Title: Advancing Understanding of Opioid-Related Overdose Mortality in Connecticut Through Simulation

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Introduction:
Despite the declines in both fatal and nonfatal opioid-related overdoses that have been observed since 2023 [1–3], opioid overdose continues to be a leading cause of preventable death among those ages 1-44 in both Connecticut and the United States [4] [1]. Specific populations may also be at higher risk of opioid overdose Connecticut, as overdose levels have been observed to "spike" for specific periods of time due to changes in drug supply and use habits [5,6]. The ongoing surveillance of the illicit opioid supply, and the effects of interventions to prevent opioid overdose are of interest to groups seeking to further reduce the risk of opioid overdose such as state agencies, policymakers, public health, and harm reduction organizations.

Rates of opioid overdose have varied across states and have been observed to be influenced by numerous factors, including the initiation of state-level policies and the spread of fentanyl [5,7,8]. Analyzing these complex trends through simulation with the aid of system dynamics (SD) models is a promising approach that can help improve understanding of how opioid use and overdose is affected by enacted policies and changes in health and prevention systems [9–11]. SD models are well suited for testing hypotheses and scenarios that are relevant to those seeking to reduce opioid-related morbidity and mortality [10–12]. In addition, simulations generated by SD models can give communities actionable data to inform local implementation of efforts to address opioid morbidity and mortality, such as expanding access to medications for opioid use disorder (MOUD) and increasing distribution of the overdose-reversal medication Naloxone.

SD modelers working with investigators in a large urban health system in Connecticut have sought to incorporate SD modeling into a randomized controlled clinical trial to evaluate the potential benefits of supporting behavior change among those who use opioids through a digital health intervention [13]. Investigators also identified potential synergies between SD modeling at the population-level and community-based engagement that is occurring as part of the clinical trial. Local study partners who are interested in the underlying dynamic complexities of opioid use, including those from state agencies, local health departments, and harm reduction, have engaged with the SD modeling team as part of an ongoing collaboration. These efforts have helped the SD modelers to obtain sufficient data to support development of simulation models for the state, which can in turn provide actionable data back to partners through an ongoing data-sharing process. Funding support for this project was provided by NIH NIDA as an HD2A Innovation and Acceleration Project.

Methods:
A simulation model of opioid morbidity and mortality developed and validated for Connecticut at the state-level for the population aged ≥12 to capture trends related to opioid morbidity and mortality for years 2009 through 2035. This model evaluates the long-term impacts of efforts to improve availability of evidence-based services to prevent opioid overdose - such as naloxone

distribution and linkage to medication-based treatments for opioid use disorder. Development of this model has been informed by our previous work investigating the dynamics of the opioid epidemic in New York State [14] and evaluating the impacts of Good Samaritan Laws in Connecticut [15]. For a full explanation of the feedback loops and equations which define this model structure, please refer to our previous publication which has focused on results from a similar SD model for New York State. We employed Vensim® DSS v10.3.2 from Ventana Systems to develop, simulate, and validate this model.

This model has been calibrated to 15 historical data sets for available years between 2009 and 2024 (see Table 1). The unique data landscape of Connecticut, and our ongoing collaboration with local partners, assisted us in gaining access to more recent measures than were previously available at the state-level for New York. Despite these differences, our calibration method yielded comparable results to the previously developed New York model in large part due to their shared model structure and assumptions. Assistance was also provided by Wake Forest School of Medicine Data Infrastructure Support Center who acted as a liaison for obtaining key IQVIA data sources. All data series were included in the payoff definition with defined weights to improve optimization.

Calibration of this model was done iteratively with input from content experts, co-investigators from Yale School of Public Health and Yale School of Medicine, and local partners. As MOUD treatment access and occurrence of fatal and nonfatal opioid overdose are the respective primary and secondary outcomes which are the focus of our study, we reviewed model outputs and revised model structure over the course of two years with the goal of achieving the most accurate calibration for these variables. Over this time, preliminary calibrations were shared with content experts and co-investigators to assist in validating model behavior. Simulations presented in this paper capture the most current version of the model, however we plan to continue updating the model as new data are made available.

