Essays on the Economics of Increasing Public Naloxone Availability to Reduce Overdose Deaths

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I declare that this thesis is my own work and has not been submitted for the award of a higher degree elsewhere.

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Abstract

Between 2013 and 2022, the opioid overdose mortality rate in the United States more than tripled from 7.9 to 25.0 deaths per 100,000, claiming 500,000 lives. This thesis is concerned with one intervention used to address this crisis: naloxone distribution to the public (i.e., non-medical professionals). Naloxone is a medication that reverses the dangerous effects of an opioid overdose. However, some theoretical and empirical evidence suggests that the protective effect of naloxone might increase risk-taking related to opioid use. The thesis begins with a meta-analysis of studies that estimated the effect of naloxone distribution on fatal overdoses by exploiting variation in state laws designed to strengthen naloxone distribution (Chapter 2). Findings indicate that laws providing immunity to prescribers and dispensers had a statistically significant, reductive effect on fatal overdoses, while laws that protected recipients of naloxone or facilitated its distribution through pharmacies had no significant effect. The thesis then estimates the effectiveness of naloxone distribution based on two large-scale naloxone giveaway events held in Pennsylvania (Chapter 3). Difference-in-differences analyses revealed a large and statistically significant decrease in fatal overdoses immediately following the first giveaway but an increase following the second. The seemingly contradictory findings are explained by the changing composition of the opioid supply between the giveaways, specifically the presence of xylazine—a non-opioid tranquilizer for which naloxone is ineffective. Finally, an economic evaluation of Pennsylvania's naloxone giveaways revealed that giveaways were cost-effective from a limited healthcare perspective and cost-saving from a broader societal perspective, but that cost-effectiveness was sensitive to increases in overdose risk (Chapter 4). Taken together, these findings suggest that naloxone distribution is a valuable tool to reduce opioid overdose deaths, but that policymakers must be aware of contextual factors (e.g., opioid supply composition) and should combine naloxone distribution with educational initiatives to prevent riskier opioid use.

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Author's Declaration

I declare that this thesis is my own work and has not been submitted for the award of a higher degree elsewhere. I offer the following additional statements about the content of this thesis:

- Chapter 3 of this thesis, The Effect of Untargeted Naloxone Distribution on Opioid Overdose Outcomes, was published in the journal Health Economics in September 2023: Dowd, William N. "The effect of untargeted naloxone distribution on opioid overdose outcomes." Health economics 32.12 (2023): 2801-2818. Only minor changes have been made to the version of the analysis presented in this thesis.
- The approach used to estimate the number of people with opioid use disorder in Chapter 4 is my work developed through a collaboration with other researchers. A manuscript describing the approach is being prepared: Dowd, W.N., Chen, Q., Chhatwal, J., Barbosa, C., Oga, E., Kulkarni, N., Xiao, J., Aldridge, A.P., Zarkin, G.A., & Knudsen, A.B. (2024). Estimating Community-Level Prevalence of Opioid Use Disorder: Extrapolating from Medicaid Claims Data and other Publicly Available Data Sources. Unpublished Manuscript. The approach is being used for other analyses to which I am a contributing author.
- An abstract describing the content of Chapter 4 was, at the time this thesis was submitted, under review for presentation the 2024 Annual Meeting for the Society for Medical Decision Making in October 2024.

Word Count

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*Consistent with Lancaster University's Postgraduate Research Regulations, this word count includes the main text of the thesis, footnotes, and data and text incorporated into diagrams, tables or figures. It excludes material preceding the main text of the thesis and material following the main text of the thesis (e.g., the appendices and the list of references).

1 Introduction

1.1 Background and Motivation

Opioids have been consumed for their analgesic and euphoric effects throughout the span of human civilization. Evidence suggests that the Sumerian civilization extracted opium from the poppy flower as least as early as the third millennium B.C.E., and written records describing the use of opium in Europe, Asia, and Africa have been found from the classical period through the renaissance (Brownstein, 1993). Although opium was used across disparate civilizations for several millennia, understanding of the substance was limited until its active ingredient—morphine—was first isolated and described in the scientific literature in 1805. As with many innovations during this period, a rapid process of development followed, leading to a proliferation of commercial products containing morphine (Brook et al., 2017). As the use of morphine expanded, so too did opioid addiction, which led to limitations on the import and sale of opium and morphine products for non-medical use in the United States and elsewhere (Brook et al., 2017).

Throughout the late nineteenth and into the twentieth century, scientists sought to develop novel opioids, in part to produce a formula that would be safer and less prone to abuse than morphine or opium (Brownstein, 1993). This led to the development of heroin in 1894, and later fully synthetic opioids such as methadone in 1937 (Boysen et al., 2023). Over the next several decades, increasingly potent synthetic opioids such as fentanyl were developed. Fentanyl has considerable utility as an analgesic, but the risks inherent in its potency were immediately evident to scientists and physicians as its approval in the United States was delayed in the face of opposition driven by concerns that it was too potent and had considerable potential for abuse (Boysen et al., 2023). Fentanyl was approved for medical use in the United States in 1968, but efforts were made to limit its appeal for recreational use by only allowing it to be distributed mixed with another substance known to reduce its euphoric effects (Stanley, 2014). Despite these efforts, fentanyl entered the illicit drug supply and was identified as a contributing cause of overdose deaths as early as 1979, but was not widespread until the second decade of the twenty-first century (Han et al., 2019).

The current epidemic of overdose deaths is contributing to more than 100,000 deaths per year, more than 75% of which involve a synthetic opioid such as fentanyl (Ahmad et al., 2024). Although prescription opioid pills and later heroin initially drove increases in drug overdose death rates in the late 1990s through around 2013 (Ciccarone, 2019), synthetic opioids such as fentanyl have contributed to an acceleration of deaths over the past decade. Given that non-

medical use of opioids has occurred for thousands of years, and opioid addiction has been documented for several centuries, it is the potency of opioids currently available that characterizes the unique challenges posed by opioids today.

Policymakers and others who aim to reduce deaths and other consequences of opioid use can intervene in three main ways. First, they can attempt to prevent non-medical opioid use though efforts to educate people of the risks or by limiting the supply of opioids (both as prescribed and through the illicit market). Second, they can encourage people who are currently addicted to opioids to stop use though treatment such as the provision of medications for opioid use disorder (MOUD). Finally, they can attempt to limit the negative consequences of drug use by engaging in harm reduction. Harm reduction interventions related to opioid use include those designed to limit the spread of bloodborne illnesses such as syringe services programs (Adams, 2020; Packham, 2022), those designed to provide information to someone about the nature of their drug supply which make an overdose less likely (e.g., drug checking services; Maghsoudi et al., 2022), and those designed to prevent an overdose from resulting in death, such as the provision of naloxone (McDonald et al., 2017). Given the potency of opioids currently available to people who use them non-medically, interventions designed to reduce overdoses—or the mortality associated with overdoses—are particularly important tools. This thesis is concerned with the question of the effectiveness and cost-effectiveness of one such intervention: increasing naloxone availability to prevent overdose deaths. To consider this question, this thesis comprises a systematic review and meta-analysis of studies that examines the effectiveness of naloxone to reduce fatal overdoses (Chapter 2), an empirical examination of the effectiveness of an untargeted naloxone giveaway strategy by applying a difference-in-differences design to data collected on large-scale naloxone giveaways in Pennsylvania (Chapter 3), and a cost-effectiveness evaluation of the Pennsylvania giveaway strategy using a simulation model (Chapter 4).

Naloxone was synthesized in 1960, around the time of the development of fentanyl and other powerful opioids (Boysen et al., 2023). Substances such as opium, heroin, and fentanyl are agonists that stimulate μ-opioid receptors in the body producing analgesic and euphoric effects that make them useful and attractive, but also potentially fatal respiratory depression (Brownstein, 1993). Naloxone is a μ-opioid antagonist that reverses those effects. Thus, naloxone can be administered to an overdose victim to restore normal respiratory function, and is “intrinsically safe,” having little effect (harmful or otherwise) on someone who has not taken opioids (Kim & Nelson, 2015; White & Irvine, 1999).

Naloxone was initially used by healthcare professionals to reverse overdoses (McDonald et al., 2017). As drug overdose deaths in the United States increased throughout the end of the twentieth and into the twenty-first century, organizations concerned with saving the lives of potential overdose victims recognized the potential value of making naloxone available to people in the community where it could be administered more quickly.[1] The Chicago Recovery Alliance began a program to distribute naloxone and train laypeople on its use in 1996. Gradually, some local and state health departments began to directly engage in naloxone distribution in the early 2000s, and the development of improvised intranasal naloxone (McDonald et al., 2017)—followed later by Narcan, a nasal formulation and now the most familiar form of naloxone in the United States—simplified the process of administering naloxone which was previously only available in injectable forms (Kolbe & Fins, 2021).

Early efforts to disseminate naloxone to laypeople demonstrated that non-professionals could in fact administer naloxone to save a life in the event of an overdose. Two analyses of Massachusetts overdose education and naloxone distribution (OEND) programs operated between 2002 and 2010 found that these programs successfully trained thousands of potential bystanders and that at least 600 overdose reversals with naloxone were reported by laypeople (Doe-Simkins et al., 2014; Walley et al., 2013).[2] The study by Walley and colleagues (2013) employed an interrupted time series design and identified a negative association between the extent of local enrollment in the OEND program and fatal overdose rates at the community level.

During this period, state policymakers recognized the potential legal or regulatory barriers that might inhibit availability of naloxone. Between 2001 and 2018, all 50 states and the District of Columbia passed at least one law to support the availability of naloxone by providing legal immunity to prescribers, dispensers, or possessors of naloxone; explicitly decriminalizing possession of naloxone; or easing the process of obtaining naloxone (e.g., by enacting a standing order making naloxone available without a prescription; Smart et al., 2021). Beginning in 2023, the U.S. Food and Drug Administration further simplified access to naloxone by approving the sale of Narcan over the counter (Tanne, 2023).

[1] After its development, naloxone was approved for the reversal of opioid overdoses by the U.S. Food and Drug Administration in 1971. It was used solely by medical professionals in the U.S. and elsewhere for two decades until it gradually became available to laypeople beginning in the 1990s despite a lack of formal approval for distribution to non-medical professionals (Kolbe & Fins, 2021; McDonald et al., 2017).

[2] Because the two study periods overlap and use data from the same state, the extent to which the reported trainees and rescues reported in the study overlapped could not be determined.

Although the general trend over the past 30 years has been characterized by increasing support for the provision of naloxone to non-medical professionals, some expressed concerns about the practice. A key reason for opposition to naloxone distribution is fears that it might encourage more or riskier drug use. Surveys of medical providers' opinions about providing naloxone to non-professionals have revealed increasingly favorable opinions (Behar et al., 2018), but even relatively recent studies have uncovered concerns about risk compensation among first responders and medical personnel (Winograd et al., 2020). Although some research contests the notion that having naloxone available could result in riskier behavior (Tse et al., 2022), qualitative research conducted with people who use opioids reveals that naloxone does represent a "a safety net" or "an excuse just to be more dangerous" to some people who use opioids (Heavey, Chang, et al., 2018). Given the safety of naloxone and its demonstrated use by laypeople to reverse overdoses, there is no doubt that availability of naloxone is unambiguously beneficial when an overdose occurs. Key questions remain about the influence that availability of naloxone has on drug use behavior and the net effects of efforts to increase naloxone availability on fatal and non-fatal overdoses in light of those effects on behavior. This thesis explores these questions using data gathered from a large-scale direct naloxone distribution intervention conducted in Pennsylvania in 2018 and 2019.

The merits of an intervention should be evaluated in terms of its costs as well as its effects. Cost-effectiveness analysis is particularly important in the case of interventions like naloxone distribution which consume scarce resources but do not prevent or cure the underlying disease (i.e., opioid use disorder). While existing economic evaluations of naloxone distribution find it to be a cost-effective intervention (see Cherrier et al., 2022 for a summary of cost-effectiveness literature),[3] the cost-effectiveness of a broad and untargeted naloxone giveaway intervention has not been evaluated, and questions remain about the link between the effect of naloxone access on drug use behavior and the economic efficiency of naloxone distribution as a harm reduction strategy.

1.2 Relevant Economic Literature

Most of the research into the effect of naloxone availability on overdose outcomes has employed microeconometric methods to exploit variation in the enactment of laws designed to facilitate access to naloxone (Smart et al., 2021).[4] These studies reached different conclusions,

[3] A more detailed discussion of prior economic evaluations of naloxone distribution is available in Chapter 4 of this thesis.

[4] The literature described in the review by Smart and colleagues is the subject of the meta-analysis in Chapter 2 of this thesis.

but one study in particular stood out in the dialog about the risks and benefits of naloxone. Using a difference-in-differences design, Doleac and Mukherjee (2022) found that enacting laws designed to increase access to naloxone caused more opioid-related emergency department visits and even more opioid-related deaths in the Midwest region of the United States. The authors discussed their findings in the context of literature on moral hazard, drawing from several previous studies exploring moral hazard associated with seat belts, automobile insurance, HIV treatment, and syringe exchange programs (Chan et al., 2016; Cohen & Dehejia, 2004; Cohen & Einav, 2003; Packham, 2022; Peltzman, 1975). As Doleac and Mukherjee describe at length, the moral hazard literature provides a valuable framework for understanding how naloxone might influence opioid use behavior when naloxone is available.

The rational addiction model, originally proposed by Becker and Murphy (1988), provides another lens through which to view the theorized impact of naloxone availability on drug use behavior. Rational addiction to a harmful good, according to Becker and Murphy, is characterized by a positive association between past consumption and current marginal utility of consumption—adjacent complementarity—and a negative association between past consumption and utility at a given level of consumption.[5] The rational addiction model describes the phenomenon of addiction as the result of forward-thinking behavior to weigh current and future costs of consuming a potentially addictive good against the rewards of doing so.

The rational addiction model represents the influence of past consumption on current utility by defining a "stock" of consumption capital. This stock is a useful construct for understanding the cumulative effect of addiction on future utility, but it is not well-suited to represent sudden death due to overdose.[6] In a study building on the original Becker and Murphy model, Orphanides and Zervos (1995) defined addiction as "the unintended occasional outcome of experimenting with an addictive good known to provide certain instant pleasure and only probabilistic future harm." In fact, the purpose of naloxone as a harm reduction intervention is to reduce the probability of *immediate* harm, thus keeping people alive to realize the potential future harm represented in the rational addiction framework.

This immediate harm seems generally to be outside of the scope of the rational addiction model, but still the model offers important insights. Consider an individual deciding whether to use

[5] Becker and Murphy explain that adjacent complementarity is related to the reinforcement characteristic of addiction and the association between past consumption and present utility at a given level of consumption is related to the tolerance characteristics of addiction.

[6] Mathematically, one could consider an overdose death to drive the stock of consumption capital to infinity and depreciation to zero, thus driving current and future utility to zero.

opioids. The rational addiction model indicates that they will choose to use opioids if the utility from doing so outweighs the costs. Part of those costs are represented by the possibility of sudden death due to overdose. If naloxone is available that risk of sudden death is reduced, and so the expected value of the costs associated with use is also reduced. As noted previously, a rational addiction is characterized by adjacent complementarity, or an increasing marginal utility of consumption as consumption stock is accumulated. Thus, for someone relatively inexperienced with opioid use (i.e., low consumption stock), the reductive effect that naloxone has on expected costs may alter the balance of cost and utility in favor of using opioids, whereas for someone with more experience (and higher marginal utility of consumption), the calculus may favor use with or without naloxone. This suggests that the potential for naloxone to alter behavior may be higher for people less experienced with drug use.[7]

A similar argument could be made with respect to the extent to which an individual discounts future costs and benefits. The rational addiction model predicts that more myopic consumers are more likely to become addicted because the future costs of current use weigh less heavily in comparison to the instantaneous benefits (Becker & Murphy, 1988). Naloxone reduces the probability of death following opioid use which reduces the expected value of the cost of use in the current period and in the future. Thus, the net present value of that reduction is lower for more myopic consumers whereas the instantaneous benefits are unaffected by one's time preference rate, and so the effect of having naloxone available on one's decision to use opioids may be greater for consumers that are more future-oriented. It is also notable that some research suggests that drug use alters one's time preference rate, causing a diminished emphasis on the future (Becker & Mulligan, 1997; Bretteville-Jensen, 1999; Grossman et al., 1998; Orphanides & Zervos, 1998), this further supports the assertion from the previous paragraph that the presence of naloxone is less likely to influence opioid use among people with more experience using opioids.

For a consumer whose affirmative decision to use opioids is in part driven by current availability of naloxone, rational choice theory suggests that expected availability of naloxone in future periods would also be a factor in the decision.[8] A consumer who expects uninterrupted access to naloxone would be more likely to use opioids in the current period than if they expect only sporadic access. Put another way, the expectation of reduced access to naloxone in the future

[7] Cawley and Ruhm (2011) provide a helpful discussion of the evolution of utility with and without consumption as the stock of past consumption increases.

[8] The association between future availability and current use is similar to the relationship between future prices of opioids and current use.

may have a similar effect on current use as the expectation of a future increase in price of opioids. Given the evolution of support for and availability of naloxone described in the previous section, culminating in the over the counter availability of Narcan (Tanne, 2023), consumers today likely feel much more secure in their access to naloxone now and in the future.

However, the framework proposed by Orphanides and Zervos (1995) suggests that current naloxone access alone might have an important effect on the decision of whether to use opioids among people with no previous experience using opioids. The Orphanides and Zervos model separated the utility function to be maximized into two components, one representing instantaneous utility from use and one representing the possible harmful side effects related to addiction and resulting from past consumption. The model introduced a parameter representing the probability of becoming addicted, which addressed a criticism of the original rational addiction model by allowing for accidental addiction driven by rational experimentation among individuals uncertain as to whether they will become addicted. As with the original rational addiction model, the potential for sudden death is not explicitly accounted for, but it stands to reason that naloxone may increase the likelihood of experimentation among those seeking to gain information about the rewards from using opioids and the likelihood that use would lead to a harmful addiction.

A recent model proposed by Cawley and Dragone (2023) extends the rational addiction model into the realm of harm reduction. The authors adopt a specific definition of harm reduction that is limited to substitutes for an addictive good. This definition of harm reduction does not align with the definition adopted earlier in the thesis, of interventions focused on addressing the consequences of drug use rather than drug use itself,[9] and excludes naloxone because it is a complement to rather than a substitute for opioids. Cawley and Dragone find that the effect of the introduction of a harm reduction intervention on total health harms is a function of its enjoyableness, its addictiveness, and its strength as a substitute for the original addictive good. Toward the end of their paper, Cawley and Dragone extend their model to the case of antagonists, which they characterize as neither enjoyable nor addictive. While naloxone is consistent with these criteria defining an antagonist, the model's treatment of antagonists suggests at least some propensity to substitute the original addictive good for the antagonist harm reduction method to stop use of the original substance. This model is perfectly consistent

[9] The example harm reduction interventions related to opioid use identified by Cawley and Dragone are methadone and buprenorphine, which are generally categorized as treatments for opioid use disorder rather than as harm reduction interventions. However, these treatments do meet the definition of harm reduction adopted by the authors.

with another opioid antagonist naltrexone, which is commonly used as a treatment for opioid use disorder. However, given the nature of naloxone as a pure complement, Cawley and Dragone's model, even when extended to the case of antagonists, does not offer insight into the effect of naloxone availability on total health harms. Despite this, Cawley and Dragone's model offers valuable insights into the conditions under which opioid agonist treatments or certain antagonists are beneficial, and an extension of the model to deal purely complementary harm reduction tools like naloxone would be most welcome.

1.3 Organization of the Thesis

This thesis begins with a review of the existing literature of the causal effect of naloxone on overdose outcomes (Chapter 2). Specifically, this chapter builds upon a recent systematic narrative review of the effect of laws related to naloxone in the United States (Smart et al., 2021) by conducting a meta-analysis of studies that examined the effects of such laws on fatal overdose outcomes overall and stratified by the nature of the laws being considered. A search identified 1,378 unduplicated records, seven of which were included in the analysis. Meta-analytic results combining all types of laws found a beneficial effect that was not statistically significant (incidence rate ratio [IRR]: 0.91, 95% CI: 0.77-1.04) but a meta-analysis of estimates from the included studies that examined the effects of laws that specifically protected prescribers and dispensers against legal liability indicated a statistically significant, reductive effect on overdose deaths (IRR: 0.85, 95% CI:0.75-0.96).

The third chapter aims to address similar questions to the studies included in the review in Chapter 2 about the effect of naloxone availability on overdose outcomes but uses a different identification strategy than the enactment of state laws. The analysis exploits a direct naloxone giveaway intervention conducted by the state of Pennsylvania in December 2018 and again in September 2019. A difference-in-differences design is employed to estimate the effects of the giveaways on fatal and non-fatal overdose outcomes in the major metropolitan areas of the state (i.e., Philadelphia and Pittsburgh) using distance to the nearest giveaway location to identify effects. Results indicate that during the first quarter after the first giveaway, the rate of overdose death fell by over 40 percent ($p<0.01$) within 3 kilometers of the nearest giveaway location relative to locations within 3 and 10 kilometers of the nearest giveaway site. However, over the two quarters following the second giveaway, overdose deaths within 3 kilometers of the nearest giveaway site increased (IRR: 1.267, $p<0.1$) relative to areas between 3 and 10 kilometers from the nearest giveaway site. The emergence of xylazine, a non-opioid tranquilizer

the effects of which naloxone does not affect (Johnson et al., 2021), is discussed as a potential explanation of the seemingly contradictory results.

The fourth chapter uses a decision model to evaluate the cost-effectiveness of the Pennsylvania giveaway intervention—the effects of which are studied in Chapter 3. An economic evaluation of the Pennsylvania giveaway strategy is warranted to determine whether an untargeted distribution strategy—rather than a strategy more directly targeting people who use drugs—is an efficient use of resources. The analysis adapts an existing decision model to the context of the five-county Philadelphia Metropolitan Area and examines three giveaway scenarios representing different frequencies of giveaways. The giveaway scenarios are represented by calibrating the model to the effects of the giveaway estimated in the previous chapter. Results indicate that conducting naloxone giveaways every quarter is a cost-effective strategy, but that these conclusions are sensitive to the relationship between increased availability of naloxone and overdose risk, particularly for individuals who have never previously overdosed on opioids. The thesis concludes with implications of findings for policy and priorities for future research.

2 Meta-analysis of Estimates of the Effect of Naloxone Access Laws on Fatal Overdoses in the United States

2.1 Introduction

The number of deaths due to opioid overdose in the United States has been trending up over the past two decades. During the last decade, rates of deaths accelerated, first due to an increase in deaths due to heroin and then, most dramatically, due to an increase in deaths due to synthetic opioids such as fentanyl (Centers for Disease Control and Prevention, 2021). Tools to address overdose deaths are arrayed into three main categories—prevention, treatment, and harm reduction. The latter category faces the strongest political headwinds, as it addresses the harmful consequences of drug use rather than addressing the act of using drugs (Hawk et al., 2015). However, as overdose death rates continued to increase into the 2010s, state governments embraced the distribution of naloxone to people who use opioids and those close to them as a key harm reduction intervention (McDonald et al., 2017). By 2018, all states had enacted some form of legislation to support the distribution of naloxone (Smart et al., 2021).

Several empirical studies have been conducted to estimate the effect of naloxone access laws (NALs) on overdose outcomes (Abouk et al., 2019; Atkins et al., 2019; Cataife et al., 2020; Doleac & Mukherjee, 2019; Erfanian et al., 2019; McClellan et al., 2018; Rees et al., 2019). The purpose of naloxone distribution as a harm reduction intervention is to prevent death due to overdose, so all studies examined the effect of NALs on opioid overdose deaths. As naloxone access laws were enacted and naloxone became more ubiquitous, some questioned whether naloxone impacts the frequency of overdose. Notably, as a harm reduction intervention, naloxone has no mechanism to prevent overdose. It is intended to be used in the event of an overdose to mitigate respiratory distress associated with an opioid overdose (White & Irvine, 1999). However, two economists reasoned that possession of naloxone among people engaged in opioid use represents a moral hazard (Doleac & Mukherjee, 2019), because it shields the individuals from some of the risk that they might experience a fatal overdose. To test this theory, they examined the effect of NALs on non-fatal overdose deaths, measured in terms of emergency department visits and hospitalizations, and one other study also examined non-fatal overdoses as an outcome (Abouk et al., 2019).

The studies that have examined the effect of NALs on opioid overdose outcomes all used a similar approach. They compiled state- or county-level panel data characterizing the status of NALs in each state over time and the outcomes for each jurisdiction over time. These studies exploited the variation in the implementation and timing of NALs across states using difference-

in-differences models to identify the effect of NALs on overdose outcomes. A recent systematic review by Smart and colleagues (2021) compiled the estimates from these studies and concluded that despite using broadly similar approaches, the evidence on the effect of NALs from these studies is mixed. The authors of the review cited different study timeframes and definitions of NAL variables as potential sources of variation.

To date, no effort has been made to combine existing estimates in a meta-analytic framework. Despite the challenges in doing so given the differences in the studies identified by the authors of the prior review, the designs of existing empirical studies examining the effect of NALs are more similar than they are different. Many of the studies included in the prior review (and incorporated into the current analysis) report various estimates of the effect of NALs under different conditions. This study aims to identify comparable estimates from causal effect estimates of the impact of NALs on fatal overdoses and summarize the effect using meta-analysis.

2.2 Methods

Overview

A systematic literature search was conducted to identify studies that estimated the effect of naloxone access laws (NALs) in the United States on fatal opioid overdoses. Estimates of the effect of NALs were extracted and standardized. Comparable estimates across included studies were analyzed using meta-analysis to estimate the effect of NALs on fatal overdoses.

Search Strategy

Searches were conducted in four databases containing peer-reviewed literature—MEDLINE, PsycINFO, EMBASE, and EconLit—and in the SSRN eLibrary to identify relevant unpublished studies. The search was structured around three domains: 1) naloxone and associated keywords, 2) drug overdoses and associated keywords, and 3) fatal events or non-fatal incidents related to overdoses. Search syntax is available in the Appendix. Studies at the intersection of these three domains were considered for inclusion in the review. In addition to database searches, studies included in a recent narrative systematic review on NALs were considered for inclusion (Smart et al., 2021).

Eligibility Criteria

Studies published in English that examined the causal effect of one or more NALs on fatal overdose rates in the United States were included in the meta-analysis. The setting was restricted to the United States to capture variation in NALs across states. For inclusion in the

meta-analysis, studies had to contain sufficient detail to identify the NALs represented by their effect estimate(s) and had to represent the U.S. population at large rather than specific subpopulations.[10]

Data Extraction

Titles and abstracts of all non-duplicated studies identified from the systematic search were reviewed and those that appeared to meet the criteria for inclusion were reviewed in full. Estimates of the causal effect of NALs on fatal or non-fatal overdose rates—a regression coefficient (β) or incidence rate ratio with a standard error—were extracted from eligible studies. In addition to the effect estimate, details about estimation procedure (e.g., the distribution used to represent the dependent variable in the regression), types of NAL (e.g., prescriber immunity and/or third party dispensing) for which effects were estimated, types of opioids (e.g., heroin and/or prescription opioids) included in the dependent variable, study timeframe, and the inclusion of other covariates in the model (such as indicators for the presence of other policies correlated with the outcomes) were also extracted. The analytic dataset comprised one row per effect estimate. Following the extraction phase, it was determined that due to a paucity of estimates of the effect of NALs on non-fatal overdoses, only effects on fatal overdoses would be considered in the analysis.

Data Preparation

Effect estimates were standardized to incidence rate ratios. Studies reported the effect of NALs on overdose outcomes as either regression coefficients (β) or incidence rate ratios. Following Smart and colleagues (2021), studies that reported effect sizes in terms of beta coefficients were converted to incidence rate ratios using Equation 2.1:

$$IRR = \frac{BaseRate + \beta}{BaseRate} \qquad \text{(Eq. 2.1)}$$

where β represents the effect size coefficient (i.e., the effect of the NAL on the outcome) reported in the study and $BaseRate$ represents the level of the outcome prior to the influence of NALs. To ensure comparability of effect estimates across studies, overdose outcomes for the year 2010 were used to represent the base rate for all studies. Base rates for fatal overdoses were computed from the Multiple Cause of Death Files accessed through the CDC WONDER system (Centers for Disease Control and Prevention, 2020). To the extent possible, base rates

[10] One study which focused on spillover effects of NALs was deemed to be sufficiently representative of the full U.S. population and included despite its exclusion of Alaska and Hawaii due to their having no neighboring states.

were computed to match the characteristics of each effect estimate. For example, base rate estimates were computed using the same ICD-10 codes as were used in the effect estimate's dependent variable.

Most studies used difference-in-differences models to estimate effects, but one study provided effect estimates that varied by the amount of time elapsed since the enactment of the NAL using an event study model. To derive a single post-enactment effect estimate that would be comparable to the other studies, the event study coefficients (for one, two, and three or more years after enactment) were averaged. To estimate the standard error around the average, the three event study coefficients were set to normal distributions defined by the point estimate and standard error of the coefficient. Values were drawn from these distributions and averaged over 1,000 iterations. The empirical distribution of these distribution draws was used to construct a 95% confidence interval around the average of event study coefficients (using the 2.5 and 97.5 percentile values), which was then converted to a standard error for use in the meta-analysis.

The types of NALs examined varied across included studies. During the data extraction phase, seven different NAL components were identified which were organized into three categories as shown in Table 1. It must be noted that the taxonomy in Table 1 differs from a similar taxonomy provided by Smart and colleagues (2021). The purpose of the taxonomy introduced in Table 1 is to organize NALs by how they impact the process of naloxone distribution (i.e., on professional willingness to distribute naloxone, on distribution itself, or on possession and utilization once distributed), whereas the taxonomy defined by Smart and colleagues organizes NALs by the individual targeted by the policy (prescribers, dispensers, or individuals receiving naloxone). Most studies provided an estimate of the effect of having any NAL within more than one of the three categories in Table 1, i.e., a "pooled" NAL estimator. Two studies only examined NALs that affected distribution of naloxone, and some studies provided both pooled estimates and estimates of the effect of individual NAL components.

Table 1: Taxonomy of Naloxone Access Law Components

Category	Included Components
Laws that protect professionals	• Prescriber immunity • Dispenser immunity
Laws that facilitate distribution of naloxone	• Third party prescriptions (i.e., prescribing to someone other than the person at risk of overdose) • Standing order (i.e., naloxone can be prescribed under a standing order, such as by a state health secretary rather than under an individual prescription) • Direct dispensing (i.e., naloxone can be dispensed by a pharmacist under his/her own authority, rather than only by a physician or other medical provider)
Laws that facilitate possession and utilization of distributed naloxone	• Possession permitted without a prescription. • Layperson immunity when administering naloxone.

Effect estimates also varied in the types of opioids used in the dependent variable. All studies provided effect estimates that estimated the effect of NALs on deaths due to any of the following: heroin (ICD-10 T40.1), other opioids (T40.2), methadone (T40.3), and other synthetic narcotics (including fentanyl; T40.4). Most studies also included deaths due to "other and unspecified narcotics" (T40.6), one excluded it presumably because deaths assigned to T40.6 could have been caused by cocaine instead of opioids (Slavova et al., 2015). Finally, all but two studies also included deaths due to opium (T40.0) in the definition of opioid overdose deaths. Its exclusion in other studies is inconsequential as only two deaths were attributed to it in 2010 (Centers for Disease Control and Prevention, 2020). In addition to using a broad definition of opioid overdose deaths (i.e., T40.0-40.4, T40.6), some studies provided estimates for narrower categories, such as heroin or fentanyl.

Identifying Comparable Effect Estimates

To identify comparable effect estimates, some estimate-level exclusion criteria were applied. First, effect estimates used in all meta-analyses had to represent the United States at large. As noted previously, the inclusion of effect estimates representing the U.S. population broadly defined was an inclusion criterion for the meta-analysis. However, some included studies estimated effects for subpopulations (e.g., effects stratified by urban/rural status, Doleac & Mukherjee, 2019). For the meta-analysis, only the estimates representing the full population were used. Second, effect estimates used in the meta-analyses had to include deaths assigned

to T40.1-T40.4 in the dependent variable. When multiple estimates were available from a given study, the estimate representing the broadest definition of opioid overdose deaths was used.

Third, whenever there were multiple estimates available from a particular study, those based on a broader set of control variables were favored over more parsimonious specifications. Additionally, a study by Rees and colleagues (2019) estimated the effect of NALs using both ordinary least squares (OLS) and Poisson regression. The OLS estimates were favored over the Poisson estimates because OLS models were used more commonly among the other studies.

Finally, one study defined a three-level mutually exclusive definition of NALs meant to represent increasing intensity of the law (Abouk et al., 2019). The top-level captured state-years in which pharmacists had direct dispensing authority, the second level captured state-years in which pharmacists had indirect dispensing authority (e.g., standing order) but not direct authority, and the third captured state-years with any other NAL but not direct or indirect dispensing authority for pharmacists (labeled "weak NALs"). This approach changes the interpretation of the lower two levels of the categorical variable such that it represents the effect of a certain type of NAL *but not a different type*. For example, the coefficient for "weak NALs" would not represent outcomes in state-years with both prescriber immunity and standing orders, thus preventing comparability to other estimates of the effects of so-called "weak NALs." As a result, only estimates representing the top level of the NAL taxonomy (direct dispensing authority) were used in meta-analysis.

Using the effect estimates that met the above criteria, eight overlapping sets of effect estimates were identified and used in separate meta-analyses. The purpose of this approach was to derive meta-analytic estimates of the effect of NALs broadly defined and to provide estimates for specific types of NALs in combination and in isolation. The eight sets are best described as four sets of two:

1a) the estimate from each study that represents the broadest set of NALs (N=7 estimates)

1b) the subset of 1a that represents all three NAL categories (N=4)

2a) all estimates that include NALs in the "laws that protect professionals" category (N=6)

2b) the subset of 2a in which the effect *only* represents the "laws that protect professionals" category (N=4)

3a) all estimates that include NALs in the "laws that facilitate distribution" category (N=10)

3b) the subset of 3a in which the effect *only* represents the "laws that facilitate distribution" category (N=8)

4a) all estimates that include NALs in the "laws that facilitate possession and utilization" category (N=5)

4b) the subset of 4a in which the effect *only* represents the "laws that facilitate possession and utilization" category (N=4)

For analyses that examined the effect of NALs of a certain type, estimates specific to that category of NALs were preferred to pooled estimates when available from a particular study. However, estimates representing multiple categories of NALs were used in sets 2a, 3a, and 4a if category-specific estimates were not available from a particular study. In sets 2b, 3b, and 4b, only category specific estimates were used. Thus, the estimates in sets 2b, 3b, and 4b are subsets of the estimates in sets 2a, 3a, and 4a, respectively.

Analysis

Random effects meta-analysis was conducted using Stata version 16.1. Restricted maximum likelihood (REML) was used to estimate the variance between effect estimates (τ^2) (Higgins & Thompson, 2004; Langan et al., 2019), and then weights were assigned to each estimate as a function of τ^2 and the standard error of a particular effect estimate θ_i^2. As a sensitivity check, the Paule-Mandel estimator of τ^2, which has been shown to produce less biased estimates than REML under certain conditions (Panityakul et al., 2013), was used and produced nearly identical results. For each meta-analysis, two closely related heterogeneity statistics—the proportion of variation attributable to estimate heterogeneity (I^2) and the ratio of total variation to sampling variation (H^2)—were computed and Cochran's Q test for heterogeneity was conducted (Higgins & Thompson, 2002).[11]

2.3 Results

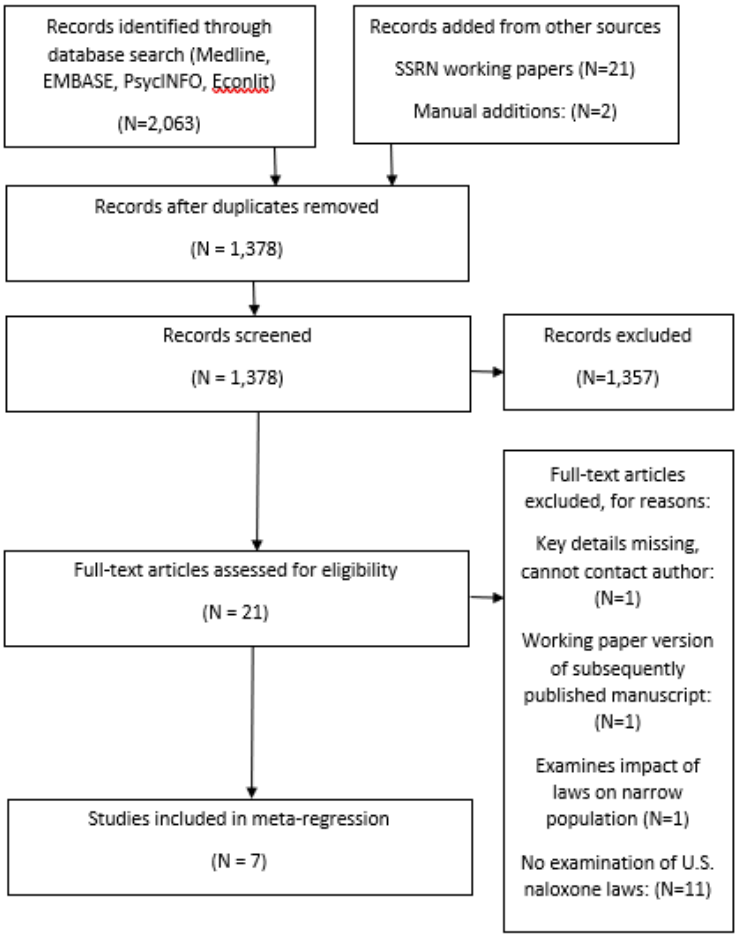
Results of Search and Study Characteristics

Seven studies were deemed eligible for inclusion in the meta-analysis out of 2,086 considered (see Figure 1). Of the 14 studies excluded after full-text review, 11 were excluded because they did not examine U.S. naloxone laws. Of the remaining three excluded after full text review, one

[11] Confidence intervals around the I^2 statistic were computed using the heterogi package in Stata (Orsini et al., 2005).

was an unpublished dissertation that did not adequately define the types of NALs considered or the types of opioids included in the dependent variable and the author could not be contacted to provide that information (Ndrianasy, 2020). One study was entirely excluded because it focused only on outcomes for individuals that had previously experienced opioid-related hospitalization (Blanchard et al., 2018). The last excluded study was a working paper version of a published study included in the review (Rees et al., 2017). Of the studies excluded after full text review, 13 were based in the U.S. and one, based in Scotland, was an uncontrolled study that found a reduction in overdose deaths associated with the implementation of a policy of naloxone provision upon release from prison (Bird et al., 2016).

