Cost-effectiveness of community-based interventions for reducing opioid overdose and non-overdose deaths: simulation modeling of HEALing Communities Study

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Summary

Background The opioid overdose crisis remains a public health emergency in the United States. Evidence-based practices—including medications for opioid use disorder (MOUD) and naloxone distribution—can reduce harms, but their community-level cost-effectiveness is uncertain and may vary locally. We aimed to evaluate the cost-effectiveness of enhanced community-level implementation of evidence-based practices for opioid use disorder (OUD).

Methods We used a validated microsimulation model of OUD, calibrated with data from the HEALing Communities Study across 26 highly impacted communities in Massachusetts, New York, and Ohio. Six intervention scenarios for 2025–2030: maintaining 2024 evidence-based practice levels (status quo); improved naloxone distribution; improved MOUD retention; improved MOUD initiation; combined initiation and retention; and combined initiation, retention, and naloxone distribution. Outcomes included opioid overdose deaths (OODs), non-overdose opioid-related deaths, quality-adjusted life years (QALYs), costs (healthcare and societal), and incremental cost-effectiveness ratios (ICERs).

Findings Maintaining 2024 evidence-based practice levels was projected to yield OODs of 39–468 per 100,000 and non-overdose deaths of 238–3018 per 100,000 across communities. Enhancing MOUD initiation, retention, and naloxone distribution reduced OODs by 15–40% and non-overdose deaths by 7–24%, producing the largest QALY gains (1006–38,292). From the healthcare perspective, improved initiation plus retention was cost-effective in all communities (ICER US$11,765–US$91,058 per QALY); from the societal perspective, all enhanced scenarios were cost-saving (US$121 million–US$4.74 billion net savings).

Interpretation Community-level enhancement of MOUD initiation and retention, and for some communities also enhancing naloxone distribution, can substantially reduce opioid-related—overdose and non-overdose—deaths. These strategies are cost-effective from a healthcare perspective and cost-saving from a societal perspective, supporting investment in comprehensive, community-tailored interventions.

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Research in context

Evidence before this study

We searched PubMed/MEDLINE, Embase, and medRxiv for studies published after 2000 using combinations of terms related to "opioid use disorder", "overdose", "cost-effectiveness", "naloxone", and "medications for opioid use disorder (MOUD)". We also reviewed reference lists of relevant articles and policy reports. Previous evaluations of opioid use disorder (OUD) interventions have mainly assessed single intervention strategies or national-level models, which limit their usefulness for local decision-making. Community-specific analyses, such as from the HEALing Communities Study (HCS) have projected reductions in opioid overdose deaths under enhanced implementation of evidence-based practices, but the associated costs and cost-effectiveness at the community level have not been quantified. In addition, prior cost-effectiveness studies have not incorporated non-overdose opioid-related deaths and broader societal costs, such as productivity losses and criminal legal costs. As a result, the overall value of comprehensive, community-tailored implementation strategies remains insufficiently characterized.

Added value of this study

Using data from the HCS, we applied a validated microsimulation model (OPSiM) that was calibrated separately for 26 highly impacted communities in Massachusetts, New York, and Ohio to project outcomes between 2025 and 2030 under six intervention scenarios: maintaining 2024 evidence-based practice levels (status quo); improved naloxone distribution; improved MOUD retention; improved MOUD initiation; combined initiation and retention; and combined initiation, retention, and naloxone distribution. We included both overdose and non-overdose opioid-related mortality and analyzed results from healthcare and societal perspectives. We identified that a combined strategy of enhancing MOUD initiation and retention, and naloxone distribution where needed, would reduce overdose deaths by 15–40% and non-overdose deaths by 7–24%. These strategies were found to be cost-effective from the healthcare perspective and cost-saving from the societal perspective, reflecting large reductions in productivity losses and criminal legal costs despite higher MOUD and naloxone spending.

Implications of all the available evidence

These findings support comprehensive, community-tailored implementation of evidence-based practices that have improved MOUD initiation and retention and expanded naloxone distribution. Such strategies can reduce opioid-related mortality, yield major health gains, and economic value. By quantifying these outcomes across different communities, our study provides a practical framework that policymakers can use to prioritize their resources in responding to the opioid crisis.

Introduction

Although opioid overdose deaths (OODs) have recently decreased, the opioid overdose crisis in the United States (US) remains a public health emergency, with annual opioid overdose deaths (OODs) reaching 80,000 in recent years.[1] Evidence-based interventions, including medications for opioid use disorder (MOUD), overdose education and naloxone distribution, and safer opioid prescribing practices, have demonstrated effectiveness in reducing fatal overdoses.[2] However, significant barriers—such as limited treatment access and retention, inadequate naloxone distribution, and substantial local variability in opioid use patterns—continue to impede their optimal implementation. These challenges underscore the need not only to identify efficacious strategies to reduce OODs, but also to recognize which interventions represent the most effective use of constrained healthcare resources.

Cost-effectiveness analyses can guide policymakers to determine how best to allocate limited resources. Prior research on the cost-effectiveness of interventions for opioid use disorder (OUD) has often centered on singular interventions or at a national level,[3–6] limiting their applicability to the multifaceted nature of the crisis, which varies across local settings. To inform practical, evidence-based decision-making, community-level modeling that combines clinical outcomes with economic resources is essential.

The Helping to End Addiction Long-term® (HEALing) Communities Study (HCS),[7,8] conducted in 67 communities across four states, provided an opportunity to evaluate the effectiveness of a community-engaged intervention to reduce OODs through increased utilization of evidence-based practices. The evidence-based practices were organized into three areas: overdose education and naloxone distribution,

effective delivery of medication for OUD (MOUD), and safer opioid prescribing practices.[8] Using HCS data, we previously estimated changes in OODs under scenarios of enhanced implementation of evidence-based practices in 26 highly impacted communities in Massachusetts, New York, and Ohio.[9] While the clinical benefits of enhanced implementation of evidence-based practices are increasingly clear, the associated costs and cost-effectiveness remain insufficiently characterized.

In this study, we aimed to fill this gap by evaluating the economic burden of opioid overdoses and assessing the cost-effectiveness of enhanced community-level interventions within the HCS communities. Our goal was to identify optimal intervention portfolios that yield the greatest health improvements while efficiently utilizing healthcare resources.

Methods

Model overview

We used a microsimulation model, the Opioid Policy Simulation Model (OPSiM), to evaluate the cost-effectiveness of community-level interventions targeting OUD. OPSiM simulated the clinical trajectory of opioid misuse, OUD, treatment, recovery, and overdose events in 26 communities (8 rural, 18 urban) across 3 US states (Massachusetts, New York and Ohio) heavily impacted by the opioid crisis, providing detailed insights into both individual–level transitions and broader community-level outcomes.[9] The model was parameterized using administrative data from the HCS from 2017 to 2024, complemented by information from peer-reviewed literature[10–18] and publicly available datasets.[19,20] We projected outcomes from 2025 to 2030 under different scenarios. We followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) for reporting model design and results.[21] The model was programmed in C++, with statistical analyses conducted in R (v4.3.1).

OPSiM pathways

OPSiM simulated monthly transitions between five mutually exclusive health states among individuals aged ≥12 years: (I) Prescription Opioid Misuse Only (i.e., no illicit opioid use), (II) Illicit Opioid Use (with or without prescription opioid misuse, without OUD), (III) OUD, (IV) MOUD (considered recovery), and (V) Recovery without MOUD (Supplementary Methods S1, Supplementary Figures S1–S2). Simulated individuals transitioned between health states based on factors such as treatment initiation, retention, relapse, and recovery. New individuals entered the simulation into either the Prescription Opioid Misuse or Illicit Opioid Use states. Community-specific data informed the initial conditions, ensuring alignment with local OUD and misuse prevalence rates and demographic characteristics. The simulated population reflected the demographic composition of HCS communities, including individuals aged ≥12 years (mean age 39.9 years, SD 13.6), with 41.1% female (range across 26 communities: 33.6%–43.5%) and non-Hispanic White as the largest racial/ethnic group, followed by non-Hispanic Black and Hispanic populations. Further details on health state definitions, transitions, and population parameterization are provided in the supplement (Supplementary Methods S1.1, S1.2, S1.3, Supplementary Tables S1–S11).

