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Effect of the New York City Overdose Prevention Program on Unintentional Heroin-related Overdose Death, 2000-2012

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Effect of the New York City Overdose Prevention Program on Unintentional Heroin-related Overdose Death, 2000-2012

by

Anne Siegler

A dissertation submitted to the Graduate Faculty in Public Health in partial fulfillment of the requirements for the degree of Doctor of Public Health, The City University of New York

2015

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**This manuscript has been read and accepted for the
Graduate Faculty in Public Health in satisfaction of the dissertation
requirement for the degree of Doctor of Public Health.**

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Abstract

Effect of the New York City Overdose Prevention Program on Unintentional Heroin-related Overdose Death, 2000-2012

by

Anne Siegler

Advisor: Nancy Sohler

Background: Drug overdose mortality is the leading cause of injury death in both the United States (US) and New York City (NYC). Heroin-related overdoses make up the majority of overdoses in NYC. Since 2006, when a law was passed that allowed for layperson administration of naloxone, an opioid antagonist, heroin-related overdose deaths have decreased in NYC. No studies to date have investigated a possible association between the implementation of this intervention and heroin-related overdose mortality.

Objectives: To investigate the possible association between overdose prevention programs (OPPs) and heroin-related overdose mortality in NYC, using interrupted time series and geospatial analytic techniques.

Methods: Using surveillance of NYC accidental drug poisoning deaths (2000-2012), a demographic profile of heroin-related overdose deaths was described prior to implementation of OPP (January 2000 – June 2006) and after implementation (July 2006 – December 2012). Interrupted time series (ITS) analyses tested for a difference in level and trend of heroin-related mortality, comparing the post-OPP period with the pre-OPP period, for NYC as a whole. Geospatial patterns of heroin-related overdose mortality were described before and after

implementation of OPP. After mapping OPP sites, NYC neighborhoods were stratified by naloxone penetration level, and using multivariable regression, we tested the hypothesis that neighborhoods with greater naloxone penetration experienced steeper declines in heroin-related overdose mortality, after controlling for neighborhood characteristics. We calculated street walking distance from the OPP to the location of each overdose fatality in one neighborhood, the Lower East Side of Manhattan, to test the hypothesis that risk increases with increasing distance. We mapped overdose rate by census tract and conducted Poisson regression.

Results: 2,142 heroin-related overdose deaths occurred in the 6.5 years prior to implementation of NYC's OPP, and 1,764 occurred in the 6.5 years after implementation, representing a 22.4% reduction in the age-adjusted mortality rate. We found, using ITS, that the level of heroin-related overdose mortality decreased by 16% (not statistically significantly different from no decrease) following implementation. When analyses were limited to only those parts of NYC with OPP, we found that neighborhoods with greatest OPP penetration saw greater decreases in overdose mortality rates, compared to neighborhoods without OPPs (-3.1 compared with -0.8). In the Lower East Side, we found that census tracts located furthest from the OPP had statistically significantly higher overdose mortality rates compared with census tracts closer to the OPP. The census tract where the OPP was located experienced the greatest decrease in heroin-related overdose death from pre-OPP to post (from 7.8 to 1.31 per 100,000 population). An individual is 1.22 times more likely to die from a heroin overdose for every 1,000 feet away from the OPP ($p=0.0002$).

Conclusions: While time series analysis of NYC as a whole did not find a statistically significant change in the level of heroin-related overdose mortality after implementation of OPP, when OPP locations were geocoded, only one-third of NYC neighborhoods had any OPP in the six years following implementation. In analyses limited to those neighborhoods of NYC with OPPs, we found statistically significant associations between OPP and heroin-related overdose mortality risk. This suggests that OPP may be contributing to decreased heroin-related overdose mortality in NYC.

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Chapter 1: Introduction

1.1. Overdose Mortality in the United States and New York City

1.1.1. Overdose Mortality in the United States

Drug overdose is an important contributor to morbidity and mortality in the United States (US). Since 1990, rates of drug overdose death have more than tripled.¹ It is now the leading cause of injury death in the US, killing more people each year than motor vehicle traffic crashes.² While rates of opioid analgesic-related overdose mortality are nearly double that of heroin-related overdose mortality (5.1 per 100,000 opioid analgesic-related deaths in 2013, compared to 2.7 per 100,000 heroin-related deaths), recent years have seen an increase in the rate of heroin-related overdose deaths, while opioid analgesic mortality has levelled. Rates of heroin-related overdose mortality has nearly quadrupled since 2000, and most of that increase occurred since 2010.³ Males and non-Hispanic whites aged 18-44 had the highest heroin-related overdose mortality rates. Additionally, nonfatal drug overdose results in a large number of emergency department visits each year. About 830,000 emergency department visits annually are due to drug poisonings, including those that involve opioids, in the US.⁴