Results:

Base Run

Base run results demonstrate a strong fit to available time series data for the state of Connecticut. Notably, the model has captured the recent decrease of opioid overdose fatalities observed after 2024, which followed the peak-period of opioid overdose deaths in the state from 2020-2023 [1]. Other key data series such as those for ED visits due to opioid overdose, naloxone adminstration, patient receiving treatment at opioid-treatment programs, and others also displayed a strong fit (see supplementary material).

Counterfactual Scenario 1: No Drop in Potency After COVID-19

In alignment with our larger study efforts, we carefully reviwed all model output files to identify and examine key parameters that were correlated with changes in opioid-related overdose over time. We also conducted multiple simulations to determine causal factors related to the dramatic decline in opioid deaths which occured after 2023. This decline has been linked to changes in potency of the opioid supply (primarily Fentanyl) and drug adulteration, although evidence for this explanation is still preliminary [16,17]. In order to test our assumption that a change in potency was affecting probability of opioid overdose death we conducted an initial scenario test which disabled conditions in the model equations which allowed for a drop in opioid potency to occur after 2023 (as show in the base run scenario). The resulting simulation represents a counterfactual sceenario, where opioid potency and supply did not experience a "shock" which initiated a decline in opioid-overdose related deaths. The results of this scenario are presented in Figure 2.

Counterfactual Scenario 2: No expansion of MOUD in Connecticut
Increasing availability of MOUD has been supported by a variety of public health initiatives and state policies such as use of opioid settlement funds and relaxation of prescribing guidelines after the COVID-19 pandemic [18–20]. Evidence that MOUD access is protective factor from experiencing opioid overdose is well-documented among a variety of populations [21–23]. Due to this evidence, and our study's emphasis on expanding MOUD access in Connecticut, we also simulated a scenario where MOUD access stayed did not expand after 2013, which is the earliest date of historic data available to us. This counterfactual scenario, where the fractional rate of MOUD initation remains at its 2013 level is presented in Figure 3.

Counterfactual Scenario 3: No expansion of Naloxone Distribution in Connecticut
Our final counterfactual scenario addresses another major policy change and public health initiative which has been to support increased distribution of Naloxone. Naloxone distribution has also been a major focus of efforts funded through abatement funds, as well as through local initatives through state agencies and harm reduction [18,24]. Our model allows Naloxone distribution to increase during two periods: 2009-2019 and 2020 and onwards. As Naloxone distribution increased greatly during the COVID-19 pandemic, we have removed the estimated effect from this additional distribution from this simulation. This captures a counterfactual scenario in which naloxone distribution remains at its 2019 level. The resulting effect of this scenario are presented in Figure 4.

Discussion:
The base run of this SD model shows a strong fit with historic data available at the state level for Connecticut. A steady increase in deaths is observered which aligns with a period of fentanyl proliferation in the State's drug supply [5]. This effect saturates in 2017, before a second increase occurs which aligns with new adulturation and use-habits in the state, including co-occuring stimulant use [25]. This is followed by the previously-discuss sharp decline in overdose fatalities which occurs beginning in 2023. The resulting decline follows an exponential trend until the end of the simulation period in 2035.

In Counterfactual Scenario 1, the removal of the change in potency of the drug supply and probability of opioid overdose that we estimate to occur after 2023 results in very different behavior from our base run. Overdose deaths continue linear growth through the end of the simulation period. This finding illustrates that these changes in opioid supply and potency were the most defining factor which lead to the continued decline in overdose deaths observed in historic data for recent years.

In comparison, as displayed in Counterfactual Scenario 2, MOUD has little effect, saving an average of only 1.3 lives per year from 2014-2035. However, a much larger effect on total overdoses (including both fatal and nonfatal) was observed (see supporting materials). Due to the degree of uncertainty in this model, further simulation and investigation would be needed to validate this finding.