The OPSiM model simulated opioid overdose events, which may be either non-fatal or fatal, with fatality probabilities varying by health state and influenced by factors such as health state, treatment type, and time since relapse. In addition to opioid overdose mortality, the model accounted for opioid-related *non-overdose* mortality due to co-occurring medical issues such as injuries, infectious diseases (e.g., HIV, hepatitis C), and other non-communicable diseases,[16] which was dependent on health state and relapse status; and *other-cause* mortality, equivalent to that of the general population not using opioids, and was based on U.S. life tables (Supplementary Methods S1.4, Supplementary Tables S12–S14).[22]

Increasing the availability of naloxone in the community can help reverse overdoses and thus prevent overdose mortality. To capture the impact of naloxone availability, we followed a saturation model used in previously published studies (Supplementary Methods S1.4.2).[5,23] We used data collected by the HCS on the number of naloxone kits distributed in each community through pharmacies[24] and community-based programs. Treatment and recovery pathways allowed individuals in the OUD state to initiate MOUD with either methadone, buprenorphine, or naltrexone, with outcomes influenced by treatment retention and relapse probabilities (Supplementary Methods S1.3).[10–15] MOUD treatment discontinuation was based on the type of MOUD and an individual's number of previous treatment episodes.

Model parameters were calibrated to match 11 targets including HCS outcome measures (overdose deaths, non-fatal overdoses, MOUD utilization and retention) and published prevalence estimates (Supplementary Methods S1.5, Supplementary Tables S15–S17, Supplementary Figures S3–S4).[25,26] Calibration was performed separately for each of the 26 communities by comparing model-predicted OOD with observed trends from 2017 to 2024 (Supplementary Methods S.2).

Intervention scenarios

We used the OPSiM model to project health and economic outcomes for six OUD intervention scenarios across communities. In *Scenario 1 (Status Quo)*, the levels of MOUD initiation and retention and naloxone distributed observed in 2024 in each community were maintained for the remaining period of the analysis (i.e., through 2030). In all other scenarios, one or more

evidence-based practice components varied from 2025 to 2030, keeping the same levels observed in 2024 for the remaining components. These enhanced implementations of evidence-based practices referred to modeled improvements in MOUD initiation, MOUD retention, and naloxone distribution, as specified in the intervention scenarios described as follows. In *Scenario 2 (Improved Naloxone)*, the number of naloxone kits distributed annually was increased such that the number of available kits was at least equal to the number of individuals with OUD in each community. Naloxone distribution was scaled relative to the estimated OUD population to ensure a comparable, community-specific implementation benchmark across settings. In *Scenario 3* (*Improved Retention*), treatment recovery support was improved, resulting in MOUD treatment retention rates at the level observed in clinical trials (6-month retention of 46% for buprenorphine and naltrexone, and 74% for methadone).[27] In *Scenario 4 (Improved Initiation)*, treatment outreach and/or capacity to scale up MOUD treatment initiation were expanded so that half of individuals with OUD were receiving MOUD. Scenarios 5 and 6 combined interventions from Scenarios 2–4. In both *Scenario 5 (Improved Initiation and Retention)* and *Scenario 6 (Improved All)*, treatment retention rates and treatment initiation rates were improved to the levels in Scenarios 3 and 4, respectively (Supplementary Methods S2), and in *Scenario 6 (Improved All)*, naloxone availability was also increased to the levels in Scenario 2.

Cost-effectiveness framework

The cost-effectiveness analysis was conducted from both *healthcare* and *societal* perspectives, capturing a comprehensive range of costs and benefits associated with OUD interventions. Costs were inflated to 2023 US$ using the medical-care specific Consumer Price Index (CPI) for healthcare costs and the standard CPI for urban consumers for other costs. Future costs and health-state utilities were discounted at an annual rate of 3%, consistent with established economic evaluation standards.[28]

From the *healthcare perspective*, costs included: MOUD costs, differentiated by medication type (buprenorphine, methadone, and naltrexone); naloxone costs, including distribution costs; emergency medical services for fatal and non-fatal overdoses; and healthcare utilization costs, stratified by outpatient, inpatient, emergency department, and residential settings. From the *societal perspective*, additional costs were included to reflect broader economic impacts: criminal legal costs for individuals in the OUD state, and productivity losses attributable to opioid misuse, opioid overdose, and other opioid-related deaths.

Economic inputs came from HCS community data, public datasets, and literature (Supplementary Methods S3, Supplementary Tables S18–S20). Costs of MOUD and naloxone were obtained from public sources.[29–31] Healthcare utilization costs were derived from HCS and data from the National Survey on Drug Use and Health (NSDUH).[19] Costs associated with productivity losses captured both differences in productivity across the model health states and productivity losses associated with an overdose event.[32] Health state-level productivity costs were estimated based on a model of the relationship between hours worked and health state, using data from NSDUH. Parameters representing the relative productivity of each state derived from NSDUH were paired with age- and sex-specific productivity estimates from the literature.[33] Age-specific criminal legal costs applied to the OUD state were derived from the literature.[34,35]

Finally, utility values for each health state were retrieved from the literature.[36] These estimates did not differentiate the utility of prescription opioid misuse and illicit opioid use without OUD vs OUD. We therefore adjusted the published estimates based on data from the National Epidemiologic Survey on Alcohol and Related Conditions-III[37] (Supplementary Methods S3).

For each community, we estimated OODs and opioid-related non-overdose deaths, quality-adjusted life years (QALYs) with the status quo (i.e., with maintained evidence-based practices) and with enhanced evidence-based practices. We also evaluated the cost-effectiveness of enhanced evidence-based practices by estimating net benefits and incremental cost-effectiveness ratios (ICERs) of enhanced evidence-based practices using willingness to pay threshold of US$100,000 per QALY, which is conservative relative to thresholds commonly applied in contemporary US cost-effectiveness evaluations.[38,39] Probabilistic sensitivity analyses were conducted to jointly characterize uncertainty in cost and utility inputs. For each community, model runs were repeated across Monte Carlo draws in which cost and health-state utility parameters were sampled from prespecified probability distributions (gamma distributions for cost parameters; beta distributions for utility parameters). For each draw, total costs, QALYs, and net monetary benefit were estimated for each intervention scenario. Uncertainty in cost-effectiveness was summarized using cost-effectiveness acceptability curves across willingness-to-pay thresholds and expected loss (regret) metrics to quantify the decision uncertainty in selecting an intervention portfolio.

Ethical approval

This study protocol (Pro00038088) was approved by Advarra Inc., the HEALing Communities Study single Institutional Review Board. The analysis used de-identified data, and the requirement for informed consent was waived.

Role of the funding source

The funder had a role in the design and conduct of the study and in the review and approval of the manuscript

through the participation of a designated Science Officer, in accordance with cooperative agreement policies. The funder had no role in the data analysis, interpretation of results, or the decision to submit the manuscript for publication.

Results

Opioid-related deaths: overdose and non-overdose mortality

Across all 26 communities, maintaining 2024 evidence-based practice levels (status quo) was projected to yield a persistently high burden of opioid-related mortality from 2025 to 2030, including both overdose and non-overdose deaths. Notably, although overdose deaths have received substantial attention, we found that non-overdose opioid-related deaths (range: 238–3018 per 100,000) were substantially higher than OOD (range: 39–468 per 100,000) in nearly every community (Table 1).