Figure 1: PRISMA Flow Diagram



All the studies used difference-in-differences to derive causal effect estimates of the effect of NALs on fatal overdoses, and two studies also examined non-fatal overdose outcomes. Data on fatal overdoses from all studies were sourced from the Centers for Disease Control National Vital Statistics System. The studies are described in greater detail in Table 2

Table 2: Characteristics of Included Studies

Study	Time Period	ICD-10 Codes for Dependent Variable	NALs Considered	NAL Categories as defined in Table 1	Time unit[a]	Geographic unit[b]	Estimation procedure	Unique features
Abouk et al., 2019	2005-2016	T40.1-T40.4, T40.6	• Direct pharmacist dispensing authority • Indirect pharmacist dispensing authority • Weak NAL (all others)	• Facilitate distribution	Month	State	OLS	NALs defined in mutually exclusive categorical indicator; event study model.
Atkins et al., 2019	1999-2016	T40.1-T40.4, T40.6	• Immunity for prescribers • Immunity for laypersons • Third party prescribing or standing orders	• All three categories (pooled)	Year	State	Poisson	
Cataife et al., 2020	1999-2014	T40.0-T40.4, T40.6	• Immunity for prescribers/dispensers • Third party prescribing • Allow dispensing without patient-specific prescription	• Protect professionals and facilitate distribution (pooled)	Year	State	OLS	Mahalanobis Distance Matching to refine comparison; focus on regional variation
Doleac and Mukherjee, 2019[c]	2010-2015	T40.0-T40.4, T40.6	• Third party prescriptions • Standing orders	• Facilitate distribution	Month	County	OLS	Focus on urban areas (though provided all area estimates used in the meta-analysis)

Study	Time Period	ICD-10 Codes for Dependent Variable	NALs Considered	NAL Categories as defined in Table 1	Time unit[a]	Geographic unit[b]	Estimation procedure	Unique features
Erfanian et al., 2019	1999-2016	T40.0-T40.4, T40.6	• Immunity for prescribers • Third party prescriptions • Allow dispensing without patient-specific prescription • Immunity for laypersons for administration • Immunity for laypersons for possession	• All three categories (pooled and separate)	Year	State	OLS	Focus on indirect effect on neighboring states; excluded Alaska and Hawaii
McClellan et al., 2018	2000-2014	T40.0-T40.4, T40.6	• Third party prescriptions • Standing orders • Immunity for laypersons for possession • Immunity for prescribers • Immunity for Dispensers	• All three categories (pooled and separate)	Year	State	Negative binomial	Unlike other studies, estimated NAL-specific models separately, rather than simultaneously
Rees et al., 2019	1999-2014	T40.0-T40.4, T40.6	• Immunity for laypersons for possession • Immunity for prescribers • Third party prescriptions • Standing orders	• All three categories (pooled and separate)	Year	State	OLS; Poisson	OLS regression used log-transformed dependent variable

[a]All estimates included time fixed effects.

[b]All estimates included geographic fixed effects except McClellan et al, which included state random effects.

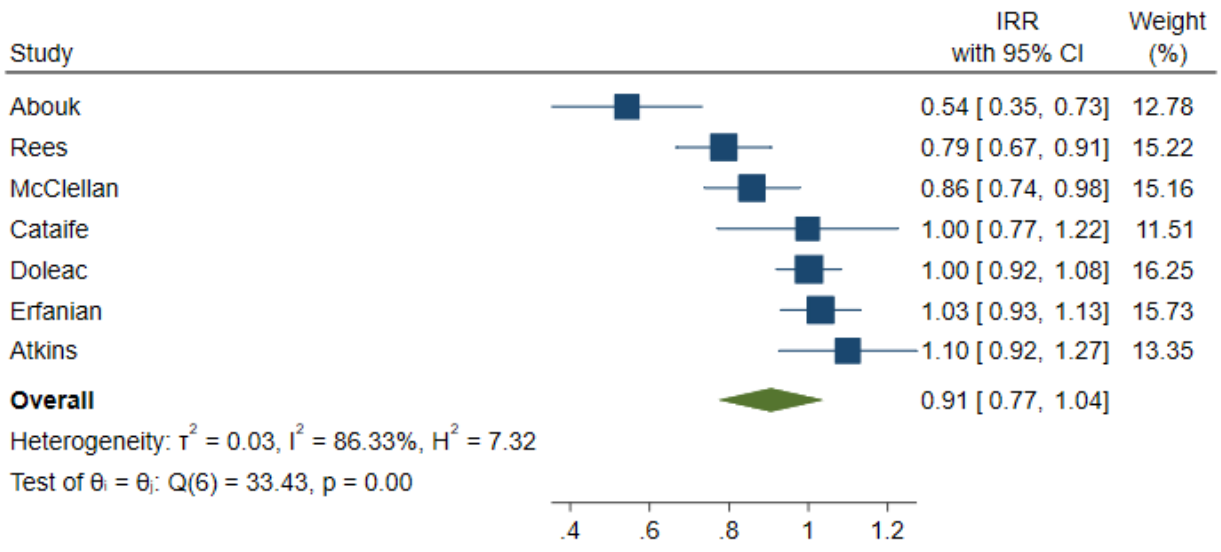
[c]Note: This is an earlier unpublished version of the *Journal of Law and Economics* paper by the same authors cited elsewhere in this thesis. The published version was unavailable at the time the review was completed.

The studies covered different time periods, with the beginning of study periods ranging from 1999 to 2010 while all analysis periods ended between 2014 and 2016. As noted, most studies included all relevant ICD-10 codes (T40.0-T40.4, T40.6) in their definition of opioid overdose deaths. Four of the seven studies examined all three categories defined in the taxonomy in Table 1, and three studies provided both pooled NAL estimates and estimates of effect for specific NAL components. Most states computed outcomes on an annual basis, but two examined monthly outcomes, and all but one study examined outcomes at the state-level while the remaining study examined county-level outcomes. OLS was the most common estimator, while two studies used Poisson regression (one of those in addition to OLS) and one used negative binomial regression. Finally, the last column of Table 2 highlights unique features of the studies not represented by the other columns in the table.

Broad Estimates of Effect of NALs

Figure 2 presents a meta-analysis of the broadest estimate from each study of the effect of NALs on fatal overdose. The overall estimate favors NALs compared to the absence of NALs (IRR: 0.91) but the estimate is not statistically significant (95% CI: 0.77—1.04). The results from the meta-analysis indicate that there is considerable heterogeneity between studies (I^2 = 86.33%, 95% CI: 65.23% - 91.22%).

Figure 2: Meta-analysis of Broadest Effect Estimate from each Study

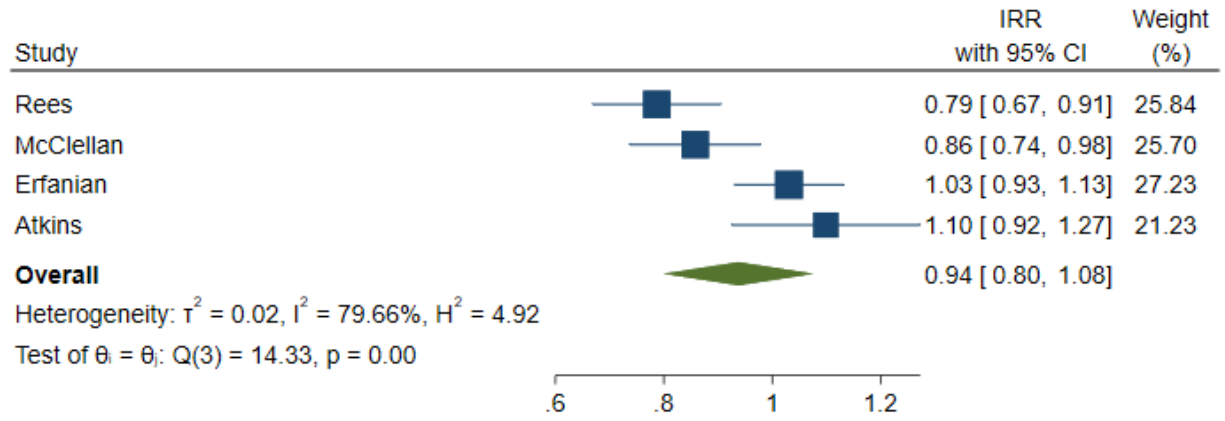


Note: 95% confidence interval of I^2: 65.23% - 91.22%

One of the potential sources of heterogeneity among the seven estimates represented in Figure 2 is the difference in the categories of NAL used in the effect estimate. Two of the studies only considered NALs from the "support distribution category," and one considered two categories but not NALs from the

"support possession and utilization" category. When the analysis was repeated excluding these three estimates to include only estimates that consider all three categories of NALs (Figure 3), the overall estimate IRR is similar (IRR: 0.94, 95% CI: 0.80-1.08). The I^2 statistic indicates a similar level of heterogeneity. The analyses underlying Figures 2 and 3 were repeated using alternative estimation procedure for the variance between effect estimates (τ2). These alternative results are available in the Appendix.

Figure 3: Meta-analysis of Estimates Representing each Category of NAL

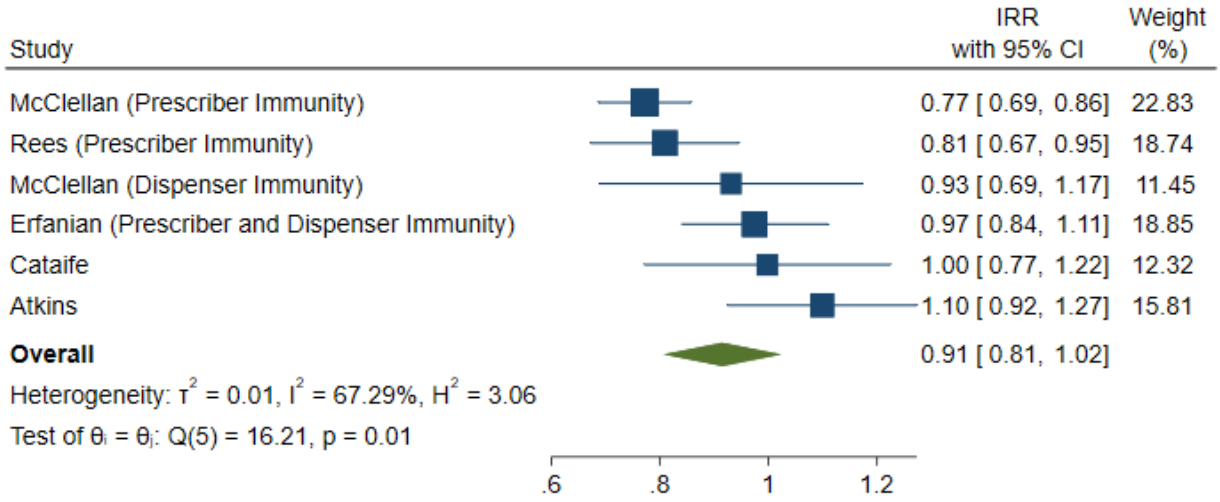


Note: 95% confidence interval of I^2: 44.04% - 92.17%

NALs to Protect Professionals from Liability when Distributing Naloxone

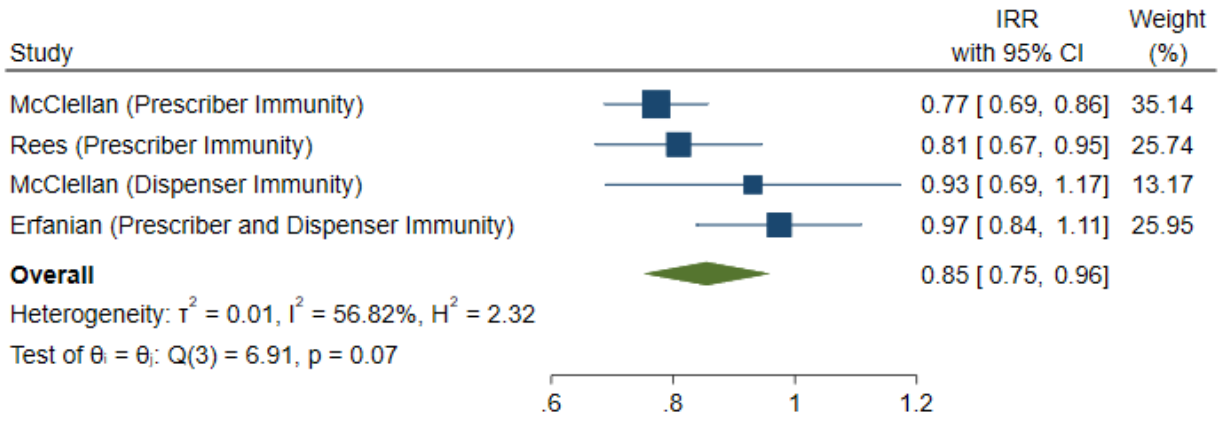
Meta-analyses of estimates of the effect of NALs geared toward protecting professionals from liability are presented in Figures 4 and 5. When all estimates that consider this category of NALs were analyzed, the resulting overall effect estimate is similar to the estimate for all NALs (Figure 4; IRR: 0.91, 95% CI: 0.81-1.02). Excluding two estimates that examine NALs that protect professionals in combination with other NALs produced a significant overall effect (Figure 5; IRR: 0.85, 95% CI: 0.75-0.96). Cochran's test for heterogeneity did not reject the null hypothesis of homogeneity (p = 0.07), but due to the small sample size and wide confidence interval around the I^2 statistic, random effect meta-analysis is still preferable to a fixed effect specification (Huedo-Medina et al., 2006).

Figure 4: Meta-analysis of Estimates Representing NALs that Protect Professionals



Note: 95% confidence interval of I^2: 27.42% - 86.89%

Figure 5: Meta-analysis of Estimates Representing only NALs that Protect Professionals

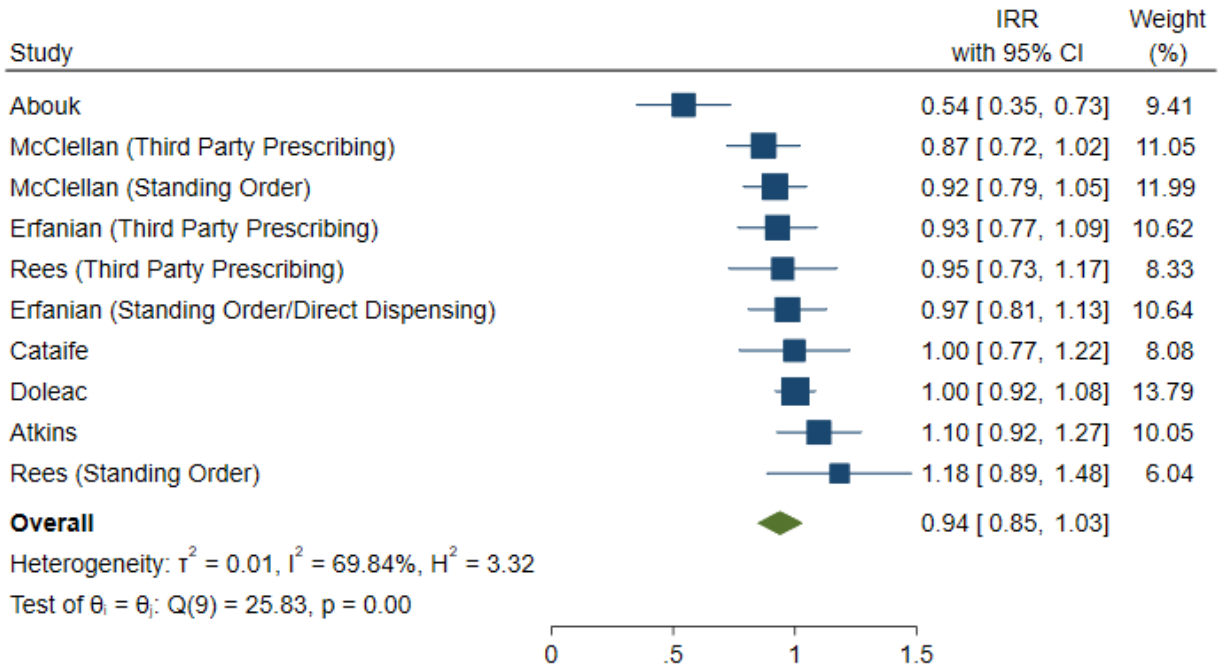


Note: 95% confidence interval of I^2: 0% - 85.60%

NALs to Facilitate Distribution of Naloxone

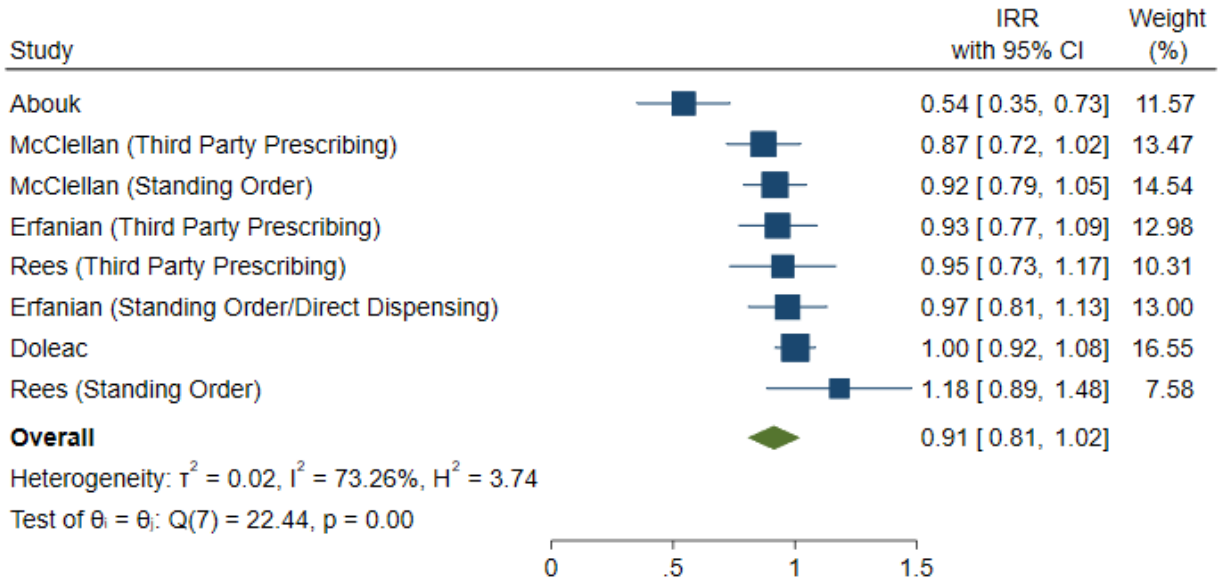
All seven studies included in the meta-analysis provided estimates of the effect of NALs that facilitate distribution of naloxone. When all estimates were used, the overall effect estimate again favors NALs but is not significant (Figure 6; IRR: 0.94, 95% CI: 0.85-1.03). When estimates from two studies that considered these NALs in combination with other types of NALs were excluded, the overall effect estimate is similar (Figure 7; IRR: 0.91, 95% CI: 0.81-1.02).

Figure 6: Meta-analysis of Estimates Representing NALs that Facilitate Distribution



Note: 95% confidence interval of I^2: 31.61% - 85.25%

Figure 7: Meta-analysis of Estimates Representing only NALs that Facilitate Distribution

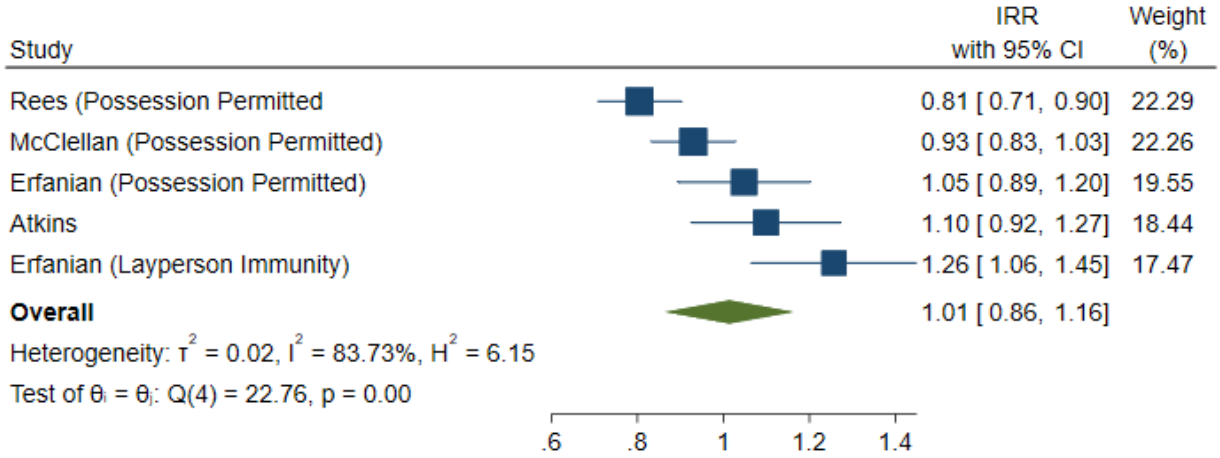


Note: 95% confidence interval of I^2: 34.75% - 85.09%

NALs to Facilitate Possession and Utilization of Naloxone

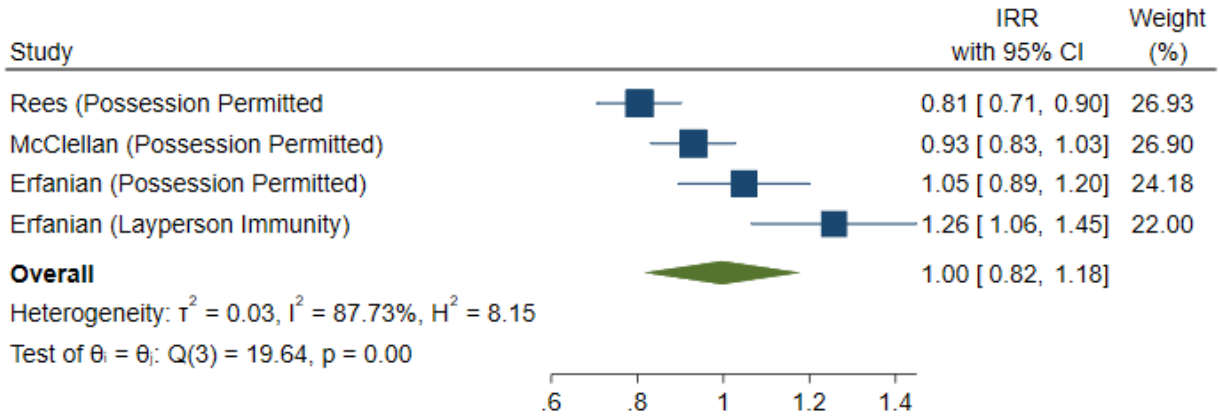
Only four studies examined the effect of NALs designed to facilitate possession and utilization of naloxone. The overall effect estimates indicate no effect in the broader set of estimates (Figure 8; IRR: 1.01, 95% CI: 0.86-1.16) and in the category-specific set of estimates (Figure 9; IRR: 1.00, 95% CI: 0.82-1.18).

Figure 8: Meta-analysis of Estimates Representing NALs that Facilitate Possession and Utilization



Note: 95% confidence interval of I^2: 59.66% - 92.34%

Figure 9: Meta-analysis of Estimates Representing Only NALs that Facilitate Possession and Utilization



Note: 95% confidence interval of I^2: 61.92% - 93.87%

2.4 Discussion

This meta-analysis described the effect of NALs on fatal overdoses using estimates from seven empirical studies published between 2018 and 2020. In general, the evidence favors the enactment of NALs as an

intervention to reduce overdose deaths, but when all types of NALs were considered, the meta-analytic estimates are not statistically significant (IRR: 0.91, 95% CI: 0.77—1.04). An exception was found for NALs that protect prescribers and dispensers from liability. A meta-analysis of estimates that defined exposure based solely on NALs that protect professionals found a significant, beneficial effect of these NALs on opioid overdose death rates (IRR: 0.85, 95% CI: 0.75-0.96). Similar analyses focused on NALs that support distribution found an effect in the positive direction but not significant (IRR: 0.91, 95% CI: 0.81-1.02), and NALs that support possession and utilization by laypeople were found to have no effect (IRR: 1.00, 95% CI: 0.82-1.18).

In the context of complicated medico-legal implications (Brodrick et al., 2016; Davis & Carr, 2017) of prescribing a drug to someone other than the person who will ultimately receive it (e.g., third-party prescribing) or dispensing a drug to someone without a prescription (e.g., standing orders), the finding of a significant, beneficial effect of NALs that protect prescribers and dispensers from liability is not unexpected. For example, despite having the legal authority to dispense naloxone under a standing order, evidence from three states—Pennsylvania (Guadamuz et al., 2019), Georgia (Nguyen et al., 2020), and California (Puzantian & Gasper, 2018)—indicates that many pharmacies are unwilling to dispense naloxone without a prescription. It is possible that NALs that have a more direct impact on the distribution of naloxone (i.e., standing orders, direct dispensing authority, and third-party prescribing) may have a limited impact without explicit protection of the professionals involved in that distribution. Future research should consider the interactions of different types of NALs with respect to overdose outcomes.

A defining characteristic of the meta-analyses presented in this chapter is the extent of heterogeneity between estimates. Despite the use of nearly identical outcomes data across studies, and despite efforts to identify estimates from studies that can be pooled in meta-analysis, statistics such as I^2 indicate that heterogeneity between studies explain a substantial amount of the variation between estimates (Higgins & Thompson, 2002); however, given the small number of estimates, I^2 values for the meta-analyses were imprecise. In a typical meta-analysis scenario where estimates comprise output from randomized controlled trials, a high level of heterogeneity might indicate that estimates represent different populations with different true effect sizes. Heterogeneity in the case of this analysis is more difficult to interpret because the estimates are not from different trials representing potentially different populations, but rather the effects were all identified by exploiting variation in the timing of NAL enactment across U.S. states.

Because the causal effect estimates used in the meta-analyses were all based on—theoretically—the same population, some discussion of sources of heterogeneity is warranted. First, as discussed by Smart and colleagues (2021), estimates came from studies in which the end of the study period varied from 2014 to 2016. Over that period, the presence of fentanyl in the illicit drug supply intensified (Centers for Disease Control and Prevention, 2021), and there is evidence that a higher dose of naloxone is often necessary to reverse overdoses involving highly potent opioids like fentanyl (Moe et al., 2020). Thus, it may be that the effect of NALs on opioid overdose deaths in the context of high diffusion of fentanyl is lower than the effect in the absence of fentanyl contributing to the heterogeneity of estimates. In addition, several states introduced NALs between 2014 and 2016 (Smart et al., 2021), so the makeup of the exposed and unexposed groups differs between studies that ended their study period in 2014 and those that continued into 2016. Second, each of the studies included in the meta-analysis had unique features as summarized in Table 2. Despite efforts to identify estimates with nearly identical definitions of fatal overdose deaths and harmonize the types of NALs examined, differences between studies remained. One study defined NALs using a hierarchical structure (Abouk et al., 2019), while another estimated effects of NALs independently rather than simultaneously (McClellan et al., 2018), each subtly changing the interpretation of the effect estimates. One study limited their scope to the contiguous United States (Erfanian et al., 2019), while another employed Mahalanobis Distance Matching in a data preprocessing step (Cataife et al., 2020), each changing the composition of the exposed and unexposed groups. These analytic decisions contribute to between-study heterogeneity. Third, some variation in the enactment dates assigned to states for various NALs was identified. For example, standing order enactment dates differed by more than 1 year for Illinois and Kentucky across two studies (Abouk et al., 2019; Doleac & Mukherjee, 2019). In summary, although the estimates that compose the meta-analyses were chosen to be as homogenous as possible, it must be noted that important differences between studies remain that limit their comparability.

This study has some limitations that must be noted. First, results for fatal overdoses are based on a relatively small number of studies, and there were an insufficient number of studies of the effect of NALs on non-fatal overdoses to support a meta-analysis for that outcome. Second, the analysis is limited to the U.S. context, so the effect of policies that support naloxone access in the rest of the world are not reflected. Finally, the analysis focuses on the effect of NALs, which is a proxy for a more direct estimate of the effect of lay possession of naloxone on overdose outcomes. The next chapter of this thesis addresses this limitation by using the case of two large scale naloxone giveaways that took place across

Pennsylvania to estimate a more direct effect of naloxone distribution to laypeople. Despite these limitations, the results from this chapter provide the first meta-analytic estimates of the effects of NALs that pool the effects estimated from previous studies. It also proposes a novel taxonomy of NALs which highlights the importance of explicit policies to protect professionals from liability if they are to support distribution of naloxone outside of their typical procedures (i.e., distribution to people without specific prescriptions). This finding may have implications beyond naloxone should future public health imperatives require a sudden broadening of access to drugs or other tools that was previously restricted.

3 The Effect of Untargeted Naloxone Distribution on Opioid Overdose Outcomes

3.1 Introduction

Between 2010 and 2019, over 340,000 people in the United States died of a drug overdose involving opioids (Hedegaard et al., 2021). The death toll has only increased since the onset of the COVID-19 pandemic, as the number of deaths attributable to opioid overdose per year increased by 61% from the December 2019 to December 2021 based on provisional data (Ahmad et al., 2022). Efforts to reduce opioid overdose deaths can be organized into interventions and policies designed to prevent non-medical use of opioids, to treat people with an opioid use disorder (OUD), and to reduce the harms associated with opioid use. The third category, harm reduction, has gained prominence as ideological resistance to it has slowly dissipated (Nadelmann & LaSalle, 2017).[12]

A key harm reduction strategy for opioid use is the distribution of naloxone. Naloxone does not prevent or treat opioid use or overdose, but reduces its consequences (i.e., death) by reversing potentially fatal respiratory depression (White & Irvine, 1999). In recent decades, the scope of naloxone availability has gradually expanded beyond medical professionals to people who use opioids and other non-professionals who may encounter an overdose victim and be able to use naloxone to render aid (McDonald et al., 2017). Only one study has estimated the effect of direct naloxone distribution on fatal and non-fatal overdoses (Walley et al., 2013), and several studies have examined the effect of state laws that facilitate access to naloxone (Smart et al., 2021).

This study examines the effect of two direct naloxone giveaways that took place in the state of Pennsylvania on fatal opioid overdoses and opioid overdose-related ED visits in the two main urban areas of the state (Philadelphia and Pittsburgh). Variation in the distance to giveaway locations at the Census tract and ZIP Code Tabulation Area (ZCTA)-levels is used to identify treated and control regions. Distance to a health-related service has been used as the basis for causal inference in previous studies (e.g., Lindo and colleagues' (2020) analysis of Texas abortion policy) and is supported in this context by a recent study in Baltimore, Maryland, that found that utilization of naloxone is associated with proximity to naloxone distribution sites (Yi et al., 2022). The effects of the two giveaways are examined separately using standard two-way fixed effects difference-in-differences and event study estimators, and combined using an estimator robust to variation in treatment timing (Callaway & Sant'Anna, 2021; Sant'Anna & Zhao, 2020).

[12] A version of this chapter was published as Dowd, W. N. (2023). The effect of untargeted naloxone distribution on opioid overdose outcomes. Health economics, 32(12), 2801-2818.

This study makes three important contributions to the literature on the distribution of naloxone to address opioid overdose. First, this study examines a unique distribution approach. Naloxone distribution generally occurs through pharmacies or overdose education and naloxone distribution (OEND) programs, which are often operated by syringe services programs (SSPs) which cater directly to people who inject drugs (Wenger et al., 2022). Conversely, Pennsylvania's naloxone giveaways focused on distributing naloxone broadly, even to people that did not use opioids themselves or have a direct connection to someone who did (Governor's Press Office, 2018). This study provides the first evidence of the effect of an untargeted naloxone distribution strategy on overdose outcomes, and its findings are applicable to other broad-based naloxone distribution strategies. Second, this study is only the second to directly estimate the causal effect of the direct provision of naloxone on overdose outcomes (Walley et al., 2013). Most of the literature on the topic focuses on the passage of state laws to support naloxone provision (Smart et al., 2021). Estimates based on a natural experiment of direct naloxone distribution improves our understanding of the effect of naloxone on overdose outcomes. Third, this study examines the effect of naloxone distribution on ED visits, to which less attention has been paid in previous studies.

This study produces evidence of a significant reduction in opioid overdose deaths in the quarter immediately following the first naloxone giveaway (IRR:0.59, p=0.01), but an opposite effect over the two quarters following the second giveaway held 9 months later (IRR:1.27, p=0.07). These apparently contradictory findings are discussed in the context of evidence suggesting that naloxone may have been less effective during the second giveaway, due in part to the increased presence of xylazine—a non-opioid veterinary tranquilizer that does not respond to naloxone—in the illicit opioid supply (Friedman et al., 2022). Some evidence of a reduction in ED visits during the second quarter after the giveaway when the effects of both giveaways are pooled (ATT: -1.12 ED visits per 10,000 population, p=0.02) was found and discussed in the context of previous studies.

The rest of this paper is organized as follows. Section 2 discusses the previous literature on the effect of distributing naloxone to the public and describes the Pennsylvania naloxone giveaways. Section 3 describes the data used for this analysis. Section 4 describes the empirical approach adopted. Section 5 presents results for two outcomes: fatal opioid overdoses and opioid overdose-related ED visits. Finally, section 6 concludes with a discussion of the results and their implications.

3.2 Background

Previous Literature

Studies have shown that naloxone can be successfully administered by people in the community. A study of a pilot OEND program in 19 Massachusetts communities between 2002 and 2009 found that out of 2,912 people who received a naloxone kit and brief education on its use, 212 reported one or more rescue attempts with a 98% success rate (as measured by an improvement in respiratory symptoms). An interrupted time series analysis found that participating communities had lower rates of opioid overdose death than communities that were not participating, and found no effect of the OEND programs on inpatient hospital admissions and emergency department visits (Walley et al., 2013). A more recent study of an OEND in Pittsburgh, Pennsylvania did not examine aggregate overdose outcomes, but did show that naloxone kits distributed through the program were used and that about 26% of recipients returned for a refill (Bennett et al., 2018).

Starting around 2010, state-level policies to facilitate the distribution and administration of naloxone by non-professionals gained momentum. These policies provided legal protection to prescribers, dispensers, and people who administer naloxone in the community, and reduced barriers to naloxone access by allowing naloxone to be dispensed without an individual prescription (e.g., by a "standing order" authorized by the state's health secretary). By 2018, all states had enacted at least one law in support of public naloxone distribution. Several studies used variation in the timing of the enactment of these naloxone access laws to identify their effect on overdose outcomes, and by extension, the effect of increased naloxone availability on those outcomes (Smart et al., 2021).

There is evidence to support the use of state-level variation in the enactment of naloxone access laws to identify the effect of naloxone access on opioid overdose outcomes. Studies have shown that the passage of naloxone access laws was associated with increased distribution of naloxone through pharmacies (Xu & Mukherjee, 2021), and with the establishment of OEND programs (Lambdin et al., 2018). However, the laws do not guarantee access to naloxone. Data suggest that naloxone distributed though pharmacies is dispensed to older Americans at a higher rate than younger Americans (Guy et al., 2019), even though older Americans die from overdose at much lower rates (Hedegaard et al., 2021). This suggests that the population most at risk of fatal overdose may be underrepresented among recipients of pharmacy-dispensed naloxone, potentially due to cost or administrative barriers (Graves et al., 2019; Peet et al., 2022). Similarly, despite the fact that naloxone access laws supported the establishment of OEND

programs, they were still only present in 8% of counties by 2014 (Lambdin et al., 2018), and are present in only six of Pennsylvania's 67 counties as of 2023 (National Harm Reduction Coalition, n.d.).

The estimated effects of naloxone access laws on opioid overdose deaths varied by study and by the specific naloxone access law(s) being evaluated but ranged from a significant reduction in deaths to no effect (Abouk et al., 2019; Atkins et al., 2019; Cataife et al., 2020; Doleac & Mukherjee, 2022; Erfanian et al., 2019; McClellan et al., 2018; Rees et al., 2019). Estimated effects of naloxone access laws on opioid overdose-related emergency department (ED) visits, albeit from fewer studies, ranged from a significant increase to no effect (Abouk et al., 2019; Blanchard et al., 2018; Doleac & Mukherjee, 2022). One of the first studies to examine the effect of naloxone on ED visits by Doleac and Mukherjee (2022) suggested that naloxone might present a moral hazard by reducing the risk of death associated with drug use. Qualitative evidence suggests that some but not all people who use drugs may use higher quantities or engage in riskier use when naloxone is available (Heavey, Chang, et al., 2018; Seal et al., 2003).[13] However, a recent review argued that there was no support for the presence of moral hazard in studies of naloxone distribution programs (Tse et al., 2022).

Pennsylvania's Naloxone Giveaways

The first naloxone giveaway was part of Pennsylvania's "Stop Overdoses in PA: Get Help Now" week. The state held several press events across the state involving the governor and high-ranking cabinet officials across several agencies, including the Departments of Health, Human Services, Corrections, Drug and Alcohol Programs, Aging, Conservation and Natural Resources, and the State Police. The giveaway and the public events held simultaneously were designed to increase naloxone possession among the general public, not just among those who use opioids or people close to them.

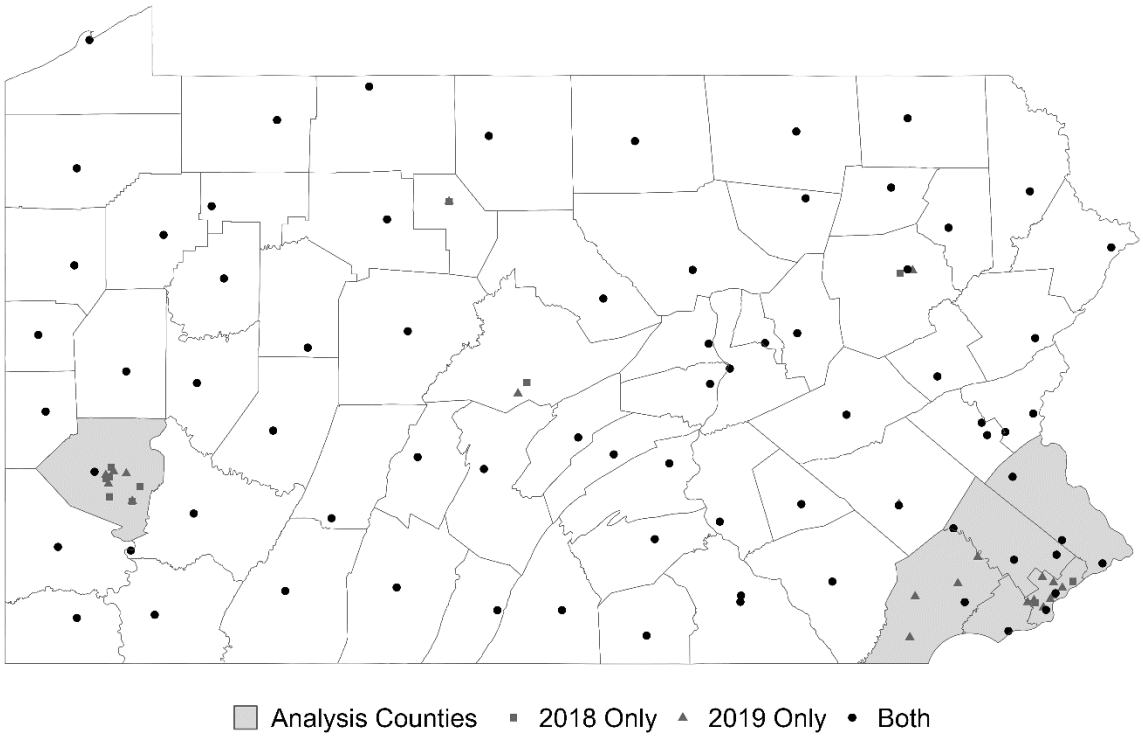
On the day of the giveaway, December 13, 2018, individuals interested in obtaining naloxone could do so at any of the 85 giveaway locations across the state (Pennsylvania Pressroom, 2018b), with at least one in each county. Individuals did not have to provide their name or any other information to obtain naloxone. Most participating locations were county or municipal health department sites, but other locations included pharmacies, libraries, fire stations, local government offices, and churches. At the time of the giveaway, state officials touted it as the biggest such giveaway ever conducted in the country (Wenner,

[13] When discussing naloxone, interview participants in the cited qualitative studies described it as "a safety net," "the anti-dope," and "an excuse just to be more dangerous, I guess, do a bigger shot." Among 82 survey participants in San Francisco, 35% "believed that, if they had naloxone, they might feel comfortable using larger amounts of heroin."