1.1.2. Overdose Mortality in New York City

Rates of heroin-related overdose (OD) death are higher in the Northeast of the US compared with southern and western parts of the US,³ and New York City (NYC) is an extreme example, where drug overdose is now the third leading cause of premature death.⁵ The Northeast reported 3.9 heroin-related overdose deaths per 100,000 in 2013 (a three-fold increase since 2007), while NYC reported a rate of 6.2 per 100,000. This rate has risen consistently for the last three years

after four years of consecutive decreases.⁶ Unlike other places, NYC experiences more ODs involving heroin, which is involved in 54% of all fatal ODs, than opioid analgesics, which are involved in 27%. Consistent with national trends, non-Hispanic white New Yorkers, males, and individuals aged 15-34 reported the highest rates of heroin-related overdose mortality. Fatal ODs represent the tip of the iceberg; non-fatal overdoses result in approximately 47,000 emergency departments visits annually in NYC alone.⁷

1.1.3. Opioid Overdose Risk

More than one hundred observational studies have been published exploring fatal and nonfatal opioid overdose risk, most employing cohort designs, mortality record review, or cross-sectional survey analysis. More than 20 risk factors have been studied, including sociodemographic characteristics (age, gender, race, socioeconomic status (SES)), comorbidities (HIV, HCV, mental illness), indicators of risk-taking behavior (criminal justice involvement, sexual risk-taking, polydrug use, history of previous overdose), and neighborhood effects (drug availability, police activity, neighborhood SES). Though no systematic review has been performed, the following factors emerge to suggest an association with opioid overdose risk: periods of abstinence, including incarceration⁸⁻¹² and drug treatment,¹³⁻¹⁵ followed by a return to use; lack of engagement in opioid replacement therapy;^{16,17} injecting opioids;^{12,14,18} use of benzodiazepines and/or alcohol with opioids;¹⁹⁻²³ mental illness;²⁴ HIV^{14,25} and HCV infection;^{12,22} history of prior overdose;^{18,24,26} and availability and use of opioids.²⁷

The following factors have not been found to be associated with opioid overdose risk: sexual orientation;^{11,22,28} housing status;^{11,22,28} health-related quality of life;²¹ and sexual risk-taking.^{21,22}

1.1.4. Evidence-based Interventions to Reduce Opioid Overdose

While recent studies have begun to assess the relationship between overdose risk and population-level interventions, such as prescription drug monitoring programs,²⁹⁻³¹ most studies to date have only assessed the effectiveness of individual-level programmatic interventions geared towards reducing opioid overdose risk. These primary prevention interventions, which are designed to “delay or prevent either the initiation of drug use or the probability of progressing from experimentation to regular use,” can be contrasted with secondary prevention interventions, which aim to “reduce drug use and/or its consequences among experienced drug users.”³² Secondary prevention interventions that aim to reduce opioid overdose risk include psychosocial, behavioral, and educational interventions. Medication-assisted interventions are those which provide naloxone hydrochloride to individuals at risk of opioid overdose and their social networks.

1.2. Overdose Prevention Programs

Overdose prevention programs are community-based programs that target individuals at risk of opioid overdose and their social networks.³³⁻³⁵ The first was in 1996.³⁴ Curricula typically include recognizing overdose, preventing overdose, discussing risk factors for overdose, teaching the appropriate response to overdose, and explaining how to administer naloxone.³⁶ These programs prescribe and dispense two doses of naloxone in an “overdose rescue kit” for use at a future overdose as a first-aid response to opioid overdose in the community setting. Trainings last from 10 minutes to one hour and are located in a variety of settings, including syringe access programs, drug treatment programs and other community-based organizations (CBOs), as well as outdoors and on street corners where drug users congregate. Trainings are usually facilitated by

health educators or other CBO staff, and naloxone is prescribed and dispensed by a physician assistant, nurse practitioner, or medical doctor.³⁷ Nearly 200 such programs around the US are operational, and since 1996 they have dispensed naloxone to over 53,000 individuals and reported over 10,000 reversals.³⁴

There are no meta-analyses of OPP studies, though one systematic review of 19 studies was recently published.³⁶ The review was unable to determine the overall effectiveness of OPPs, however, and reported that the overall quality of the studies was fair, with substantial methodological problems.³⁶ Follow-up was infrequent, and often only among those who returned for clinical services. Study periods were often short, and sample sizes were small. No studies used randomized designs. The review did find, however, that participation in OPPs was associated with overdose reversals, as well as with increased knowledge and ability to respond to an opioid overdose and to administer naloxone.