Our analysis of Naloxone simulated a much greater effect on opioid overdoses from 2020-2035, although this diminished somewhat in future years. The model estimates that the increase in Naloxone distribution which occurs after 2019 is responsible for preventing an annual average of 29 opioid-related overdose deaths per year. These preliminary results will require more investigation, but this initial estimate has provided us with evidence that recent Naloxone distribution has contributed to ongoing declines in opioid-related fatality.

The observable effect of drug potency change far outweighs the other two effects simulated in our counterfactual scenarios. However, we did not test the full removal of the effects of MOUD access or naloxone distribution which would theorhetically have a greater effect on model behavior. Likewise, if drug potency was kept to a defined range, or defined as a constant in the model, it would see a more limite effect in our results.

As the drug supply evolves in Connecticut changing drug potency will continue to be a concern for policy makers and people who use opioids, as evidenced by Scenario 1. This analysis chose only to examine a portion of the loops and factors which make up the overall Connectictut state model. The loops responsible for driving change in this analysis are Opioid Availability (B1) and Demand Driving Supply (R2). For future analyses, the interacting effects of social influence and community awareness will also be incorporate.

[Insert Figure 5]

Limitations:
While these findings are unique, the imbalance between the effects of changing potency and policy changes related to naloxone and MOUD point to the need for further investigation. Development of confidence intervels, and refined scenario testing, can help address uncertainty in the model results. Additionally many factors related change of potency and adulturation of the drug supply are outside the model of our boundary, such the effects of stimulant use. Drug markets are known to complex, and the network effects of the changes in supply and demand for opioids are not fully capture by current model structure. Further analysis is needed to improving understand the underlying dynamic relationships responsible for these trends.

Conclusion:
Traditional public health surveillance may be limited in its ability to identify the causal relationships that have influenced changes in opioid overdose mortalitiy and morbidity in recent years. Scenario testing through simulation using SD models can help overcome this barrier, and give decsion-makers rapid access to actionable data when addressing drug-related fatalities.