2018). State officials reported that 6,105 naloxone kits, each containing two doses of the naloxone nasal spray Narcan were distributed across the state on the day of the giveaway (Pennsylvania Pressroom, 2018a) and that hundreds were later provided to people on waiting list, bringing the total to over 7,000 (Pennsylvania Pressroom, 2019a).

The state held a second naloxone giveaway on September 18 and 25, 2019 at 95 locations across the state, with at least one location in each county (Pennsylvania Pressroom, 2019c). As with the 2018 giveaway, naloxone distribution coincided with other events to raise awareness about opioid use disorder and the risk of overdose. Nearly 6,800 kits were distributed across the two days (Pennsylvania Pressroom, 2019b). Distribution locations by giveaway are shown in Figure 10.

Figure 10: Map of Naloxone Giveaway Locations



This map shows locations where naloxone was available during giveaway events in December 2018 and September 2019. The shaded counties are the focus of this analysis, including Allegheny County (representing Pittsburgh in the western part of the state) and the Philadelphia area in the southeast, represented by Philadelphia County and the four "collar" counties (Bucks, Chester, Delaware, and Montgomery) that make up Metropolitan divisions within the Philadelphia Metropolitan Statistical Area.

3.3 Data

Outcome Variables

Data on opioid overdose deaths and ED visits attributable to opioid overdose were provided by the Pennsylvania Bureau of Health Statistics & Registries and the Office of Drug Surveillance and Misuse Prevention, respectively. The Pennsylvania Department of Health, under which these agencies are situated, specifically disclaims responsibility for any analyses, interpretations, or conclusions of this research. Opioid overdose deaths were defined as those with underlying cause of death codes representing accidental (ICD-10: X40-X44) or undetermined (Y10-Y14) poisoning and a contributing cause of death code representing opioids (T40.0-T40.4, T40.6). Counts of opioid overdose deaths were obtained at the Census tract-quarter level for 2017-2020. The Census tract identified the location of the incident, not the residence of the decedent.

ED visits attributable to opioid overdose were identified using the state's syndromic surveillance system which combines information from diagnosis codes, triage notes, and chief complaints to classify ED visits (Office of Drug Surveillance and Misuse Prevention, 2022). Quarterly counts of ED visits attributable to opioid overdose between 2017 and 2020 were obtained at the level of the ZIP code of the patient's residence. Counts between 1 and 4 were suppressed, so logical imputation using unsuppressed values for other time periods (i.e., months) for the same ZIP code was used for suppressed quarters. ZIP code-level counts were aggregated to ZCTAs, which are more readily assigned to a spatial geometry. To avoid the potential for a disproportionately large influence of ZCTA-quarters with very high rates of ED visits due to small denominators, ZCTAs with a minimum population below 100 over the study period were excluded and ED visits from that ZCTA were reassigned to the closest neighboring ZCTA.

Treatment Variables

The addresses of naloxone distribution sites by county were published by the state in press releases prior to each giveaway. Addresses of other free sources of naloxone in Pennsylvania and neighboring states were obtained from the National Harm Reduction Coalition's directory of naloxone providers (National Harm Reduction Coalition, n.d.). Addresses were geocoded to obtain longitude and latitude coordinates.

Control Variables

Demographic and socioeconomic data were drawn from the American Community Survey (ACS) for 2017-2020 at the Census tract and ZCTA-levels (United States Census Bureau, 2022a).[14] ACS variables include the proportion of the population by gender, age group, race, ethnicity, and educational attainment, as well as the median household income and unemployment rate in the region. ACS estimates were based on the five most recent survey estimates (e.g., 2017 estimates were based on the ACS from 2013-17). Due to the completion of the 2020 Decennial Census and subsequent redrawing of some Census tract boundaries, tract-level estimates were not comparable between 2017-19 and 2020. Thus, 2019 ACS data were applied to 2020 observations. For tracts or ZCTA observations with missing demographic or socioeconomic data, the county-level average was applied.

Control variables related to opioid overdose were taken from the Pennsylvania Opioid Data Dashboard (OpenData PA, 2022). These measures were at the county-level and measured as rates per 10,000 population. These measures included the prevalence of OUD diagnoses among Medicaid beneficiaries; rates of opioid prescribing and additional risky prescribing rates (> 90 mg morphine equivalence opioid prescriptions, overlapping opioid and benzodiazepine prescriptions and individuals receiving prescriptions from 3 or more prescribers and dispensers); law enforcement seizures (kilograms of heroin and fentanyl seized per 10,000 population); treatment measures (rates of treatment intakes through state hotline, Medicaid beneficiaries receiving MOUD, and buprenorphine prescriptions); and measures related to alternative sources of naloxone (rates of naloxone receipt among Medicaid beneficiaries and rates of EMS naloxone administration). One additional county-level treatment-related control was the number of substance use disorder treatment facilities per 10,000 population from the National Directory of Drug and Alcohol Abuse Treatment Facilities (Substance Abuse and Mental Health Services Administration, n.d.). Most opioid overdose-related controls were measured on a quarterly or monthly basis (month-level rates were averaged within quarter to produce quarterly measures). The four controls measured on an annual basis—rates of Medicaid beneficiaries with an OUD diagnosis, receiving MOUD, or filling a naloxone prescription, and the number of treatment facilities per 10,000 population—were applied to all four quarters in a year.

[14] ACS data were obtained using the tidycensus R package, see Walker, K., & Herman, M. (2022). tidycensus: Load US Census boundary and attribute data as 'tidyverse' and 'sf'-ready data frames. R package version 1.2.3. https://walker-data.com/tidycensus/.

Sample

The main sample for this analysis comprises Census tracts and ZCTAs in six Pennsylvania counties: Allegheny, Bucks, Chester, Delaware, Montgomery, and Philadelphia. These six counties represent the two major urban areas in the state: Pittsburgh (Allegheny County) and Philadelphia (including Philadelphia proper and its four "collar counties"). Philadelphia's four collar counties, along with the city itself, make up the Metropolitan Divisions—large subdivisions of metropolitan statistical areas (MSA)—within the Philadelphia MSA. Although several counties other than Allegheny comprise the Pittsburgh MSA, they are dissimilar from the Philadelphia suburbs in terms of population size and density. These six counties comprise 1,400 of the state's 3,217 Census tracts, 317 of its 1,774 ZCTAs,[15] and 42.1% of its population.

Restricting the focus of the analysis to urban areas strengthens the research design, which relies on defining exposure to the intervention based on distance from the geographic center of a relatively small geographic region—a Census tract or ZCTA—from a giveaway location. Distance from the geographic center of a region becomes less representative of the distance from all points in that region as the physical size of a region grows.[16] Census tracts are statistical subdivisions of counties drawn by the Census bureau as contiguous areas with a population of between 1,200 and 8,000 people (United States Census Bureau, 2022b), and ZCTAs are geographic representations of one or more ZIP code mail delivery routes. Naturally, as population density increases, the physical size of these regions decreases. Census tracts in the six counties that comprise the main sample for this analysis average 5.3 km^2 (median: 1.7 km^2) compared to 59.7 km^2 (median: 15.2 km^2) in the 61 other counties. Similarly, ZCTAs in the six counties average 23.2 km^2 (median: 9.5 km^2) compared to 65.3 km^2 (median: 33.8 km^2) elsewhere. However, it must be noted that restricting the analysis to urban areas limits the generalizability of the estimated effects; the main results of this study should be assumed to be applicable to rural areas.

The analysis period began in the second quarter of 2017 and ran through the end of the first quarter of 2020. The period began in the second quarter of 2017 because some covariates were unavailable prior to April 2017. The analysis period ended after the first quarter of 2020 due to the onset of the COVID-19 pandemic, which may have changed how naloxone was used in the community due to social distancing measures (Collins et al., 2020). The post-giveaway period for the 2018 giveaway was defined to begin in the first quarter of 2019, and the post-giveaway period for the 2019 giveaway was defined to begin in the

[15] ZCTAs can cross county lines; for this analysis, a ZCTA was included if the majority of its population resides in the six-county area.

[16] Notwithstanding this caveat, estimates representing the other 61 counties are available in the appendix.

last quarter of 2019. Over the analysis period, there were 7,737 opioid overdose deaths and 15,835 opioid overdose-related ED visits in the six-county area.

Descriptive Statistics

Descriptive statistics for the tract-level analysis are shown in Table 3.[17] The average population in the 1,400 tracts within the six-county area was 52% female, 31% aged 24 and younger, 69% white, and 7% Hispanic. Sixty-two percent had completed some college, about 7% were unemployed, and the median household had income of over $73,000. Treated regions for giveaway #2 had considerably lower percentages of white residents and higher percentages of black residents than the control regions. Treated regions in both giveaways had higher educational attainment and median household incomes.

Table 3: Descriptive Statistics

Characteristic	Full six-county region (N=1,400 tracts)	Giveaway #1		Giveaway #2	
		Control (N=593 tracts)	Treated (N=154 tracts)	Control (N=593 tracts)	Treated (N=217 tracts)
Gender					
Male	0.48 (0.04)	0.48 (0.03)	0.49 (0.05)	0.48 (0.03)	0.48 (0.05)
Female	0.52 (0.04)	0.52 (0.03)	0.51 (0.05)	0.52 (0.03)	0.52 (0.05)
Age					
Under 15	0.18 (0.05)	0.17 (0.04)	0.18 (0.05)	0.17 (0.04)	0.19 (0.05)
15-24	0.13 (0.09)	0.12 (0.05)	0.13 (0.09)	0.12 (0.05)	0.14 (0.09)
25-44	0.27 (0.08)	0.26 (0.06)	0.28 (0.07)	0.26 (0.07)	0.27 (0.06)
45-64	0.27 (0.06)	0.28 (0.04)	0.25 (0.05)	0.28 (0.04)	0.26 (0.05)
65 and Older	0.16 (0.06)	0.17 (0.06)	0.15 (0.06)	0.17 (0.06)	0.15 (0.06)
Race					
White	0.69 (0.29)	0.72 (0.28)	0.70 (0.22)	0.79 (0.20)	0.51 (0.33)
Black	0.20 (0.28)	0.19 (0.27)	0.20 (0.20)	0.12 (0.18)	0.38 (0.32)
Other Race	0.11 (0.10)	0.10 (0.08)	0.11 (0.08)	0.09 (0.07)	0.11 (0.09)
Hispanic	0.07 (0.12)	0.05 (0.06)	0.09 (0.10)	0.05 (0.05)	0.09 (0.12)

[17] Descriptive statistics for the ZCTA-level ED visit analysis are not shown but are nearly identical to the tract-level analysis.

Characteristic	Full six-county region (N=1,400 tracts)	Giveaway #1		Giveaway #2	
		Control (N=593 tracts)	Treated (N=154 tracts)	Control (N=593 tracts)	Treated (N=217 tracts)
Educational Attainment					
Less than High School Diploma	0.09 (0.08)	0.07 (0.06)	0.11 (0.07)	0.06 (0.05)	0.12 (0.08)
High School Diploma	0.29 (0.12)	0.28 (0.11)	0.36 (0.09)	0.28 (0.11)	0.33 (0.10)
Some College	0.62 (0.18)	0.65 (0.15)	0.52 (0.14)	0.66 (0.14)	0.54 (0.15)
Unemployment Rate	0.07 (0.05)	0.06 (0.04)	0.08 (0.06)	0.05 (0.04)	0.09 (0.05)
Median Household Income (thousands $)	73.47 (36.66)	77.67 (33.22)	55.46 (20.13)	83.41 (34.23)	55.16 (23.44)
County-Level Controls (rate per 10,000)					
Individuals Diagnosed with OUD[a]	427.88 (97.30)	430.89 (97.11)	450.50 (104.23)	427.21 (98.12)	411.14 (93.67)
Opioid Prescriptions	1388.10 (219.73)	1393.80 (215.57)	1402.80 (223.75)	1372.40 (220.39)	1352.16 (207.97)
Opioid Prescriptions > 90 MME	37.94 (11.45)	37.71 (11.11)	36.12 (10.54)	36.33 (10.71)	38.79 (11.58)
Individuals With Overlapping Opioid and Benzodiazepine Prescriptions	53.93 (14.22)	53.97 (13.57)	52.49 (12.93)	51.96 (13.42)	53.88 (14.84)
Individuals Seeing 3+ Prescribers and 3+ Dispensers	3.73 (1.10)	3.72 (1.08)	3.74 (1.10)	3.61 (1.08)	3.59 (1.04)
Kilograms Heroin Seized	0.01 (0.02)	0.01 (0.02)	0.01 (0.02)	0.01 (0.02)	0.01 (0.02)
Kilograms Fentanyl Seized	0.01 (0.08)	0.01 (0.06)	0.01 (0.07)	0.02 (0.09)	0.02 (0.09)
Intakes to State "Get Help Now" Hotline	0.58 (0.26)	0.56 (0.25)	0.52 (0.24)	0.51 (0.24)	0.56 (0.27)
Buprenorphine Prescriptions	199.23 (69.39)	201.21 (67.61)	204.59 (74.09)	193.28 (71.08)	183.34 (61.31)
Individuals receiving MOUD[a]	247.69 (86.22)	251.04 (85.10)	267.34 (90.28)	246.92 (86.53)	231.52 (80.40)
SUD Treatment Facilities	0.38 (0.10)	0.36 (0.10)	0.36 (0.09)	0.35 (0.10)	0.38 (0.11)
Naloxone Prescriptions[a]	70.93 (25.58)	70.52 (23.70)	69.36 (23.05)	66.64 (24.00)	69.09 (26.64)
Naloxone Administrations by EMS	0.42 (0.37)	0.40 (0.35)	0.36 (0.32)	0.35 (0.33)	0.41 (0.39)

N=16,800 Census tract-quarters (6 urban counties from Q2 2017 – Q1 2020; 1,400 tracts * 12 quarters). Weighted by tract population.

[a]Rates are for Medicaid beneficiaries.

More than 420 out of every 10,000 Medicaid beneficiaries had an OUD diagnosis in the past year. More than 1 opioid prescription for 10 people was written, but risky prescribing was less common. Heroin and fentanyl seizures averaged about 1 kg per million people over the period but varied widely. Treatment intakes through the state's Get Help Now hotline averaged about 1 per 20,000 population per quarter, but nearly 200 buprenorphine prescriptions were written per 10,000 population, and nearly 250 people per 10,000 Medicaid beneficiaries (or more than half of the population with an OUD diagnosis) received MOUD. Finally, 70 people for every 10,000 Medicaid beneficiaries filled a naloxone prescription, and EMS personnel administered naloxone about once per 20,000 population per quarter on average across the six-county area.[18]

3.4 Empirical Framework

Main Approach

The main empirical approach exploited region-level variation in distance to naloxone distribution sites and other sources of free naloxone to identify the effect of the naloxone giveaways on fatal opioid overdoses and opioid overdose-related ED visits. Two-way fixed effects difference-in-differences and event study estimators were used to examine the effects of each giveaway separately, and then an estimator robust to staggered exposure to treatment was used to evaluate the effects of the giveaways together (Callaway & Sant'Anna, 2021; Sant'Anna & Zhao, 2020). This analysis adopted an intent-to-treat perspective, as outcomes of people who obtained naloxone during the giveaways were not available.

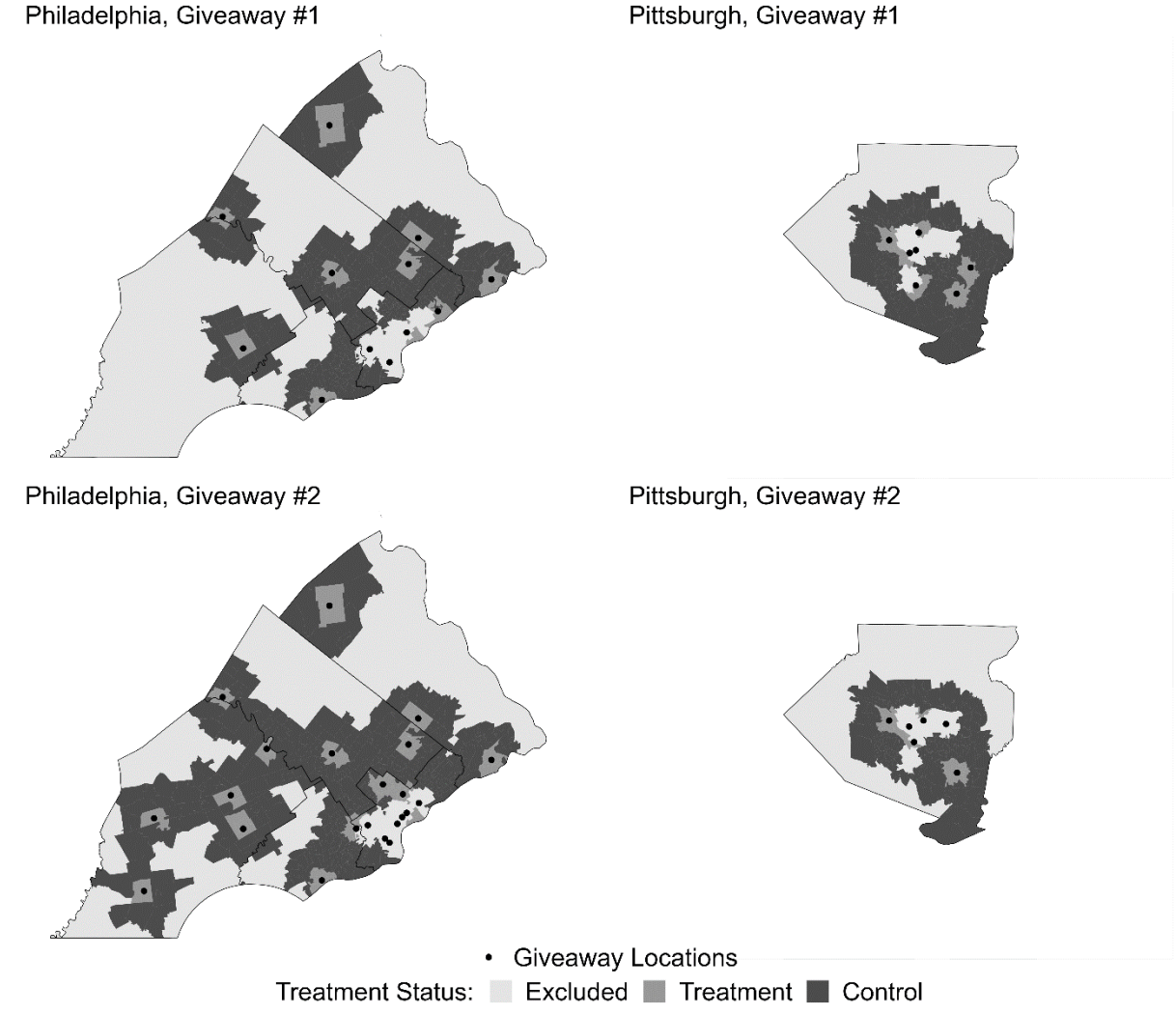
The treatment status of each Census tract (for the fatal overdose analysis) and ZCTA (for the ED visit analysis) was defined based on two distances: 1) the distance from the center of the tract/ZCTA to the nearest giveaway location and 2) the distance from the center of the tract/ZCTA to the nearest alternative source of free naloxone.[19] Based on those two distances, tracts and ZCTAs were defined as either "treated", if they were within 3km from the nearest giveaway location and more than 3km from any alternative source of free naloxone; "control", if they were between 3km and 10km from the nearest

[18] Compared to the rest of the state, the population in the six-county area had fewer opioid prescriptions (261.17 fewer per 10,000 people, $p<0.01$), more receipt of prescriptions from 3 or more prescribers or dispensers (0.65 more per 10,000 people, $p = 0.03$), and more naloxone fills (20.51 more per 10,000 Medical Assistance beneficiaries, $p=0.01$). There were no statistically significant differences on any of the other opioid overdose-related control variables.

[19] Tract and ZCTA geographies, including their center points, were obtained from U.S. Census Bureau shapefiles through the tigris package in R, see Walker, K. E. (2016). tigris: An R package to access and work with geographic data from the US Census Bureau. All distances for this analysis were calculated from longitude and latitude coordinates using the raster package in R, see Hijmans, R. J., Van Etten, J., Cheng, J., Mattiuzzi, M., Sumner, M., Greenberg, J. A., ... & Hijmans, M. R. J. (2015). Package 'raster'. R package, 734.

giveaway location and more than 3km from any alternative source of free naloxone; or excluded if they were within 3km of an alternative source of free naloxone or more than 10km from the nearest giveaway location. Regions within 3km of an alternative, more permanent source of free naloxone were excluded under the assumption that a temporary naloxone giveaway would not affect people in those locations, and regions more than 10km from a giveaway location were excluded to maximize the comparability of treatment and control regions.[20] Because some distribution locations were only used for one of the two giveaways, some regions' treatment status varied between giveaways. Treated and control tracts for both giveaways in the Philadelphia (five counties) and Pittsburgh (Allegheny County) areas are shown in Figure 11. An analogous map for the ZCTA-level analysis of opioid overdose-related ED visits is shown in Appendix Figure A3.1.

Figure 11: Treated and Control Regions for Census Tract-Level Analysis

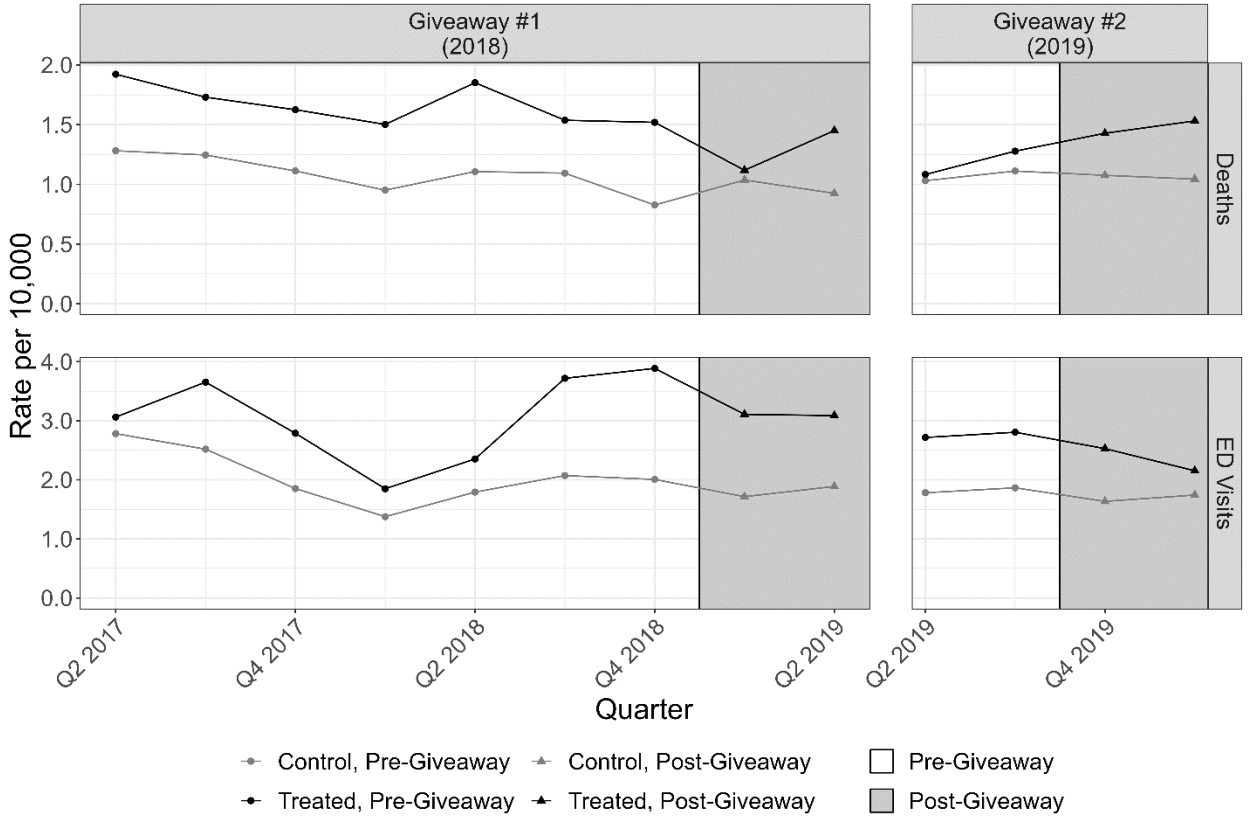


[20] The distance thresholds and exclusions used in the main analysis were varied in a sensitivity analysis.

This figure shows treated and control regions for the Census-tract level analysis of the effect of each of the two giveaways on opioid overdose deaths. Excluded regions are Census tracts within 3km of an existing source of free naloxone or more than 10km from a giveaway location, treated regions are Census tracts more than 3km from an existing source of free naloxone but within 3km of a giveaway location, and control regions are Census tracts more than 3km from an existing source of free naloxone but between 3km and 10km of the nearest giveaway location.

Unadjusted trends expressed in rates per 10,000 population for both outcomes in both giveaway periods are shown in Figure 12. The charts indicate that treated regions had higher rates of both outcomes, but do not suggest the presence of differential trends in the pre-giveaway periods. However, unadjusted trend plots offer only limited support for the common trends assumption, and other evidence such as event study plots and robustness checks to gauge the sensitivity of key findings to the common trends assumption are warranted.

Figure 12: Unadjusted Outcome Trends



This plot shows unadjusted outcomes over time for treated and control regions. Opioid overdose deaths are shown in the top two panels and opioid overdose-related ED visits are shown in the bottom two panels. The 2018 giveaway is represented in the left two panels and the 2019 giveaway is represented in the right two panels. Dependent variables are expressed as rates of events (i.e., opioid overdose deaths or opioid overdose-related ED visits) per 10,000.

The effect of the giveaway was measured using a standard two-way fixed effects estimator as shown in Equation 3.1:

$$y_{rt} = \alpha + \gamma_r + \lambda_t + \delta(Trt_r * Post_t) + X'_{rt}\beta + \varepsilon_{rt} \qquad \text{(Eq. 3.1)}$$

where y_{rt} is the outcome for region r at time t, α is the intercept, γ_r and λ_t are region and time fixed effects, respectively, X'_{rt} represents the time-varying region-level characteristics related to OUD prevalence, prescribing, law enforcement seizures, treatment, and naloxone access as described in section 3.3[21], and ε_{rt} represents the error term. To maintain parsimony and to avoid potential bias from control variables affected by the treatment (Angrist & Pischke, 2009), control variables represented by X'_{rt} are included in robustness checks but not the main results. δ is the treatment effect being estimated, based on an interaction of a dummy variable representing treated regions (Trt_r) and post-giveaway time periods ($Post_t$). The outcome y_{rt} for the fatal overdose analysis was the count of deaths that occurred in each Census tract and quarter, and the outcome for the ED visit analysis was the count of ED visits by residents of a given ZCTA in a given quarter.

To assess pre-existing trends in treated and control regions prior to the giveaways and to examine how effects vary over time after the giveaway, an event study was used to incorporate leads and lags (Equation 3.2):

$$y_{rt} = \alpha + \gamma_r + \lambda_t + \sum_{\tau=-q}^{-2} \delta_\tau (Trt_r * T_\tau) + \sum_{\tau=0}^{m} \delta_\tau (Trt_r * T_\tau) + X'_{rt}\beta + \varepsilon_{rt} \quad \text{(Eq. 3.2)}$$

which replaces the single treatment effect from Equation 3.1 with terms representing the difference between treated and control regions in each period before and after the giveaway (excluding the period just prior to the giveaway, τ = -1, which is normalized to 0). As in the case of Equation 3.1, control variables represented by X'_{rt} were omitted from the main analysis and introduced in robustness checks.

Because both outcomes were counts of events (i.e., fatal overdoses and ED visits, respectively), Equations 3.1 and 3.2 were estimated using fixed effects Poisson regression. Standard errors adjusted for clustering at the level of the geographic region. Because the outcomes were influenced by the number of people in a region, an exposure variable was specified (i.e., the natural logarithm of this variable is included in the model with coefficient constrained to 1). For the fatal overdose analysis, because the dependent variable is based on event location not decedent residence, and because some tracts have 0 population (i.e., industrial or commercial areas), tract-level population could not be used. Instead, each tract's population was proportionally allocated to all tracts within 10km to produce an exposure variable that was highly correlated with tract population (r = 0.51) and with county population (when exposure is added up at the

[21] Tract- and ZCTA-level demographic and socioeconomic characteristics from the American Community Survey were not included in the main output because they change very little over the period of analysis and because they were unavailable for tracts in 2020. They were added in a sensitivity analysis.

county-level; r=0.99).[22] Because the dependent variable for the ED visit analysis was based on the residence of people presenting to the ED, the ZCTA-level population was suitable to represent exposure for the ED visit analysis. Equations 3.1 and 3.2 were re-estimated using fixed effects linear regression with the dependent variable expressed as the count of events—fatal overdoses or ED visits—per 10,000 people.

Equations 3.1 and 3.2 were used to estimate the effects of each giveaway separately. The period of analysis for the 2018 giveaway was from the second quarter of 2017 through the second quarter of 2019, and the period of analysis for the 2019 giveaway was from the second quarter of 2019 through the first quarter of 2020. Thus, the analysis periods for both giveaways each have two post-giveaway quarters. A short follow-up period was chosen for two reasons. First, the giveaways were temporary, so it would not be reasonable to define a lengthy post-implementation period as would be appropriate for the types of policies usually studied using a similar design. The short (6 month) follow-up period focuses on the time that the intervention is expected to have an effect, and Equation 3.2 allows for immediate effects to be differentiated from delayed effects. Second, because the intention of Equations 3.1 and 3.2 was to estimate the effect of both giveaways separately, periods for the analysis for the respective giveaways were chosen to limit the potential of one giveaway to confound the estimate of the effect of the other. A key consequence of this is a limited pre-intervention period for the 2019 giveaway, which comprised only two quarters.

Finally, the overall effect of the naloxone giveaways was analyzed using an estimator that accounts for variation across regions in terms of the timing of exposure to a giveaway (Callaway & Sant'Anna, 2021; Sant'Anna & Zhao, 2020). The doubly robust difference-in-differences approach, henceforth the CS estimator, uses a two-stage approach of a generalized propensity score followed by an outcome regression. The CS estimator is robust to misspecification of either stage of the procedure and produces an estimate of the average treatment effect on regions exposed to the giveaway using regions never exposed to the giveaway as controls, thus avoiding bias produced by the two-way fixed effects estimator in cases where units are treated at different time periods (Borusyak et al., 2021; De Chaisemartin & d'Haultfoeuille, 2020; Goodman-Bacon, 2021; Sun & Abraham, 2021). The specific estimator used for this

[22] The proportion of a donor tract's population to a given recipient tract, p_t, is done according to the function, $p_t = a_t/\text{sum}(a)$, where a_t is 10,000 minus the distance between the donor tract and the recipient tract in meters and sum(a) is the sum of the quantity a for all tracts within 10km of the donor tract. The donor tract allocates a proportion of its population to itself, the quantity a_t is equal to 10,000 (because the distance is 0 meters).

analysis, based on inverse probability tilting for the first stage and weighted least squares for the second, was shown to produce relatively unbiased estimates—especially in comparison to conventional two-way fixed effect difference-in-differences—with high efficiency in Monte Carlo simulations (Sant'Anna & Zhao, 2020).

The dependent variable for the doubly robust estimate was identical to that which was used for Equations 3.1 and 3.2 when estimated using linear regression: the count of events—fatal overdoses or ED visits—per 10,000 people. Pre-treatment covariates used for the first stage propensity score model included tract- or ZCTA-level demographic characteristics (gender, age, race/ethnicity), educational attainment, and unemployment rates, as well as county-level OUD prevalence, risky prescribing measures (> 90 mg morphine equivalence opioid prescriptions, overlapping opioid and benzodiazepine prescriptions), and EMS naloxone administrations.[23] As with the giveaway-specific estimates, the effect of the giveaway was only measured for two post-intervention quarters.[24]

Robustness Tests

Several robustness checks were conducted to establish the validity of the approach and to assess the sensitivity of findings to analytic assumptions. First, as noted in the previous section, Equations 3.1 and 3.2 were estimated both using fixed effects Poisson regression and fixed effects linear regression. Second, to test the sensitivity of results to the common trends assumption, a postestimation procedure proposed by Rambachan and Roth (2022) was used to re-estimate standard errors for event study (Equation 3.2) and doubly-robust estimator coefficients. This approach, which accounts for uncertainty in differences in group trends, was applied to significant coefficients to identify the approximate maximum deviation from parallel in the post-giveaway period—as a proportion of the maximum observed deviation from parallel in the pre-giveaway period—under which the coefficient remained significant. Third, to test for selection effects, the analysis of the first giveaway was repeated restricting the control regions to those exposed to the second giveaway but not the first. This is similar to a wait-list control design, as both treatment and control regions were ultimately chosen to have giveaway locations nearby. If main findings were driven by selection, this alternative approach would be expected to produce results closer to a null effect. Fourth,

[23] The set of covariates used for the doubly robust estimator was restricted to key covariates because the estimator did not converge on the full set of covariates. All covariates listed here were used for the fatal overdose outcome. For the ED visit outcome, only demographic characteristics, educational attainment, and OUD prevalence were used.
[24] The doubly-robust estimator was implemented using the Stata package csdid, see Rios-Avila, F., Sant'Anna, P., & Callaway, B. (2022). CSDID: Stata module for the estimation of Difference-in-Difference models with multiple time periods.

Equation 3.1 was re-estimated with demographic and socioeconomic controls added as covariates, with demographic and socioeconomic controls and no opioid overdose-related controls, and with no controls. Fifth, Equation 3.1 was re-estimated for the fatal overdose outcome using the tract population as the exposure variable, rather than the exposure variable constructed using distance-based allocation. This analysis excluded tracts with populations under 1,000 (3.2% of tracts). Sixth, a permutation test was conducted in which treatment status was reshuffled among regions and Equations 3.1 and 3.2 were re-estimated 100 times each. The coefficients δ from Equation 3.1 and δ_0 from Equation 3.2 (representing the event study estimate for the first post-giveaway quarter) from the observed data were plotted against 100 estimates based on treatment status permutations. Finally, several analyses were conducted to explore sensitivity to treatment status definitions: 1) Equation 3.1 was re-estimated using alternative criteria to define the treatment status of regions with respect to the giveaways using alternative distance thresholds (i.e., 1km and 5km) and removing sample exclusions; 2) outcomes were regressed on quarter and region fixed effects alone (i.e., using time as the only treatment indicator) on samples defined by increasing proximity to giveaway sites using a regression discontinuity in time (RDiT) approach (Hausman & Rapson, 2018); and 3) Equation 3.1 was re-estimated with distance to the nearest giveaway site as a continuous intensity of treatment measure replacing the binary treatment indicator.

3.5 Results

Fatal Overdose Results

Effect estimates from Equation 3.1 are presented as IRRs in Table 4 for both giveaways. No statistically significant effect of the 2018 giveaway on fatal overdoses was detected in the first two quarters after the giveaway, but an increase in opioid overdose deaths (IRR:1.27, p=0.07) was found for the 2019 giveaway. Notably, when Equation 3.1 was re-estimated using fixed effects linear regression, a statistically significant reduction in deaths was detected for the treated region after the 2018 giveaway (-0.31 deaths per 10,000, p = 0.04, Appendix Table A3.1) and an increase was detected after the 2019 giveaway (+0.31 deaths per 10,000, p = 0.07). Results for Equation 3.1 for the rest of the state are available in Appendix Table A3.2.