Enhancing evidence-based practice levels led to meaningful reductions in both overdose and non-overdose opioid-related deaths (Table 1). Increases in MOUD initiation and retention (Scenario 5) and the combination of all interventions (Scenario 6) consistently generated the largest decreases in mortality. For instance, Scenario 6 (improved initiation, retention, and naloxone distribution) reduced OOD by 15–40% and opioid-related non-overdose deaths by 7–24% across communities. Although the relative declines in non-overdose deaths were generally smaller than those in overdose deaths, the absolute reductions were substantial, highlighting that comprehensive evidence-based practice improvements can mitigate a broader range of opioid-related fatal outcomes than previously emphasized (Supplementary Table S21).

Cost-effectiveness of evidence-based practices: healthcare and societal perspectives

All intervention scenarios increased QALYs relative to the status quo; however, improved naloxone only resulted in the smallest increase in QALYs (range: 0–58 total QALYs across communities) among all scenarios evaluated. In contrast, improving treatment initiation and retention and naloxone distribution consistently generated the largest health gains, with incremental QALY increases ranging from 1006 to 38,292 across communities compared with the status quo (Table 2). Improvements in both MOUD initiation and retention had a synergistic effect on improvement in QALYs, resulting in higher QALY improvement than the sum of individual improvement observed by MOUD retention only and MOUD initiation only in every community.

Compared to the status quo, all scenarios of evidence-based practice implementation resulted in increased opioid-related healthcare spending (Supplementary Table S22). Naloxone distribution already surpassed OUD prevalence in 11 of the 26 communities (i.e., no need for further naloxone improvement); improving naloxone distribution was implemented in the remaining 15 communities. From a healthcare perspective, the scenario with improved treatment initiation and retention (Scenario 5) and the scenario with improved treatment initiation and retention and naloxone distribution (Scenario 6) were the most cost-effective options, resulting in the highest net benefit in every community (Supplementary Table S23). Among the communities where naloxone improvement was implemented (15 communities), Scenario 6 was cost-effective in 12 communities, with ICERs ranging from US$32,670 to US$91,058 per QALY gained. Scenario 4 was cost-effective for the remaining three communities. In the other 11 communities where naloxone was not enhanced, Scenario 5 was the most cost-effective. ICERs for this scenario were between US$11,765 and US$52,791 per QALY gained (Table 3). In contrast, scenarios focusing on single interventions (e.g., improved initiation, improved retention, or improved naloxone) offered limited health gains at higher relative costs. The results of the community-level cost-effectiveness analyses are shown in Supplementary Figure S5.

Opioid-related costs burden

Fig. 1 illustrates per-capita healthcare expenditures related to opioid misuse across the 26 communities with the status quo and the scenario with improvement in all three evidence-based practice areas (Scenario 6). With the status quo, annual per-capita spending generally ranged from approximately US$700 in lower-prevalence communities to over US$4000 in communities with the highest OUD burden. After enhancing MOUD initiation and retention and naloxone distribution, these expenditures rose further, surpassing US$6000 per capita in the most heavily affected communities.

Fig. 2 and Supplementary Tables S24–S25 summarize 6-year healthcare spending associated with opioid misuse in each community. With the status quo scenario (maintaining 2024 evidence-based practice levels), healthcare expenditures related to opioid misuse were predominantly driven by acute and hospital-based services. For example, Community 6 had over 65% of its total expenditure (US$1070 million) in inpatient and emergency settings, reflecting a system primarily responding to OUD-related crises through inpatient admissions and emergency visits. With enhanced initiation, retention, and naloxone distribution, there was a shift in the composition of healthcare spending. Although total expenditure generally increased across most communities, much of this rise was attributable to greater investments in MOUD and naloxone. These investments coincided with reductions in emergency department and inpatient utilization.