Figure 1: *Baseline Model Results*

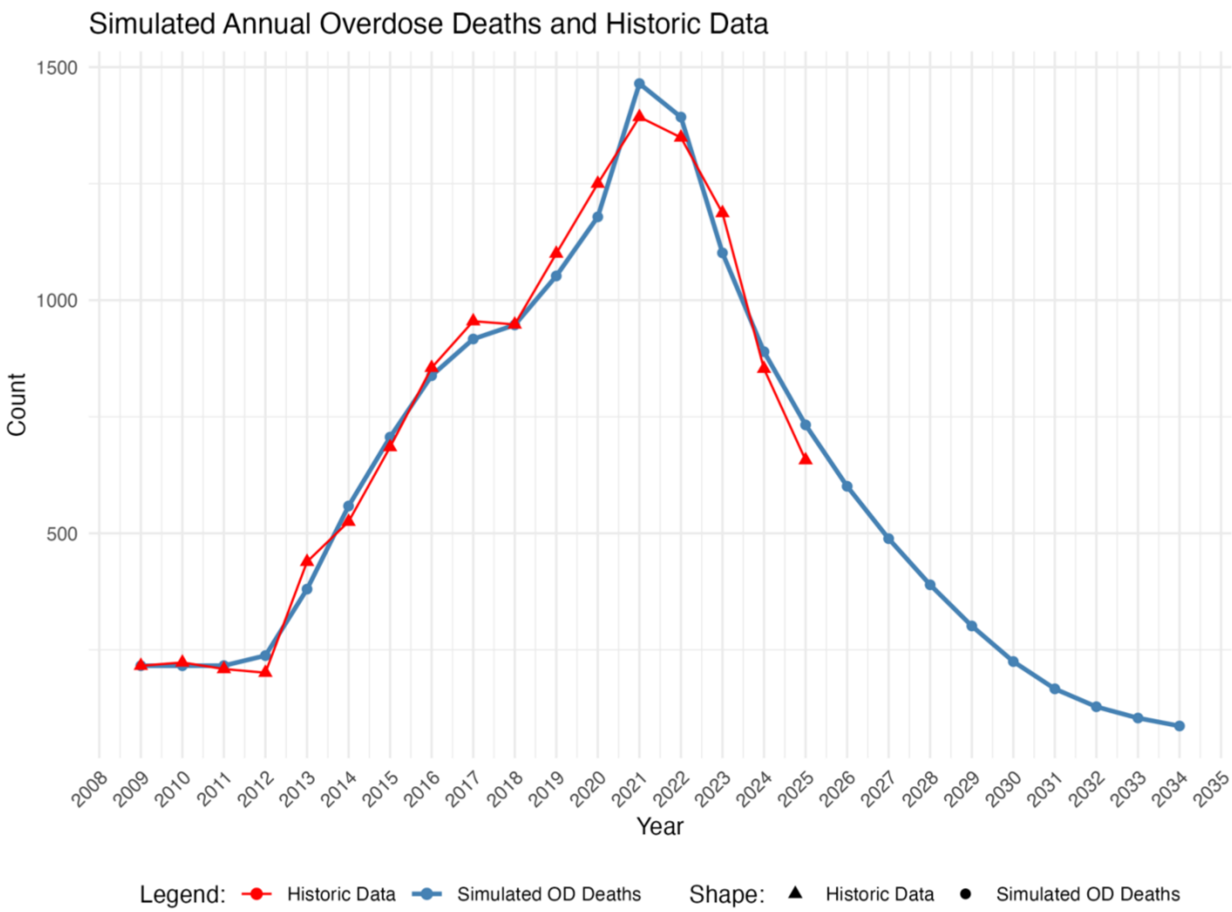