Table 4: Effect of Naloxone Giveaways on Overdose Deaths

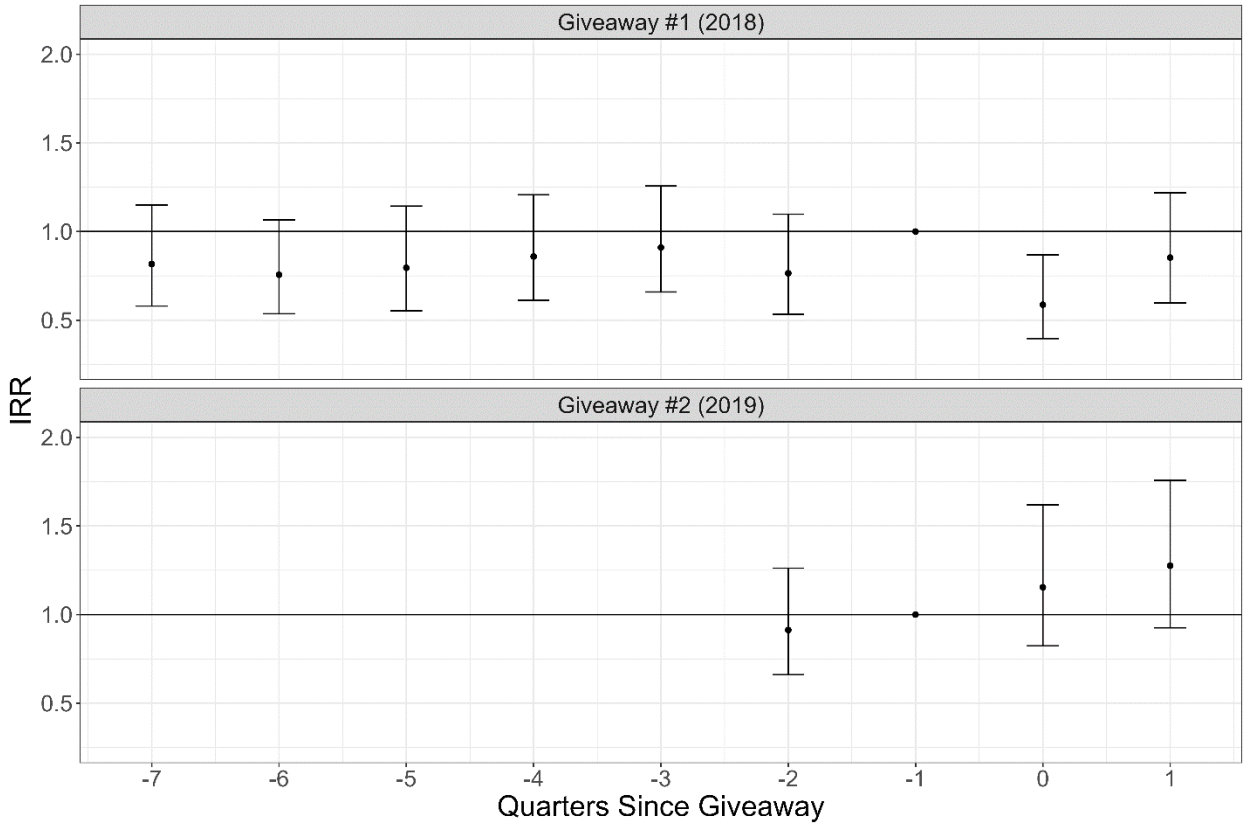
	Giveaway #1 (2018)	Giveaway #2 (2019)
Treatment x Post	0.853	1.267*
	[0.690,1.056]	[0.985,1.629]
Observations	6066	2420

* p<0.10, ** p<0.05, *** p<0.01

This table shows incidence rate ratios from fixed effects Poisson regression of Equation 3.1: Census tract-quarter level opioid overdose deaths on an interaction term identifying observations of tracts treated during the naloxone giveaway (Treatment x Post), Census tract fixed effects, and quarter fixed effects. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the Census tract level. Tracts with no recorded opioid overdose deaths over the analysis period are excluded.

When effects were allowed to vary over time in an event study (Equation 3.2), a large and statistically significant decrease in deaths in the first post-giveaway quarter after the 2018 giveaway was detected (IRR:0.59, p=0.01, Figure 13). This result holds at the 5% significance level if the deviation from parallel in the post-giveaway period was no greater than 75% of the largest observed deviation in the pre-giveaway period (IRR CI: 0.30–0.99), and at the 10% level if the post-giveaway deviation was no greater than 100% of the largest observed pre-giveaway deviation (IRR CI: 0.29–0.98). None of the other post-giveaway coefficients were statistically significant for either giveaway. Event study coefficients for the periods preceding both giveaways were not statistically significant, providing support for the common trends assumption. Event study results estimated using fixed effects linear regression, which are consistent with Poisson estimates, are shown in Appendix Figure A3.2. Results for the rest of the states are shown in Appendix Figure A3.3.

Figure 13: Event Study Estimates for Effect of Naloxone Giveaways on Overdose Deaths

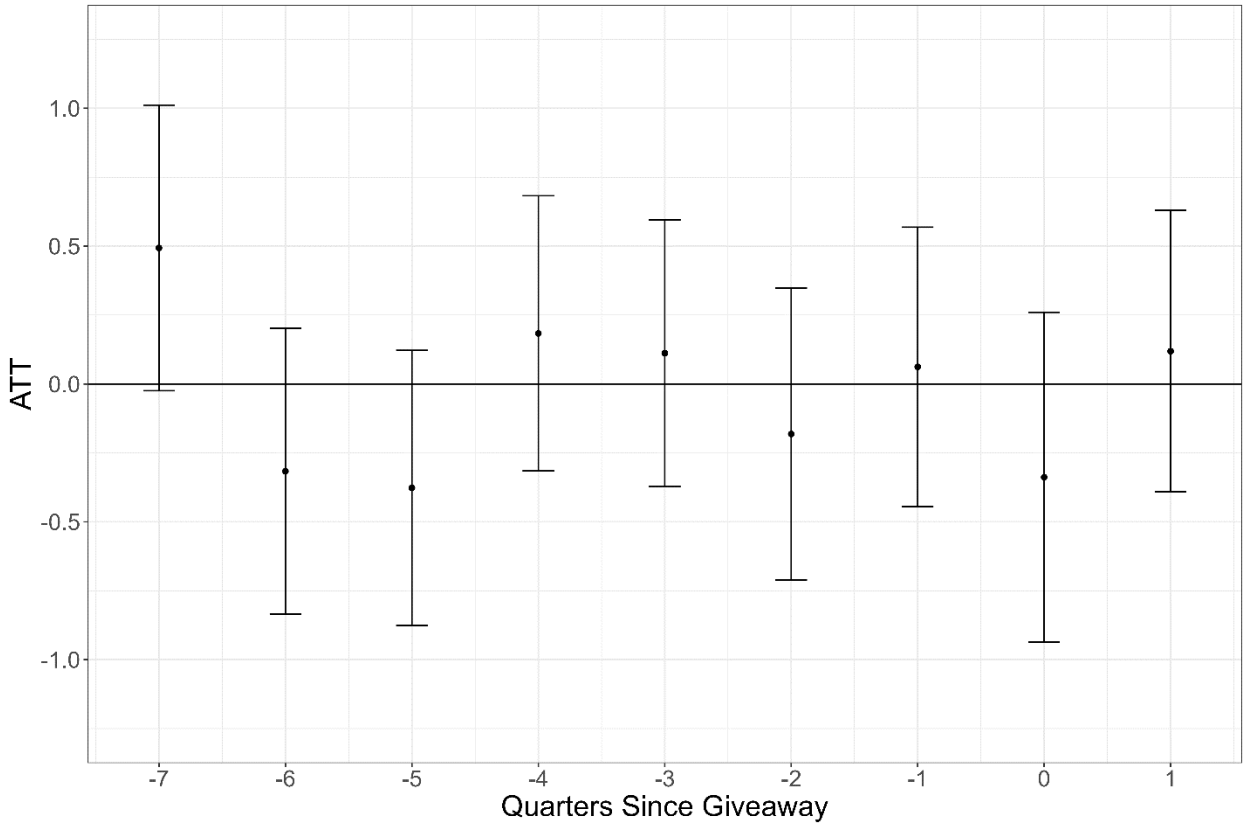


This figure shows incidence rate ratios (IRRs) from a fixed effect Poisson event study regression of Equation 3.2: Census tract-quarter level opioid overdose deaths. The regression controls for Census tract and quarter fixed effects. The point represents the

coefficient estimate (IRR) and the error bars represent 95% confidence intervals based on standard errors adjusted for clustering at the Census tract level. Tracts with no recorded opioid overdose deaths over the analysis period are excluded.

Finally, when the effects of the two giveaways were examined together, 154 tracts were treated during the 2018 giveaway, 95 tracts were treated during the 2019 giveaway but not the 2018 giveaway, and 582 were not treated during either giveaway. Dynamic treatment effects estimated using the CS estimator identified no statistically significant effect of the giveaways on opioid overdose deaths (Figure 14).

Figure 14: Combined Dynamic Treatment Effect of Naloxone Giveaways on Overdose Deaths from Doubly Robust Estimator



This figure shows dynamic treatment effects combining both naloxone giveaways using the doubly robust estimator developed by Callaway, Sant'Anna, and Zhao. The dependent variable is untransformed opioid overdose deaths per 10,000 population. The model adjusts for time-invariant (pre-treatment) differences between Census tracts in demographic (gender, age, race/ethnicity) and socioeconomic (educational attainment, median household income, and unemployment rate) characteristics, and OUD prevalence among individuals receiving Medical Assistance, rates of high-dose opioid prescriptions and overlapping opioid and benzodiazepine prescriptions, and rates of EMS naloxone administration. The point represents the estimate of the average treatment effect on the treated (ATT) and the error bars represent 95% confidence intervals based on standard errors adjusted for clustering at the Census tract level.

Repeating the analysis of the effect of the 2018 giveaway on opioid overdose deaths using later-treated tracts as controls was not suggestive of selection bias in the main results. Estimates from Equation 3.1 (Appendix Table A3.3) and Equation 3.2 (Appendix Figure A3.4) were statistically significant and had higher magnitudes than analogous main analysis estimates. Results from Equation 3.1 were generally unchanged

when controls were added to the model (Appendix Table A3.4). Estimating Equation 3.1 using tract population as the exposure variable produced nearly identical results to the main analysis (Appendix Table A3.5). A permutation test for Equation 3.2 in the 2018 giveaway (Appendix Figure A3.5) supported the finding that the giveaway reduced deaths in the first post-giveaway quarter, as the estimated reduction in deaths was larger than any permutation. Permutation tests for the 2019 giveaway are also shown in Appendix Figure A3.6.

Changing the definition of treatment and control regions had a minor effect on the magnitude and significance of estimated effects (Appendix Table A3.6). For both giveaways, increasing the distance threshold from 3km to 5km reduced the magnitude of the effect supporting the relationship between proximity to the giveaway locations and effect on deaths. Appendix Table A3.7 containing RDiT results provides further evidence for this, showing that average deaths in the post-giveaway quarters relative to the quarter prior to the giveaway increased as the sample was progressively restricted to include tracts closer to a giveaway location. This relationship is particularly strong for the first quarter following the 2018 giveaway. Finally, using distance from giveaway as an intensity of treatment measure in place of the binary treatment indicator in Equation 3.1 yields a similar conclusion, as distance from the giveaway location was significantly associated with overdose deaths in both giveaways and the direction of the effect was the same as in Table 2 (Appendix Table A3.8). For the 2018 giveaway, deaths increased as distance from the giveaway location increased (IRR: 1.02 per 1km, $p<0.01$). For the 2019 giveaway, deaths decreased as distance from the giveaway location increased, but this effect was not statistically significant (IRR: 0.98, $p=0.10$).

Emergency Department Visit Results

Effect estimates from Equation 3.1 for the ED visit analysis are shown in Table 5. No statistically significant effects on ED visits related to opioid overdose were detected over the first two quarters following the 2018 giveaway, but a reduction in ED visits was identified for the two quarters following the 2019 giveaway (IRR:0.81, $p=0.05$). When Equation 3.1 was re-estimated using fixed effects linear regression, the reduction in ED visits following the 2019 giveaway was not significant even at the 10% level ($p=0.25$, Appendix Table A3.9). Based on event study coefficients from Equation 3.2, no statistically significant effect was detected using fixed effects Poisson regression (Figure 15) or fixed effects linear regression (Appendix Figure A3.7). Estimates from Equation 3.1 and Equation 3.2 for the rest of the state are available in Appendix Table A3.10 and Appendix Figure A3.8, respectively.

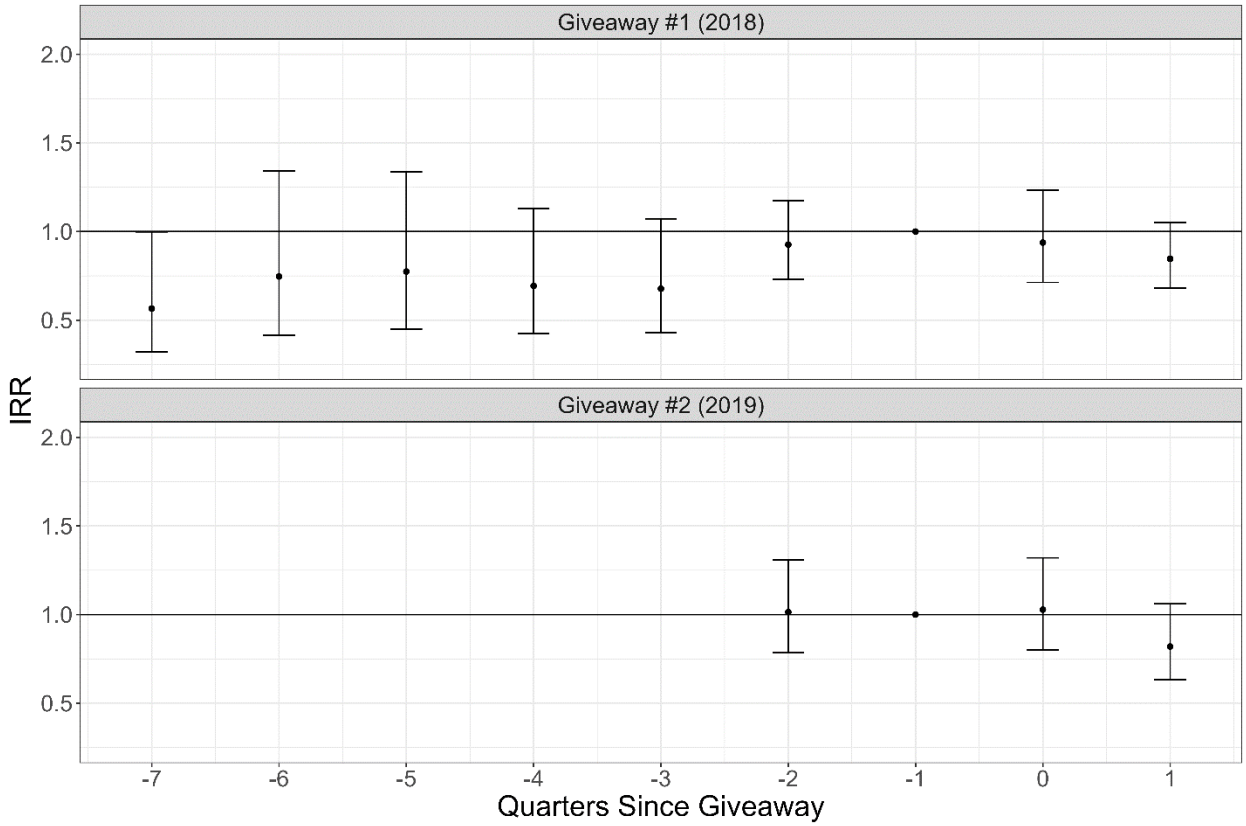
Table 5: Effect of Naloxone Giveaways on Opioid Overdose-related Emergency Department Visits

	Giveaway #1 (2018)	Giveaway #2 (2019)
Treatment x Post	1.166	0.809*
	[0.821,1.657]	[0.653,1.003]
Observations	1359	668

* p<0.10, ** p<0.05, *** p<0.01

This table shows incidence rate ratios from fixed effects Poisson regression of Equation 3.1: ZCTA-quarter level emergency department (ED) visits attributable to opioid overdose on an interaction term identifying observations of ZCTAs treated during the naloxone giveaway (Treatment x Post), ZCTA fixed effects, and quarter fixed effects. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the ZCTA level. ZCTAs with no recorded opioid overdose-related ED visits over the analysis period are excluded.

Figure 15: Event Study Estimates for Effect of Naloxone Giveaways on Emergency Department Visits

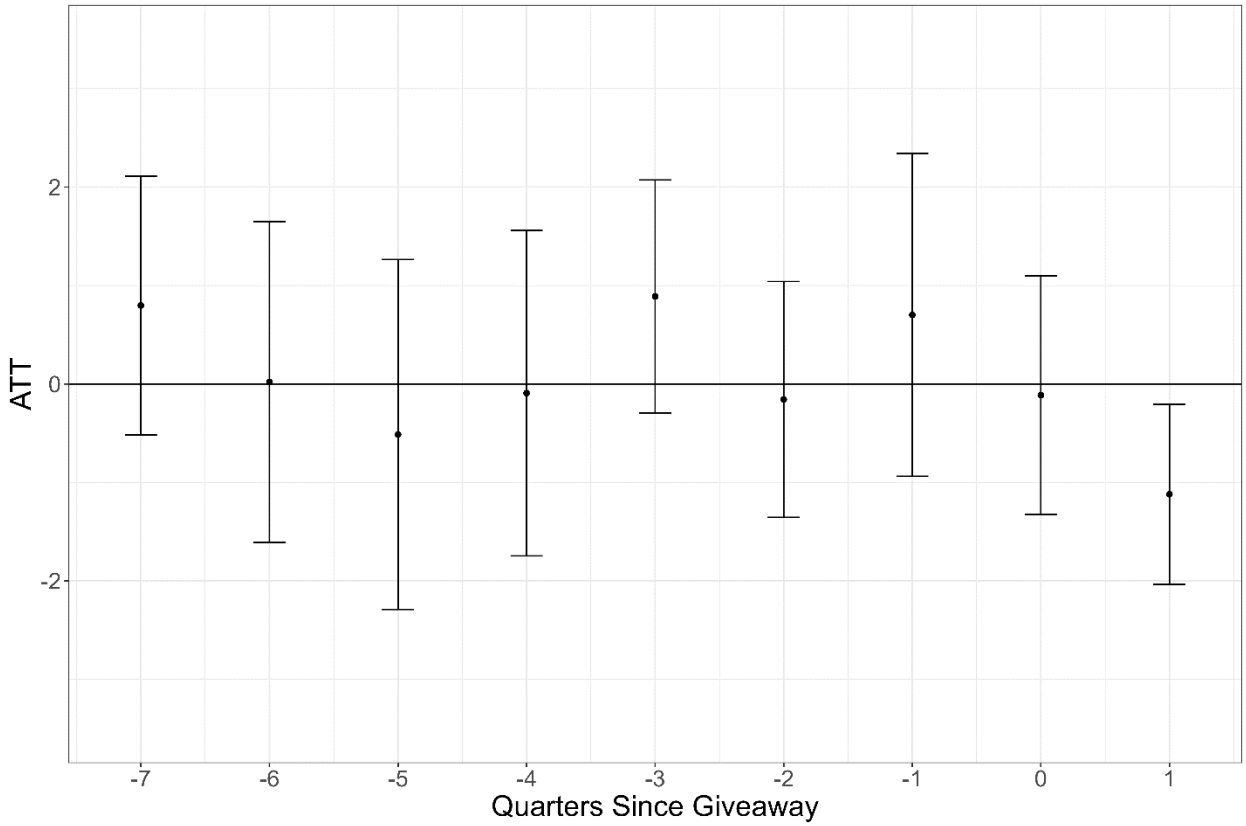


This figure shows incidence rate ratios (IRRs) from a fixed effects Poisson event study regression of Equation 3.2: ZCTA-quarter level emergency department (ED) visits attributable to opioid overdose. The regression controls for ZCTA and quarter fixed effects. The point represents the coefficient estimate (IRR) and the error bars represent 95% confidence intervals based on standard errors adjusted for clustering at the ZCTA level. ZCTAs with no recorded opioid overdose-related ED visits over the analysis period are excluded.

The combined effect of the two giveaways on opioid overdose-related ED visits was evaluated using the doubly robust CS estimator (Figure 16). Twenty-six ZCTAs were treated during the 2018 giveaway, 19 were treated during the 2019 giveaway but not the 2018 giveaway, and 145 ZCTAs were not treated during either giveaway. These results suggest no immediate effect of the giveaway on opioid-related ED visits

but a reduction in the second quarter after the giveaways (ATT: -1.12 ED visits per 10,000 population, p=0.02); however, this effect is not statistically significant when uncertainty about common trends is accounted for and bounded at 25% of the maximum observed deviation from parallel in the pre-giveaway period.

Figure 16: Combined Dynamic Treatment Effect of Naloxone Giveaways on Emergency Department Visits from Doubly Robust Estimator



This figure shows dynamic treatment effects combining both naloxone giveaways using the doubly robust estimator developed by Callaway, Sant'Anna, and Zhao. The dependent variable is untransformed emergency department visits attributable to opioid overdose per 10,000 population. The model adjusts for time-invariant (pre-treatment) differences between ZCTAs in demographic (gender, age, race/ethnicity) and socioeconomic (educational attainment) characteristics, and OUD prevalence among individuals receiving Medical Assistance. The point represents the estimate of the average treatment effect on the treated (ATT) and the error bars represent 95% confidence intervals based on standard errors adjusted for clustering at the ZCTA level.

Like the main analysis, repeating the estimation of Equation 3.1 (Appendix Table A3.11) and Equation 3.2 (Appendix Figure A3.9) for the first giveaway using ZCTAs defined as treated in the second giveaway as the comparison group produced results that were not statistically significant. Results from Equation 3.1 were generally robust to the inclusion of control variables, though including opioid-overdose related controls decreased the magnitude of the effect for the 2019 giveaway from 0.809 to 0.895 and removed marginal statistical significance (Appendix Table A3.12). Permutation tests support the findings of no

significant effect of the 2018 (Appendix Figure A3.10) giveaway on ED visits but provide some support for the overall reduction over the first two quarters following the 2019 giveaway (Appendix Figure A3.11).

Changing the definition of treatment and control regions had a minimal effect on the results. None of the distance thresholds or alternative definitions of the control group produced a statistically significant effect from Equation 3.1 for the 2018 giveaway. Although changing the distance threshold from 3km to 5km eliminated the marginally significant result for the 2019 giveaway (Appendix Table A3.13), the magnitude was essentially unchanged. RDiT models of ED visits on quarter and ZCTA fixed effects indicated a decline in ED visits across the six-county region in the quarters after the giveaways with increasing magnitude in areas closer to giveaway sites in the second post-giveaway quarter (Appendix Table A3.14). When distance is used as an intensity of treatment measure in place of the binary treatment indicator in Equation 3.1, no statistically significant effect was detected (Appendix Table A3.15)

3.6 Discussion

This study is the first to examine the effect of large-scale public naloxone giveaways. The results provide consistent evidence that the first giveaway caused a large and significant reduction in opioid overdose deaths in the quarter immediately following it. That result holds across several robustness tests. The results also indicate that the second giveaway was associated with an increase in opioid overdose deaths, significant at the 10% level, over the two quarters following the giveaway. This finding is also consistent across several robustness checks, but the magnitude of the effect is less precise than for the 2018 giveaway. Because the effects on overdose deaths are in opposite directions, it is not surprising that when the effects of the giveaways are measured together using the CS estimator, no statistically significant effects are detected. The effects of the giveaways in terms of opioid overdose-related ED visits are less certain. The results provide some evidence of a reduction in ED visits following the 2019 giveaway and for the second post-giveaway quarter when the experiences of the two giveaways were pooled using the CS estimator, but those results are less robust to alternative estimation procedures (i.e., linear regression) and highly sensitive to deviations from the common trends assumption, respectively.

It is difficult to compare these findings to the previous literature on the topic given the unique nature of the intervention studied. The goal of the Pennsylvania giveaways was to increase naloxone possession among the general population by establishing naloxone as a universal public health tool like CPR training or automated external defibrillators. The only other study of the causal effect of direct naloxone distribution came from an OEND program in Massachusetts. In that study, 69% of the participants

reported active substance use, 34% had overdosed, and 74% had witnessed an overdose. The population who participated in the Pennsylvania giveaways likely had considerably lower levels of substance use and overdose experience. Despite the difference in the nature of the interventions, the results from the Massachusetts study in terms of overdose deaths are aligned with the results from the current study with respect to the first giveaway, both having suggested a protective effect of naloxone distribution on opioid overdose deaths. Similarly, studies that identified the effect of providing naloxone to non-professionals using variations in the timing of naloxone access laws also generally found that naloxone had a protective effect on deaths, or that it had no statistically significant effect at all. Thus, the finding of an increase in deaths following the second naloxone giveaway seems to contradict existing evidence.

It is striking that the same approach applied to two naloxone giveaways held about 9 months apart would produce such different results with respect to fatal overdoses. One possibility is that the nature of the opioid supply may have changed between the first and second giveaways, reducing the effectiveness of naloxone. Changes in the drug supply are particularly difficult to measure, but there is some evidence of such a change between the giveaways. According to Overdose Information Network (ODIN) data (OpenData PA, 2022), overdose survival conditional on naloxone administration in the six-county area fell from 93.6% immediately following the first giveaway (Q1 2019) to 91.5% immediately following the second (Q4 2019). Although this is not a large difference in absolute terms, the 91.5% survival rate in Q4 2019 is the lowest on record from 2018 (the earliest period for ODIN data) through the end of the first quarter of 2020. Over the same period, the number of overdose incidents reported to ODIN increased from 172 to 235, and the average dose of naloxone administered per incident increased from 6.7mg to 7.7mg ($p = 0.09$)—and the median dose from 4mg to 8mg. All of this suggests an increase in the potency of the opioid supply, which may have reduced the effectiveness of a dose of naloxone.

Additionally, the presence of xylazine—a veterinary tranquilizer—in the drug supply in Philadelphia increased considerably during the period of the giveaways. Xylazine was detected in 18% of heroin and/or fentanyl overdoses in Philadelphia in 2018, compared to 31% in 2019 (Johnson et al., 2021). Qualitative research conducted with people who use opioids indicated that some seek out opioids with xylazine as an additive because the combination produces a “heroin-like effect” rather than the “short-lived high” produced by fentanyl (Friedman et al., 2022). Like opioids, xylazine has respiratory depressive effects, but naloxone does not reverse respiratory depression caused by xylazine (Kariisa et al., 2021). If people who obtained naloxone were more likely to seek out and use opioids with xylazine due to the perception of naloxone as a “safety net,” that could contribute to the increase in deaths due to the ineffectiveness of

naloxone to reverse xylazine overdose. Given the considerable change in the opioid supply and its potential impact on the effectiveness of naloxone, the evidence based on the first giveaway may be more reliable than the evidence from the pooled estimator, particularly for understanding the effect of a naloxone giveaway in a market with little to no exposure to xylazine. The pooled estimator could be interpreted as a weighted average of the effect of naloxone giveaways in two distinct environments, which may not be applicable to any specific context. However, the contrast between the two sets of giveaway-specific estimates and the effects from the pooled estimator suggest that the effectiveness of the intervention to reduce overdose deaths is sensitive to contextual factors, so decisionmakers should consider the prevailing conditions when interpreting the results of this study. Effect estimates from the second giveaway and from the pooled estimator may become increasingly important depending on the spread of xylazine and the potential emergence of new adulterants in the opioid supply.

In terms of the ED visit outcome, the findings from this study also differ from previous literature. The Massachusetts OEND study found no effect on that outcome (Walley et al., 2013), but studies of naloxone access laws generally found an increase in ED visits associated with passage of the laws (Abouk et al., 2019; Doleac & Mukherjee, 2022). To the contrary, this study found limited evidence of a decrease in ED visits in areas exposed to the giveaway. As noted, the totality of analyses conducted in this study provide less confidence for this effect than for the fatal overdose outcome, and thus results with respect to ED visits should be interpreted with caution. Notwithstanding this caveat, it is important not to equate a potential reduction in ED visits with a reduction in risky opioid use. Some previous studies have suggested that naloxone represents a moral hazard (Abouk et al., 2019; Doleac & Mukherjee, 2022), and the argument that the presence of naloxone may cause some subset people who use opioids to take more risks has some support in qualitative literature (Heavey, Chang, et al., 2018; Seal et al., 2003). Opponents of that view dispute the notion that people engage in drug use drugs differently when naloxone is present (Greene, 2018), but no one has suggested a mechanism through which naloxone should reduce drug use or risk-taking. Any reduction in ED utilization associated with naloxone distribution is likely due to a lower propensity to seek professional assistance following an overdose due to the ability to reverse the overdose using naloxone on hand (Koester et al., 2017).

There are some important limitations to this analysis that must be noted. First, in addition to the suppression criteria applied to the ED visit outcome, two out of 171 EDs in the state do not provide data, and visit classifications are often made based on free text fields which may result in misclassification (Office of Drug Surveillance and Misuse Prevention, 2022). Second, data on the number of kits distributed

at each giveaway location were not available, so local dose effects could not be studied. Third, people obtaining naloxone were not followed-up with after the giveaways. This was an intentional decision to increase the likelihood that people would go to the giveaway locations to obtain naloxone, but it prevents analysis of the outcomes of individuals who specifically participated in the giveaways. Fourth, it is possible that by limiting the post-giveaway period to six months, the analysis could have underestimated the effect of the giveaways, as naloxone has a relatively long shelf life and has been shown to be effective beyond its expiration date (Pruyn et al., 2019). However, the decision to limit the post-giveaway period, made primarily to support the independent analysis of the two giveaways, is supported by evidence suggesting that 74% of people who obtain naloxone use or lose it within six months (Kinnard et al., 2021). Finally, estimation of the effect of the second giveaway is challenging because the two giveaways were held only nine months apart. To address this, the pre-giveaway period was limited to two quarters for the analysis of the second giveaway to avoid overlapping with the period immediately following the first giveaway. This limits the ability to evaluate the common trends assumption for those analyses and does not eliminate the risk that the naloxone kits distributed during the first giveaway could have confounded estimates of the effect of the second giveaway. Importantly, this limitation only applies to the analysis specific to the second giveaway. The analysis of the first giveaway was not affected because the follow-up period was limited to only two quarters, and the analysis of the combined effect of the giveaways was not affected because the control group was made up of regions that were never defined as treated in either giveaway.

Despite these limitations, this study provides an estimate of the effect of a novel approach to naloxone distribution on opioid overdose outcomes and further evidence about the effect of public naloxone distribution in general, including other, novel approaches to naloxone distribution through mail delivery (Yang et al., 2021) and vending machines, such as the one recently placed in one of the naloxone giveaway distribution sites in Philadelphia (Feldman, 2022). In summary, the findings from this study indicate that naloxone giveaways such as those conducted in Pennsylvania have the potential to generate large and immediate reductions of opioid overdose deaths. This finding, based on the first giveaway, is robust to several sensitivity analyses. In addition, this study finds no evidence of an increase in emergency department utilization related to opioid overdose following the giveaways. Thus, while policymakers must consider various responses to the ongoing opioid overdose epidemic, this study suggests that untargeted naloxone giveaways should be among the interventions considered. However, policymakers must also contend with an ever-changing drug supply, and evidence from this study suggests that naloxone

giveaways were ineffective when a non-opioid tranquilizer emerged as a common additive to illicit opioids in the Philadelphia area prior to the second giveaway. More research is needed to understand how to protect people from sudden changes to the composition of opioids, whether different naloxone products such as the higher-dose Kloxxado or the naloxone alternative Opvee (nalmefene) are more or less effective than Narcan (Hill et al., 2022; Krieter et al., 2019), and how to educate people who use opioids on the limitations of naloxone, such as its ineffectiveness to reverse the effects of xylazine.

4 The Cost-Effectiveness of Naloxone Giveaways

4.1 Introduction

Harm reduction is an important component of efforts to reduce opioid overdose mortality, which continues to claim the lives of more than 200 Americans every day (Ahmad et al., 2024). Interventions to increase the availability of naloxone in the community—as well as other well-established harm reduction interventions[25] such as syringe exchange programs, test strip provision, and community drug testing—have the primary aim to reduce the consequences of drug use rather than to reduce drug use itself. Although these interventions all share an emphasis on the harms associated with drug use, the way in which they interact with drug use, overdose, and death due to overdose is different. Syringe exchange programs reduce the risk of transmission of bloodborne diseases such as HIV and hepatitis B and C (Adams, 2020; Packham, 2022), which in turn reduces the risk that someone who uses injection drugs could further transmit those diseases and reduces the costs associated with treatment for those diseases. Interventions such as fentanyl test strip provision and community drug testing interact early in the cause-and-effect pathway between deciding to use drugs and the potential consequences (Maghsoudi et al., 2022). These interventions convey information to the person considering drug use about the nature of the product that they have obtained, which could trigger responses including but not limited to the decision to use less or to forego using the substance at all (Krieger et al., 2018). Naloxone's mechanism of action is different, in that it only has value in the event of an overdose.[26] Because naloxone reduces the probability of death conditional on an overdose, it is reasonable to suggest that some people might be more willing to engage in drug use—thus risking potential overdose—if they have naloxone than if they do not. This notion is supported by qualitative research in which some participants noted that they or their acquaintances were willing to use a higher quantity or take more risk when naloxone is available (Heavey, Chang, et al., 2018; Seal et al., 2003).

People who use opioids and those who seek to improve their health and wellbeing must contend with stigma. Stigma contributes to perceptions that people who use opioids have less value in society and

[25] Some researchers and institutions adopt a broad definition of harm reduction to include things like medications to treat opioid use disorder. This thesis adopts a definition of harm reduction that is distinct from treatment, similar to the definition provided by the National Institute on Drug Abuse, see: https://nida.nih.gov/research-topics/harm-reduction.

[26] Supervised injection facilities—places where people who use drugs can go to ensure that someone will render aid if they overdose—are somewhat similar in that their principal benefit is to reduce the likelihood of death conditional on an overdose, but they also provide access to other treatment and harm reduction resources, see Levengood et al., (2021).

should be ashamed of their condition. This leads to prejudice and discrimination that manifests itself in barriers to treatment and other key services (Cheetham et al., 2022). Given its emphasis on reducing the harms associated with drug use rather than preventing or treating it, harm reduction interventions such as those designed to increase naloxone availability have been particularly challenged by the stigma around opioid use (Adeosun, 2023). Any proposal to use public funds faces scrutiny, but opposition to certain initiatives—such as providing free naloxone—can be intensified by stigma (RAND Corporation, 2023). An economic evaluation is always warranted when evaluating uses of public funds, but is a particularly useful tool to alleviate hesitation to support a particular intervention exacerbated by stigma by presenting the benefits and costs of the intervention in a neutral way without recourse to normative arguments. This chapter aims to evaluate the cost-effectiveness of the intervention described in the previous chapter (i.e., large-scale untargeted naloxone giveaways) to establish whether it is an efficient use of scarce resources and whether and at what frequency it should be conducted.

Several studies have examined the cost-effectiveness of naloxone distribution in various contexts. Early studies evaluated naloxone distribution to heroin users in the United States, Russia, and the United Kingdom. All three found naloxone distribution to be highly cost-effective in base-case analyses, with incremental cost-effectiveness ratios (ICERs) relative to no naloxone distribution of $438, $94, and £899 per quality-adjusted life year (QALY) respectively (Coffin & Sullivan, 2013a, 2013b; Langham et al., 2018). A more recent study examined the cost effectiveness of naloxone distribution alone and in combination with treatments for OUD in the United States. When naloxone distribution alone was compared to no intervention, the cost per QALY gained was $51,000 (Fairley et al., 2021). The difference in ICERs among these studies highlights the importance of perspective when evaluating the costs and benefits of naloxone distribution. The analyses by Coffin and Sullivan and Langham and colleagues tracked only the costs of naloxone and healthcare interactions specifically related to overdose and thus produced relatively low ICERs. On the other hand, the analysis by Fairley et al. also captured healthcare and criminal justice costs attributable to OUD, which often continue to accrue following an overdose reversed by naloxone. As Fairley and colleagues point out, because naloxone keeps people alive but does not treat their OUD (or reduce or eliminate costs associated with OUD), costs per QALY gained are relatively high given the perspective they adopted.

Other studies examined naloxone distribution in specific settings or to specific groups. Naloxone distribution in syringe services programs in the United States was found to be cost effective with an ICER of $323 per QALY (Uyei et al., 2017). Naloxone distribution to secondary schools in Toronto, Canada was

found to be cost-effective when the combination of overdose frequency and naloxone effectiveness was sufficiently high (e.g., when at least one overdose occurred per year across all 112 schools and naloxone reduced mortality after an overdose by at least 40%) (Cipriano & Zaric, 2018). Two studies examined the cost-effectiveness of naloxone distribution to people receiving prescription opioids. One study found that biannual distribution of naloxone to this population in the United States generated additional QALYs relative to no naloxone distribution at a cost of $84,799 per QALY (Acharya et al., 2020). Another estimated a cost of 38,200 Australian dollars per death averted (Nielsen et al., 2022). Although deaths averted cannot be converted directly to QALYs, the implied ICER from the Australian study is much lower than from the American study. The difference is likely due to the overdose rate (assumed to be 5% per year in the Australian study and considerably lower in the American study). Finally, a study compared distribution strategies between emergency medical services (EMS) personnel, police and fire personnel, and laypeople likely to witness an overdose (Townsend et al., 2020). The results indicated that high levels of naloxone distribution to all three groups was cost-effective (ICER: $15,950 from healthcare perspective and dominant from societal perspective), and that distribution to laypeople and EMS should be prioritized.

This study contributes to an understanding of the cost-effectiveness of naloxone distribution by complementing many of the previous economic evaluations of naloxone distribution. Many previous studies considered distribution strategies targeted to people who use opioids or people who are very likely to encounter people who have overdosed on opioids. To the contrary, this study examines the cost-effectiveness of an untargeted distribution strategy in which people were encouraged to pick up naloxone as a precaution, even if they were not especially likely to encounter a situation where it would be needed. In addition, this is only the second study to examine the implications of a potential increase in overdose risk associated with naloxone availability. One previous modeling study conducted a threshold analysis and found that a scenario that included maximizing public naloxone distribution was preferred to strategies that only involved distribution to police and other first responders if the public distribution strategy increased naloxone by at least 23% (Townsend et al., 2020). The current study adopts a more flexible approach, using calibration to identify different sets of several key parameters[27] that, in the model, reproduce the levels of outcomes observed before and after the giveaway intervention. Following this, relationships between parameter sets resulting from calibration and cost-effectiveness results are

[27] The calibrated parameters are along the use, overdose, and death cause-and-effect pathway discussed earlier. They are calibrated because they are not known with certainty and include the probability of overdose and responses to overdose, such as whether the overdose was witnessed (i.e., whether the victim used alone), whether naloxone was available and administered, whether an ambulance was called, and whether the victim went to the hospital.

characterized, which provides valuable insights into potential secondary consequences of the intervention that may modify its net benefit to society.

4.2 Methods

Overview

This study evaluated the cost-effectiveness of Pennsylvania's first naloxone giveaway held in December 2018 in 85 locations across the state. During the one-day event, officials handed out naloxone to anyone who wished to obtain it free of charge and without requiring any personal information. By the end of the day, over 6,000 kits were distributed, and approximately 1,000 additional kits were handed out soon thereafter to people on a waiting list (i.e., to people who visited a giveaway site that had run out of naloxone). More information about the nature of the giveaway is available in the previous chapter (Section 3.2).