Only one study to date has assessed the relationship between OPPs and overdose mortality at the population level. This study used interrupted time series (ITS) and found that, in Massachusetts, communities that had implemented OPPs had lower rates of overdose death compared to communities without OPPs.³⁸ (One other study has been published that suggests population-level changes; however, no outside factors were controlled for and detailed analysis was provided).³⁹

1.3. Gaps in the Current Literature

While studies suggest that OPPs improve individuals' knowledge of overdose risk and their ability to respond to an overdose, there is a lack of systematic testing of the effectiveness of the intervention. The recently published systematic review (described above) reported that “well-designed studies are needed to evaluate the extent to which [OPPs] reduce drug-related morbidity and mortality... and determine the population-level benefits of [OPPs].”³⁶

The one study assessing the relationship between OPPs and overdose mortality at the population level was an interrupted time series analysis that suggested that OPPs in Massachusetts are associated with reduced opioid overdose mortality rates.³⁸ The evidence of these benefits of OPPs would be strengthened if studies found similar evidence in other settings as well. We believe replication of these findings in NYC would be particularly interesting because of the differences between Massachusetts and NYC. For example, the laws and regulations that allow for prescription of naloxone to trained laypersons are different, and allow for standing orders and non-clinical dispensing of naloxone in Massachusetts, while in New York until 2014, naloxone could only be prescribed by medical doctors, physician assistants, and nurse practitioners, making access less widely available. The Massachusetts study evaluated the effects of naloxone across 19 communities, many of which are less urban, less densely populated, and have a lower prevalence of injection drug use than NYC. A study specific to NYC would be of value to ascertain the effectiveness of naloxone in an urban center where naloxone may be less widely available but the population is denser and incidence of drug overdose is greater.

In NYC, heroin-related overdose deaths decreased steadily each year following the implementation of the OPP, in 2006, until 2010. No studies have determined the cause of this decrease though a number of outside factors could possibly explain the declining rates: decreased rates of heroin use, particularly if there was a shift to opioid analgesic use; increased access to and utilization of medication-assisted therapy such as methadone and buprenorphine; decreased prevalence of loss of tolerance due to incarceration or detoxification; decreased prevalence of polydrug use, such as benzodiazepine or alcohol use with heroin. Several changes occurred in NYC while overdose prevention was implemented. A timeline of key policy events during the study period that could have influenced overdose mortality is found in Appendix I.

I hypothesize that implementation of NYC's OPP was causally associated with the decrease in heroin-related overdose mortality beginning in 2006. Employing a population-level analysis of the relationship between this intervention and overdose mortality in NYC could help determine the intervention's effectiveness and inform policy, both in NYC and nationally.

1.4. Overview of the Dissertation

1.4.1. Overall Goals

While small-scale evaluations of NYC's overdose prevention program have been conducted,⁴⁰⁻⁴² no study has evaluated the population-level effects of the intervention on overdose mortality. The proposed dissertation will address this gap by examining the overdose prevention program in NYC at the population level.

This dissertation repeats the Massachusetts methodology in the NYC context, using interrupted time series analysis, to evaluate intervention effects over time. Then, the dissertation adds a novel analysis by employing spatial statistics to describe the program and its effectiveness across neighborhoods, hypothesizing that those neighborhoods that experienced more overdose prevention programming saw steeper declines in heroin-related mortality after controlling for other neighborhood-level differences.

Last, the dissertation zooms in to a specific neighborhood in Manhattan, the Lower East Side (LES). The Lower East Side Harm Reduction Center (LESHRC) has the longest-running overdose prevention program in the city, which has been described elsewhere in the literature.⁴⁰ The LES is home to a population representative of New Yorkers overall; mortality and premature mortality rates, proportion of residents by age, living in poverty, foreign-born, White, Hispanic, without health insurance, and proportion of people who report fair or poor health, mental illness, and serious psychological distress are all similar to that of NYC overall.⁴³ The rate of drug-related deaths and drug-related hospitalizations are also similar to those of NYC as a whole.⁴³ Using a method tested in Vancouver, a spatial analysis will describe risk of overdose mortality as a function of distance from a naloxone dispensing site and test the hypothesis that risk of heroin-related overdose increases with distance from the overdose prevention program.⁴⁴

This study uses robust toxicology data to isolate the targeted population by looking only at heroin-specific mortality. Data such as these, which are only available by matching death certificates to medical examiner records, are rarely available in other jurisdictions, and will offer

this study a more targeted study population, as well as allow for the controlling of other substances contributing to the overdose.