Figure 2: *Counterfactual Scenario 1*

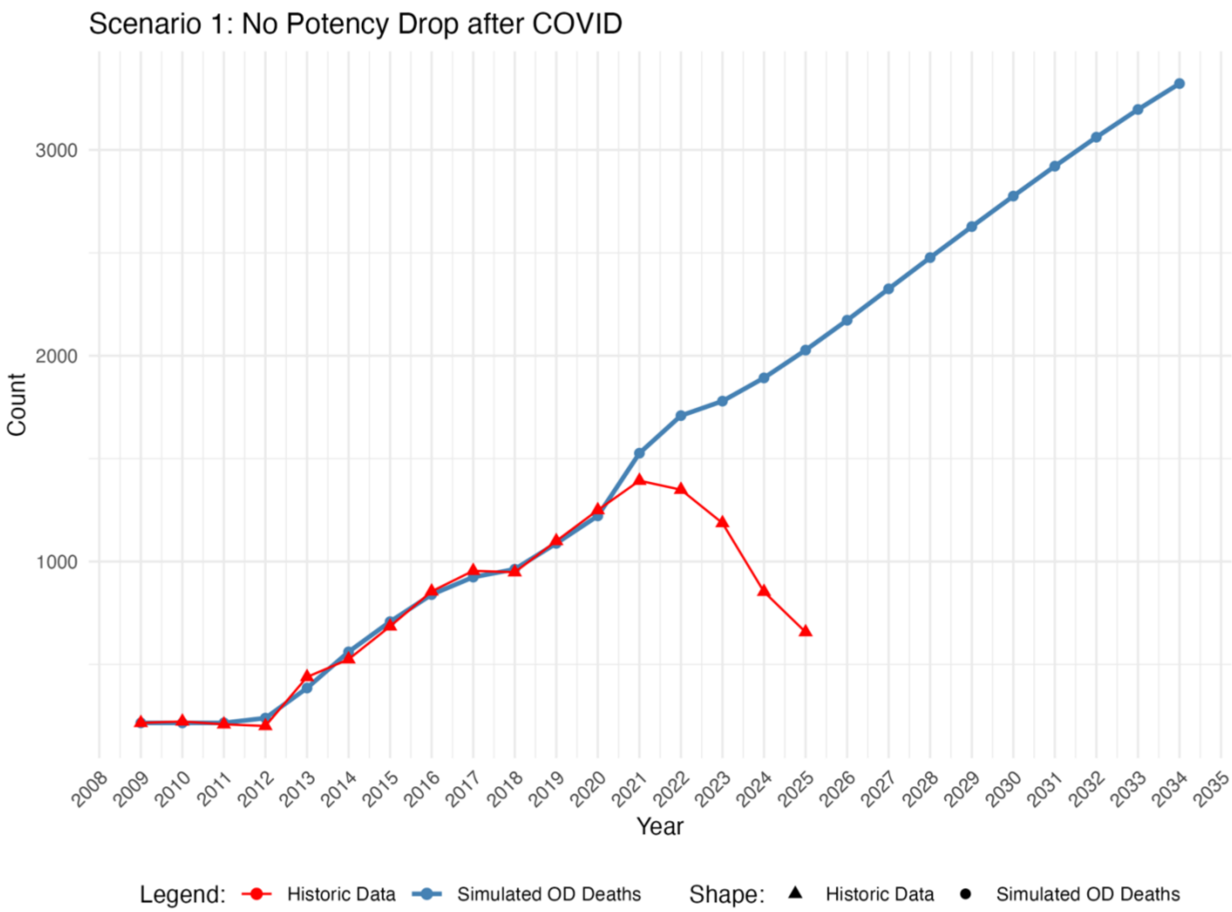


Figure 3: *Counterfactual