A decision model was developed to evaluate the cost-effectiveness of the giveaway intervention among people with opioid use disorder in the Philadelphia metropolitan area, composed of Philadelphia and its surrounding counties: Bucks, Chester, Delaware, and Montgomery. The model was used to compare four strategies: 1) a no giveaway scenario, 2) a one-time naloxone giveaway, 3) naloxone giveaways once a year for three years, and 4) naloxone giveaways once a quarter for three years. The model represented the giveaway intervention by incorporating all the costs of the intervention (naloxone, other materials, staff time, and participant time) and by calibrating the model to produce the effects of the giveaway as estimated in the previous chapter by varying parameters likely to be affected by the giveaway, such as the probability that naloxone would be administered by a bystander and the probability that emergency services would be called. The analysis examined cost-effectiveness from two perspectives consistent with best practices for cost effectiveness analysis (Neumann et al., 2016): first, a healthcare system perspective that captures only the costs incurred in that sector (i.e., the cost of the giveaway intervention, medical interventions following overdoses, and healthcare utilization attributable to opioid use), and second, a broader societal perspective that captures costs in the healthcare sector and beyond (i.e., productivity, consumption, and criminal justice). Cost-effectiveness was measured in terms of cost per quality-adjusted life year (QALY) over time horizons of 5 and 10 years.[28] All costs were represented in 2023 dollars and

[28] A lifetime time horizon was not adopted for this analysis as five- and ten-year horizons are sufficient to capture the costs and benefits of giveaway interventions implemented for three years. The three-year duration for the periodic giveaway scenarios (annually and quarterly) was chosen as a conservative measure to avoid projecting effects from the observed giveaways too far into the future given uncertainty around the future dynamics of the opioid epidemic.

costs and QALYs were discounted at 3% annually. An impact inventory (Neumann et al., 2016; Table A4.1), which provides more detail on the specific costs captured in each perspective, and a Consolidated Health Economic Evaluation Reporting Standards table (Husereau et al., 2022; Table A4.2), which offers a standardized accounting of the components of the analysis, are available in the Appendix.

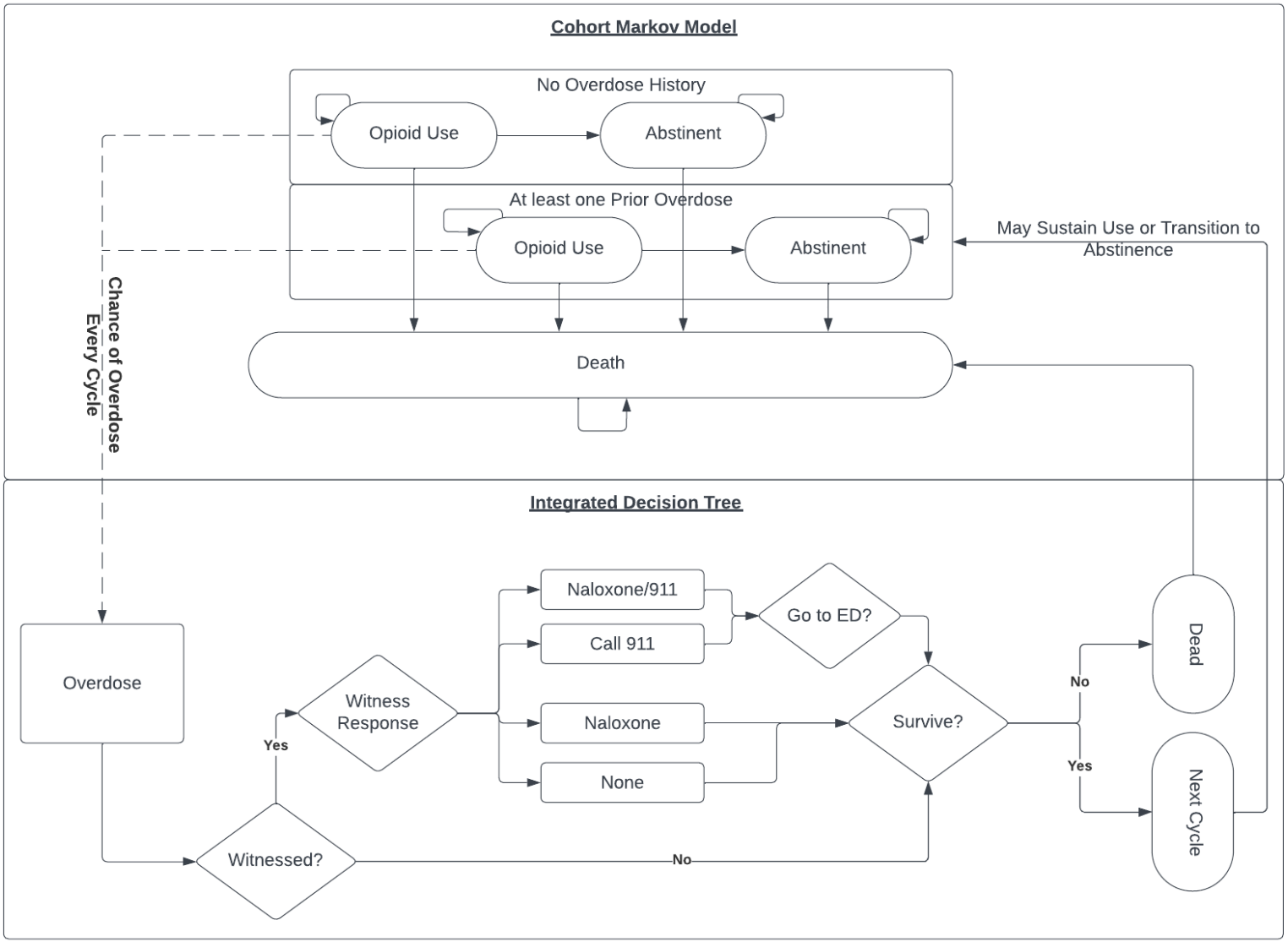
Model Structure

The analysis was conducted using a decision model that is similar in structure to other models used for cost-effectiveness studies of naloxone distribution (Coffin & Sullivan, 2013a, 2013b; Langham et al., 2018; Townsend et al., 2020). A cohort Markov model—a type of decision model structured around transitions among mutually-exclusive disease states (Briggs et al., 2006)–was used to model transitions among opioid use, abstinence, and death states. The model comprised two sets of opioid use and abstinence states, one for people who had never experienced an opioid overdose and one for people with prior opioid experience, and one absorbing state representing death. The use of two distinct sets of use and abstinence states helps to overcome the main limitation of the Markov model: that transitions are a function of current health state and do not account for history (Briggs et al., 2006). The structure of this model allows for the application of different transition probabilities and consequences to subsets of the cohort that had and had not experienced an overdose. The cohort Markov model is described in the top panel of Figure 17.

At model initialization, the cohort was divided among the two opioid use states. Transitions occurred each quarter: individuals in abstinence states could remain abstinent, transition to use, or die, and individuals in the use state could continue using, transition to abstinence, die from a cause other than overdose, or overdose. Overdoses and related consequences were governed by an integrated decision tree. An overdose could either be witnessed or unwitnessed. If the overdose was witnessed, the witness could intervene by administering naloxone, calling 911, doing both, or doing neither. When 911 was called, the overdose victim could be transported to the emergency room. The overdose victim would either survive or die;[29] if they survived, they would be returned to one of the two states representing people who had at least one prior overdose (i.e., abstinence or use). The decision model is described in the bottom panel of Figure 17.

[29] The probability of death following an overdose was a function of the victim's state in the Markov model, the presence or absence of a witness, and interventions applied by a witness (if any).

Figure 17: Model Structure



Model Parameters

Population. The model population was set to the estimated number of people in the five-county area with OUD estimated based on the number of people on Medicaid with an OUD diagnosis, estimates from the National Survey on Drug Use and Health (NSDUH) of healthcare utilization and OUD prevalence stratified by Medicaid beneficiary status and by age group (Substance Abuse and Mental Health Services Administration (SAMHSA), n.d.-a, n.d.-b), population data from the U.S. Census (United States Census Bureau, 2022a), and estimates of misdiagnosis and underdiagnosis from clinical algorithm validation studies (Chadd et al., 2021; Ranapurwala et al., 2021).[30]

To account for age differences among people with OUD, the population was divided into four age cohorts with starting ages of 25, 35, 45, and 55, respectively. The population was allocated to these groups based on the age distribution of people who used opioids non-medically in Pennsylvania from the NSDUH. These groups differed in terms of overdose history; the percentage of the cohort that had previously overdosed ranged from 26%–59% for the 25-year-old and 55-year-old cohorts, respectively. The proportion with overdose experience for each age group was estimated by running the model for an 18-year-old cohort with no prior overdoses and examining the model state distribution over time. Each age cohort entered the model separately and outcomes were aggregated to represent the full population.

State Transitions. Probabilities of transition from opioid use to an abstinence and vice-versa were taken from Townsend et al. (2020) and converted to represent a quarterly cycle length. These probabilities were equivalent for people with and without overdose history. Transition out of the set of states defined by no history of an overdose only occurred following an overdose (see *Overdose Parameters* section) while in the opioid use state or death. Following a first overdose—if survived—people transitioned into the set of states defined by prior overdose history. Transition from opioid use to abstinent states was assumed to be independent of overdose, so the probability of transitioning from the opioid use state to the abstinence state was the same for someone who experienced an overdose that cycle as for someone who did not experience an overdose. The assumption of equivalent transition probabilities between use and abstinence and vice-versa was made to maintain consistency with the validated model developed by Townsend and colleagues. The authors of that study note a lack of available evidence to support differentiating these probabilities.

[30] A manuscript describing this approach to estimating OUD prevalence is in development (Dowd et al., 2024).

Death could be due to overdose or to other causes. Probability of death due to overdose is explained in the *Overdose Parameters* section. Parameters for causes of death other than overdose were taken from Townsend et al. (2020) and were derived from meta-analyses of mortality rates associated with being in or out of medication treatment for OUD (Sordo et al., 2017). Following Townsend et al. (2020), mortality rates for being in treatment were applied to the abstinent states, and mortality rates for being out of treatment were applied to the opioid use cases.

Overdose Parameters. As noted previously, an integrated decision tree governed overdoses and related events and outcomes for people in the opioid use states. Initial values of the decision tree parameters are described in this section, but several parameters were allowed to vary during the calibration process (see *Model Calibration* section).

The probability of experiencing an overdose was taken from Townsend et al. (2020) and converted to a quarterly cycle length. Overdose probability was more than four times higher for those who had previously overdosed (0.09) than those who had never overdosed (0.02). The probability that an overdose was witnessed (0.62) was taken from a modeling study by Irvine and colleagues (2022), who estimated epidemic-specific probabilities of witnessed overdoses. The probability corresponding to a fentanyl dominated epidemic was chosen to best represent the Philadelphia area. The probability that a witness would possess and use naloxone (0.13) was estimated based on Pennsylvania ODIN data that reported 8.2% of overdoses resulted in layperson administration of naloxone.[31] The probability that a witness would call 911 was assumed to be 0.5 based on Townsend et al. (2020), and the probability that a 911 call would lead to an emergency department (ED) visit was 0.59 (Zozula et al., 2022).

Overdose death probability parameters were based on Townsend et al. (2020). The probability of death following an overdose in which naloxone was not administered and 911 was not called was 0.05 for a first overdose and 0.16 for a repeat overdose. The relative risk (RR) of death when naloxone was administered was 0.48. The relative risk of death when the witness did not administer naloxone but did call 911 was 0.59.[32] The relative risk of death when the witness administers naloxone and calls 911 was assumed to be

[31] 0.13 was obtained by dividing 0.082 (the proportion of overdoses reversed by a bystander with naloxone) by 0.62 (the proportion of overdoses witnessed).

[32] This relative risk was estimated assuming that emergency medical services (EMS) have naloxone in their possession 75% of the time and administer naloxone 89% of the time when they have it, for a total of 67% of incidents. EMS was assumed to reduce the risk of death by 20% by other means when they do not administer naloxone. Thus, the relative risk when 911 is called was computed as a weighted average of the relative risk when naloxone is

the product of the relative risks of witness-administered naloxone (0.48) and EMS intervention without naloxone (0.8), yielding a relative risk of death after witness-administered naloxone and a 911 call of 0.38.

Costs and Utilities. Healthcare sector costs included costs of the naloxone giveaway, the cost of ambulance callouts and emergency department visits, and excess healthcare costs associated with opioid use. Costs of the naloxone giveaway included staff time, naloxone, and other materials. Staff costs were estimated using the published list of giveaway sites (12) and operating hours (7.5 per site) and assumed that each site was operated by two staff. Total compensation for healthcare and social assistance workers employed by state and local governments ($52.34) was used to value staff time (Bureau of Labor Statistics, 2023). Naloxone costs were computed based 2,159 kits distributed in the five county area and a unit cost of $70.95 per kit (two doses), based on published estimates of $380,000 in expenditures for 6,105 naloxone kits (Finnerty, 2019) and inflated to 2023 dollars. Other materials provided to giveaway participants (i.e., a copy of the Surgeon General's standing order for naloxone and a magnet detailing overdose response strategies) were valued at $1.92 based on high volume pricing from a large office supply retailer. The cost of an ambulance callout was based on the Pennsylvania Medical Assistance fee schedule ($400) (Pennsylvania Department of Human Services, 2023), and the cost of an emergency department visit for an opioid overdose was taken from Yokell et al. (2014) and inflated to 2023 dollars ($24,134). Following Townsend et al. (2020), this estimate was based on a weighted average of cases that required hospitalization those that were treated and released. Finally, excess healthcare costs associated with current opioid use ($3,218 per quarter) or previous opioid use ($1,697) were applied to the opioid use and abstinent states, respectively (Townsend et al., 2020).[33]

Additional costs applied when a societal perspective was adopted included net productivity, criminal justice costs, and opportunity costs for participating in the naloxone giveaway. Net productivity was computed as age-specific average annual productivity (Grosse et al., 2019) minus age-specific consumption from the Bureau of Labor Statistics Consumer Expenditure Survey (Bureau of Labor Statistics, 2022).[34] Productivity was reduced by 17.5 percent for people in the current opioid use state

administered (0.48) and the relative risk when EMS is present but does not administer naloxone (0.8): 0.48 * 0.67 + 0.8 * 0.33 = 0.59.

[33] These values represent the extent to which the average healthcare costs of people represented in the model exceed those that would be expected of those without OUD. For the estimated incremental costs for people engaging in active use, direct costs related to overdose were excluded.

[34] Consumption data are presented at the level of the "consumer unit." A consumer unit can be one, financially independent person, or two or more people living together making expenditure decisions jointly (i.e., like a household). To estimate age-specific per-person expenditures, estimates for single person consumer units were

(U.S. Department of Justice National Drug Intelligence Center, 2011), and a productivity cost of $810 was applied to each overdose based on average absenteeism costs (Inocencio et al., 2013). Productivity entered the cost calculation as a negative value, such that it defrayed other costs. Age-specific criminal justice costs represented incremental costs associated with opioid use (Murphy, 2020). Finally, the opportunity cost of the public's participation in the naloxone giveaway were applied based on the assumption that individuals who participated in the giveaway spent half an hour obtaining naloxone, and their time was valued at the average total compensation for civilian workers ($43.07 per hour) (Bureau of Labor Statistics, 2023).

Health utility weights were derived from Rhee and Rosenheck (2019), who computed utilities for individuals with current or past OUD. Utilities from this study were chosen over other alternatives because they were based on data from the National Epidemiologic Survey on Alcohol and Related Conditions-III, a general population survey conducted in the United States, rather than small and potentially ungeneralizable samples (i.e., from clinical trials). Rhee and Rosenheck mapped participant responses to the 12-item Short Form Survey (SF-12; Brazier & Roberts, 2004) to EQ-5D health utility values ranging from 0 (death) to 1 (perfect health) using an established algorithm (Gray et al., 2006). These weights, when applied to life years, produce QALYs, the main outcome for the analysis. A health utility of 0.73 was applied to time spent in an opioid use state, and a health utility of 0.82 was applied to time spent in an abstinent state.

Model Calibration. A three-stage calibration sequence was used to conduct the analysis. The first stage calibrated the model to represent the five-county Philadelphia area by modifying key parameters so that the model produced the same number of quarterly opioid overdose deaths (484) and overdose-related ED visits (1022) as were reported in the five-county area in the average quarter in 2018. The set of baseline parameters that resulted from the first calibration stage represented a quarter with no naloxone giveaway. The second and third stages further calibrated baseline model parameters to produce sets of giveaway parameters that represented the first and second quarters of the giveaway, respectively. The calibration targets for the second stage were based on the effects of the giveaway on overdose deaths and overdose-related ED visits for the first and second giveaway quarters estimated in the previous chapter.

used. Multi-person consumer unit data could not be used to estimate age-specific consumption in the absence of microdata that described each consumer unit.

The calibration process only allowed a subset of model parameters to change. These nine parameters were identified as the most likely to vary from place to place, and thus the most appropriate to modify when the objective is to calibrate a model validated at the national level to a specific locale. All parameters chosen for calibration were related to overdose events, and were the probability of overdose (varied by previous overdose experience), the probabilities of different reactions to an overdose (i.e., the probability that the overdose was witnessed, that a witnessed had and administered naloxone, whether the witness called 911, and whether a 911 call led to an ED visit), and the probability of death for an overdose with no intervention (varied by previous overdose experience). To avoid major deviations from initial parameter values based primarily on a previously validated model, these values were only allowed to vary by +/- 10% in the first stage.

For the second and third stages of the calibration sequence, constraints on parameters were set to align with the anticipated direction(s) that they might change following a naloxone giveaway intervention. The probability of overdose was allowed to increase by up to 50%, the probability that an overdose was witnessed was allowed to increase by up to 20%, and the probability that the witness would have and administer naloxone was allowed to increase by up to 400%. None of these parameters were allowed to decrease during the second or third stages, as a naloxone giveaway should not be expected to cause fewer overdoses, fewer witnessed overdoses, or fewer lay naloxone administrations. Other parameters representing responses to overdoses—witness calling 911 or a 911 call leading to an ED visit—were allowed to increase by 10% or decrease by 20% because the direction of a potential effect of the giveaway on these decisions is ambiguous. On one hand, the educational component of the intervention might lead to a greater likelihood of calling 911. On the other hand, having naloxone or other new information could make witnesses and victims more confident to handle an overdose and its aftermath without medical assistance. It is important to note that the ranges over which each parameter was allowed to vary were assumed. Because the intervention directly increased the availability of naloxone, the probability that the witness would have and administer naloxone had the widest range. Other parameters varied over narrower ranges because they were at best indirectly affected by the intervention. The probability of death from an overdose without intervention was not allowed to change at all during the second and third stages of the calibration sequence (i.e., first-stage calibration values were used for these probabilities), as the giveaway only influenced how witnessed responded to overdoses, not the underlying probability of death from overdose.

Calibration was carried out using simulated annealing as implemented in R using the optimization package (Husmann & Lange, 2023). Simulated annealing is an iterative optimization algorithm that minimizes an objective function by initializing with starting values of parameters (i.e., values from the "Model Parameters" section for first stage calibration and values resulting from the first stage for second and third stage calibration) and randomly perturbing them within a search space (i.e., the parameter bounds specified in the preceding paragraphs) (Henderson et al., 2003; Kirkpatrick et al., 1983). The approach is called simulated annealing because it mimics the annealing process in metallurgy, in which a material is heated to a high temperature and allowed to cool gradually, producing a better product. In simulated annealing during early iterations (i.e., the high temperature phase), perturbations that *increase* the objective function are allowed at a higher probability than during later iterations (i.e., the low temperature phase). The advantage of allowing perturbations that increase the objective function is that it reduces the likelihood of getting stuck in a local optimum within the search space and—over a sufficient number of iterations—increases the likelihood of identifying the global minimum (Henderson et al., 2003; Kirkpatrick et al., 1983).

The objective function for the simulated annealing process was the sum of squared differences between the number of opioid overdose deaths and opioid-related ED visits produced by the model and their respective target values. As noted previously, the target values for the first calibration stage were quarter-level averages for the five-county areas in 2018. For the second and third stages, incidence rate ratios estimated in the previous chapter were applied to 2018 values to produce target overdose deaths and opioid-related ED visit counts for the first and second quarters following the giveaways. Because the effect estimates were based on distance to the giveaway location, the incidence rate ratios were applied only to the proportion of the recorded deaths and ED visits from 2018 that occurred within areas defined as treated in the previous chapter (i.e., within 3 kilometers of a giveaway location and more than 3 kilometers from another source of free naloxone).[35] Consistent with the effect estimates from Chapter 3, other parts of the five-county area were assumed to be unaffected by the giveaways.

[35] Treated regions accounted for 13.5% of deaths and 10.7% of ED visits in 2018.

Analysis

Main Analysis. Incremental cost-effectiveness ratios (ICERs) were computed from the model output for both time horizons and both perspectives.[36] ICERs were defined as the difference in cost divided by the difference in QALYs for a given strategy compared to the next less expensive undominated strategy. A strategy was dominated if it produced fewer QALYs than a less expensive strategy and was dominated by extension if its ICER was higher than a more effective strategy (Drummond et al., 2015). The amount society should be willing to pay for an additional QALY is a normative decision; however, values of $50,000 or $100,000 are common thresholds for whether an intervention should be considered cost-effective (Grosse, 2008; Neumann et al., 2014).

Due to the stochastic nature of the calibration process, a different set of calibrated parameters is produced each time the process is completed. To account for potential influence of the calibration process on results, the ICERs described above were computed from the average of 100 sets of outcomes, each from a distinct calibration sequence. The extent of variation of results based on individual calibration sequences was examined graphically, and characteristics of calibration sequences that produced anomalous results were described using a regression analysis.

Sensitivity Analysis. One-way sensitivity analyses (OWSAs) were conducted to identify parameter values that, when changed from their initial value, had the largest influence on the cost-effectiveness of the intervention (Briggs et al., 2012). Because overdose parameters were calibrated to observed overdose death and opioid-related ED visit targets, population and overdose parameters were excluded from one-way sensitivity analysis. To conduct OWSAs, a single model parameter was successively increased and then decreased from its base value and costs and QALYs were computed using the single modified parameter and all other parameters at their base values for the no giveaway and quarterly giveaway strategies. Resulting costs and QALYs were converted to net monetary benefit (NMB), which is the product of QALYs and an assumed willingness to pay for a QALY ($50,000[37]) minus costs (Briggs et al., 2006). Incremental NMB (INMB) for the quarterly and no giveaway strategies for each OWSA iteration was plotted for the high and low values of each of the included parameters in a tornado diagram.

[36] Main results are calibrated to the point estimates of the effects of the giveaway on fatal and non-fatal overdoses from the previous chapter. As a sensitivity check, the main analysis was repeated using the upper and lower bounds of the 95% confidence intervals of the effect estimates.

[37] As noted above, common willingness to pay values range from $50,000 to $100,000. For this analysis, $50,000 was chosen as a conservative valuation.

Probabilistic sensitivity analysis (PSA) was conducted to examine the extent to which the conclusions of the main results are sensitive to parameter uncertainty (Briggs et al., 2012). The PSA accounts for both conventional parameter uncertainty (i.e., the values used as point estimates for parameters are not known with certainty) as well as parameter uncertainty driven by the stochastic optimization process described above. In each PSA iteration, initial values of parameters were drawn from a distribution, and then parameter sets were produced using a modified process that omitted the first stage and instead calibrated the initial values drawn from distributions to the effects of the giveaway as in the second and third stages of the full calibration process. It was necessary to omit the first stage of the calibration process because it was not always possible to attain targets based on observed data parameters were drawn from distributions. Importantly, because the calibration process took place within each PSA iteration after values were redrawn from distributions, it was not necessary to avoid drawing values from distributions for parameters related to calibration as it was for the OWSA.

After drawing parameter values from distributions and conducting the calibration process, the model was evaluated, and NMB was calculated for each strategy, time horizon, and perspective. Expected loss curves (ELCs) were produced from the output of the PSA iterations (Alarid-Escudero et al., 2019). For each iteration, loss attributed to a particular strategy was computed as the difference between the NMB of the strategy with the highest NMB and the NMB of the strategy (Equation 4.1):

$$L_{si} = \max(Q * WTP - C)_i - (Q_{si} * WTP - C_{si}) \qquad \text{(Eq. 4.1)},$$

where L_{si} is loss for strategy s in iteration i, $\max(Q * WTP - C)_i$ is the highest NMB (i.e., QALYs [Q] time willingness to pay [WTP] minus costs [C]) among all strategies in iteration i, and $(Q_{si} * WTP - C_{si})$ is the NMB for strategy s in iteration i. Expected loss for a particular strategy (EL_s) was then computed as the average loss across all iterations (Equation 4.2):

$$EL_s = \frac{1}{N} * \sum_{i=1}^{N} L_{si} \qquad \text{(Equation 4.2)}.$$

Expected loss was evaluated over different values of WTP ranging from \$0 to \$100,000, and the resulting curves were plotted.[38] The strategy with the lowest expected loss at a given WTP is cost-effective given that WTP.

[38] Expected loss curves were plotted using the dampack package in R (Alarid-Escudero et al., 2021).

ELCs have two key advantages over cost effectiveness acceptability curves (CEACs), which are traditionally used to represent results of a PSA (Alarid-Escudero et al., 2019). First, ELCs explicitly rank strategies from highest to lowest expected NMB at any given value of WTP and better represent circumstances when expected NMB is similar between two strategies. CEACs, which represent the proportion of iterations for which a strategy has the highest NMB, can sometimes give the impression that a strategy is greatly preferred to another when it is not and can even produce a different ranking of strategies. Second, the frontier formed by strategies with the lowest expected loss across the range of WTP values also represents the expected value of perfect information, or the cost of uncertainty about parameter values, which provides a sense of the return to future research efforts conducted to refine parameter values.

Parameter inputs to the model including base values, low and high values for OWSAs, and distributions for PSA are described in Table 6.

Table 6: Model Parameters

Parameter	Base Value	OWSA -Low	OWSA -High	PSA Distribution	Mean	SD	Source
Population							
Count of people with OUD	102,927			Normal	102,927	5,572	Computed, see *Model Parameters: Population*
Proportion of OUD population - Age 25 Cohort	0.309			Dirichlet[a]			Computed based on National Survey on Drug Use and Health
Proportion of OUD population - Age 35 Cohort	0.301			Dirichlet[a]			Computed based on National Survey on Drug Use and Health
Proportion of OUD population - Age 45 Cohort	0.140			Dirichlet[a]			Computed based on National Survey on Drug Use and Health
Proportion of OUD population - Age 55 cohort	0.250			Dirichlet[a]			Computed based on National Survey on Drug Use and Health
Proportion with no overdose history - Age 25 cohort	0.745			Beta	0.745	0.100	Computed from model; standard deviation assumed
Proportion with no overdose history - Age 35 cohort	0.592			Beta	0.592	0.100	Computed from model; standard deviation assumed
Proportion with no overdose history - Age 45 cohort	0.487			Beta	0.487	0.100	Computed from model; standard deviation assumed
Proportion with no overdose history - Age 55 cohort	0.407			Beta	0.407	0.100	Computed from model; standard deviation assumed
State Transition							
Probability of transition from use to abstinent state	0.040	0.020	0.060	Beta	0.040	0.013	Townsend et al.
Probability of transition from abstinent to use state	0.040	0.020	0.060	Beta	0.040	0.004	Townsend et al.

Parameter	Base Value	OWSA -Low	OWSA -High	PSA Distribution	Mean	SD	Source
Non-overdose mortality, use state 25-34	0.005						Townsend et al.; Sordo et al.
Non-overdose mortality, abstinent state 25-34	0.002						Townsend et al.; Sordo et al.
Non-overdose mortality, use state 35+	0.008						Townsend et al.; Sordo et al.
Non-overdose mortality, abstinent state 35+	0.003						Townsend et al.; Sordo et al.
Overdose Parameters							
Probability of overdose, no prior overdose[b]	0.018			Beta	0.018	0.007	Townsend et al.
Probability of overdose, prior overdose[b]	0.085			Beta	0.085	0.019	Townsend et al.
Probability overdose is witnessed[b]	0.620			Beta	0.620	0.080	Irvine et al.
Probability witness has and uses naloxone[b]	0.133			Beta	0.133	0.030	Computed, see *Model Parameters: Overdose Parameters*
Probability witness who does not use naloxone calls 911[b]	0.500			Beta	0.500	0.170	Townsend et al.
Probability witness who does use naloxone calls 911[b]	0.500			Beta	0.500	0.175	Townsend et al.
Probability 911 call leads to an ED visit[b]	0.593			Beta	0.593	0.170	Zozula et al.; standard deviation assumed
Probability of mortality after first overdose, no witness[c]	0.054			Beta	0.054	0.010	Townsend et al.
Probabiity of mortality after repeat overdose, no witness[c]	0.164			Beta	0.164	0.030	Townsend et al.
Relative risk of mortality if witness gives naloxone	0.480			Beta	0.480	0.100	Townsend et al.
Relative risk of mortality if witness calls 911	0.586			Beta	0.586	0.100	Computed based on Townsend et al.
Relative risk of mortality if witness gives naloxone and calls 911	0.384			Beta	0.384	0.100	Computed based on Townsend et al.
Costs and Utilities							
Cost of Ambulance	$400	$320	$480	Gamma	$400	$100	Pennsylvania Department of Human Services; standard deviation assumed
Cost of ED Visit	$24,134	$19,308	$28,961	Gamma	$24,134	$6,034	Townsend et al.; Yokell et al.; standard deviation assumed
Health costs associated with use	$3,218	$2,574	$3,861	Gamma	$3,218	$804	Townsend et al.; standard deviation assumed
Health costs for people in recovery (no current use)	$1,697	$1,357	$2,036	Gamma	$1,697	$424	Townsend et al.; standard deviation assumed
Cost of a naloxone kit	$70.95	$56.76	$85.14	Gamma	$70.95	$17.74	Computed based on Finnerty; standard deviation assumed
Hourly compensation for giveaway personnel	$52.34	$41.87	$62.81	Gamma	$52.34	$13.09	Bureau of Labor Statistics Employer Costs for Employee

Parameter	Base Value	OWSA -Low	OWSA -High	PSA Distribution	Mean	SD	Source
							Compensation; standard deviation assumed
Personnel per site	2	1	4				Assumed
Additional costs of materials handed out	$1.92	$1.54	$2.30	Gamma	$1.92	$0.48	Assumed
Hours spent getting naloxone	0.500	0.250	0.750	Gamma	0.500	0.125	Assumed
Hourly compensation for public	$43.07	$34.46	$51.68	Gamma	$43.07	$10.77	Bureau of Labor Statistics Employer Costs for Employee Compensation; standard deviation assumed
Productivity, 25-34	$20,376						Grosse et al., 2019
Productivity, 35-44	$27,412						Grosse et al., 2019
Productivity, 45-54	$26,257						Grosse et al., 2019
Productivity, 55-64	$21,417						Grosse et al., 2019
Productivity multiplier[d]	1	0.8	1.2	Normal	1	0.1	Assumed
Consumption, 25-34	$12,511						Bureau of Labor Statistics Consumer Expenditure Survey
Consumption, 35-44	$14,704						Bureau of Labor Statistics Consumer Expenditure Survey
Consumption, 45-54	$13,330						Bureau of Labor Statistics Consumer Expenditure Survey
Consumption, 55-64	$11,251						Bureau of Labor Statistics Consumer Expenditure Survey
Consumption multiplier[d]	1	0.8	1.2	Normal	1	0.1	Assumed
Productivity reduction proportion associated with current use	0.175	0.140	0.210	Normal	0.175	0.018	U.S. Department of Justice National Drug Intelligence Center; standard deviation assumed
Productivity cost of overdose	$810	$648	$972	Gamma	$810	$202	Inocencio et al.; standard deviation assumed
Criminal justice cost associated with use, 25-34	$1,388						Murphy
Criminal justice cost associated with use, 35-44	$1,925						Murphy
Criminal justice cost associated with use, 45-54	$1,740						Murphy
Criminal justice cost associated with use, 55-64	$1,612						Murphy
Criminal justice cost multiplier[d]	1	0.8	1.2	Normal	1	0.1	Assumed
Health utility for current use state	0.730	0.584	0.876	Beta	0.730	0.031	Rhee and Rosenheck
Relative increase in health utility for someone in abstinent state	1.123	1.000	1.250	Normal	1.123	0.021	Rhee and Rosenheck

Parameter	Base Value	OWSA -Low	OWSA -High	PSA Distribution	Mean	SD	Source
Giveaway Effect Parameters							
Giveaway effect on deaths, first giveaway quarter	0.587			Normal	0.587	0.117	Computed (previous chapter)
Giveaway effect on deaths, second giveaway quarter	0.853			Normal	0.853	0.155	Computed (previous chapter)
Giveaway effect on ED visits, first giveaway quarter	0.938			Normal	0.938	0.131	Computed (previous chapter)
Giveaway effect on ED visits, second giveaway quarter	0.846			Normal	0.846	0.093	Computed (previous chapter)

[a] These parameters which divided the OUD population into four age cohorts are drawn from a Dirichlet distribution for PSA to maintain their sum of 1. Parameters in the Dirichlet distribution were the probabilities expressed as percents.
[b] These seven parameters were allowed to vary during all calibration stages. See *Model Calibration* section.
[c] These two parameters were allowed to vary during the first calibration stage. See *Model Calibration* section.
[d] In OWSA and PSA, variation in age-specific productivity, consumption, and criminal justice costs was expressed using multipliers. The base value of the multiplier was 1 so as not to affect the parameter values in the main analyses.

4.3 Results

ICERs for the healthcare perspective are shown in Table 7. The no giveaway strategy was the least expensive, followed by one, annual, and quarterly giveaway strategies. Strategies with more giveaways also generated more QALYs than those with less. Under a five-year time horizon, the one giveaway strategy was dominated by extension. The cost per QALY gained under the annual giveaway strategy compared to the no giveaway strategy was $20,336, and the cost per QALY gained for the quarterly giveaway strategy compared to the annual giveaway strategy was $23,648. Under a ten-year time horizon, both the one time and annual giveaway strategies were dominated by extension. The cost per QALY gained under the quarterly giveaway strategy was $19,454 compared to the no giveaway strategy. ICERs vary when different assumptions about the effects of the intervention are made. When the upper bound is used for giveaway effectiveness, ICERs for the quarterly giveaway strategy relative to the next most effective strategy were about $15,000 for both time horizons (Appendix Table A4.3). However, when the lower bound is used for effectiveness, ICERs exceeded $100,000 for both time horizons (Appendix Table A4.4).

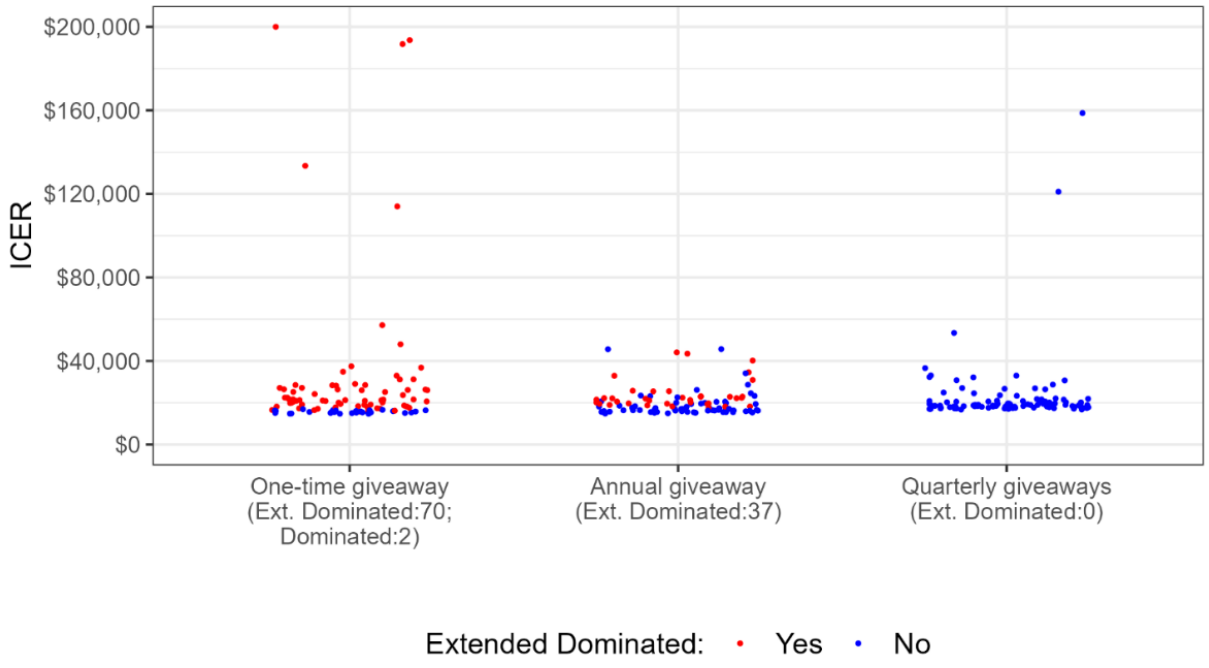
Table 7: Incremental Cost Effectiveness Ratio, Healthcare Perspective

Strategy	Cost	Effect (QALYs)	Incremental Cost	Incremental Effect	ICER
Five-Year Time Horizon					
No Giveaways	$5,417.4M [$5,415.5M–$5,419.5M]	333.7K [333.6K–333.8K]	-	-	-
One Giveaway	$5,419.3M [$5,417.5M–$5,421.4M]	333.8K [333.7K–333.9K]	-	-	Ext. Dom.
Annual Giveaways	$5,421.5M [$5,419.7M–$5,423.8M]	333.9K [333.8K–334.0K]	$4.1M	201.9	$20,336
Quarterly Giveaways	$5,430.1M [$5,428.0M–$5,432.7M]	334.3K [334.1K–334.4K]	$8.9M	363.1	$23,648
Ten-Year Time Horizon					
No Giveaways	$8,860.8M [$8,855.8M–$8,866.6M]	584.0K [583.5K–584.5K]	-	-	-
One Giveaway	$8,863.3M [$8,858.4M–$8,869.0M]	584.1K [583.6K–584.6K]	-	-	Ext. Dom
Annual Giveaways	$8,867.3M [$8,862.5M–$8,872.4M]	584.3K [583.8K–584.8K]	-	-	Ext. Dom
Quarterly Giveaways	$8,881.7M [$8,876.8M–$8,886.9M]	585.1K [584.4K–585.6K]	$20.9M	1,075.7	$19,454

Note: Brackets contain 95% credible intervals around costs and effects from 100 calibration sequences (i.e., the 2.5th and 97.5th percentile values of the distribution yielded by the 100 calibration sequences).

Figure 18 plots ICERs for each strategy relative to the next less expensive strategy for each of the 100 calibration sequences under the ten-year time horizon. This presentation is practical because the rank of the strategies in terms of cost was consistent across all 100 calibration sequences. In order to illustrate the range of results across calibration sequences, Figure 18 plots ICERs even if the strategy was dominated by extension but omits two values for the one-time giveaway scenarios from calibration sequences in which that strategy was completely dominated by the no giveaway scenario. Figure 18 shows that ICERs for all strategies are highly concentrated despite each of the 100 sequences having unique parameters. However, there are some outlier values, particularly for the one giveaway and quarterly giveaway strategies.