Community	Maintain 2024 EBP Levels (Scenario 1)	Improved naloxone (Scenario 2)	Improved retention (Scenario 3)	Improved initiation (Scenario 4)	Improved initiation & retention (Scenario 5)	Improved all (Scenario 6)
C1: INT	–	*Nalo: 0%*	*Rete: 28%*	*Init: 184%*	*Init: 116%, Rete: 210%*	*Init: 116%, Rete: 210%, Nalo: 0%*
C1: OOD	**259**	**0 [0%]**	**−7 [−3%]**	**−30 [−12%]**	**−42 [−16%]**	**−42 [−16%]**
C1: OND	**3018**	**0 [0%]**	**−66 [−2%]**	**−297 [−10%]**	**−393 [−13%]**	**−393 [−13%]**
C2: INT	–	*Nalo: 23%*	*Rete: 229%*	*Init: 202%*	*Init: 29%, Rete: 511%*	*Init: 29%, Rete: 511%, Nalo: 23%*
C2: OOD	**232**	**−10 [−4%]**	**−35 [−15%]**	**−11 [−5%]**	**−72 [−31%]**	**−78 [−34%]**
C2: OND	**1629**	**0 [0%]**	**−150 [−9%]**	**−201 [−12%]**	**−383 [−24%]**	**−383 [−24%]**
C3: INT	–	*Nalo: 165%*	*Rete: 139%*	*Init: 781%*	*Init: 365%, Rete: 1131%*	*Init: 365%, Rete: 1131%, Nalo: 165%*
C3: OOD	**265**	**−52 [−20%]**	**−9 [−3%]**	**−31 [−12%]**	**−65 [−25%]**	**−105 [−40%]**
C3: OND	**2412**	**4 [0%]**	**−55 [−2%]**	**−328 [−14%]**	**−484 [−20%]**	**−483 [−20%]**
C4: INT	–	*Nalo: 49%*	*Rete: 38%*	*Init: 151%*	*Init: 73%, Rete: 182%*	*Init: 73%, Rete: 182%, Nalo: 49%*
C4: OOD	**248**	**−29 [−12%]**	**−9 [−4%]**	**−26 [−10%]**	**−40 [−16%]**	**−65 [−26%]**
C4: OND	**2193**	**1 [0%]**	**−79 [−4%]**	**−188 [−9%]**	**−300 [−14%]**	**−299 [−14%]**
C5: INT	–	*Nalo: 0%*	*Rete: 55%*	*Init: 145%*	*Init: 41%, Rete: 186%*	*Init: 41%, Rete: 186%, Nalo: 0%*
C5: OOD	**468**	**0 [0%]**	**−31 [−7%]**	**−44 [−9%]**	**−87 [−19%]**	**−87 [−19%]**
C5: OND	**1875**	**0 [0%]**	**−96 [−5%]**	**−172 [−9%]**	**−291 [−16%]**	**−291 [−16%]**
C6: INT	–	*Nalo: 20%*	*Rete: 47%*	*Init: 149%*	*Init: 54%, Rete: 182%*	*Init: 54%, Rete: 182%, Nalo: 20%*
C6: OOD	**321**	**−8 [−2%]**	**−18 [−6%]**	**−30 [−9%]**	**−55 [−17%]**	**−61 [−19%]**
C6: OND	**1799**	**1 [0%]**	**−69 [−4%]**	**−158 [−9%]**	**−241 [−13%]**	**−242 [−13%]**
C7: INT	–	*Nalo: 0%*	*Rete: 44%*	*Init: 231%*	*Init: 133%, Rete: 280%*	*Init: 133%, Rete: 280%, Nalo: 0%*
C7: OOD	**143**	**0 [0%]**	**−5 [−3%]**	**−17 [−12%]**	**−26 [−18%]**	**−26 [−18%]**
C7: OND	**1622**	**0 [0%]**	**−43 [−3%]**	**−167 [−10%]**	**−239 [−15%]**	**−239 [−15%]**
C8: INT	–	*Nalo: 84%*	*Rete: 174%*	*Init: 298%*	*Init: 105%, Rete: 600%*	*Init: 105%, Rete: 600%, Nalo: 84%*
C8: OOD	**190**	**−22 [−12%]**	**−17 [−9%]**	**−13 [−7%]**	**−53 [−28%]**	**−69 [−36%]**
C8: OND	**1022**	**2 [0%]**	**−49 [−5%]**	**−126 [−12%]**	**−200 [−20%]**	**−199 [−19%]**
C9: INT	–	*Nalo: 0%*	*Rete: 56%*	*Init: 228%*	*Init: 111%, Rete: 287%*	*Init: 111%, Rete: 287%, Nalo: 0%*
C9: OOD	**208**	**0 [0%]**	**−9 [−4%]**	**−21 [−10%]**	**−37 [−18%]**	**−37 [−18%]**
C9: OND	**1338**	**0 [0%]**	**−35 [−3%]**	**−130 [−10%]**	**−180 [−13%]**	**−179 [−13%]**
C10: INT	–	*Nalo: 84%*	*Rete: 31%*	*Init: 191%*	*Init: 131%, Rete: 233%*	*Init: 131%, Rete: 233%, Nalo: 84%*
C10: OOD	**57**	**−9 [−16%]**	**−2 [−4%]**	**−7 [−12%]**	**−10 [−18%]**	**−17 [−30%]**
C10: OND	**932**	**0 [0%]**	**−20 [−2%]**	**−106 [−11%]**	**−139 [−15%]**	**−138 [−15%]**
C11: INT	–	*Nalo: 19%*	*Rete: 65%*	*Init: 274%*	*Init: 133%, Rete: 349%*	*Init: 134%, Rete: 349%, Nalo: 19%*
C11: OOD	**131**	**−3 [−2%]**	**−6 [−5%]**	**−14 [−11%]**	**−25 [−19%]**	**−27 [−21%]**
C11: OND	**1081**	**0 [0%]**	**−32 [−3%]**	**−103 [−10%]**	**−158 [−15%]**	**−158 [−15%]**
C12: INT	–	*Nalo: 0%*	*Rete: 54%*	*Init: 173%*	*Init: 72%, Rete: 223%*	*Init: 72%, Rete: 223%, Nalo: 0%*
C12: OOD	**274**	**0 [0%]**	**−15 [−5%]**	**−27 [−10%]**	**−50 [−18%]**	**−50 [−18%]**
C12: OND	**1006**	**0 [0%]**	**−32 [−3%]**	**−82 [−8%]**	**−122 [−12%]**	**−122 [−12%]**
C13: INT	–	*Nalo: 60%*	*Rete: 143%*	*Init: 188%*	*Init: 33%, Rete: 355%*	*Init: 33%, Rete: 355%, Nalo: 60%*
C13: OOD	**135**	**−14 [−10%]**	**−15 [−11%]**	**−9 [−7%]**	**−33 [−24%]**	**−43 [−32%]**
C13: OND	**591**	**0 [0%]**	**−34 [−6%]**	**−64 [−11%]**	**−101 [−17%]**	**−101 [−17%]**
C14: INT	–	*Nalo: 0%*	*Rete: 64%*	*Init: 238%*	*Init: 125%, Rete: 327%*	*Init: 125%, Rete: 327%, Nalo: 0%*
C14: OOD	**163**	**0 [0%]**	**−8 [−5%]**	**−17 [−10%]**	**−34 [−21%]**	**−34 [−21%]**
C14: OND	**628**	**0 [0%]**	**−17 [−3%]**	**−68 [−11%]**	**−93 [−15%]**	**−93 [−15%]**
C15: INT	–	*Nalo: 6%*	*Rete: 61%*	*Init: 209%*	*Init: 110%, Rete: 292%*	*Init: 110%, Rete: 292%, Nalo: 6%*
C15: OOD	**111**	**−1 [−1%]**	**−6 [−5%]**	**−11 [−10%]**	**−22 [−20%]**	**−23 [−21%]**
C15: OND	**562**	**0 [0%]**	**−12 [−2%]**	**−56 [−10%]**	**−73 [−13%]**	**−72 [−13%]**
C16: INT	–	*Nalo: 114%*	*Rete: 41%*	*Init: 76%*	*Init: 26%, Rete: 118%*	*Init: 26%, Rete: 118%, Nalo: 114%*
C16: OOD	**82**	**−17 [−21%]**	**−6 [−7%]**	**−5 [−6%]**	**−13 [−16%]**	**−28 [−34%]**
C16: OND	**496**	**0 [0%]**	**−12 [−2%]**	**−30 [−6%]**	**−42 [−8%]**	**−41 [−8%]**
C17: INT	–	*Nalo: 0%*	*Rete: 135%*	*Init: 141%*	*Init: 30%, Rete: 315%*	*Init: 30%, Rete: 315%, Nalo: 0%*
C17: OOD	**82**	**0 [0%]**	**−9 [−11%]**	**−4 [−5%]**	**−18 [−22%]**	**−18 [−22%]**
C17: OND	**471**	**0 [0%]**	**−26 [−6%]**	**−46 [−10%]**	**−74 [−16%]**	**−74 [−16%]**
C18: INT	–	*Nalo: 60%*	*Rete: 69%*	*Init: 319%*	*Init: 186%, Rete: 440%*	*Init: 186%, Rete: 440%, Nalo: 60%*
C18: OOD	**39**	**−6 [−15%]**	**−2 [−5%]**	**−4 [−10%]**	**−8 [−20%]**	**−12 [−31%]**
C18: OND	**536**	**1 [0%]**	**−9 [−2%]**	**−54 [−10%]**	**−71 [−13%]**	**−71 [−13%]**

(Table 1 continues on next page)

Community	Maintain 2024 EBP Levels (Scenario 1)	Improved naloxone (Scenario 2)	Improved retention (Scenario 3)	Improved initiation (Scenario 4)	Improved initiation & retention (Scenario 5)	Improved all (Scenario 6)
(Continued from previous page)						
C19: INT	–	*Nalo: 38%*	*Rete: 68%*	*Init: 283%*	*Init: 143%, Rete: 372%*	*Init: 142%, Rete: 372%, Nalo: 38%*
C19: OOD	**95**	**−7 [−7%]**	**−4 [−4%]**	**−10 [−10%]**	**−19 [−20%]**	**−24 [−25%]**
C19: OND	**403**	**0 [0%]**	**−8 [−2%]**	**−36 [−9%]**	**−48 [−12%]**	**−47 [−12%]**
C20: INT	–	*Nalo: 162%*	*Rete: 122%*	*Init: 194%*	*Init: 50%, Rete: 344%*	*Init: 50%, Rete: 344%, Nalo: 162%*
C20: OOD	**99**	**−18 [−18%]**	**−9 [−9%]**	**−7 [−7%]**	**−23 [−23%]**	**−36 [−36%]**
C20: OND	**453**	**0 [0%]**	**−24 [−5%]**	**−50 [−11%]**	**−79 [−17%]**	**−78 [−17%]**
C21: INT	–	*Nalo: 0%*	*Rete: 84%*	*Init: 377%*	*Init: 216%, Rete: 546%*	*Init: 216%, Rete: 546%, Nalo: 0%*
C21: OOD	**42**	**0 [0%]**	**−2 [−5%]**	**−4 [−9%]**	**−9 [−21%]**	**−9 [−21%]**
C21: OND	**453**	**0 [0%]**	**−8 [−2%]**	**−46 [−10%]**	**−62 [−14%]**	**−62 [−14%]**
C22: INT	–	*Nalo: 0%*	*Rete: 170%*	*Init: 226%*	*Init: 63%, Rete: 478%*	*Init: 63%, Rete: 478%, Nalo: 0%*
C22: OOD	**123**	**0 [0%]**	**−12 [−10%]**	**−7 [−6%]**	**−31 [−25%]**	**−31 [−25%]**
C22: OND	**353**	**0 [0%]**	**−17 [−5%]**	**−38 [−11%]**	**−59 [−17%]**	**−59 [−17%]**
C23: INT	–	*Nalo: 0%*	*Rete: 226%*	*Init: 435%*	*Init: 150%, Rete: 892%*	*Init: 150%, Rete: 892%, Nalo: 0%*
C23: OOD	**63**	**0 [0%]**	**−4 [−6%]**	**−4 [−6%]**	**−16 [−25%]**	**−16 [−25%]**
C23: OND	**336**	**0 [0%]**	**−13 [−4%]**	**−44 [−13%]**	**−65 [−19%]**	**−65 [−19%]**
C24: INT	–	*Nalo: 35%*	*Rete: 86%*	*Init: 149%*	*Init: 46%, Rete: 250%*	*Init: 46%, Rete: 250%, Nalo: 35%*
C24: OOD	**103**	**−6 [−6%]**	**−9 [−9%]**	**−8 [−8%]**	**−22 [−21%]**	**−26 [−25%]**
C24: OND	**352**	**0 [0%]**	**−14 [−4%]**	**−29 [−8%]**	**−47 [−13%]**	**−47 [−13%]**
C25: INT	–	*Nalo: 14%*	*Rete: 259%*	*Init: 555%*	*Init: 217%, Rete: 1234%*	*Init: 217%, Rete: 1234%, Nalo: 14%*
C25: OOD	**71**	**−2 [−3%]**	**−4 [−6%]**	**−4 [−6%]**	**−19 [−27%]**	**−20 [−28%]**
C25: OND	**319**	**0 [0%]**	**−9 [−3%]**	**−37 [−12%]**	**−54 [−17%]**	**−54 [−17%]**
C26: INT	–	*Nalo: 0%*	*Rete: 62%*	*Init: 184%*	*Init: 92%, Rete: 265%*	*Init: 92%, Rete: 265%, Nalo: 0%*
C26: OOD	**110**	**0 [0%]**	**−5 [−5%]**	**−8 [−7%]**	**−17 [−15%]**	**−17 [−15%]**
C26: OND	**238**	**0 [0%]**	**−3 [−1%]**	**−14 [−6%]**	**−17 [−7%]**	**−17 [−7%]**