Scenario 2*

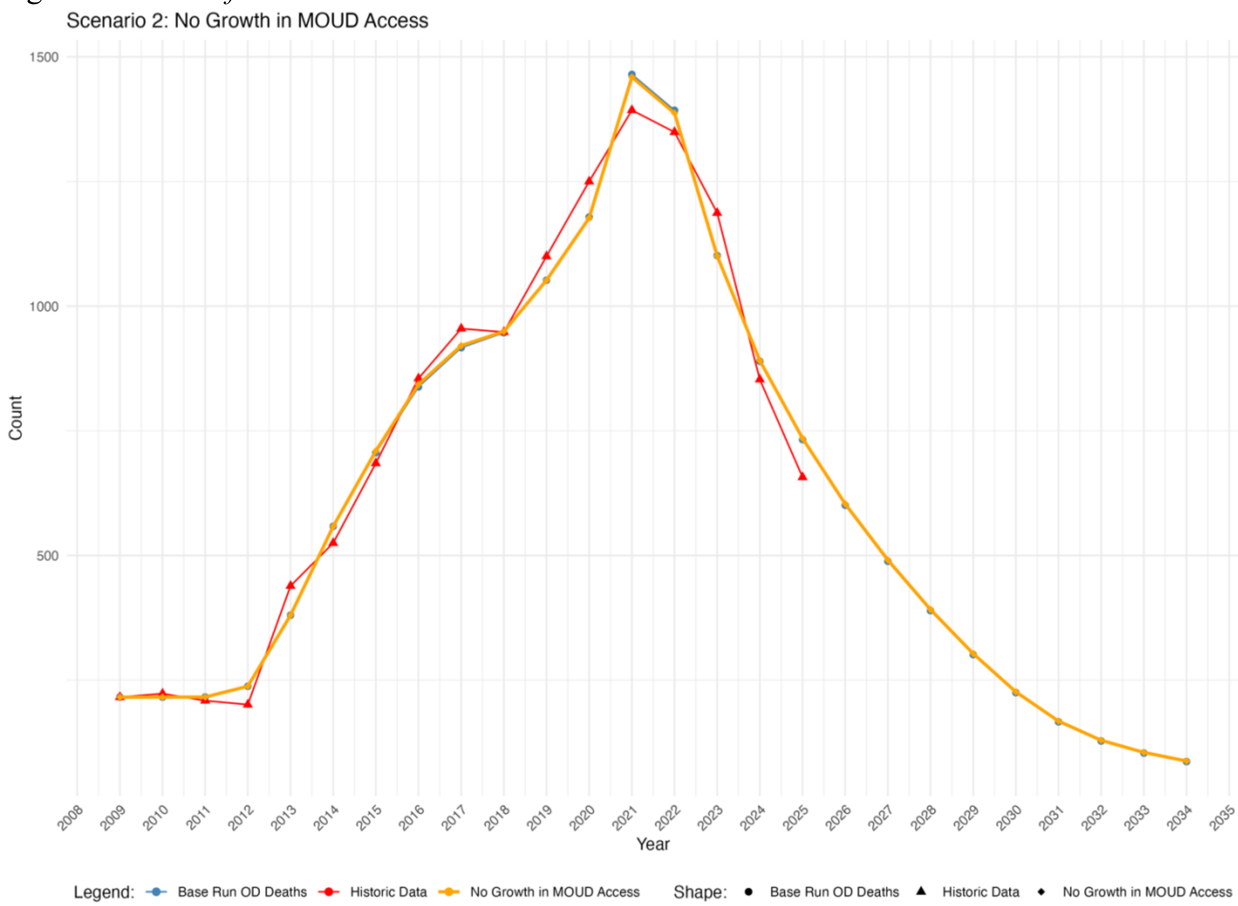


Figure 4: *Counterfactual Scenario 3*