Figure 18: Variation of Healthcare Perspective ICERs across 100 Calibration Sequences, Ten-Year Time Horizon



ICERs for the societal perspective are shown in Table 8. Costs are negative in the societal perspective due to the inclusion of net productivity which offset healthcare, criminal justice, and opportunity costs. Under both the five- and ten-year time horizons, the quarterly giveaway strategy dominated all other strategies as the least expensive and most effective strategy using default effectiveness estimates and those representing an upper bound on effectiveness (Appendix Table A4.5). However, when effect estimates representing the lower bound of giveaway effectiveness were used (Appendix Table A4.6), ICERs for the quarterly giveaway strategy were $88,000 and $164,000 for the five- and ten-year time horizon, respectively.

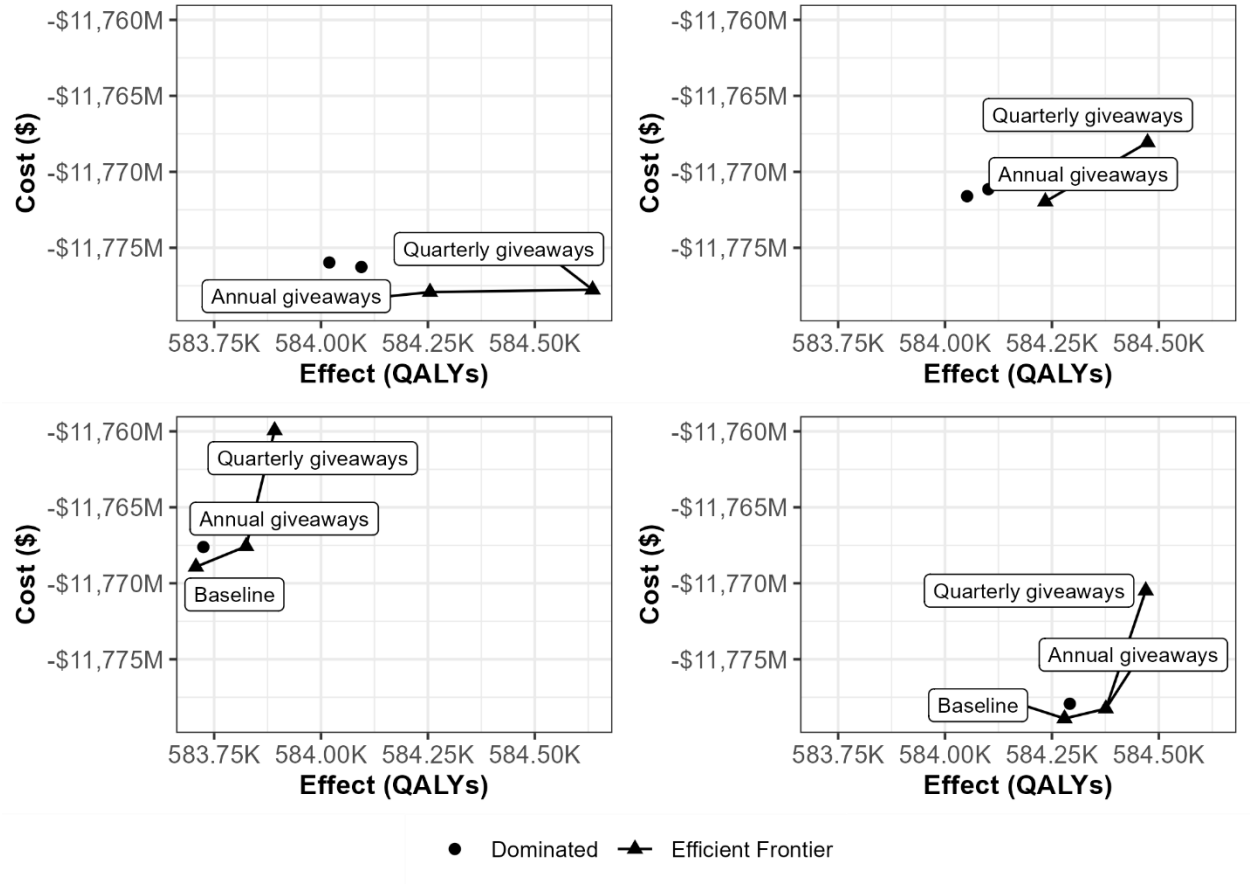
Table 8: Incremental Cost Effectiveness Ratio, Societal Perspective

Strategy	Cost	Effect (QALYs)	Incremental Cost	Incremental Effect	ICER
		Five-Year Time Horizon			
Quarterly Giveaways	-$5,544.8M [-$5,551.1M–-$5,535.0M]	334.3K [334.1K–334.4K]	-	-	-
Annual Giveaways	-$5,542.0M [-$5,547.5M–-$5,536.1M]	333.9K [333.8K–334.0K]	-	-	Dom.
One Giveaway	-$5,540.9M [-$5,545.8M–-$5,535.8M]	333.8K [333.7K–333.9K]	-	-	Dom.
No Giveaways	-$5,539.9M [-$5,544.5M–-$5,534.8M]	333.7K [333.6K–333.8K]	-	-	Dom.
		Ten-Year Time Horizon			
Quarterly Giveaways	-$11,793.8M [-$11,811M–-$11,769.1M]	585.1K [584.4K–585.6K]	-	-	-
Annual Giveaways	-$11,781.7M [-$11,797.1M–-$11,766.1M]	584.3K [583.8K–584.8K]	-	-	Dom.
One Giveaway	-$11,778.4M [-$11,792.3M–-$11,763.4M]	584.1K [583.6K–584.6K]	-	-	Dom.
No Giveaways	-$11,776.3M [-$11,789.4M–-$11,762.2M]	584.0K [583.5K–584.5K]	-	-	Dom.

The quarterly giveaway strategy dominated all other strategies across most of the 100 calibration sequences. There were 12 exceptions under a five-year time horizon, though the quarterly giveaway strategy would still be considered cost effective in all 12.[39] Under a ten-year time horizon, the quarterly giveaway strategy dominated in all but four calibration sequences. The quarterly strategy was still the most effective in all sequences, but its ICER ranged from $417 to $114,498. Cost effectiveness frontiers for the four calibration sequences in which the quarterly giveaway strategy did not dominate all others are shown in Figure 19.

[39] In all 12 exceptions, the quarterly giveaway strategy was the most effective and had ICERs under $20,000.

Figure 19: Societal Perspective Cost Effectiveness Frontiers for Calibration Sequences Resulting in Non-Dominance of Quarterly Giveaway Strategy, Ten-Year Time Horizon



Further review of the calibration sequences that produced anomalous results in Figures 18 and 19 uncovered a common characteristic: a considerable increase in the probability of overdose in the first post-giveaway quarter among people who had not previously overdosed. A linear regression model of the INMB of the quarterly giveaway strategy compared to the no giveaway strategy revealed a significant association between the dependent variable (INMB) and the probability of overdose among people with no prior overdose across all 100 iterations ($p<0.001$). This suggests that the effect of naloxone giveaways on overdose risk is an important driver of the cost-effectiveness of the intervention.

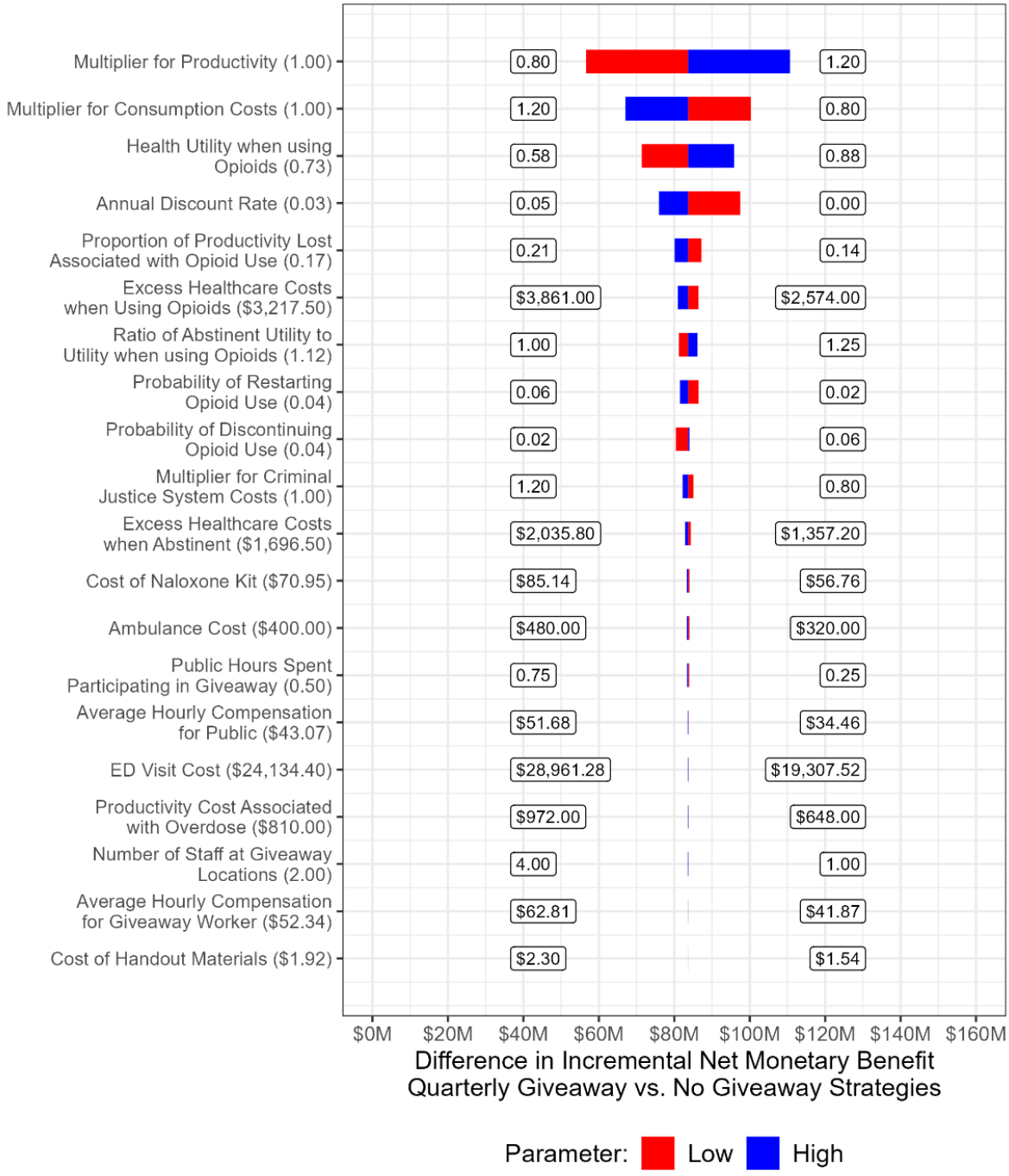
A tornado plot displaying the model parameters that had the most influence on the INMB of the quarterly giveaway strategy compared to the no giveaway strategy from a societal perspective is shown in Figure 20. Several of the most influential parameters, including the two most influential, were related to net productivity. Increasing or decreasing productivity estimates by 20% increased or decreased the INMB of the quarterly giveaway strategy relative to the no giveaway strategy by $27.0 million, respectively. Increasing or decreasing the consumption estimates changed INMB by $16.6 million, but in opposite

directions from productivity. Decreasing average productivity loss for people engaged in opioid use by 20% increased INMB by about $3.5 million and increasing productivity loss by 20% decreased IMNB by the same amount. Taken together, these findings indicate that IMNB is sensitive to deviations from base values of parameters related to productivity, and that the higher the net productivity of the population, the higher the INMB of strategies with more giveaways.

Health utility was also influential and positively associated with INMB. An increase (decrease) of 20% from the base utility value increased (decreased) IMNB by $12.3 million. Similarly, increasing the ratio of health utility when abstinent to health utility when using opioids by 20% increased IMNB by $2.4 million. Finally, changing the discount rate from the base value of 3% to 0% increased IMNB of the quarterly giveaway strategy to the no giveaway strategy by $13.8 million, and increasing it to 5% decreased IMNB by $7.7 million. Notably, even though some parameters have a sizable influence on the specific IMNB value, all the OWSA iterations produce IMNBs that are well above $0. Thus, the finding that a quarterly giveaway strategy is cost-effective at a willingness to pay of $50,000 per QALY is robust to any of the alternative parameter values tested using OWSA.

A tornado plot describing the most influential parameters from the healthcare perspective is available in the appendix (Figure A4.1). Given the narrower perspective, several of the parameters from Figure 20, including the two most influential relating to net productivity, had no effect from the healthcare perspective. However, among common parameters, the relative degree of influence was similar between the two perspectives and the directional effects of varying those parameters was identical, but the magnitude of the change in IMNB was lower than from the societal perspective. The most influential parameter from the healthcare perspective was the health utility value for the opioid use states. The ratio of utility between use and abstinence states was also relatively influential. As from the societal perspective, increasing health utility in the opioid use state or increasing the difference in utility between the abstinence and use states increased the IMNB of the quarterly strategy relative to the no giveaway strategy. The effects of varying the discount rate and the excess healthcare costs attributable to active opioid use were also in line with their effects from the societal perspective. As in the societal perspective, none of the alternative parameter values in the OWSA produced an IMNB less than $0 given a willingness to pay for an additional QALY of $50,000.

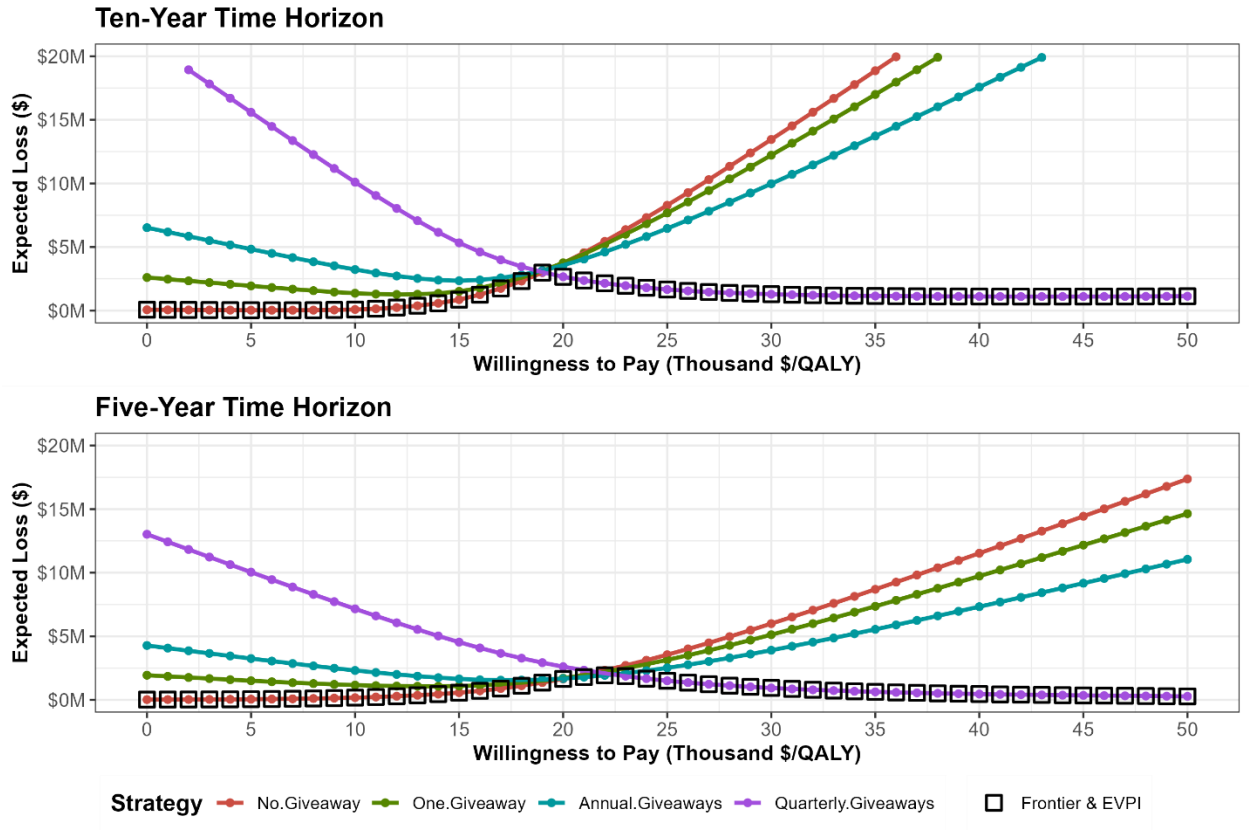
Figure 20: One-way Sensitivity Analysis, Societal Perspective, Ten-Year Time Horizon



The effect of joint uncertainty of all parameters is represented by the expected loss curves from the healthcare perspective in Figure 21. The PSA underlying the expected loss curves accounts both for uncertainty of parameters fixed outside the calibration sequence and uncertainty driven by the calibration process itself. Under both time horizons, the no giveaway strategy was cost effective for willingness to

pay below $18,000 per QALY, though the difference in expected loss is quite narrow for a willingness to pay values starting around $10,000 per QALY. Starting at a willingness to pay value of $19,000 for the ten-year time horizon and $22,000 for the five-year time horizon, the quarterly giveaway strategy is cost effective with increasing certainty as willingness to pay increases. The key difference between the time horizons is the rate at which the gaps in expected loss between the quarterly giveaway strategy and the other strategies grow as willingness to pay increases. The gap first reaches $5 million around a willingness to pay value of $27,000 for the ten-year time horizon and $38,000 for the five-year time horizon. Notwithstanding this difference, the quarterly giveaway strategy is clearly cost-effective at common threshold levels of willingness to pay (i.e., $50,000 or $100,000 per QALY). Expected loss curves for the societal perspective are available in the appendix and indicate that the quarterly giveaway strategy is cost-effective at all willingness to pay values.

Figure 21: Expected Loss Curves, Healthcare Perspective



4.4 Discussion

This analysis compared three naloxone giveaway strategies—a one-time giveaway, annual giveaways for three years, and quarterly giveaways for three years—against a no giveaway strategy. Results indicate

that naloxone giveaways are cost-effective if they generate effects on fatal and non-fatal overdoses in line with Pennsylvania's first giveaway in 2018. In addition, conducting giveaways at a higher frequency—up to quarterly—is cost-effective compared to conducting less frequent events. These results hold under a relatively narrow healthcare perspective and are strengthened—and giveaways become cost-saving—when a broader societal perspective is adopted that considers productivity, consumption, criminal justice costs, and costs of participants' time to obtain naloxone during the giveaways. From a healthcare perspective, ICERs for giveaway strategies were lower when the analysis was conducted over ten years compared to five years, suggesting that people who may have had an overdose reversed by naloxone obtained at a giveaway survived long after the giveaways ended. However, results were sensitive to assumptions concerning the effect of the giveaways on overdose outcomes as using lower bound effectiveness estimates produced ICERs larger than $100,000 from both the healthcare and societal perspectives.

Deterministic sensitivity analyses examining the influence of economic parameters found that productivity and consumption (for the societal perspective), health utility, and the discount rate had the most influence on the net monetary benefit of the quarterly giveaway strategy when compared to the no giveaway strategy. However, all the one-way sensitivity analysis iterations produced a positive net monetary benefit. Findings were also robust to parameter uncertainty, as probabilistic sensitivity analyses concluded with high confidence that the quarterly giveaway strategy is cost effective at any willingness to pay per QALY from the societal perspective and for willingness to pay of about $30,000 from the healthcare perspective.

There are two important implications of these findings for policymakers to consider when considering naloxone distribution strategies. First, although higher frequency giveaways scenarios produced larger net benefits than one-time giveaways at conventional values of willingness to pay, a single naloxone giveaway was still highly cost-effective relative to no giveaway. Thus, policymakers should not be deterred from holding a single naloxone giveaway even if budget constraints limit their ability to commit to future giveaways.

Second, although the analyses provide strong evidence for the cost-effectiveness of naloxone giveaways given effects in line with estimates from the previous chapter, a minority of model iterations produced results that were distinct from the rest. Although many of these iterations produced ICERs considered cost-effective under standard thresholds, the estimated net monetary benefit of giveaway strategies was

markedly lower than other iterations. The defining characteristic of these iterations was an elevated risk of overdose in the first quarter following a giveaway among people who had not previously overdosed. Previous studies have explored whether availability of naloxone causes people to use opioids more often or at higher doses. Some qualitative research indicates that some people are willing to take more risks when it comes to drug use when naloxone is available (e.g., Heavey, Chang, et al., 2018) and one econometric analysis found increased emergency department utilization following the enactment of certain laws designed to increase access to naloxone and suggested that naloxone may represent a moral hazard (Doleac & Mukherjee, 2022). On the other hand, several other studies have found no evidence of risk compensation when people who use opioids have access to naloxone (Tse et al., 2022). It is important to note that this analysis does not shed light on the debate about whether naloxone availability causes increased risk taking among people who use drugs, but it does offer two related insights. First, the naloxone giveaway intervention that had a beneficial effect on overdose deaths may also have increased the rate of overdose, as there were several combinations of calibrated parameters that produced a higher overdose rate (relative to no giveaway) while also reproducing the beneficial effects on overdose outcomes from the giveaway. Second, if the giveaway resulted in higher overdose rates, its economic efficiency would be lower than if there was no increase in overdose rates, despite no difference in the effect on overdose outcomes. Based on these insights, there is an economic incentive for policymakers to reduce the likelihood of increases in overdose rates following naloxone giveaways; thus, naloxone giveaways should be combined with education and other prevention initiatives to reduce the likelihood of these unintended consequences.

The ICERs estimated in this study are situated within the span of ICERs from other previous studies, which ranged from under $100 to over $80,000 per QALY. Because the model used to conduct the current analysis was adapted from the work of Townsend and colleagues (2020), it is to be expected that the estimates presented here are closest to Townsend and colleagues. Both these results and those from the Townsend study found that the highest intensity distribution strategy dominated all others from the societal perspective and had ICERs in the $15,000-$20,000 range from the healthcare perspective.[40] The difference between these estimates and those of other studies can be explained by differences in perspective. The earliest cost-effectiveness analyses of naloxone adopted a very narrow healthcare perspective which did not account for excess healthcare costs for people with OUD (Coffin & Sullivan,

[40] Because Townsend et al. used a lifetime time horizon, the best comparison is to the ten-year time horizon (ICERs of $15,950 (2017 dollars) and $19,454 (2023 dollars), respectively.

2013a, 2013b; Langham et al., 2018), and thus estimated considerably lower ICERs than those estimated in this study. On the other hand, the study by Fairley and colleagues (2021) estimated a positive ICER for overdose education and naloxone distribution ($51,000) compared to no treatment from the societal perspective while this analysis found that naloxone giveaway strategies dominated no giveaway strategies. The key difference in the perspective between the two studies is the inclusion of productivity in the current study which captures benefits to society of longevity following averted overdose deaths. The analysis by Fairley and colleagues only tracks healthcare and criminal justice costs, and thus did not account for the value of longevity separate from QALYs. That the exclusion of net productivity could produce such different results regarding the cost-effectiveness of naloxone distribution is supported by the one-way sensitivity analysis in which parameters related to productivity comprised three of the five most influential.

The results of this analysis also indicate that the economic efficiency of the naloxone giveaway intervention compares well to other interventions targeting OUD and its consequences. Most economic evaluations of medications for opioid use disorder compare different combinations of pharmacological and non-pharmacological treatments against each other (Onuoha et al., 2021), but one study conducted in the UK estimated costs of £13,923 per QALY for buprenorphine and £14,206 per QALY for methadone (2016 pounds sterling) from the healthcare perspective (Kenworthy et al., 2017). These correspond to ICERS of $23,164 and $23,635 in 2023 dollars at current exchange rates, respectively. In addition, a simulation-based analysis projecting the cost-effectiveness of hypothetical supervised injection facilities established in Toronto and Ottawa, Canada found that establishing a single facility[41] in each city would generate QALYs at an incremental cost of $10,763 in Toronto and $6,127 in Ottawa (2012 Canadian dollars) equivalent to $9,989 and $5,686 in 2023 dollars at current exchange rates.

There are three important limitations of this analysis that must be noted. First, the analysis used a state transition model that represented a closed cohort of people with OUD in the Philadelphia region at a point in time. Because the model was not an individual-level simulation, it was limited in how it could represent individual-level heterogeneity and history. However, this limitation was offset by the use of distinct states representing people with and without prior overdoses and multiple age cohorts. In addition, because the model represented a closed cohort it did not account for new cases of OUD. This means that the results from the current study likely represent a lower bound of the cost-effectiveness for multiple giveaway

[41] The analysis of hypothetical Canadian supervised injection facilities found that the cost per QALY would increase with the establishment of additional facilities.

scenarios since the cost of a giveaway was assumed to remain the same, but its potential impact fell as time passes as people in the cohort transitioned to abstinence or died. On the other hand, if naloxone giveaways cause an increase in the incidence of OUD, the estimates of the cost-effectiveness of giveaway scenarios could be overly optimistic. There is no evidence to suggest that naloxone giveaways would cause more people to use opioids or develop OUD, but it is possible that some people would be more willing to experiment with using opioids non-medically if naloxone was available as a contingency. The use of a closed cohort model also contributed to the decision to limit the duration of periodic giveaways in the annual and quarterly giveaway scenarios to three years and to limit the time horizon of the analysis to ten years.

Second, the calibration process which allowed the model to represent the naloxone giveaways was based on assumed ranges over which key model parameters may have changed following the giveaways compared to before the giveaways. Due to the lack of individual-level data available for this intervention, it was not possible to estimate those parameters. However, it is important to note that because the second and third calibration stages use the parameters from the first calibration stage (i.e., parameters representing no giveaway) as initial values, the optimization algorithm does not favor solutions with large deviations from the base case over those with smaller deviations. It should be noted that this calibration approach was chosen in favor of a more direct approach of directly setting the parameter that was most likely to be affected by the giveaway – the probability that a witness to an overdose has and administers naloxone. That approach was taken by previous modeling studies such as the analysis by Townsend and colleagues (2020) which defined its scenarios based on the availability of naloxone. The purpose of this analysis was to evaluate the cost-effectiveness of a particular intervention, not just the cost-effectiveness of increasing naloxone availability in general. The giveaway intervention increased the availability of naloxone and likely increased the probability that it would be administered by a witness to an overdose, but also may have affected other probabilities, such as the probabilities of overdose, of overdose being witnessed (i.e., the likelihood of people opting to use opioids with someone else present), and of different responses to overdoses. Because the effects of the intervention on all these parameters could not be measured, a more neutral calibration approach was adopted.

Third, the scenarios are based on a naloxone giveaway from 2018. Much has changed in the intervening years both with respect to the nature of opioid use and the availability of naloxone. The drug supply has become more potent as the presence of fentanyl and other synthetic opioids more than doubled between 2018 and 2021 (Kilmer et al., 2022). Naloxone can effectively reverse overdoses caused by synthetic

opioids, and although some data suggest that an equivalent dose of naloxone can successfully reverse an overdose on low or high potency opioids (Carpenter et al., 2020), other studies suggest that people who use drugs or who may be in a position to reverse an overdose often fear that a single dose of naloxone may be insufficient (Abdelal et al., 2022). In addition, the introduction of other additives such as xylazine, which is not an opioid and thus not responsive to naloxone, was particularly notable in the Philadelphia area (Johnson et al., 2021). These drug supply changes may alter the cost-effectiveness of a naloxone giveaway if held today. Furthermore, changes in naloxone availability since the 2018 giveaway would likely alter the cost-effectiveness of a specific naloxone giveaway intervention. Total naloxone dispensed by pharmacies increased by nearly 900% between 2016 and 2021 (American Medical Association, 2022), and can now be obtained over the counter without a prescription (Food and Drug Administration, 2023). Outside of pharmacies, naloxone is available through innovative distribution strategies, such as mail order delivery (Barnett et al., 2021). Naloxone giveaways are likely to be cost-effective in situations where they have a meaningful impact on the probability that naloxone will be present at the scene of a witnessed overdose. Because naloxone is available through more channels today, a naloxone giveaway may have less influence on the probability that naloxone is available immediately following an overdose than it did in 2018. Thus, the specific giveaway intervention may be less cost-effective if evaluated in the current context of baseline naloxone availability. Thus, policymakers should consider the merits of giveaways compared to alternative strategies to increase access to naloxone, such as subsidizing the cost of mail order or over the counter naloxone.

Despite these limitations, this analysis provides valuable information to policymakers considering interventions to increase naloxone availability in their communities, particularly interventions aimed at the general public like the Pennsylvania giveaway. Results indicate that giveaways are cost-effective, that higher frequency giveaways are preferable to one-time or lower frequencies, and that the biggest threat to the cost-effectiveness of naloxone distribution strategies is the possibility that it may cause the probability to overdose to increase among some people who use drugs. Although this analysis cannot shed light on whether naloxone has such an effect, it suggests that communities that engage in naloxone distribution should take reasonable steps to prevent riskier use. Future research should establish whether people who use opioids change their use patterns when naloxone is available and should study the effectiveness and cost-effectiveness of other novel distribution strategies such as mail-order naloxone and vending machines (Barnett et al., 2021; Feldman, 2022).

5 Conclusion

This thesis sought to generate new insights about the effectiveness and cost-effectiveness of actions to increase the availability of naloxone to address the ongoing opioid overdose epidemic. In the four years roughly coinciding with the conduct of the research contained in this thesis (June 2019 to June 2023) over 300,000 Americans died from an opioid overdose. This represents an increase of nearly 60 percent over the death toll from the preceding four years (Ahmad et al., 2024). Naloxone is an important but highly specialized tool to reduce mortality associated with opioid overdose. It neither prevents nor aids in the discontinuation of opioid use, but it can be used in the event of overdose to save a life.

For much of the time since it was developed, naloxone was used exclusively by healthcare professionals. Gradually, efforts were made to deploy naloxone directly into the hands of people likely to witness overdoses in the community (McDonald et al., 2017). Policymakers in the United States reacted by changing policies to accommodate naloxone distribution to and possession by non-professionals. Prior to the completion of this thesis, most of what was known about the effectiveness of naloxone in the United States was based on observational studies (Doe-Simkins et al., 2014; Walley et al., 2013) and quasi-experimental studies that exploited variations in the timing and enactment of state laws related to naloxone (Smart et al., 2021). Chapter 2 of this thesis contributes to the latter part of the literature by conducting a meta-analysis of effect estimates of naloxone access laws on fatal overdose rates from quasi-experimental studies. The results from the meta-analysis indicate that the effect of naloxone access laws broadly defined is inconclusive (IRR for opioid overdose deaths: 0.91, 95% CI: 0.77—1.04), but suggest that naloxone access laws that protect prescribers and dispensers from liability may reduce overdose deaths (IRR: 0.85, 95% CI: 0.75-0.96).

Chapter 3 of this thesis exploited two large-scale naloxone giveaway events sponsored by the state of Pennsylvania as the basis for a natural experiment, and conducted a difference-in-differences analysis to estimate the effect of the giveaways on fatal and non-fatal overdoses in areas very close to giveaway sites (i.e., within 3km) compared to areas slightly more distant (i.e., between 3km and 10km). Results indicated an immediate (i.e., within the first three months after the giveaway) reduction in opioid overdose deaths in areas within 3km of giveaway sites compared to areas between 3km and 10km (IRR: 0.59, $p<0.01$) after the first giveaway held in December 2018, but some evidence of an increase in overdose deaths in areas within 3km of giveaway sites compared to more distant controls over the first two quarters following the second giveaway held in September 2019 (IRR:1.27, $p=0.07$). The increasing presence of xylazine—a non-opioid tranquilizer that produces similar depressive effects on one's respiratory system but is unaffected

by naloxone (Friedman et al., 2022; Johnson et al., 2021)—in the drug supply between the first and second giveaways is offered as an explanation for these seemingly contradictory findings.

Chapter 4 extended the findings from the previous chapter by estimating the cost-effectiveness of the novel giveaway intervention held in Pennsylvania. An existing decision model (Townsend et al., 2020) was adapted to the specific context of the first Pennsylvania naloxone giveaway in Philadelphia and surrounding counties. The model was used to evaluate scenarios ranging from no naloxone giveaways to giveaways held every quarter. The model was calibrated to estimates from chapter 3 to represent the effects of the giveaways on overdose outcomes. The analysis contributed to the literature on the cost effectiveness of increasing availability of naloxone by examining a novel, "untargeted" distribution strategy. Results indicated that quarterly giveaways comprise a cost-effective strategy from the healthcare perspective if willingness to pay for a quality-adjusted life year exceeds approximately $20,000, and that from a broader, societal perspective, quarterly giveaways are cost-saving. The analysis also examined connections between key parameters and the cost-effectiveness results based on variations resulting from model calibration. This process revealed an important association between risk of an individual's first overdose following a naloxone giveaway and the cost-effectiveness of the intervention. While this insight does not indicate whether the naloxone giveaway or naloxone availability in general causes an increased risk of overdose, it demonstrates that the economic efficiency of the intervention would be affected by such behaviors.

Taken together, the research in this thesis produces several important policy implications. First, the results of the literature review suggest that efforts to distribute naloxone through professional channels may have been strained by uncertainty among prescribers and dispensers about the legality of providing naloxone to laypeople. Although the availability of naloxone over the counter likely reduces the direct impact of laws designed to protect prescribers and dispensers from liability, ensuring that medical professionals are aware of and comfortable with naloxone distribution will likely increase the reach of interventions and policies designed to increase its availability. Additionally, the importance of ensuring that professionals that have a role in providing services to people who use opioids are not unduly constrained by fear of legal liability has implications beyond naloxone. For example, some clinicians are hesitant to prescribe buprenorphine, an effective treatment for OUD, due to concern about government intrusion or legal liability (Klusaritz et al., 2023; Nyaku et al., 2024). The findings from the analysis of NALs suggests that efforts to clarify policies regarding buprenorphine prescriptions or make liability protections explicit may reduce barriers to treatment availability.

Second, the seemingly contradictory effectiveness results of the two Pennsylvania giveaways held less than a year apart suggests the importance of contextual factors. As noted in chapter 3, a potential explanation of these findings is the sudden increase of the presence of xylazine in the opioid supply in the Philadelphia area throughout 2019. This underscores a need for policymakers and others involved in the distribution of naloxone to emphasize education about the proper use and limitations of naloxone. Many harm reduction organizations that provide naloxone do provide education (Wenger et al., 2022)—and those efforts have been shown to increase knowledge related to overdose (Heavey, Burstein, et al., 2018)—but events like the Pennsylvania giveaways and over the counter availability may provide less of an opportunity to educate recipients. Policymakers and other organizations engaged other approaches, such as public health communication campaigns, to fill the gap. This finding also underscores the need for public health authorities to conduct surveillance on the characteristics local drug supply. Research has established an association between the chemical characteristics of the local drug supply and overdose death rates, but information obtained from law enforcement or medical examiner laboratories is not optimally disseminated to inform public health (Zibbell et al., 2023). For example, a pilot drug testing and dissemination effort in Rhode Island demonstrated the value of rapid drug test data (i.e., by identifying xylazine and other substances not known to be present in the drug supply) and the feasibility of rapid dissemination of drug test data to public health authorities (Collins et al., 2023). Given the dynamic drug supply and the effect changing drug supply composition has on the effectiveness of naloxone distribution, policymakers should support efforts to obtain timely data on the drug supply and encourage broad dissemination of those data.

Third, the results of the cost-effectiveness analysis conducted in chapter 4 suggest that events to distribute naloxone at relatively high frequencies constitute an efficient use of resources. Contrary to other avenues though which naloxone was available prior to the giveaways, the Pennsylvania giveaway events encouraged people to obtain naloxone even if they did not necessarily expect to need it. The finding that this intervention was cost-effective even though much of the naloxone handed out during the giveaways may never have been used, is an important one. Even though naloxone has become much more readily available in the time since the giveaways, policymakers should note the unique benefits of a no-cost, no-questions-asked, untargeted approach to naloxone distribution like the Pennsylvania giveaways. Future cost-effectiveness research should compare giveaways to alternative strategies for broad-based naloxone distribution, including mail-order delivery, permanent vending machines, and subsidies for over-the-counter purchase.

There are two key opportunities for future research to build upon the work reflected in this thesis. First, although the research into the Pennsylvania giveaways produced important insights, the available data did not allow for a direct investigation into the effect that the availability of naloxone may have on individual use behaviors. Following previous efforts to examine this question empirically (Abouk et al., 2019; Doleac & Mukherjee, 2022) , chapter 3 considered the effect of the naloxone giveaways on both fatal and non-fatal overdoses. An increase in non-fatal overdoses may suggest an increased propensity to overdose, but the findings with respect to non-fatal overdoses following the Pennsylvania giveaways were in the opposite direction. As discussed in the discussion of those results and elsewhere in this thesis, there is no theoretical basis by which naloxone should reduce overdoses, so a reduction in ED utilization should not be taken as evidence of a reduction in risk-taking associated with naloxone availability. Given the difficulties in obtaining data representative of total overdoses (i.e., because many overdoses are never recorded at all), more definitive research in this area would likely require both qualitative and quantitative methodologies. Considering what existing theory suggests about an increased potential for risk taking among relatively novice users discussed in this thesis's introduction and the finding from the cost-effectiveness analysis of sensitivity of results to the risk of first-time overdose, future research in this area should focus on the effect of naloxone availability on behaviors among those considering initiating opioid use and those with relatively little experience with opioid use. Valuable data that could help to inform the relationship between naloxone availability and drug use behavior includes qualitative interviews, particularly with people who only recently initiated drug use, about their experience with naloxone and the importance they place on its availability under different circumstances, such as when using for the first time or when using a higher dose or drugs from a different supplier. In addition, a questionnaire meant to capture information on recent episodes of drug use, distributed to people who use opioids by a trusted intermediary (e.g., a harm reduction organization) in a way that maintains anonymity could be used to understand associations between the presence of naloxone and drug use activity. Such a questionnaire could also be leveraged for effectiveness research alongside intervention trials or in the context of a suitable natural experiment.

Second, a logical follow-up to the cost-effectiveness analysis presented in chapter 4 is a distributional cost-effectiveness analysis (Asaria et al., 2016). The data available to study the effects of the Pennsylvania giveaways on fatal and non-fatal overdoses did not include demographic characteristics, so it was not possible to conduct such a distributional analysis. A distributional cost-effectiveness analysis of an intervention like Pennsylvania's naloxone giveaways, or of other efforts to distribute naloxone is

particularly important given emerging evidence of existing disparities in access to naloxone for racial and ethnic minorities (Khan et al., 2023; Nolen et al., 2022).