Conducting both a time series analysis as well as a geospatial analysis, each controlling for confounders that could alternatively explain the decrease in heroin-related overdose mortality rate, together can build a case for a causal association between NYC's opioid overdose prevention program and decreased risk for heroin-related overdose mortality.

Evidence of a protective effect could be used to shape policy and direct resources towards OD prevention interventions in NYC as well as other cities affected by opioid overdose. Because these programs are some of the most promising interventions to address the growing burden of overdose mortality, they may prove a crucial element to reversing the current national mortality trends.

1.4.2. Specific Aims

Aim 1. Describe the average rate of heroin-related overdose mortality in NYC in the seven years preceding the implementation of the NYC overdose prevention program (OPP) (2000- June 2006) and the six years following the implementation of the OPP (July 2006-2012), and test one hypothesis.

A descriptive analysis was conducted to assess the rate of heroin-related overdose deaths at the city level, before and after implementation of OPP.

Hypothesis 1. Implementation of the OPP in 2006 reduced the rate of heroin-related overdose mortality, after accounting for factors other than the OPP that might explain temporal change in overdose mortality, between 2000 and 2012.

To assess the effect of the intervention over time while controlling for other factors, interrupted time-series (ITS) analysis was conducted using segmented regression. The exposure was the NYC OPP and the outcome was the number of unintentional drug poisoning deaths involving heroin. The unit of analysis was six-month intervals.

The intervention was evaluated using segmented regression to assess (a) a change in level immediately after the intervention is implemented, and (b) a change in slope from the pre-intervention period to the post-intervention period.⁴⁵ The level and trend of the outcome prior to the intervention served as a comparison to the level and trend of the outcome after the intervention was implemented.⁴⁶

Aim 2. Describe geospatial patterns of heroin-related overdose mortality before (2000-2006) and after (2007-2012) the implementation of OPP, and test two hypotheses.

To analyze the effect of the intervention using spatial statistics, the locations of the outcome were geocoded and maps were created to detect visual trends in the spatial distribution of the data, a process known as exploratory spatial data analysis (ESDA). Choropleth maps were

created for two time periods, one aggregating years 2000 to 2006, and a second aggregating years 2007 to 2012, to represent the magnitude of overdose mortality within each neighborhood.

Clusters of overdose in space were detected with SaTScan™, a software program, using the geocoded locations of heroin-related deaths. SaTScan™ “performs geographical surveillance... to detect spatial...disease clusters and [assesses] if they are statistically significant” and tests whether overdoses are randomly distributed over space.⁴⁷ Overdose clusters that were significantly elevated with respect to all of NYC, as a reference, were mapped.

Hypothesis 2. The reduction in heroin-related overdose mortality rate between the seven years preceding the implementation of the OPP (2000-2006) and the six years following its implementation (2007-2012) was greater in NYC neighborhood tabulation areas in which the OPP was implemented compared with neighborhood tabulation areas in which no OPP was implemented.

Overdose prevention programs were implemented more heavily in some neighborhoods of NYC and less heavily or not at all in others. If all NYC neighborhoods are analyzed as a whole, the effects of the intervention will be diluted by those neighborhoods that did not experience the intervention. In order to address this issue, neighborhoods were organized into four strata: no, low, medium, and high naloxone penetration, a score compiled by summing naloxone doses shipped. This approach allowed for the detection of a potential dose-response relationship between the intervention and its effects. A similar approach was used in the previously mentioned Massachusetts study.³⁸

In order to control for differences in neighborhoods, multivariable regression was conducted, using the following neighborhood-level characteristics: proportion of the neighborhood population that identifies as White and non-White, proportion over age 60, proportion female, proportion of single-person households, and persons per acre. A final fitted regression model was used to predict heroin-related mortality risk by neighborhood tabulation area.