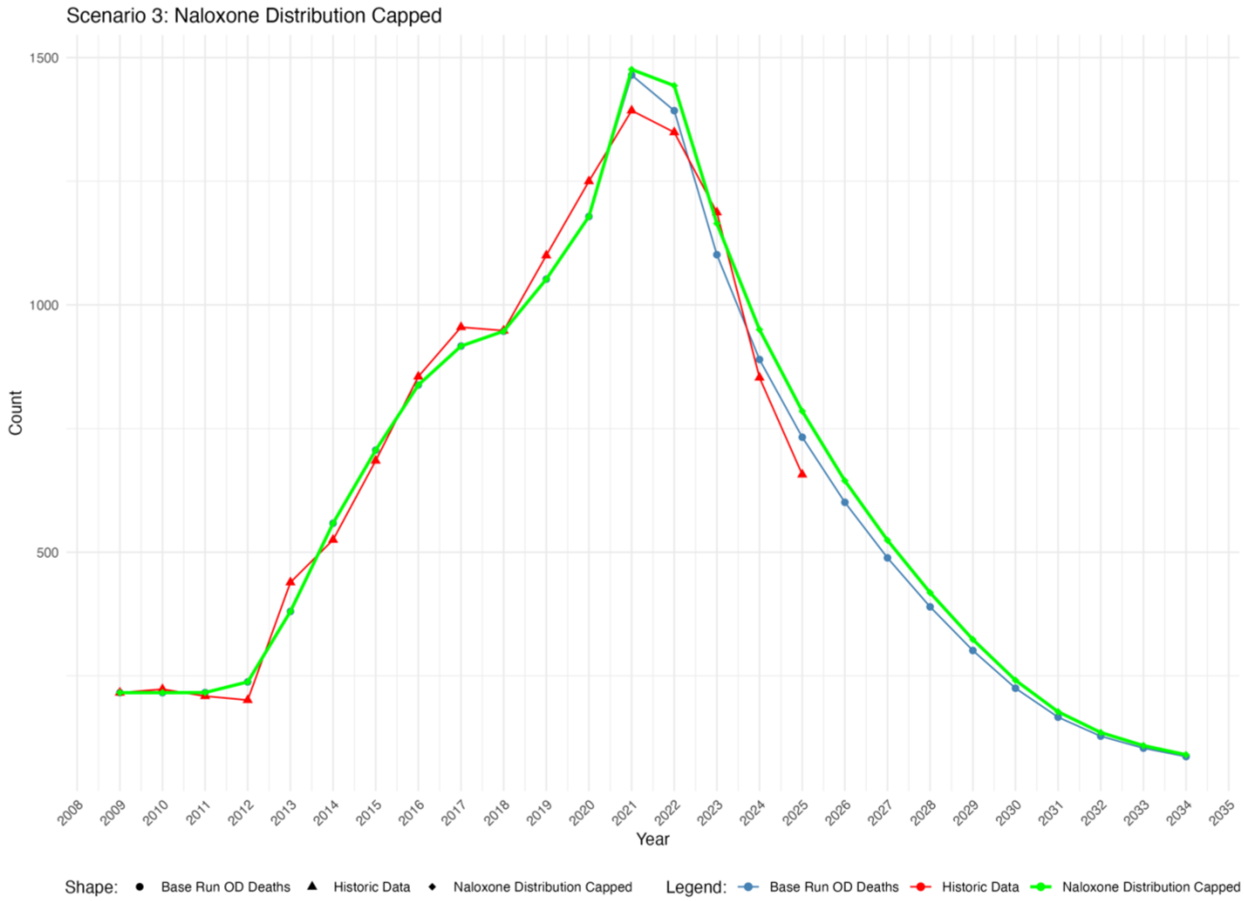
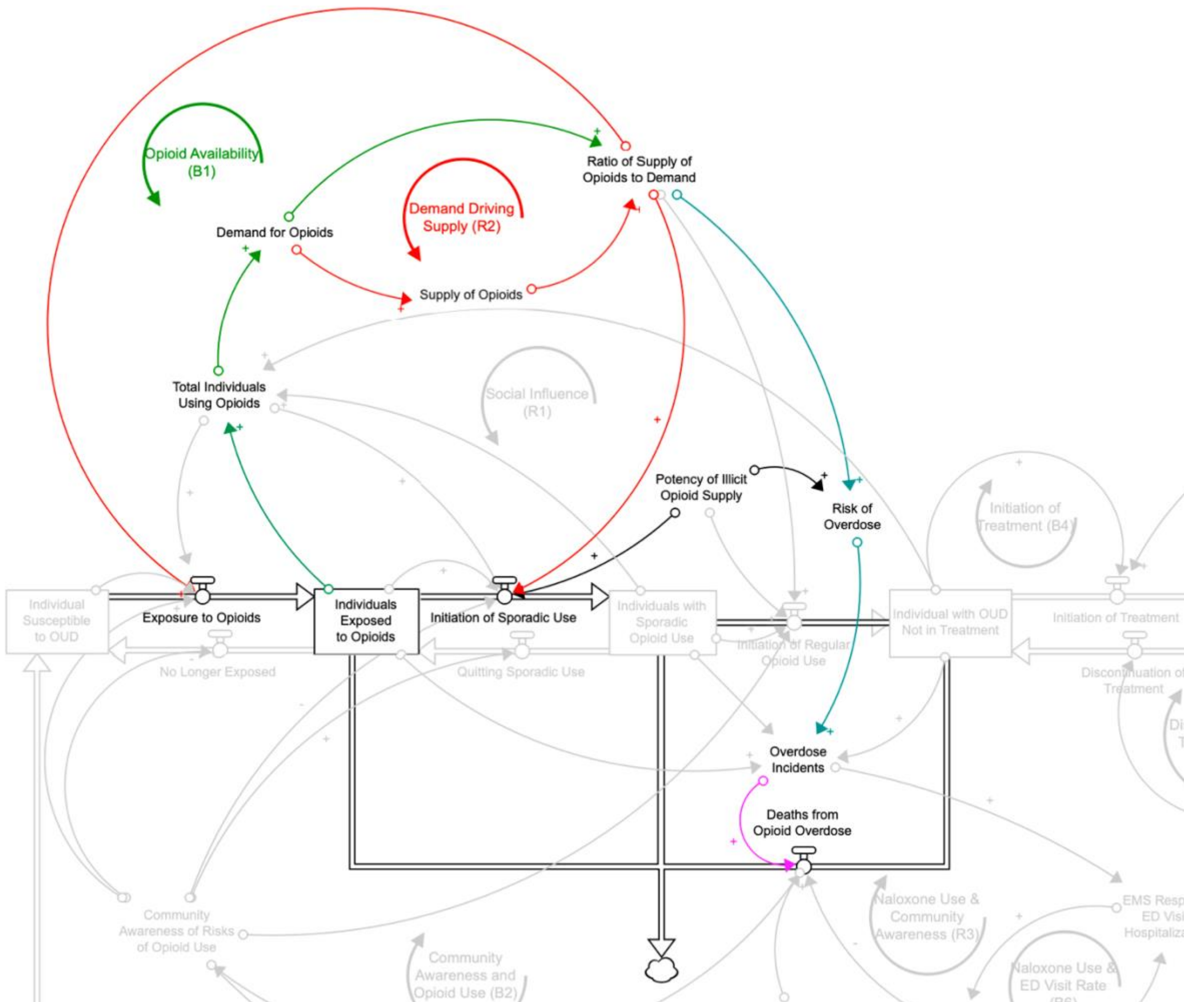