The work contained in this thesis makes important contributions to the literature on the effectiveness and cost-effectiveness of efforts to increase the availability of naloxone. Chapter 2 expanded upon a previous systematic review of the literature on the causal effects of NALs (Smart et al., 2021) to provide meta-analytic estimates of the effects of those laws on fatal overdoses. It also proposed a taxonomy for NALs that categorizes how each law interacts with the naloxone distribution process and highlights the importance of ensuring that professional practitioners involved in the distribution of naloxone are explicitly protected from legal liability. Chapter 3 provided a fresh look at the causal effect of naloxone availability on fatal and non-fatal overdoses. It was the first to study the effects of untargeted naloxone distribution that emphasized uptake of naloxone among the general public, not just people who use opioids or those with close connections to people who use drugs. Whereas several previous studies exploited variation in enactment of laws supportive of naloxone to identify effects of naloxone, the empirical analysis in chapter 3 estimated the effect of naloxone availability based on direct distribution of thousands of naloxone kits during state-sponsored giveaway events. The results from chapter 3 also offered insights into the consequences of the increasing presence of xylazine in the opioid supply in the period between the two giveaways. Finally, given the findings from chapter 3 regarding the effectiveness of the initial Pennsylvania giveaway as well as the novelty of the strategy to increase the availability of naloxone, chapter 4 considered whether naloxone giveaways represented an efficient use of resources and if so, at what frequency they should be conducted. In addition to providing conventional cost-effectiveness estimates of the giveaway intervention, the analysis in chapter 4 utilized a multi-stage calibration strategy to represent the effects of the giveaways on the probability of overdose and responses to those overdoses that could not be measured. This approach indicated that a naloxone giveaway that a meaningful increase in overdose risk may have occurred despite the overall beneficial effects of the giveaways. More importantly, results show that increased overdose risk would detract from the economic efficiency of the giveaway intervention, thus demonstrating the practical importance of limiting shifts in behavior toward greater risk. The insights from this thesis can be used to combat the ongoing opioid overdose crisis and to inform future research priorities.

Research Ethics

The research contained in this thesis was approved by the Faculty of Health and Medicine Research Ethics Committee of Lancaster University.

Appendix Material for Chapter 2

Search Syntax

Table A2.1 MEDLINE Syntax

S1	(MH "Naloxone+") OR (narcan OR naloxone OR naloxon)
S2	(MH "Drug Overdose") OR overdos*
S3	(MH "Mortality+") OR (mortalit* OR (overdose* N5 death*)))
S4	(nonfatal OR non-fatal OR repeat* OR suspected OR acute) N5 overdose*
S5	S3 OR S4
S6	S1 AND S2 AND S5 (Limiter: English Language)

Table A2.2 PsycINFO Syntax

S1	DE ("Naloxone") OR (narcan or naloxone or naloxon)
S2	DE "Drug Overdoses" OR overdos*
S3	(DE "Mortality Risk" OR DE "Mortality Rate" OR DE "Death and Dying") OR (mortalit* OR (overdose* N5 death*)))
S4	(nonfatal OR non-fatal OR repeat* OR suspected OR acute) N5 overdose*
S5	S3 OR S4
S6	S1 AND S2 AND S6 (Limiter: English Language)

Table A2.3 EMBASE Syntax

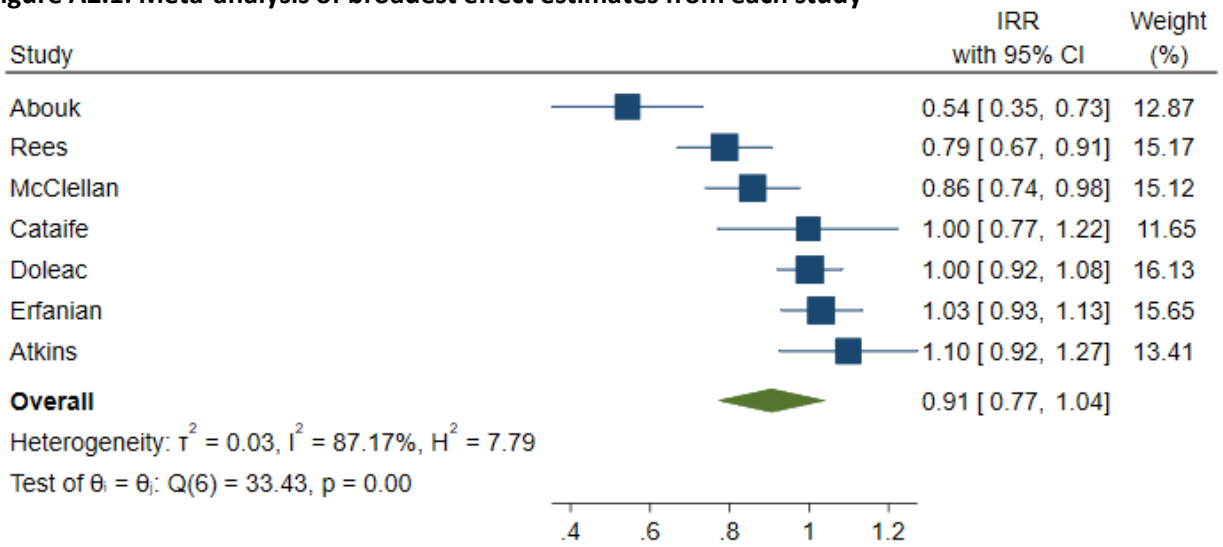
S1	exp naloxone/
S2	(narcan or naloxone or naloxone).af.
S3	S1 or S2
S4	drug overdose/
S5	“overdos*”.af.
S6	S4 OR S5
S7	Mortality/
S8	(mortalit* or (overdos* adj5 death*)).af.
S9	S7 or S8
S10	((nonfatal or non-fatal or repeat* or suspected or acute) adj5 overdose*).af.
S11	S3 AND S6
S12	S9 OR S10
S13	S11 AND S12 (Limiter: English Language)

Because EconLit and the SSRN e-Library included fewer relevant references, a very broad search using the keyword “naloxone” was used and all hits were manually reviewed.

Alternative Meta-Analysis Output

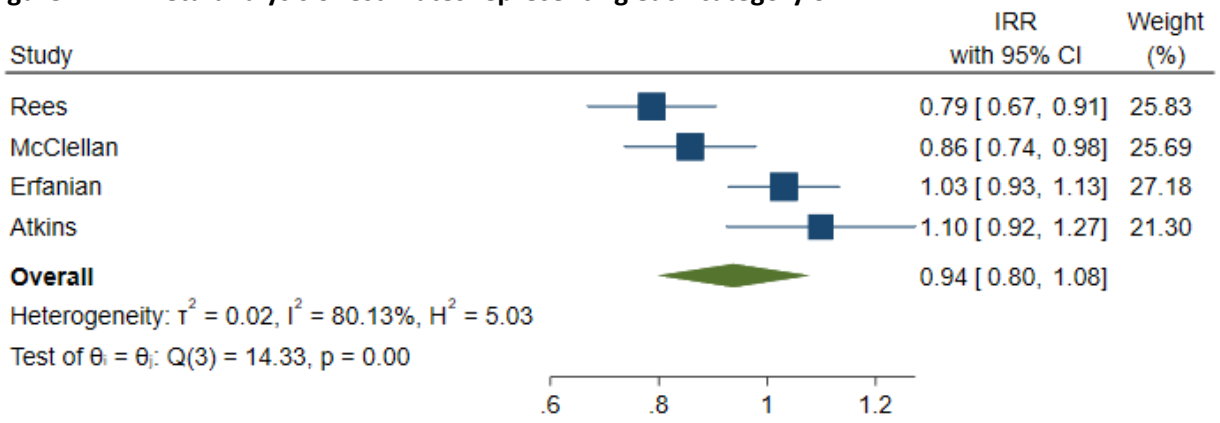
The figures below correspond to Figures 2 and 3 in Chapter 2 showing the broadest effect estimates available from the included studies. The use of the Paule-Mandel estimator produces slightly different estimate weights but substantively equivalent results.

Figure A2.1: Meta-analysis of broadest effect estimates from each study



Note: 95% confidence interval of I^2: 65.23% - 91.22%

Figure A2.2: Meta-analysis of estimates representing each category of NAL



Note: 95% confidence interval of I^2: 44.04% - 92.17%

Appendix Material for Chapter 3

Tables

Table A3.1. Effect of Naloxone Giveaways on Overdose Deaths, Linear Regression

	Giveaway #1 (2018)	Giveaway #2 (2019)
Treatment x Post	-0.313**	0.308*
	[-0.608,-0.017]	[-0.021,0.638]
Observations	6723	3240

* p<0.10, ** p<0.05, *** p<0.01

This table shows effects in opioid overdose deaths per 10,000 population from fixed effects linear regression of Equation 3.1: Census tract-quarter level opioid overdose deaths on an interaction term identifying observations of tracts treated during the naloxone giveaway (Treatment x Post), Census tract fixed effects, and quarter fixed effects. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the Census tract level.

Table A3.2. Effect of Naloxone Giveaways on Overdose Deaths, Rest of State

	Giveaway #1 (2018)		Giveaway #2 (2019)	
	3km Threshold	15km Threshold	3km Threshold	15km Threshold
Treatment x Post	0.976	0.996	1.054	1.130
	[0.816,1.168]	[0.870,1.141]	[0.849,1.309]	[0.950,1.343]
Observations	6543	14031	2360	4904

* p<0.10, ** p<0.05, *** p<0.01

This table shows incidence rate ratios from fixed effects Poisson regression of Equation 3.1: Census tract-quarter level opioid overdose deaths on an interaction term identifying observations of tracts treated during the naloxone giveaway (Treatment x Post), Census tract fixed effects, and quarter fixed effects. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the Census tract level. Tracts with no recorded opioid overdose deaths over the analysis period are excluded. Columns 1 and 3 show results using the standard distance threshold used in the main analysis (treated: within 3km of giveaway site; control: between 3km and 10km of a giveaway site). Columns 2 and 4 include all tracts within 15km of a giveaway site in the treatment group and all other tracts as controls.

Table A3.3. Effect of Naloxone Giveaways on Overdose Deaths, Alternative Control Group

	Giveaway #1 (2018)
Treatment x Post	0.671**
	[0.474,0.952]
Observations	1908

* p<0.10, ** p<0.05, *** p<0.01

This table shows incidence rate ratios from fixed effects Poisson regression of Equation 3.1: Census tract-quarter level opioid overdose deaths on an interaction term identifying observations of tracts treated during the naloxone giveaway (Treatment x Post), Census tract fixed effects, and quarter fixed effects. The treatment group is the same as in the main analysis, but the control group is restricted to Census tracts that are within 3km of distribution locations during the 2019 giveaway. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the Census tract level. Tracts with no recorded opioid overdose deaths over the analysis period are excluded.

Table A3.4. Effect of Naloxone Giveaways on Overdose Deaths, Alternative Covariates

	Giveaway #1 (2018)				Giveaway #2 (2019)	
	Main Results	All Controls	ACS Controls Only	Overdose-Related Controls Only	Main Results	Overdose-Related Controls Only
Treatment x Post	0.853	0.826*	0.834*	0.847	1.267*	1.272*
	[0.690,1.056]	[0.666,1.023]	[0.673,1.034]	[0.684,1.049]	[0.985,1.629]	[0.987,1.639]
Observations	6066	6066	6066	6066	2420	2420

* p<0.10, ** p<0.05, *** p<0.01

This table shows incidence rate ratios from fixed effects Poisson regression of Equation 3.1: Census tract-quarter level opioid overdose deaths on an interaction term identifying observations of tracts treated during the naloxone giveaway (Treatment x Post), Census tract fixed effects, and quarter fixed effects, and various time-varying controls. The main results include no controls beyond the tract and quarter fixed effects, the "all controls" column includes results controlling for the county-level opioid-overdose related controls along with tract-level demographic and socioeconomic controls from the American Community Survey (ACS), the "ACS controls" column includes only demographic and socioeconomic controls and excludes the county-level opioid-overdose related controls, and the "overdose-related" columns exclude all control variables. ACS controls were not used for the 2019 giveaway because ACS data were not available in 2020 for the tracts used in this analysis. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the Census tract level. Tracts with no recorded opioid overdose deaths over the analysis period are excluded.

Table A3.5. Effect of Naloxone Giveaways on Overdose Deaths, Alternative Exposure Variable

	Giveaway #1 (2018)		Giveaway #2 (2019)	
	Main Results	Tract Population as Exposure	Main Results	Tract Population as Exposure
Treatment x Post	0.853	0.86	1.267*	1.266*
	[0.690,1.056]	[0.694,1.066]	[0.985,1.629]	[0.984,1.628]
Observations	6066	5967	2420	2400

* p<0.10, ** p<0.05, *** p<0.01

This table shows incidence rate ratios from fixed effects Poisson regression of Equation 3.1 for opioid overdose deaths using different measures to represent exposure. The first and third column repeat the main results for the 2018 and 2019 giveaways, respectively. The second and fourth columns show the results when tract population is used. For these results, tracts with a population of less than 1,000 at any point in the analysis period are excluded.

Table A3.6. Effect of Naloxone Giveaways on Overdose Deaths, Alternative Treatment Regions

	Main Results	1km Distance Threshold	5km Distance Threshold	Remove 10km Restriction	Remove Alt. Naloxone Restriction	Remove Both Restrictions
			Giveaway #1 (2018)			
Treatment x Post	0.853	0.859	0.900	0.825*	0.957	0.937
	[0.690,1.056]	[0.617,1.196]	[0.729,1.111]	[0.672,1.013]	[0.822,1.113]	[0.811,1.082]
Observations	6066	8109	4878	8442	8802	11178
			Giveaway #2 (2019)			
Treatment x Post	1.267*	1.274*	1.079	1.262*	1.174*	1.164*
	[0.985,1.629]	[0.985,1.650]	[0.843,1.380]	[0.989,1.610]	[0.989,1.394]	[0.990,1.369]
Observations	2420	3196	1952	3036	3452	4068

* p<0.10, ** p<0.05, *** p<0.01

This table shows incidence rate ratios from fixed effects Poisson regression of Equation 3.1 for opioid overdose deaths under different treatment and control region definitions. The first column repeats the main analysis for the 2018 (top) and 2019 (bottom) giveaways. The second column uses a 1km distance to define both inclusion in the treatment region and exclusion due to proximity to alternative naloxone. The third column uses a 5km distance to define both inclusion in the treatment region and exclusion due to proximity to alternative naloxone. The fourth column uses the default 3km distance threshold and removes the restriction on the control group that limits to regions that are 10km or less from a giveaway location. The fifth column uses the default 3km distance threshold and removes the exclusion of tracts within 3km of alternative sources of free naloxone. Finally, the sixth column combines the fourth and fifth by using the default 3km distance threshold but removing both restrictions. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the Census tract level. Tracts with no recorded opioid overdose deaths over the analysis period are excluded.

Table A3.7. Regression Discontinuity in Time for Overdose Deaths

	Full Six-county Region	Within 10km	Within 5km	Within 3km	Within 2km
			2018 Giveaway		
First Giveaway Quarter	1.131	1.088	0.973	0.736*	0.704
	[0.975,1.311]	[0.919,1.288]	[0.761,1.242]	[0.524,1.033]	[0.447,1.107]
Second Giveaway Quarter	1.108	1.066	1.05	0.954	0.889
	[0.964,1.274]	[0.909,1.250]	[0.840,1.311]	[0.705,1.292]	[0.616,1.283]
Observations	8442	6066	2655	1287	684
			2019 Giveaway		
First Giveaway Quarter	1.016	1.014	1.024	1.117	1.046
	[0.884,1.168]	[0.869,1.183]	[0.826,1.269]	[0.841,1.483]	[0.741,1.477]
Second Giveaway Quarter	1.000	1.019	1.053	1.198	1.292
	[0.871,1.149]	[0.877,1.185]	[0.866,1.281]	[0.921,1.558]	[0.933,1.789]
Observations	3036	2420	1300	708	392

* p<0.10, ** p<0.05, *** p<0.01

This table shows results from regression discontinuity in time models of Census tract-quarter level opioid overdose deaths on Census tract and quarter fixed effects estimated using Poisson regression. The coefficients are incidence rate ratios representing the within-tract difference in the outcome in a post-giveaway quarter relative to the quarter immediately before the giveaway. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the Census tract level. The top panel represents the 2018 giveaway and the bottom panel the 2019 giveaway. The columns from left to right represent areas that are progressively closer to giveaway locations.

Table A3.8. Effect of Naloxone Giveaways on Overdose Deaths, Continuous Distance as Treatment Intensity

	Giveaway #1 (2018)		Giveaway #2 (2019)	
	Poisson (IRR)	Linear Regression	Poisson (IRR)	Linear Regression
Treatment x Post	1.017***	0.022***	0.980*	-0.024**
	[1.005,1.029]	[0.009,0.036]	[0.956,1.004]	[-0.047,-0.000]
Observations	8442	9450	3036	4200

* p<0.10, ** p<0.05, *** p<0.01

This table shows results from fixed effects regressions of Equation 3.1: Census tract-quarter level opioid overdose deaths on an interaction term of the distance from the tract to the nearest giveaway location and an indicator of the post-giveaway period (Distance x Post), Census tract fixed effects, and quarter fixed effects. The model is estimated using Poisson (columns 1 and 3) and linear (columns 2 and 4) regression. Poisson results are shown as incidence rate ratios (IRR), and linear regression results are shown as effects in opioid overdose deaths per 10,000 population. The coefficients represent the effect of being an additional 1km from a giveaway location. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the Census tract level.

Table A3.9. Effect of Naloxone Giveaways on Opioid Overdose-related Emergency Department Visits, Linear Regression

	Giveaway #1 (2018)	Giveaway #2 (2019)
Treatment x Post	0.109	-0.751
	[-0.795,1.014]	[-2.026,0.523]
Observations	1458	744

* p<0.10, ** p<0.05, *** p<0.01

This table shows effects in opioid-related emergency department (ED) visits per 10,000 population from fixed effects linear regression of Equation 3.1: ZCTA-quarter level ED visits attributable to opioid overdose on an interaction term identifying observations of ZCTAs treated during the naloxone giveaway (Treatment x Post), ZCTA fixed effects, and quarter fixed effects. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the ZCTA level.

Table A3.10. Effect of Naloxone Giveaways on Opioid Overdose-related Emergency Department Visits, Rest of State

	Giveaway #1 (2018)		Giveaway #2 (2019)	
	3km Threshold	15km Threshold	3km Threshold	15km Threshold
Treatment x Post	1.218	1.055	0.771**	0.973
	[0.863,1.719]	[0.878,1.268]	[0.619,0.962]	[0.821,1.154]
Observations	2106	8037	848	2992

* p<0.10, ** p<0.05, *** p<0.01

This table shows incidence rate ratios from fixed effects Poisson regression of Equation 3.1: ZCTA-quarter level emergency department (ED) visits attributable to opioid overdose on an interaction term identifying observations of ZCTAs treated during the naloxone giveaway (Treatment x Post), ZCTA fixed effects, and quarter fixed effects. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the ZCTA level. ZCTAs with no recorded opioid overdose-related ED visits over the analysis period are excluded. Columns 1 and 3 show results using the standard distance threshold used in the main analysis (treated: within 3km of giveaway site; control: between 3km and 10km of a giveaway site). Columns 2 and 4 include all ZCTAs within 15km of a giveaway site in the treatment group and all other ZCTAs as controls.

Table A3.11. Effect of Naloxone Giveaways on Opioid Overdose-related Emergency Department Visits, Alternative Control Group

	Giveaway #1 (2018)
Treatment x Post	0.847
	[0.545,1.316]
Observations	342

* p<0.10, ** p<0.05, *** p<0.01

This table shows incidence rate ratios from fixed effects Poisson regression of Equation 3.1: ZCTA-quarter level emergency department (ED) visits attributable to opioid overdose on an interaction term identifying observations of ZCTAs treated during the naloxone giveaway (Treatment x Post), ZCTA fixed effects, and quarter fixed effects. The treatment group is the same as in the main analysis, but the control group is restricted to ZCTAs that are within 3km of distribution locations during the 2019 giveaway. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the ZCTA level. ZCTAs with no recorded opioid overdose-related ED visits over the analysis period are excluded.

Table A3.12. Effect of Naloxone Giveaways on Opioid Overdose-related Emergency Department Visits, Alternative Covariates

	Giveaway #1 (2018)				Giveaway #2 (2019)	
	Main Results	All Controls	ACS Controls Only	Overdose-Related Controls Only	Main Results	Overdose-Related Controls Only
Treatment x Post	1.116	1.139	1.149	1.098	0.809*	0.895
	[0.821,1.165]	[0.880,1.472]	[0.778,1.697]	[0.846,1.424]	[0.653,1.003]	[0.732,1.095]
Observations	1359	1359	1359	1359	668	668

* p<0.10, ** p<0.05, *** p<0.01

This table shows incidence rate ratios from fixed effects Poisson regression of Equation 3.1: ZCTA-quarter level emergency department visits attributable to opioid overdose on an interaction term identifying observations of ZCTAs treated during the naloxone giveaway (Treatment x Post), ZCTA fixed effects, and quarter fixed effects, and various time-varying controls. The main results include no controls beyond the ZCTA and quarter fixed effects, the "all controls" column includes results controlling for the county-level opioid-overdose related controls along with ZCTA-level demographic and socioeconomic controls from the American Community Survey (ACS), the "ACS controls" column includes only demographic and socioeconomic controls and excludes the county-level opioid-overdose related controls, and the "overdose-related" columns exclude all control variables. ACS controls were not used for the 2019 giveaway because ACS data were not available in 2020 for the ZCTAs used in this analysis. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the ZCTA level. ZCTAs with no recorded opioid overdose deaths over the analysis period are excluded.

Table A3.13. Effect of Naloxone Giveaways on Opioid Overdose-related Emergency Department Visits, Alternative Treatment Regions

	Main Results	1km Distance Threshold	5km Distance Threshold	Remove 10km Restriction	Remove Alt. Naloxone Restriction	Remove Both Restrictions
Giveaway #1 (2018)						
Treatment x Post	1.166	1.055	1.233	1.129	1.073	1.047
	[0.821,1.657]	[0.724,1.538]	[0.923,1.647]	[0.798,1.597]	[0.916,1.258]	[0.898,1.219]
Observations	1359	1656	1143	2241	1719	2601
Giveaway #2 (2019)						
Treatment x Post	0.809*	0.856*	0.811	0.805**	0.853**	0.851**
	[0.653,1.003]	[0.715,1.025]	[0.611,1.075]	[0.654,0.992]	[0.732,0.993]	[0.735,0.985]
Observations	668	800	572	912	828	1072

* p<0.10, ** p<0.05, *** p<0.01

This table shows incidence rate ratios from fixed effects Poisson regression of Equation 3.1 for opioid overdose-related ED visits under different treatment and control region definitions. The first column repeats the main analysis for the 2018 (top) and 2019 (bottom) giveaways. The second column uses a 1km distance to define both inclusion in the treatment region and exclusion due to proximity to alternative naloxone. The third column uses a 5km distance to define both inclusion in the treatment region and exclusion due to proximity to alternative naloxone. The fourth column uses the default 3km distance threshold and removes the restriction on the control group that limits to regions that are 10km or less from a giveaway location. The fifth column uses the default 3km distance threshold and removes the exclusion of ZCTAs within 3km of alternative sources of free naloxone. Finally, the sixth column combines the fourth and fifth by using the default 3km distance threshold but removing both restrictions. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the ZCTA level. ZCTAs with no recorded opioid overdose deaths over the analysis period are excluded.

Table A3.14. Regression Discontinuity in Time for Opioid Overdose-related Emergency Department Visits

	Full Six-county Region	Within 10km	Within 5km	Within 3km	Within 2km
			2018 Giveaway		
First Giveaway Quarter	0.849***	0.840***	0.817***	0.801*	0.76
	[0.766,0.942]	[0.749,0.941]	[0.710,0.940]	[0.629,1.021]	[0.541,1.068]
Second Giveaway Quarter	0.935	0.901*	0.928	0.796***	0.739***
	[0.840,1.041]	[0.796,1.019]	[0.792,1.088]	[0.682,0.929]	[0.614,0.890]
Observations	2241	1359	549	225	90
			2019 Giveaway		
First Giveaway Quarter	0.874**	0.886**	0.822**	0.901	0.821
	[0.782,0.976]	[0.787,0.997]	[0.700,0.965]	[0.735,1.105]	[0.605,1.115]
Second Giveaway Quarter	0.880**	0.877**	0.805**	0.769**	0.626***
	[0.781,0.991]	[0.772,0.996]	[0.680,0.953]	[0.628,0.943]	[0.468,0.836]
Observations	912	668	288	144	52

* p<0.10, ** p<0.05, *** p<0.01

This table shows results from regression discontinuity in time models of ZCTA-quarter level emergency department (ED) visits attributable to opioid overdose on ZCTA and quarter fixed effects estimated using Poisson regression. The coefficients are incidence rate ratios representing the within-ZCTA difference in the outcome in a post-giveaway quarter relative to the quarter immediately before the giveaway. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the ZCTA level. The top panel represents the 2018 giveaway and the bottom panel the 2019 giveaway. The columns from left to right represent areas that are progressively closer to giveaway locations.

Table A3.15. Effect of Naloxone Giveaways on Opioid Overdose-related Emergency Department Visits, Continuous Distance as Treatment Intensity

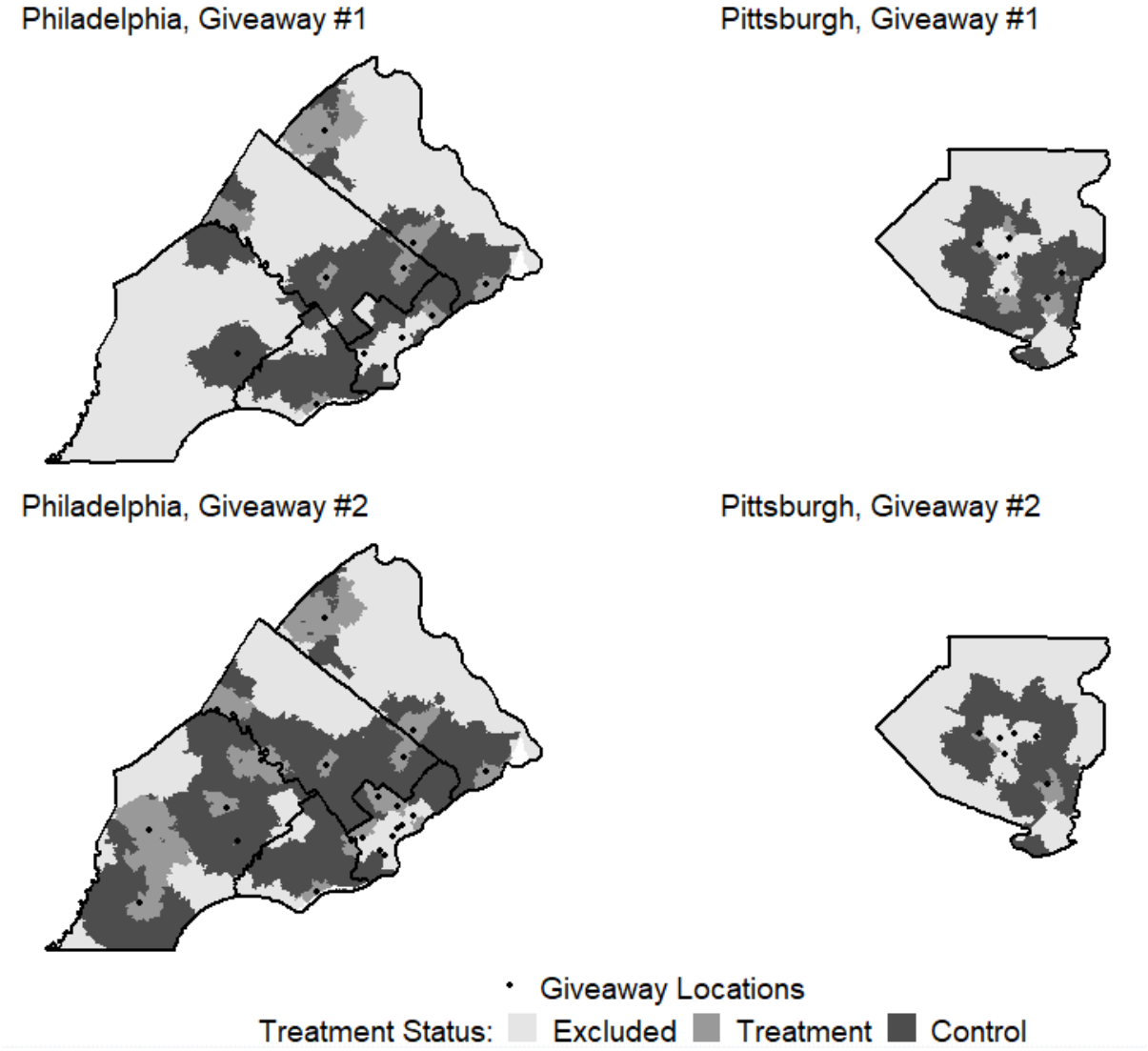
	Giveaway #1 (2018)		Giveaway #2 (2019)	
	Poisson (IRR)	Linear Regression	Poisson (IRR)	Linear Regression
Treatment x Post	1.011	0.052	1.019	-0.047
	[0.988,1.034]	[-0.010,0.114]	[0.995,1.044]	[-0.106,0.011]
Observations	2241	2493	912	1108

* p<0.10, ** p<0.05, *** p<0.01

This table shows results from fixed effects regressions of Equation 3.1: ZCTA-quarter level emergency department (ED) visits attributable to opioid overdose on an interaction term of the distance from the ZCTA to the nearest giveaway location and an indicator of the post-giveaway period (Distance x Post), ZCTA fixed effects, and quarter fixed effects. The model is estimated using Poisson (columns 1 and 3) and linear (columns 2 and 4) regression. Poisson results are shown as incidence rate ratios (IRR), and linear regression results are shown as effects in ED visits per 10,000 population. The coefficients represent the effect of being an additional 1km from a giveaway location. 95% confidence intervals shown in brackets are based on standard errors adjusted for clustering at the ZCTA level.

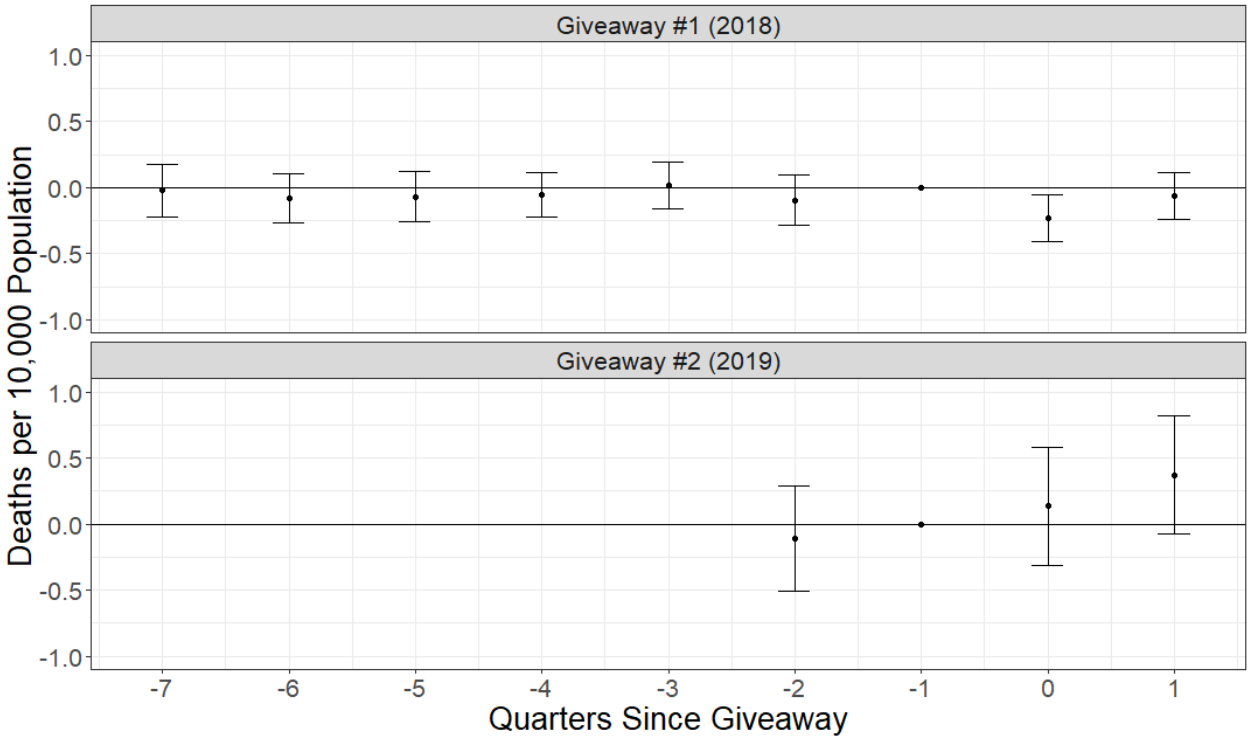
Figures

Figure A3.1. Treated and Control Regions for ZCTA-Level Analysis



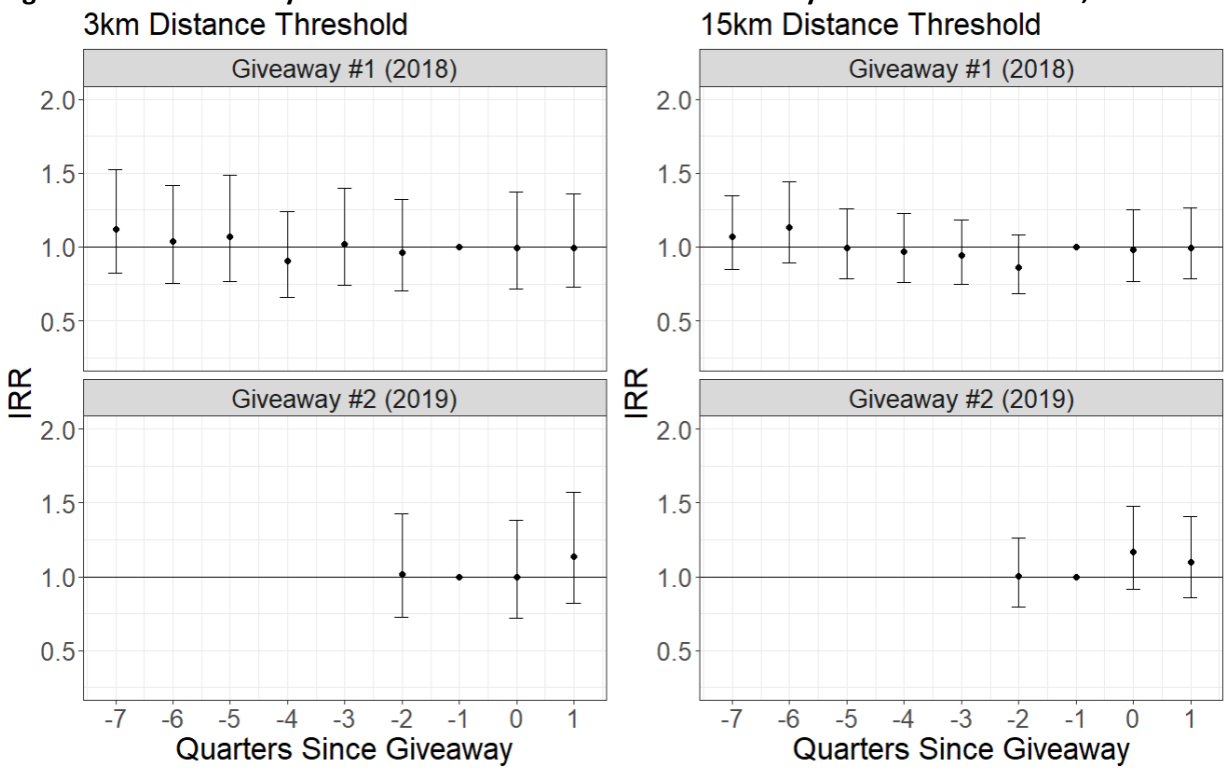
This figure shows treated and control regions for the ZCTA-level analysis of the effect of each of the two giveaways on opioid-related ED visits. Excluded regions are ZCTAs within 3km of an existing source of free naloxone or more than 10km from a giveaway location, treated regions are ZCTAs more than 3km from an existing source of free naloxone but within 3km of a giveaway location, and control regions are ZCTAs more than 3km from an existing source of free naloxone but between 3km and 10km of the nearest giveaway location.

Figure A3.2. Event Study Estimates for Effect of Naloxone Giveaways on Overdose Deaths, Linear Regression



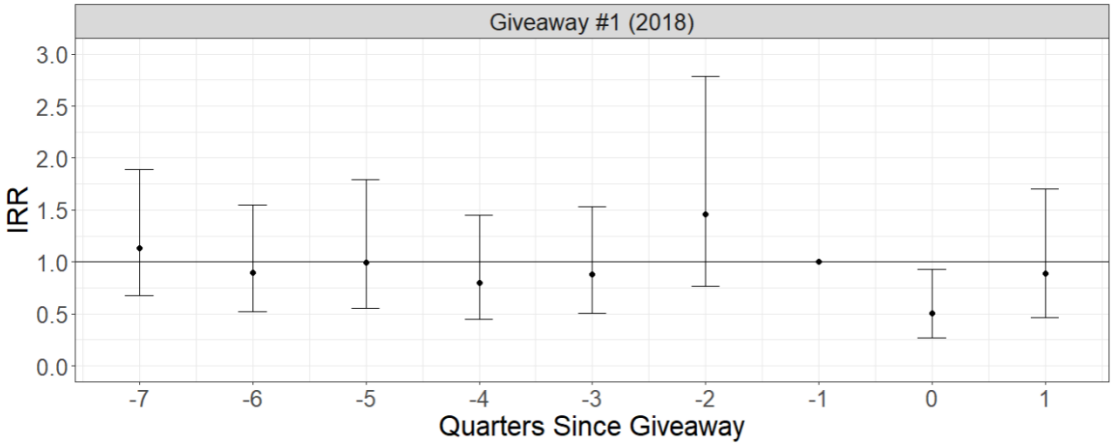
This figure shows effects in opioid overdose deaths per 10,000 population from an event study estimated using fixed effects linear regression of Equation 3.2. The regression controls for Census tract and quarter fixed effects. The point represents the coefficient estimate and the error bars represent 95% confidence intervals based on standard errors adjusted for clustering at the Census tract level.