Abbreviations: C = Community; EBP = Evidence-Based Practice; Init = Improved Initiation; INT = Intervention; Nalo = Improved Naloxone Distribution; OND = Opioid-Related Non-Overdose Deaths; OOD = Opioid-Related Overdose Deaths; Rete = Improved Retention. Percentages in brackets represent the relative change compared to the "Maintain 2024 EBP Levels" scenario. Negative percentages indicate a reduction in deaths, while positive percentages indicate an increase. Communities are in order of decreasing OUD prevalence in the "Maintain 2024 EBP Levels" scenario.

Table 1: **Opioid-related overdose and non-overdose deaths (per 100,000) under status quo (Scenario 1) and changes for Scenarios 2–6 between 2025 and 2030.**

From a societal perspective, all enhanced evidence-based practice scenarios were projected to generate cost savings across every community. When reductions in criminal legal costs and productivity losses were included, net savings ranged from US$121 million to US$4.74 billion over six years (Supplementary Table S26). These societal gains occurred despite higher direct health care spending. For example, in Community 6, health care costs rose by US$416 million (from US$1.07 billion to US$1.49 billion), yet total societal costs fell by US$2.39 billion (from US$10.02 billion to US$7.63 billion), demonstrating a substantial overall economic benefit. Supplementary Tables S27–S28 summarize 6-year societal costs associated with opioid misuse in each community.

Sensitivity analysis

Supplementary Figure S6 displays the probability that each intervention scenario is the cost-effective option from a healthcare perspective at a willingness-to-pay threshold of US$100,000 per QALY gained, stratified by community. Across all 26 communities, Scenario 6 consistently demonstrated the highest probability of being cost-effective, which exceeded 50% in most communities. Supplementary Figure S7 presents the expected loss associated with each intervention scenario. Expected loss can be interpreted as the financial penalty or "regret" of not selecting the cost-effective strategy. In all communities, Scenario 6 consistently exhibited the lowest expected loss, clustered near zero on the horizontal axis.

Discussion

In this community-level decision analytic modeling study, we found that enhancing the implementation of evidence-based practices for OUD—increasing MOUD initiation and retention, with naloxone distribution in some communities—was a highly cost-effective strategy to combat the opioid overdose crisis. From a societal perspective, these interventions are projected to be net cost-saving. Importantly, while reductions in overdose deaths were expected, our findings underscore that non-overdose opioid-related deaths, which have been relatively underemphasized in public health strategies, also decline substantially.

Previous cost-effectiveness analyses of OUD intervention have focused on comparing MOUD approaches