Figure 5: *Overview of key loops and variables informing scenario analyses*



These key loops include Opioid Availability (B1) and Demand Driving Supply (R2). The effects of these loops and of the variable "Potency of Illicit Opioid Supply" are illustrated in the diagram.

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TABLE 1 Opioid-related historical data series used in model development and calibration.

Model variable	Data sources	Years Utilized
Annual overdose deaths	Connecticut Office of the Chief Medical Examiner	2009-2024
Annual overdoses resulting in ED visit or hospitalization	NEMSIS Annual Reporting (provided in aggregate by Connecticut Department of Public Health)	2014-2024
Annual naloxone administrations by Community Overdose Prevention Programs	Connecticut Department of Public Health CT Syringe Services Program, Connecticut Department of Consumer Protection, Connecticut Department of Correction	2016-2024 (not available in 2019)
Annual naloxone administrations by EMS and law enforcement	NEMSIS Annual Reporting (provided in aggregate by Connecticut Department of Public Health)	2014-2024
Annual naloxone administrations by bystanders	NEMSIS Annual Reporting (provided in aggregate by Connecticut Department of Public Health)	2020-2024
Suspected opioid overdoses responded to by EMS and transported to hospital	NEMSIS Annual Reporting (provided in aggregate by Connecticut Department of Public Health)	2020-2024
Annual number of naloxone kits distributed at pharmacies or drug treatment centers	IQVIA Xponent Longitudinal Prescription Transaction Data for Opioid, Medications for Opioid Use Disorder, and Naloxone; Prescription Data Monitoring System, CT Department of Mental Health and Addiction Services	2009-2024
Total patients receiving MOUD at Opioid Treatment Programs (OTPs)	SAMHSA N-SSATS; Prescription Data Monitoring System, CT Department of Mental Health and Addiction Services	2009-2024 (not available in 2014 and 2018)
Patients receiving ≥1 buprenorphine prescription for OUD	IQVIA Xponent Longitudinal Prescription Transaction Data for Opioid, Medications for Opioid Use Disorder, and Naloxone; Prescription Data Monitoring	2009-2024

	System, CT Department of Mental Health and Addiction Services	
Annual discharge episodes from MOUD, behavioral treatment, and detoxification treatment	CT Department of Mental Health and Addiction Services	2009-2023
Annual number of individuals exposed to prescription opioids	IQVIA Xponent Longitudinal Prescription Transaction Data for Opioid, Medications for Opioid Use Disorder, and Naloxone; SAMHSA NSDUH	2015-2024 (not available in 2020)
Annual number of individuals exposed to illicit opioids	IQVIA Xponent Longitudinal Prescription Transaction Data for Opioid, Medications for Opioid Use Disorder, and Naloxone; SAMHSA NSDUH; NFLIS-Drug Public Data Query System US DEA	2015-2024 (not available in 2020)
Annual number of individuals incidentally exposed to opioids	SAMHSA NSDUH and NFLIS (Northeast Region, and Connecticut State)	2015-2024 (not available in 2020)
Annual rate of sporadic use among individuals initially exposed to opioids	SAMHSA NSDUH (National)	2015-2024 (not available in 2020)
Annual rate of regular opioid use among individuals already using opioids sporadically	SAMHSA NSDUH (National)	2015-2024 (not available in 2020)
Total population	US Census Bureau	2009-2025