Figure A3.3. Event Study Estimates for Effect of Naloxone Giveaways on Overdose Deaths, Rest of State



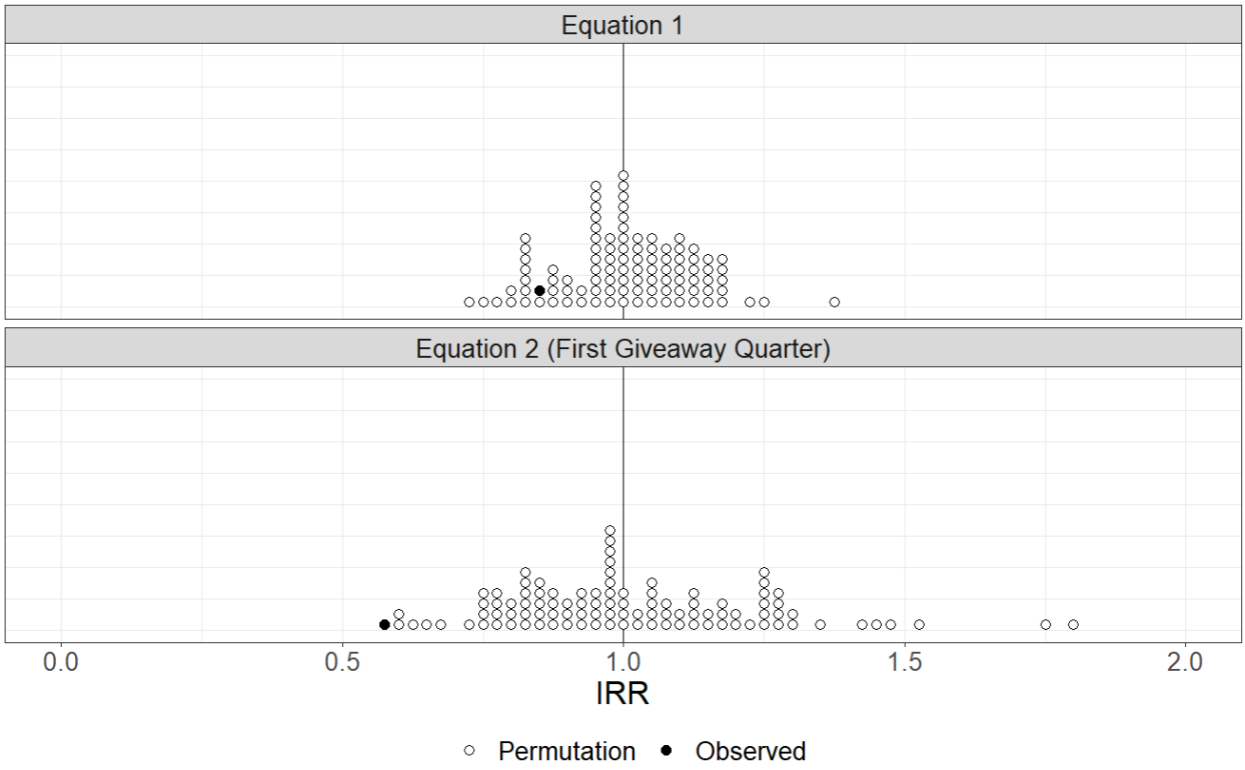
This figure shows incidence rate ratios from a fixed effect Poisson event study regression of Equation 3.2 for Census tract-quarter level opioid overdose deaths. The regression controls for Census tract and quarter fixed effects. The point represents the coefficient estimate (IRR), and the error bars represent 95% confidence intervals based on standard errors adjusted for clustering at the Census tract level. Tracts with no recorded opioid overdose deaths over the analysis period are excluded. The left two panels show results using the standard distance threshold used in the main analysis (treated: within 3km of giveaway site; control: between 3km and 10km of a giveaway site) for the 2018 (top) and 2019 (bottom) giveaways, respectively. The right two panels include all tracts within 15km of a giveaway site in the treatment group and all other tracts as controls.

Figure A3.4. Event Study Estimates for Effect of Naloxone Giveaways on Overdose Deaths, Alternative Control Group



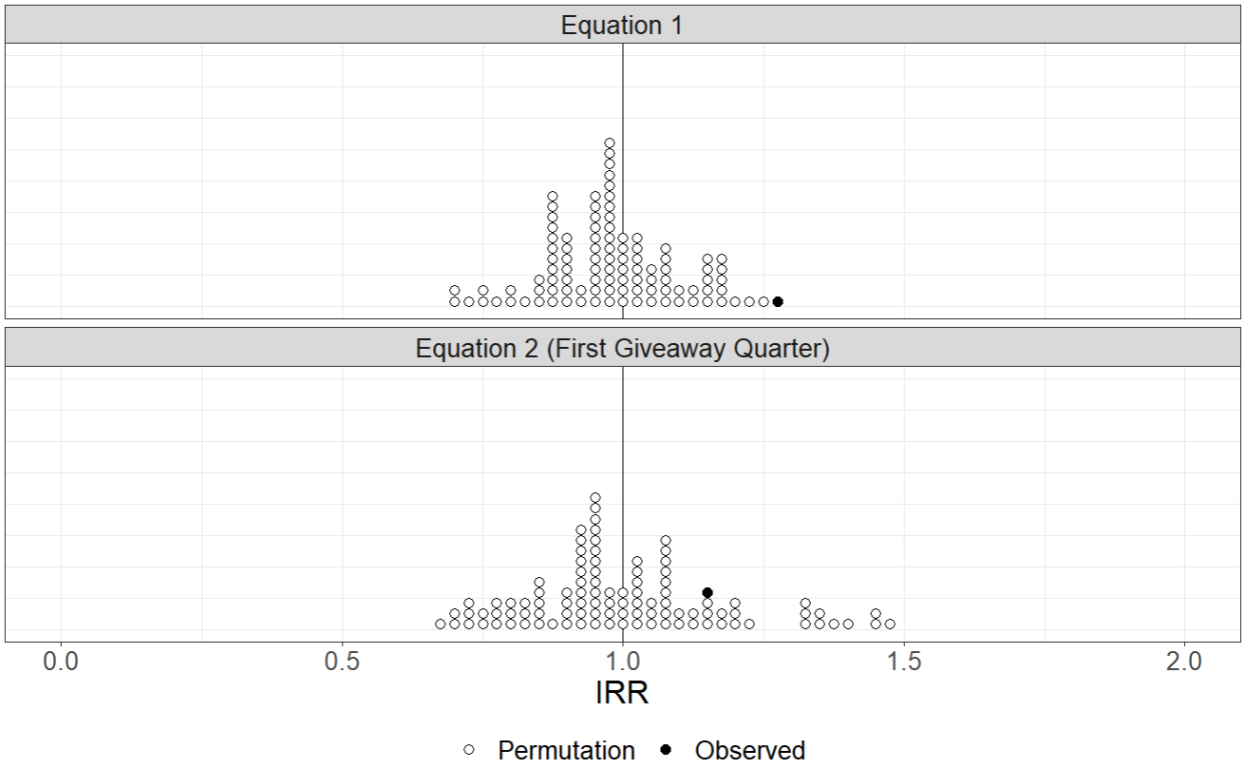
This figure shows incidence rate ratios (IRRs) from a fixed effect Poisson event study regression of Equation 3.2: Census tract-quarter level opioid overdose deaths. The regression controls for Census tract and quarter fixed effects. The treatment group is the same as in the main analysis, but the control group is restricted to Census tracts that are within 3km of distribution locations during the 2019 giveaway. The point represents the coefficient estimate (IRR) and the error bars represent 95% confidence intervals based on standard errors adjusted for clustering at the Census tract level. Tracts with no recorded opioid overdose deaths over the analysis period are excluded.

Figure A3.5. Permutation Test Results for Effect of Naloxone Giveaways on Overdose Deaths, 2018 Giveaway



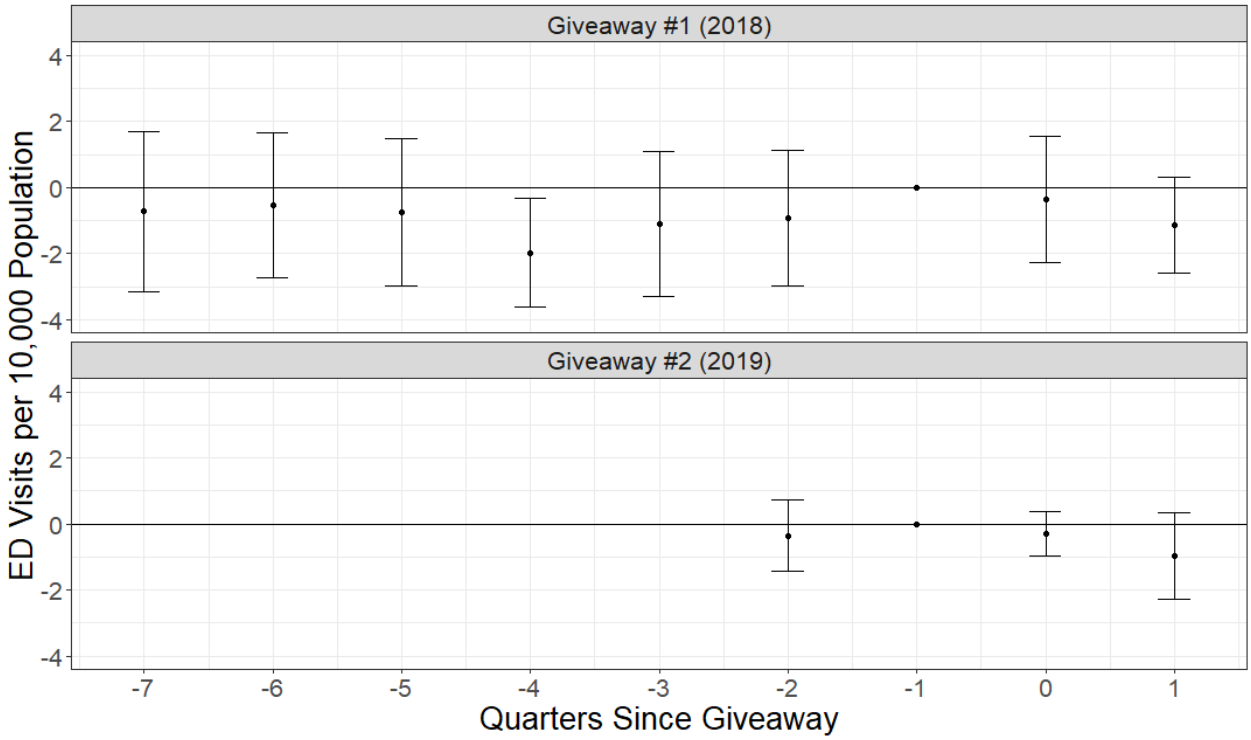
This figure shows results from permutation tests of Equation 3.1 and Equation 3.2 for the opioid overdose death analysis for the 2018 giveaway. Each hollow circle represents one instance of the model run with randomly reshuffled tract treatment assignment. The solid circle represents the observed IRR for the effect estimate from Equation 3.1 and for the first post-giveaway quarter in Equation 3.2.

Figure A3.6. Permutation Test Results for Effect of Naloxone Giveaways on Overdose Deaths, 2019 Giveaway



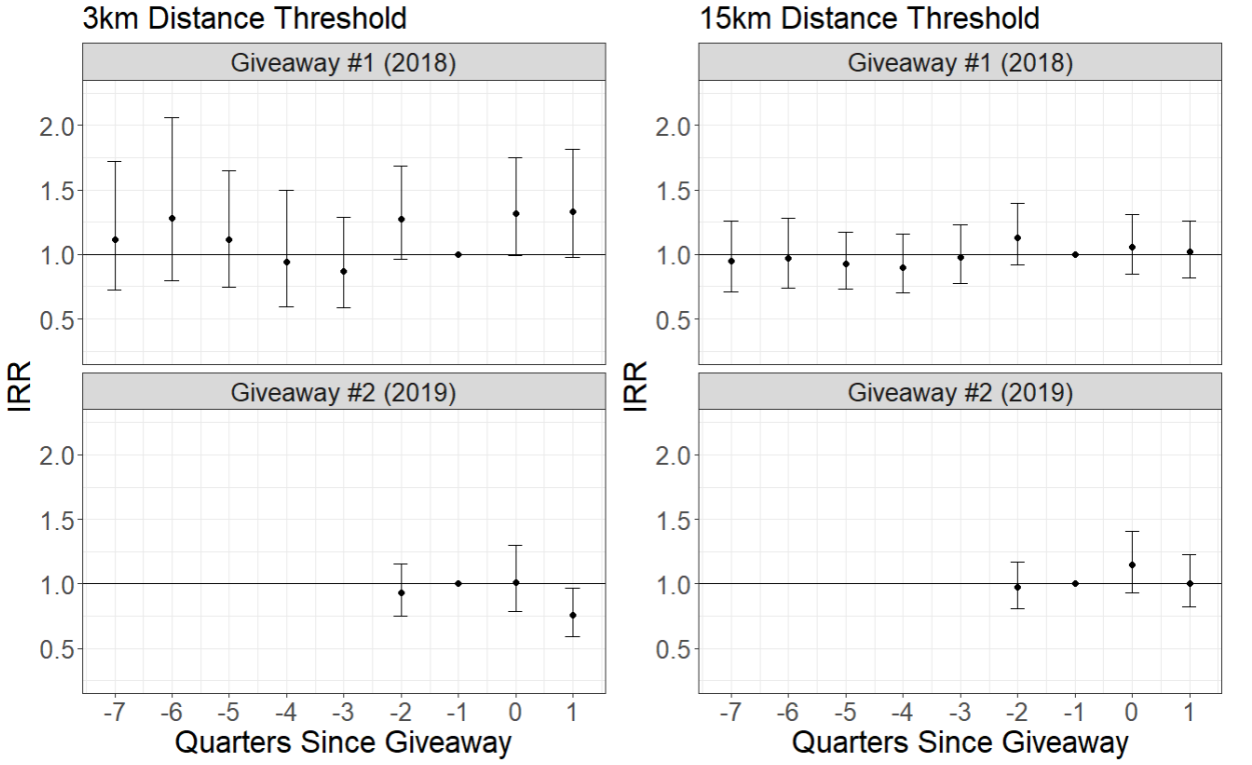
This figure shows results from permutation tests of Equation 3.1 and Equation 3.2 for the opioid overdose death analysis for the 2019 giveaway. Each hollow circle represents one instance of the model run with randomly reshuffled tract treatment assignment. The solid circle represents the observed IRR for the effect estimate from Equation 3.1 and for the first post-giveaway quarter in Equation 3.2.

Figure A3.7. Event Study Estimates for Effect of Naloxone Giveaways on Opioid Overdose-related Emergency Department Visits, Linear Regression



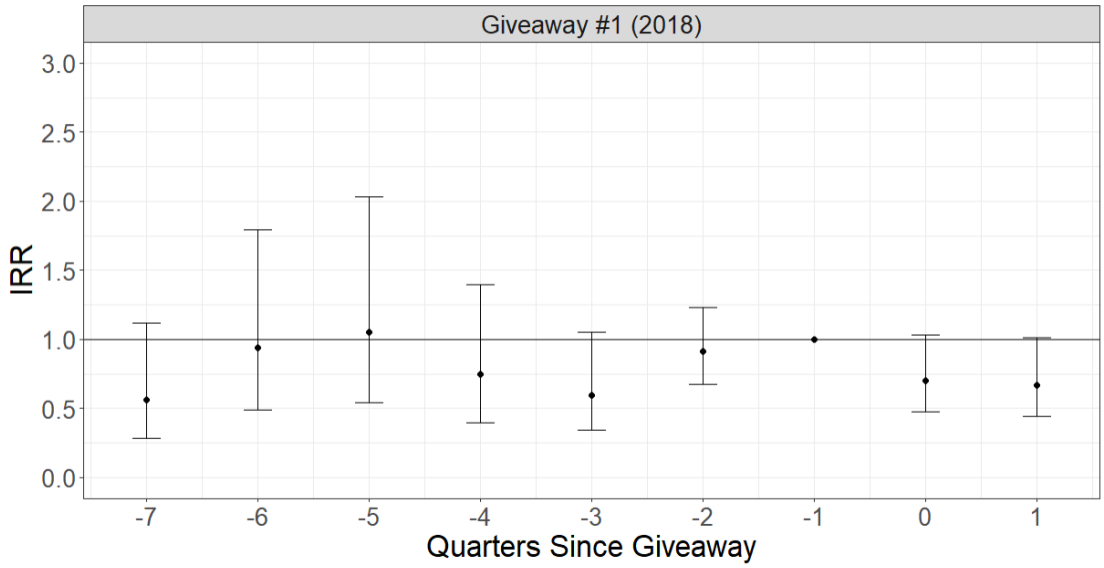
This figure shows effects in emergency department (ED) visits attributable to opioid overdose per 10,000 population from an event study estimated using fixed effects linear regression of Equation 2. The regression controls for ZCTA and quarter fixed effects. The point represents the coefficient estimate and the error bars represent 95% confidence intervals based on standard errors adjusted for clustering at the ZCTA level.

Figure A3.8. Event Study Estimates for Effect of Naloxone Giveaways on Opioid Overdose-related Emergency Department Visits, Rest of State



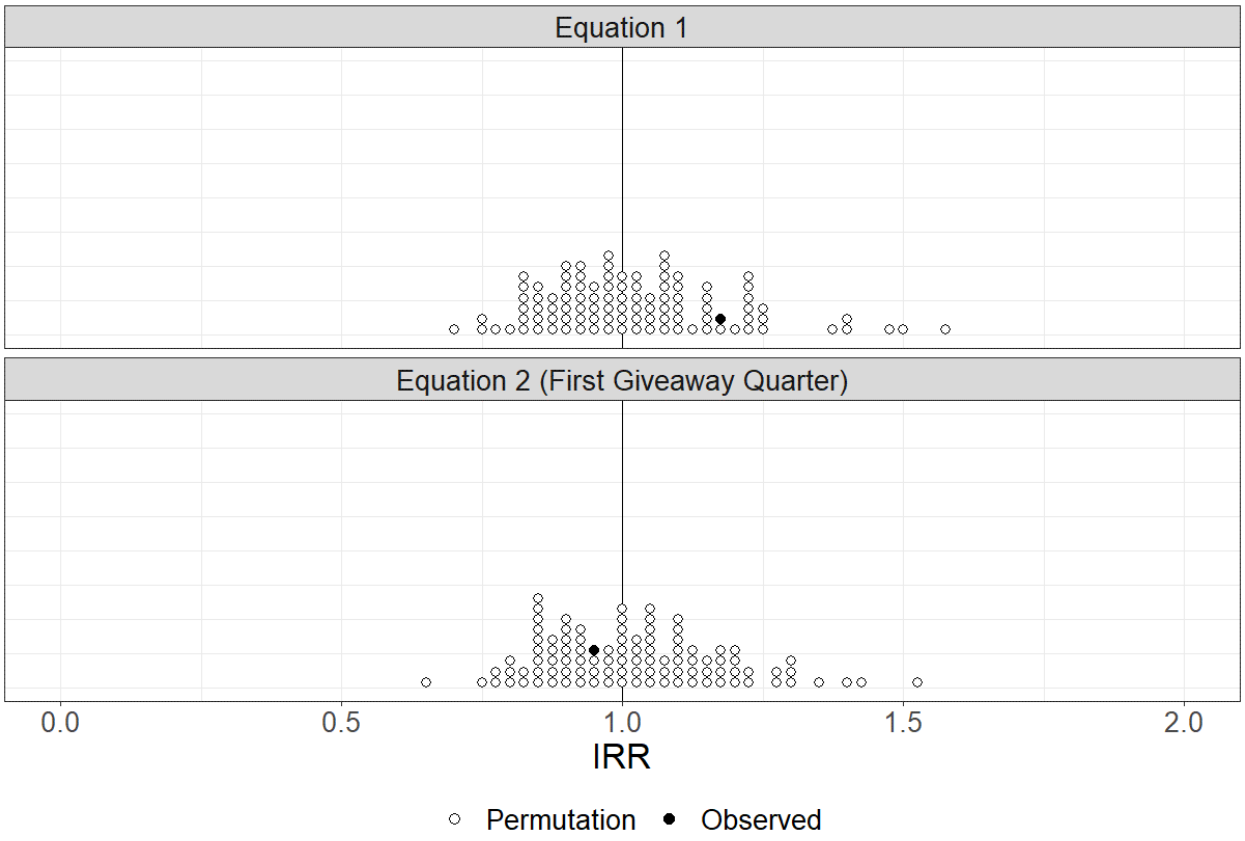
This figure shows incidence rate ratios from a fixed effect Poisson event study regression of Equation 3.2 for ZCTA-quarter level opioid overdose-related ED visits. The regression controls for ZCTA and quarter fixed effects. The point represents the coefficient estimate (IRR), and the error bars represent 95% confidence intervals based on standard errors adjusted for clustering at the ZCTA level. ZCTAs with no recorded opioid overdose-related ED visits over the analysis period are excluded. The left two panels show results using the standard distance threshold used in the main analysis (treated: within 3km of giveaway site; control: between 3km and 10km of a giveaway site) for the 2018 (top) and 2019 (bottom) giveaways, respectively. The right two panels include all ZCTAs within 15km of a giveaway site in the treatment group and all other ZCTAs as controls.

Figure A3.9. Event Study Estimates for Effect of Naloxone Giveaways on Emergency Department Visits, Alternative Control Group



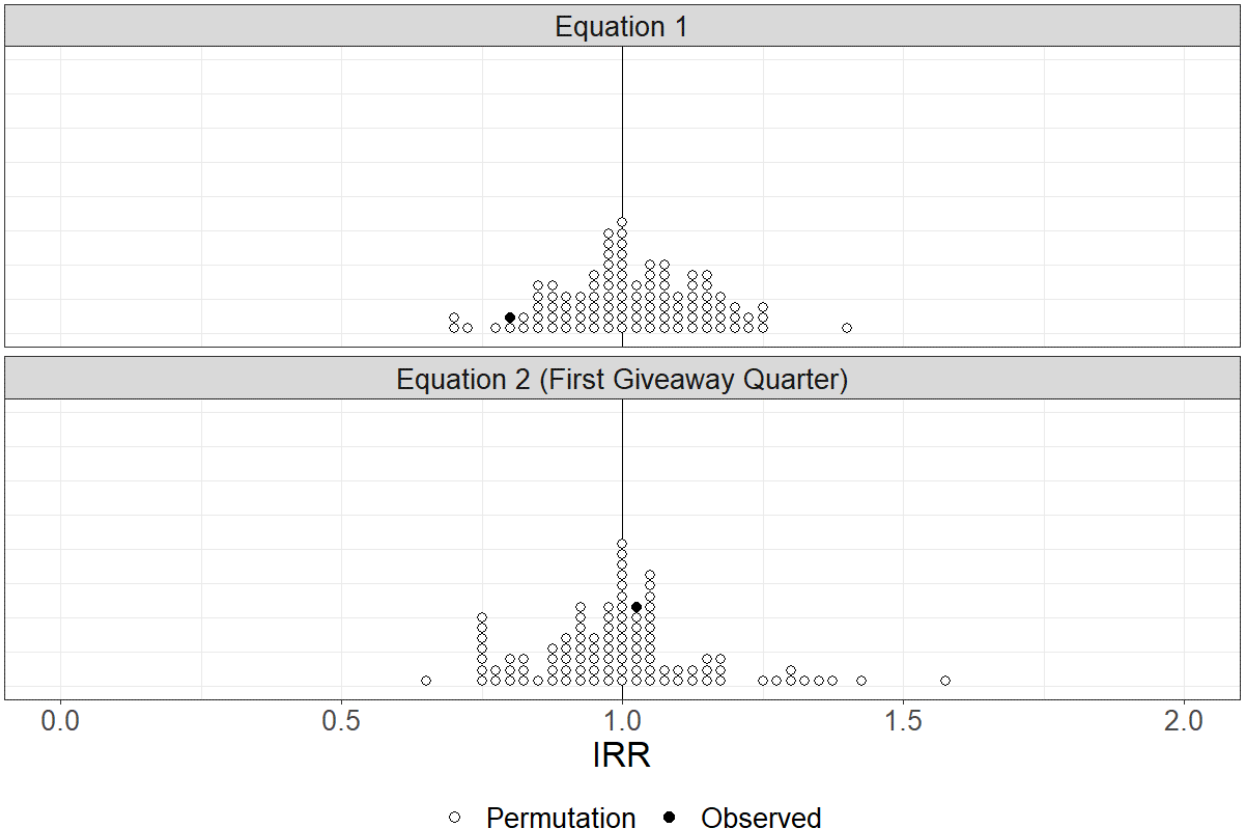
This figure shows incidence rate ratios (IRRs) from a fixed effects Poisson event study regression of Equation 3.2: ZCTA-quarter level emergency department (ED) visits attributable to opioid overdose. The regression controls for ZCTA and quarter fixed effects. The treatment group is the same as in the main analysis, but the control group is restricted to ZCTAs that are within 3km of distribution locations during the 2019 giveaway. The point represents the coefficient estimate (IRR) and the error bars represent 95% confidence intervals based on standard errors adjusted for clustering at the ZCTA level. ZCTAs with no recorded opioid overdose-related ED visits over the analysis period are excluded.

Figure A3.10. Permutation Test Results for Effect of Naloxone Giveaways on Opioid Overdose-related Emergency Department Visits, 2018 Giveaway



This figure shows results from permutation tests of Equation 3.1 and Equation 3.2 for the opioid overdose-related ED visit analysis for the 2018 giveaway. Each hollow circle represents one instance of the model run with randomly reshuffled ZCTA treatment assignment. The solid circle represents the observed IRR for the effect estimate from Equation 3.1 and for the first post-giveaway quarter in Equation 3.2.

Figure A3.11. Permutation Test Results for Effect of Naloxone Giveaways on Opioid Overdose-related Emergency Department Visits, 2019 Giveaway



This figure shows results from permutation tests of Equation 3.1 and Equation 3.2 for the opioid overdose-related ED visit analysis for the 2019 giveaway. Each hollow circle represents one instance of the model run with randomly reshuffled ZCTA treatment assignment. The solid circle represents the observed IRR for the effect estimate from Equation 3.1 and for the first post-giveaway quarter in Equation 3.2.

Appendix Material for Chapter 4

Tables

Table A4.1: Impact Inventory

Sector	Type of Impact	Healthcare Sector	Societal
Formal Healthcare Sector			
Health	*Health outcomes (effects)*		
	Longevity effects	Y	Y
	Health-related quality of life effects	Y	Y
	Other health effects	N	N
	Medical costs		
	Paid for by third party payers	Y	Y
	Paid for by patients out of pocket	Y	Y
	Future related medical costs	Y	Y
	Future unrelated medical costs	Y	Y
Informal Healthcare Sector			
Health	Patient time costs	N/A	Y
	Unpaid caregiver time costs	N/A	N
	Transportation costs	N/A	N
Non-Healthcare Sectors			
Productivity	Labor market earnings lost	N/A	Y
	Cost of unpaid labor market earnings due to illness	N/A	Y
	Cost of uncompensated household production	N/A	Y
Consumption	Future consumption unrelated to health	N/A	Y
Social Services	Cost of social services as part of intervention	N/A	N
Legal or Criminal Justice	Cost of crimes related to intervention	N/A	Y
Education	Impact of intervention on educational achievement of population	N/A	N
Housing	Cost of home improvements, remediation	N/A	N
Environment	Production of toxic waste pollution by intervention	N/A	N
Other	Other impacts (if applicable)	N/A	N

Table A4.2: CHEERS 2022 Checklist

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Chapter title
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	N/A
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction section
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	N/A
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Model Parameters: Population
Setting and location	6	Provide relevant contextual information that may influence findings.	Overview and Model Parameters: Population
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Overview
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Overview
Time horizon	9	State the time horizon for the study and why appropriate.	Overview
Discount rate	10	Report the discount rate(s) and reason chosen.	Overview
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Model Parameters: Costs and Utilities
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Model Parameters: Costs and Utilities
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Model Parameters: Costs and Utilities
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Model Parameters: Costs and Utilities
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Model Parameters: Costs and Utilities
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Model Structure and Figure 1
Analytics and assumptions	17	Describe any methods for analyzing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Model Structure, Model Parameters, and Model Calibration
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Model Parameters: Population

Topic	No.	Item	Location where item is reported
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	N/A
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	Analysis: Sensitivity Analysis
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	N/A
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Model Parameters and Table 1
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarize them in the most appropriate overall measure.	Table 2 and 3
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Results and Figures 4 and 5
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	N/A
Discussion			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	N/A
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	N/A

Note: Generated using https://don-husereau.shinyapps.io/CHEERS/

Table A4.3: Incremental Cost Effectiveness Ratio, Healthcare Perspective, Upper Bound of Intervention Effectiveness

Strategy	Cost	Effect (QALYs)	Incremental Cost	Incremental Effect	ICER
		Five Year Time Horizon			
No Giveaways	$5,417.3M [$5,415.3M–$5,419.3M]	333.7K [333.6K–333.8K]	-	-	-
One Giveaway	$5,419.5M [$5,417.5M–$5,421.4M]	333.9K [333.8K–334.0K]	-	-	Ext. Dom.
Annual Giveaways	$5,421.6M [$5,419.9M–$5,423.6M]	334.1K [334.0K–334.2K]	$4.3M	381.5	$11,277
Quarterly Giveaways	$5,428.5M [$5,426.7M–$5,430.7M]	334.5K [334.4K–334.6K]	$6.9M	465.9	$14,829
		Ten Year Time Horizon			
No Giveaways	$8,860.7M [$8,854.6M–$8,865.8M]	584.0K [583.5K–584.4K]	-	-	-
One Giveaway	$8,864.6M [$8,858.6M–$8,869.5M]	584.3K [583.8K–584.7K]	-	-	Ext. Dom
Annual Giveaways	$8,870.2M [$8,864.5M–$8,874.8M]	584.7K [584.2K–585.1K]	$9.4M	711.9	$13,249
Quarterly Giveaways	$8,884.9M [$8,879.9M–$8,889.2M]	585.7K [585.2K–586.2K]	$14.7M	993.3	$14,782

Table A4.4: Incremental Cost Effectiveness Ratio, Healthcare Perspective, Lower Bound of Intervention Effectiveness

Strategy	Cost	Effect (QALYs)	Incremental Cost	Incremental Effect	ICER
		Five Year Time Horizon			
No Giveaways	$5,417.4M [$5,415.6M–$5,419.7M]	333.7K [333.6K–333.8K]	-	-	-
One Giveaway	$5,418.7M [$5,416.8M–$5,420.9M]	333.7K [333.5K–333.8K]	-	-	Dom.
Annual Giveaways	$5,420.7M [$5,418.4M–$5,422.8M]	333.6K [333.5K–333.7K]	-	-	Dom.
Quarterly Giveaways	$5,431.0M [$5,427.9M–$5,434.2M]	333.8K [333.7K–334.0K]	$13.6M	126.6	$107,418
		Ten Year Time Horizon			
No Giveaways	$8,860.8M [$8,856.3M–$8,867.0M]	584.0K [583.5K–584.4K]	-	-	-
One Giveaway	$8,861.2M [$8,856.6M–$8,867.5M]	583.9K [583.4K–584.3K]	-	-	Dom.
Annual Giveaways	$8,862.2M [$8,857.8M-$8,868.5M]	583.7K [583.1K–584.3K]	-	-	Dom.
Quarterly Giveaways	$8,875.2M [$8,870.7M–$8,881.3M]	584.1K [583.3K–584.7K]	$14.5M	76.1	$189,936

Table A4.5: Incremental Cost Effectiveness Ratio, Societal Perspective, Upper Bound of Intervention Effectiveness

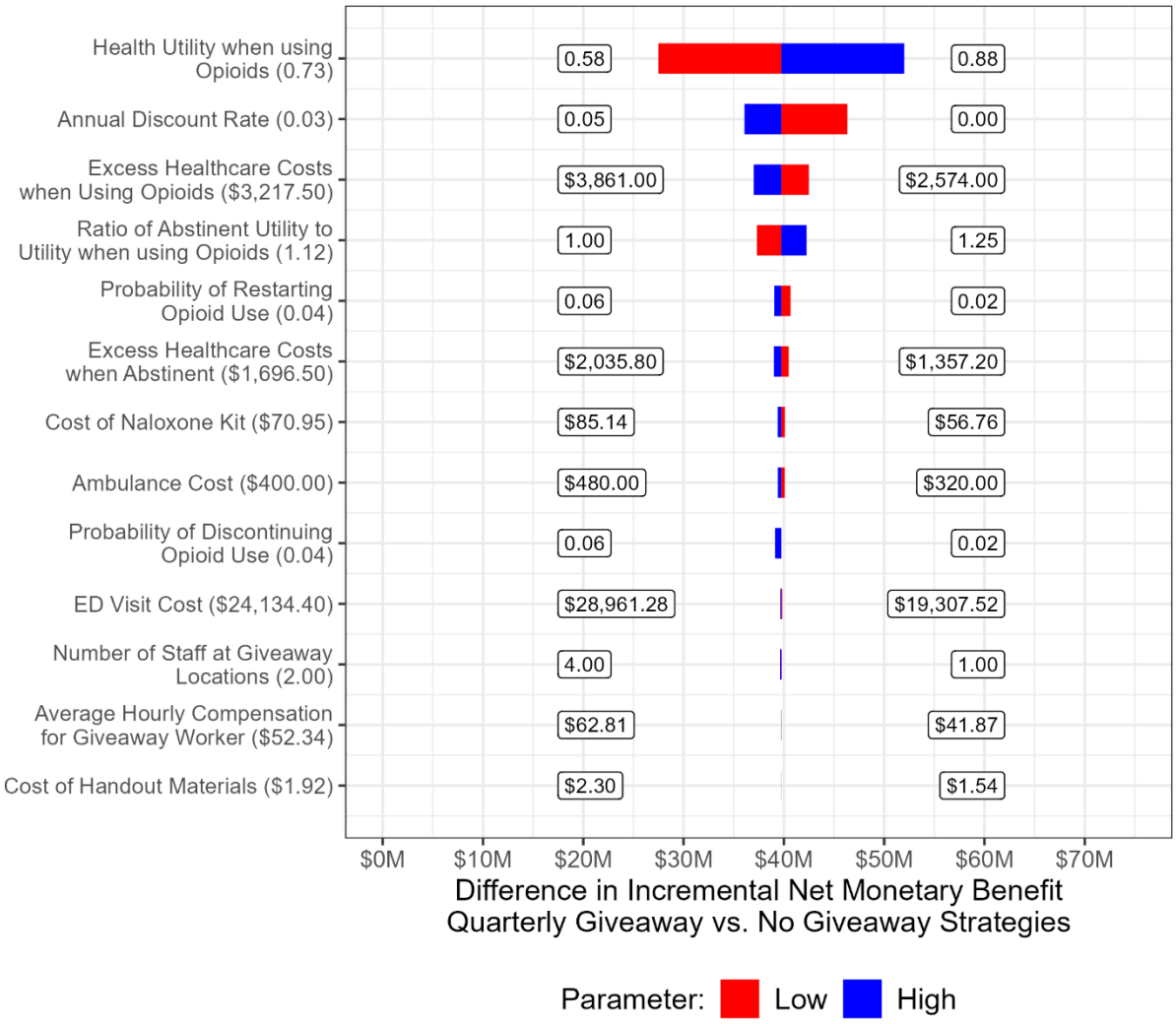
Strategy	Cost	Effect (QALYs)	Incremental Cost	Incremental Effect	ICER
Five Year Time Horizon					
Quarterly Giveaways	-$5,556.4M [-$5,561.1M–-$5,550.7M]	334.5K [334.4K–334.6K]	-	-	-
Annual Giveaways	-$5,548.4M [-$5,552.9M–-$5,543.3M]	334.1K [334.0K–334.2K]	-	-	Dom.
One Giveaway	-$5,544.0M [-$5,548.5M–-$5,539.5M]	333.9K [333.8K–334.0K]	-	-	Dom.
No Giveaways	-$5,540.3M [-$5,545.1M–-$5,536.0M]	333.7K [333.6K–333.8K]	-	-	Dom.
Ten Year Time Horizon					
Quarterly Giveaways	-$11,814.6M [-$11,827.0M–-$11,798.5M]	585.7K [585.2K–586.2K]	-	-	-
Annual Giveaways	-$11,793.8M [-$11,806.6M–-$11,779.2M]	584.7K [584.2K–585.1K]	-	-	Dom.
One Giveaway	-$11,784.1M [-$11,797.0M–-$11,769.9M]	584.3K [583.8K–584.7K]	-	-	Dom.
No Giveaways	-$11,777.3M [-$11,790.6M–-$11,764.3M]	584.0K [583.5K–584.4K]	-	-	Dom.

Table A4.6: Incremental Cost Effectiveness Ratio, Societal Perspective Lower Bound of Intervention Effectiveness

Strategy	Cost	Effect (QALYs)	Incremental Cost	Incremental Effect	ICER
Five Year Time Horizon					
No Giveaways	-$5,539.8M [-$5,545.2M–-$5,535.9M]	333.7K [333.6K–333.8K]	-	-	-
One Giveaway	-$5,536.7M [-$5,542.4M–-$5,531.7M]	333.6K [333.5K–333.8K]	-	-	Dom.
Annual Giveaways	-$5,533.2M [-$5,539.9M–-$5,527.4M]	333.6K [333.5K–333.7K]	-	-	Dom.
Quarterly Giveaways	-$5,528.6M [-$5,537.6M–-$5,518.7M]	333.8K [333.7K–334.0K]	$11.2M	126.6	$88,390
Ten Year Time Horizon					
No Giveaways	-$11,776.1M [-$11,789.8M–-$11,764.3M]	584.0K [583.5K–584.4K]	-	-	-
One Giveaway	-$11,771.0M [-$11,785.5M–-$11,757.7M]	583.9K [583.4K–584.3K]	-	-	Dom.
Annual Giveaways	-$11,764.9M [-$11,781.4M–-$11,748.8M]	583.7K [583.1K–584.3K]	-	-	Dom.
Quarterly Giveaways	-$11,763.7M [-$11,784.9M–-$11,739.7M]	584.1K [583.3K–584.7K]	$12.4M	76.1	$163,570

Figures

Figure A4.1. One-way Sensitivity Analysis, Healthcare Perspective, Ten-Year Time Horizon



List of Acronyms and Abbreviations

Abbreviation	Definition
ACS	American Community Survey
ATT	Average Treatment Effect on the Treated
CDC	Centers for Disease Control
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence Interval
CS	Callaway and Sant'Anna Estimator
ED	Emergency Department
ELC	Expected Loss Curve
EMS	Emergency Medical Services
EQ-5D	EuroQoL Group Five-Dimensional Quality of Life Scale
ICD	International Classification of Diseases
ICER	Incremental Cost-Effectiveness Ratio
INMB	Incremental Net Monetary Benefit
IRR	Incidence Risk Ratio
MME	Morphine Milligram Equivalents
MOUD	Medication for Opioid Use Disorder
MSA	Metropolitan Statistical Area
NAL	Naloxone Access Law
NMB	Net Monetary Benefit
NSDUH	National Survey on Drug Use and Health
ODIN	Overdose Information Network
OEND	Overdose Education and Naloxone Distribution
OLS	Ordinary Least Squares
OUD	Opioid Use Disorder
OWSA	One-way Sensitivity Analysis
PA	Pennsylvania
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Year
RDiT	Regression Discontinuity in Time
REML	Restricted Maximum Likelihood
RR	Relative Risk
SF-12	12-item Short Form Survey
SSP	Syringe Services Program
WONDER	Wide-ranging Online Data for Epidemiologic Research
WTP	Willingness to Pay
ZCTA	ZIP Code Tabulation Area

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