Community	Maintain 2024 EBP Levels (Scenario 1)	Improved naloxone (Scenario 2)	Improved retention (Scenario 3)	Improved initiation (Scenario 4)	Improved initiation & retention (Scenario 5)	Improved all (Scenario 6)
C1	–	*Nalo: 0%*	*Rete: 28%*	*Init: 184%*	*Init: 116%, Rete: 210%*	*Init: 116%, Rete: 210%, Nalo: 0%*
	44,769	**+0 [0%]**	**+545 [1%]**	**+2266 [5%]**	**+3129 [7%]**	**+3129 [7%]**
C2	–	*Nalo: 23%*	*Rete: 229%*	*Init: 202%*	*Init: 29%, Rete: 511%*	*Init: 29%, Rete: 511%, Nalo: 23%*
	62,265	**+10 [0%]**	**+3150 [5%]**	**+2919 [5%]**	**+7476 [12%]**	**+7483 [12%]**
C3	–	*Nalo: 165%*	*Rete: 139%*	*Init: 781%*	*Init: 365%, Rete: 1131%*	*Init: 365%, Rete: 1131%, Nalo: 165%*
	63,787	**+49 [0%]**	**+918 [1%]**	**+4421 [7%]**	**+7577 [12%]**	**+7626 [12%]**
C4	–	*Nalo: 49%*	*Rete: 38%*	*Init: 151%*	*Init: 73%, Rete: 182%*	*Init: 73%, Rete: 182%, Nalo: 49%*
	40,913	**+0 [0%]**	**+862 [2%]**	**+1795 [4%]**	**+3062 [7%]**	**+3062 [7%]**
C5	–	*Nalo: 0%*	*Rete: 55%*	*Init: 145%*	*Init: 41%, Rete: 186%*	*Init: 41%, Rete: 186%, Nalo: 0%*
	27,347	**+0 [0%]**	**+770 [3%]**	**+1196 [4%]**	**+2225 [8%]**	**+2225 [8%]**
C6	–	*Nalo: 20%*	*Rete: 47%*	*Init: 149%*	*Init: 54%, Rete: 182%*	*Init: 54%, Rete: 182%, Nalo: 20%*
	101,730	**+16 [0%]**	**+2402 [2%]**	**+4494 [4%]**	**+7752 [8%]**	**+7768 [8%]**
C7	–	*Nalo: 0%*	*Rete: 44%*	*Init: 231%*	*Init: 133%, Rete: 280%*	*Init: 133%, Rete: 280%, Nalo: 0%*
	33,828	**+0 [0%]**	**+467 [1%]**	**+1748 [5%]**	**+2576 [8%]**	**+2576 [8%]**
C8	–	*Nalo: 84%*	*Rete: 174%*	*Init: 298%*	*Init: 105%, Rete: 600%*	*Init: 105%, Rete: 600%, Nalo: 84%*
	42,391	**+19 [0%]**	**+1273 [3%]**	**+2140 [5%]**	**+4481 [11%]**	**+4501 [11%]**
C9	–	*Nalo: 0%*	*Rete: 56%*	*Init: 228%*	*Init: 111%, Rete: 287%*	*Init: 111%, Rete: 287%, Nalo: 0%*
	61,358	**+2 [0%]**	**+1083 [2%]**	**+2956 [5%]**	**+4766 [8%]**	**+4765 [8%]**
C10	–	*Nalo: 84%*	*Rete: 31%*	*Init: 191%*	*Init: 131%, Rete: 233%*	*Init: 131%, Rete: 233%, Nalo: 84%*
	32,161	**+8 [0%]**	**+320 [1%]**	**+1522 [5%]**	**+2065 [6%]**	**+2071 [6%]**
C11	–	*Nalo: 19%*	*Rete: 65%*	*Init: 274%*	*Init: 133%, Rete: 349%*	*Init: 134%, Rete: 349%, Nalo: 19%*
	20,085	**+2 [0%]**	**+344 [2%]**	**+1034 [5%]**	**+1667 [8%]**	**+1668 [8%]**
C12	–	*Nalo: 0%*	*Rete: 54%*	*Init: 173%*	*Init: 72%, Rete: 223%*	*Init: 72%, Rete: 223%, Nalo: 0%*
	39,174	**+19 [0%]**	**+683 [2%]**	**+1764 [5%]**	**+2749 [7%]**	**+2766 [7%]**
C13	–	*Nalo: 60%*	*Rete: 143%*	*Init: 188%*	*Init: 33%, Rete: 355%*	*Init: 33%, Rete: 355%, Nalo: 60%*
	33,550	**+13 [0%]**	**+1218 [4%]**	**+1316 [4%]**	**+3028 [9%]**	**+3039 [9%]**
C14	–	*Nalo: 0%*	*Rete: 64%*	*Init: 238%*	*Init: 125%, Rete: 327%*	*Init: 125%, Rete: 327%, Nalo: 0%*
	468,662	**+0 [0%]**	**+8207 [2%]**	**+23,868 [5%]**	**+38,292 [8%]**	**+38,292 [8%]**
C15	–	*Nalo: 6%*	*Rete: 61%*	*Init: 209%*	*Init: 110%, Rete: 292%*	*Init: 110%, Rete: 292%, Nalo: 6%*
	155,814	**+8 [0%]**	**+2670 [2%]**	**+7243 [5%]**	**+11,681 [7%]**	**+11,688 [8%]**
C16	–	*Nalo: 114%*	*Rete: 41%*	*Init: 76%*	*Init: 26%, Rete: 118%*	*Init: 26%, Rete: 118%, Nalo: 114%*
	18,267	**+14 [0%]**	**+386 [2%]**	**+532 [3%]**	**+993 [5%]**	**+1006 [6%]**
C17	–	*Nalo: 0%*	*Rete: 135%*	*Init: 141%*	*Init: 30%, Rete: 315%*	*Init: 30%, Rete: 315%, Nalo: 0%*
	42,693	**+0 [0%]**	**+1375 [3%]**	**+1377 [3%]**	**+3262 [8%]**	**+3262 [8%]**
C18	–	*Nalo: 60%*	*Rete: 69%*	*Init: 319%*	*Init: 186%, Rete: 440%*	*Init: 186%, Rete: 440%, Nalo: 60%*
	30,249	**+7 [0%]**	**+422 [1%]**	**+1651 [5%]**	**+2530 [8%]**	**+2536 [8%]**
C19	–	*Nalo: 38%*	*Rete: 68%*	*Init: 283%*	*Init: 143%, Rete: 372%*	*Init: 142%, Rete: 372%, Nalo: 38%*
	239,809	**+58 [0%]**	**+4040 [2%]**	**+12,510 [5%]**	**+20,035 [8%]**	**+20,100 [8%]**
C20	–	*Nalo: 162%*	*Rete: 122%*	*Init: 194%*	*Init: 50%, Rete: 344%*	*Init: 50%, Rete: 344%, Nalo: 162%*
	58,746	**+42 [0%]**	**+1776 [3%]**	**+2324 [4%]**	**+4918 [8%]**	**+4958 [8%]**
C21	–	*Nalo: 0%*	*Rete: 84%*	*Init: 377%*	*Init: 216%, Rete: 546%*	*Init: 216%, Rete: 546%, Nalo: 0%*
	47,646	**+0 [0%]**	**+644 [1%]**	**+2580 [5%]**	**+4084 [9%]**	**+4084 [9%]**
C22	–	*Nalo: 0%*	*Rete: 170%*	*Init: 226%*	*Init: 63%, Rete: 478%*	*Init: 63%, Rete: 478%, Nalo: 0%*
	48,086	**+0 [0%]**	**+1536 [3%]**	**+2016 [4%]**	**+4445 [9%]**	**+4445 [9%]**
C23	–	*Nalo: 0%*	*Rete: 226%*	*Init: 435%*	*Init: 150%, Rete: 892%*	*Init: 150%, Rete: 892%, Nalo: 0%*
	87,278	**+0 [0%]**	**+2167 [2%]**	**+4152 [5%]**	**+8936 [10%]**	**+8936 [10%]**
C24	–	*Nalo: 35%*	*Rete: 86%*	*Init: 149%*	*Init: 46%, Rete: 250%*	*Init: 46%, Rete: 250%, Nalo: 35%*
	25,230	**+9 [0%]**	**+669 [3%]**	**+939 [4%]**	**+1863 [7%]**	**+1870 [7%]**
C25	–	*Nalo: 14%*	*Rete: 259%*	*Init: 555%*	*Init: 217%, Rete: 1234%*	*Init: 217%, Rete: 1234%, Nalo: 14%*
	78,087	**+4 [0%]**	**+1660 [2%]**	**+3995 [5%]**	**+8396 [11%]**	**+8402 [11%]**
C26	–	*Nalo: 0%*	*Rete: 62%*	*Init: 184%*	*Init: 92%, Rete: 265%*	*Init: 92%, Rete: 265%, Nalo: 0%*
	260,949	**+0 [0%]**	**+4085 [2%]**	**+9766 [4%]**	**+16,119 [6%]**	**+16,119 [6%]**

Abbreviations: C = Community; EBP = Evidence-Based Practice; Init = Improved Initiation; Nalo = Improved Naloxone Distribution; QALY = Quality-Adjusted Life-Year; Rete = Improved Retention. Percentages in brackets represent the relative change compared to the "Maintain 2022 EBP Levels" scenario. Negative percentages indicate a reduction in QALYs, while positive percentages indicate an increase.

Table 2: **Total (Scenario 1) and incremental (Scenarios 2–6) QALYs associated with opioid misuse between 2025 and 2030.**

Community	Maintain 2024 EBP levels (Scenario 1)	Improved Naloxone (Scenario 2)	Improved Retention (Scenario 3)	Improved Initiation (Scenario 4)	Improved Initiation & Retention (Scenario 5)	Improved All (Scenario 6)
C1[a]	–	[a]	Weakly dominated	$19,392	$43,834	[a]
C2	–	Weakly dominated	$11,371	Weakly dominated	$13,668	$108,535
C3	–	Weakly dominated	Weakly dominated	$19,187	$27,266	$53,540
C4	Weakly dominated	–	Weakly dominated	$14,301	weakly dominated	$32,670
C5[a]	–	[a]	Dominated	$17,877	$ 39,326	[a]
C6	–	Weakly dominated	Weakly dominated	$19,429	$37,799	$74,743
C7[a]	–	[a]	Weakly dominated	$13,273	$39,440	[a]
C8	–	Weakly dominated	$11,445	Weakly dominated	$12,788	$56,117
C9[a]	–	[a]	Weakly dominated	$19,680	$32,430	[a]
C10	–	Weakly dominated	Weakly dominated	$6659	$26,983	$124,503
C11	–	Weakly dominated	Weakly dominated	$14,248	$39,185	$123,115
C12[a]	–	[a]	Weakly dominated	$17,828	$ 52,791	[a]
C13	–	Weakly dominated	Weakly dominated	Weakly dominated	$20,509	$65,618
C14[a]	–	[a]	Weakly dominated	$8009	$ 18,045	[a]
C15	–	Weakly dominated	Weakly dominated	$8384	$13,436	$64,803
C16	–	Weakly dominated	Weakly dominated	$8446	$14,727	$46,136
C17[a]	–	[a]	$12,530	Weakly dominated	$16,354	[a]
C18	–	Weakly dominated	Weakly dominated	$3847	$10,774	$91,058
C19	–	Weakly dominated	Weakly dominated	$11,099	$25,968	$67,164
C20	–	Weakly dominated	Weakly dominated	Weakly dominated	$16,339	$49,063
C21[a]	–	[a]	Weakly dominated	$6633	$15,297	[a]
C22[a]	–	[a]	$9887	Weakly dominated	$11,765	[a]
C23[a]	–	[a]	$16,722	Weakly dominated	$18,163	[a]
C24	–	Weakly dominated	Weakly dominated	$6453	$14,635	$51,363
C25	–	Weakly dominated	$7979	Weakly dominated	$10,077	$83,387
C26[a]	–	[a]	Dominated	$2161	$12,378	[a]

Abbreviations: C = Community; EBP = Evidence-Based Practice; ICER = Incremental Cost-Effectiveness Ratio. [a]Naloxone improvement scenarios were excluded as communities have already implemented enhanced naloxone distribution. Therefore, Scenarios 1 & 2, and Scenarios 5 & 6 are equivalent. Green: Cost-effective scenario. Orange: dominated (not cost-effective) scenario.

Table 3: **ICERs of different levels of EBPs across 26 communities.**

at a national level.[40,41] In line with recent modeling efforts,[3–6,9] our results underscore the importance of tailored, multifaceted strategies at the community level that consider local epidemic dynamics and current levels of interventions. Importantly, we expanded this work to evaluate the cost-effectiveness of multiple strategies at the community level and found that scaling up evidence-based practices was not only cost-effective from a healthcare perspective, but they were cost-saving from societal perspective—an important finding that justifies investment in combating the opioid overdose crisis.

An important insight from our analysis is the substantial—and often underrecognized—burden of non-overdose opioid-related mortality. The finding that non-overdose opioid-related deaths (ranging from 238 to 3018 per 100,000) substantially outnumbered overdose deaths (39–468 per 100,000) in nearly all communities underscores the importance of broadening outcome metrics beyond overdose deaths alone. It also highlights the importance of multifaceted interventions that address the full spectrum of opioid-related harm.

From a healthcare perspective, interventions improving MOUD initiation and retention, alone or in combination with naloxone distribution, were consistently cost-effective strategies across nearly all communities. By contrast, single-focus strategies, such as improved naloxone distribution alone, often yielded limited QALY gains at higher relative costs, underscoring that a piecemeal approach is less efficient than a comprehensive intervention scenario. We also found that in 3 of our 15 communities, enhancing naloxone distribution alongside increased MOUD initiation and retention was less cost-effective than increasing MOUD initiation and retention only. Communities need to be aware of their own level of evidence-based practice implementation in judging whether further enhancements are cost-effective.

Although we estimated that implementation of evidence-based practices would generally increase total healthcare spending—particularly through higher MOUD expenditures—this investment would partially be offset by reductions in high-cost hospital-based care. Over time, shifting resources from reactive, episodic services to proactive, evidence-based interventions can be both clinically and economically advantageous. We found that communities with the highest OUD prevalence bore the greatest upfront costs but also could gain the most in terms of reduced mortality.

Furthermore, when examined from a societal perspective, all enhanced implementation scenarios

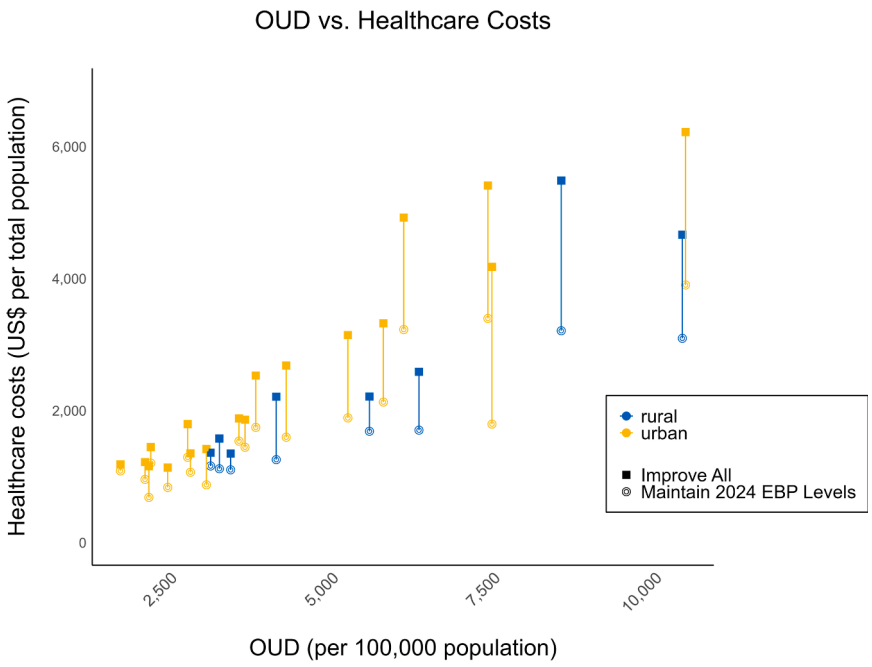

Fig. 1: Per capita cost (US$) associated with opioid misuse in each community increases with increase in OUD prevalence (population 12 years old and older). Abbreviations: EBP = Evidence-Based Practice; OUD = Opioid Use Disorder.

were cost saving, reflecting reductions in productivity losses and criminal legal costs that outweighed increases in health care expenditures. These findings reinforce the value of community-level investments in comprehensive OUD treatment strategies, not only to improve population health but also to generate broader societal economic benefits.

While the HCS reported a non-statistically significant 9% reduction in OODs during the comparison period from July 2021 through June 2022, our study shows the evidence-based practice interventions can be a good value for money.[42] The HCS lacked the power to detect reductions smaller than 40%, had short duration of the implementation, faced COVID-19 disruptions, and was impacted by the evolving illicit drug market that resulted in a national surge in the number of fentanyl-related overdose deaths.[43] Despite the lack of significance in the 1-year comparison period for the main study outcome, the detailed multi-year community-level data collected as part of the HCS offers an unparalleled opportunity to model the relationships between evidence-based practices and opioid-related outcomes and project future QALYs and costs under different scenarios of evidence-based practice implementation.[9]

The magnitude of increases in MOUD initiation and retention modeled here warrants careful interpretation. Sustained population-level increases exceeding 50% in either initiation or long-term retention have rarely been observed outside of highly targeted or time-limited interventions. While programs such as emergency department–initiated buprenorphine, jail- and prison-based initiation, and low-threshold treatment models have demonstrated meaningful short-term gains in treatment uptake, maintaining engagement over time—particularly in fentanyl-dominated drug markets—has proven far more challenging. Barriers include limited treatment capacity, workforce shortages, fragmented care transitions, housing instability, co-occurring mental illness, and persistent stigma. Even in jurisdictions that have relaxed regulatory barriers, achieving and sustaining large-scale improvements in retention likely requires coordinated investments across healthcare delivery, social services, and community-based support systems.

Our targets for initiation and retention are aspirational and would require coordinated structural and programmatic changes to be approached in practice. Recent reforms and service models make progress plausible on a scale. These include: permanent expansion of methadone take homes, telehealth initiation, and modernized OTP admission criteria under the 2024 SAMHSA Final Rule[44,45]; low threshold buprenorphine, including mobile and syringe service delivery, reaching high risk groups with meaningful retention[46–48]; contingency management improving adherence in randomized trials[49]; rapid induction extended release buprenorphine improving early retention, including in the fentanyl era[50]; emergency department initiation to capture patients at crisis contact points[51]; and nurse led and integrated primary care models that expand prescriber capacity and reduce downstream costs.[52,53] By

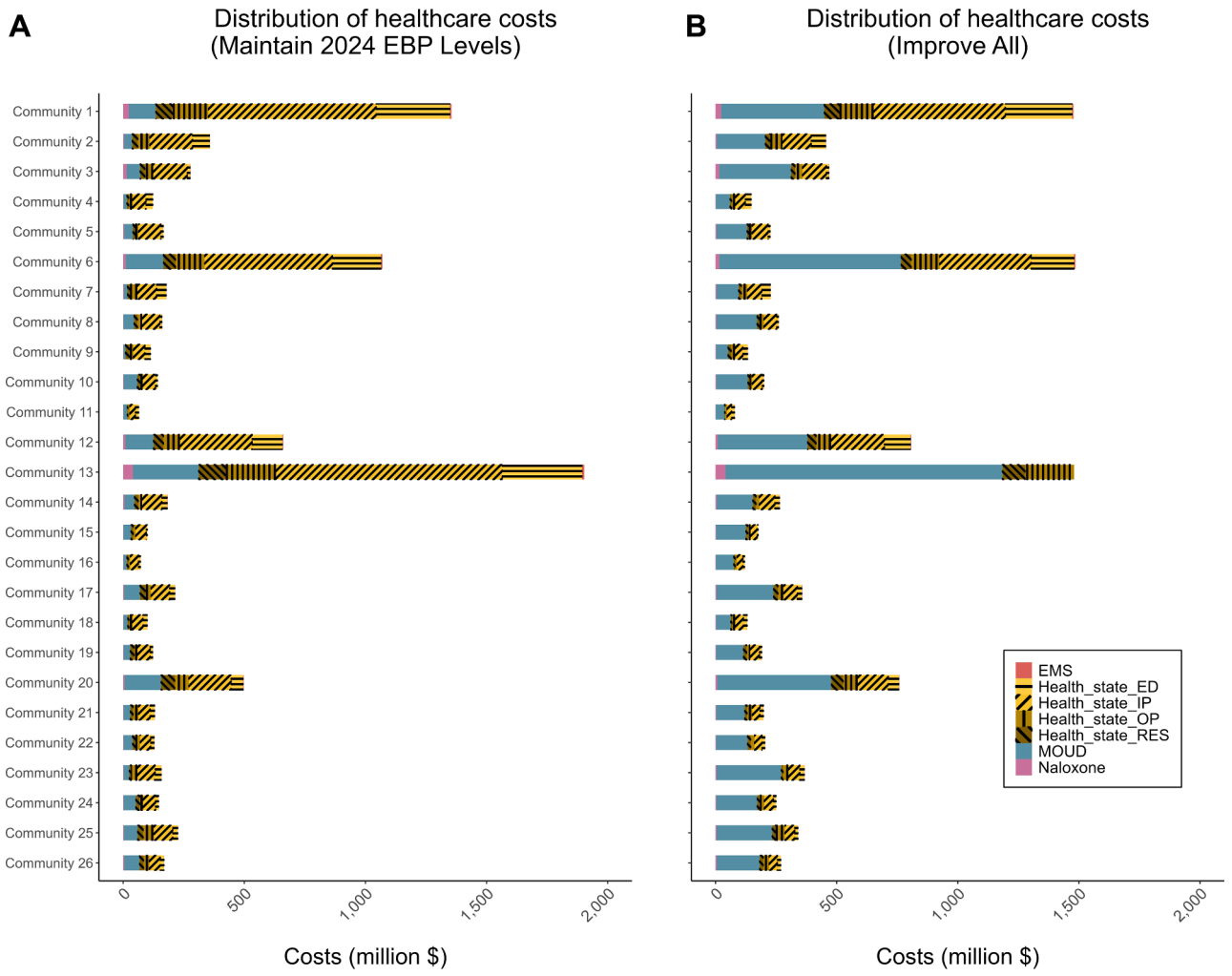

Fig. 2: Total 5-year healthcare costs associated with opioid misuse in each community (A) Maintain 2024 EBP levels; (B) Improve all interventions. Abbreviations: EBP = Evidence-Based Practice; ED = Emergency Department; EMS = Emergency Medical Services; IP = Inpatient; MOUD = Medications for Opioid Use Disorder; OP = Outpatient; RES = Residential Services.

contrast, elimination of the X waiver alone did not meaningfully increase buprenorphine dispensing, underscoring the need for multi-component implementation—financing, workforce, contingency management, and low barrier design—to translate policy into real-world gains.[54]

This study has limitations. First, our analysis did not account for barriers to MOUD treatment and naloxone distribution, including financial, regulatory, and social stigma barriers and we did not account for potential capacity constraints. Second, estimates of MOUD treatment benefits are based largely on observational studies and may be affected by non-random treatment entry and exit, with residual confounding potentially overstating observed effects.[17,18] Third, several model inputs were informed by the NSDUH, which is designed to represent the noninstitutionalized civilian population. As such, it underrepresents individuals at highest risk of opioid-related overdose and non-overdose mortality, including those who are incarcerated, unhoused, or otherwise socially marginalized. The field would benefit from sustained investment in complementary epidemiological surveillance systems designed to better capture these populations, which would strengthen future modeling and policy analyses.[55] Fourth, we did not explicitly incorporate heterogeneity in overdose risk related to drug dose, potency, or route of administration (e.g., injection versus non-injection use), which may influence both fatal overdose risk and intervention effectiveness. Fifth, we did not explicitly model other evidence-based practices such as prevention through communication campaigns or recovery-related behavioral interventions. Sixth, we did not incorporate the costs borne by families and child welfare systems when parents die from overdoses. Seventh, the model was calibrated with data

up to 2024. It is possible that the reduction in overdose deaths has been driven, in part, by an increase in the uptake of evidence-based practices or changes in the drug supply, which are topics for further investigation. Finally, given the five-year projection horizon, long-term QALY gains from averted deaths are likely understated.

In conclusion, enhanced community-level implementation of evidence-based practices—particularly improvements in MOUD initiation and retention, combined with appropriate naloxone distribution—was projected to reduce opioid-related overdose and non-overdose deaths across communities, while remaining cost-effective or cost-saving. These results provide strong evidence that investments in comprehensive, community-tailored OUD strategies represent high-value approaches to addressing the opioid crisis.

Contributors

JC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing—original draft, Writing—review & editing, and responsible for the decision to submit the manuscript; MS: Conceptualization, Data curation, Formal analysis, Methodology, Software, Visualization, Writing—original draft, Writing—review & editing; QC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing; WD: Conceptualization, Data curation, Formal analysis, Methodology, Writing—original draft, Writing—review & editing; JX: Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing—review & editing; GAZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing—original draft, Writing—review & editing; AA: Data curation, Formal analysis, Methodology, Writing—review & editing; JAB: Formal analysis, Methodology, Writing—review & editing; MC: Formal analysis, Methodology, Writing—review & editing; NF: Formal analysis, Writing—review & editing; LAF: Writing—review & editing; AH: Formal analysis, Methodology, Writing—review & editing; KMK: Formal analysis, Methodology, Writing—review & editing; CEK: Writing—review & editing; ML: Formal analysis, Writing—review & editing; BPL: Formal analysis, Writing—review & editing; EO: Funding acquisition, Writing—review & editing; SMR: Writing—review & editing; JHS: Funding acquisition, Writing—review & editing; BRS: Formal analysis, Methodology, Writing—review & editing; EES: Methodology, Writing—review & editing; LES: Writing—review & editing; JV: Data curation, Formal analysis, Writing—review & editing; ABK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing; CB: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing—original draft, Writing—review & editing.

Data sharing statement

The data that support the findings of this study are available from Medicaid and States. Restrictions apply to the availability of these data, which were used under license for this study.

Declaration of interests

MC and KK have received personal fees for consulting in opioid litigations. All other authors have nothing to report.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2026.101480.

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