Hypothesis 3. Within the neighborhood of an OPP at a community-based organization in the Lower East Side of Manhattan, risk of heroin-related overdose death increases with increasing distance from a naloxone dispensing site.

The Lower East Side's OPP piloted the overdose prevention initiative beginning in 2004, prior to the passage of the state Opioid Overdose Prevention law. The program has dispensed 2,478 doses of naloxone in 2004-2012. To assess the effect of distance from naloxone dispensing locations on heroin-related poisoning risk, the street network distance was measured from location of each overdose fatality to LESHRC, where naloxone doses were dispensed. During this time period, LESHRC was the largest distributor of naloxone for the Lower East Side neighborhood. Years 2000-2003 (before the program began dispensing naloxone) and 2004-2012 (when the program was actively dispensing naloxone) were aggregated, and risk of overdose death was estimated by calculating the sum of OD deaths that occurred in each census tract by the population of that census tract. Choropleth maps were produced, and the rate of overdose death was plotted against distance to the OPP.

1.4.3. Organization of the Dissertation

The dissertation consists of four subsequent chapters. Chapter 2 (Aim 1, Hypothesis 1) describes heroin-related overdose mortality in NYC as a whole in the years prior to OPP implementation (January 2000 - June 2006) and the years since OPP implementation (July 2006 – December 2012). It then evaluates the intervention temporally, using interrupted time series analysis to assess the relationship between the passage of the OPP law in 2006 and the change in level and slope of heroin-related overdose mortality in NYC. Chapter 3 (Aim 2, Hypothesis 2) evaluates the intervention spatially by comparing NYC neighborhoods with the intervention to those neighborhoods without the intervention. This chapter employs three geospatial analytic tools: mapping, cluster detection, and regression. Chapter 4 (Aim 2, Hypothesis 3) investigates one particular neighborhood in NYC, the Lower East Side, to test the hypothesis that overdose risk is a function of distance from the intervention site. Chapter 5 summarizes the key findings from Chapters 2 through 4, discusses overall strengths and limitations, and provides suggestions for future research. It concludes with implications for policy in NYC and nationally.

1.4.4. Significance of the Dissertation

New York City is one of a limited number of jurisdictions to dispense naloxone to non-medically trained community members at risk of opioid overdose and was one of the first to begin doing so. As such, it now has one of the largest and most mature overdose prevention initiatives in the US. Increasingly other areas of the United States, both urban and rural, are beginning to experience opioid overdose burden and will be exploring interventions to curb this trend. While NYC is unique in many ways, such as its dense population and the scale and history of the drug trade and use, lessons learned from this inquiry will have applicability to other areas of the United States

impacted by opioid overdose epidemics. To date, only one study has evaluated the effects of this intervention over time at the population level and took place in Massachusetts.³⁸ This study would replicate the methods of that study in the NYC context, and add to it by exploring the effects of the intervention spatially. Lessons learned could be used to direct NYC policy and resources, as well as those in other cities and states.

1.5. Study Population and Data Sources

1.5.1. Study Population

Because this is an ecologic study, the study population is the population of New York City from 2000 to 2012. The exposure is the overdose prevention intervention. This intervention includes both a short educational component and the dispensation of two doses of naloxone to each trained responder, either in an intramuscular or intranasal formulation. For the purposes of this study, the intervention will be quantified by the doses of naloxone dispensed in NYC during the study period, from the program's pilot beginning in 2004 in one neighborhood, its legalization and implementation in 2006 to the study end, 2012, the most recent year for which mortality data is available.

1.5.2. Data Sources

Measures of the overdose prevention program are estimated using a proxy: the number of naloxone doses shipped to each of the NYC overdose prevention programs from the suppliers. During the study period, over 55,000 doses of naloxone were shipped in NYC. Data on naloxone doses shipped comes from two administrative datasets at these suppliers: the New York State Department of Health - AIDS Institute (via their supplier AmFAR) and the NYC

Department of Health and Mental Hygiene (DOHMH) Bureau of Alcohol and Drug Use Prevention, Care and Treatment.

Overdose mortality data came from an ongoing, surveillance database of unintentional drug poisoning deaths comprised of two linked data sources: death certificates and medical examiner records. This database is housed and the sources are linked at DOHMH. This dataset is a complete record of all unintentional overdose deaths in New York City in 2000-2012. The NYC Office of the Chief Medical Examiner is responsible for investigating all deaths believed to be homicides, suicides or accidents; deaths of a suspicious unnatural nature; and deaths not attended by a physician. Drug overdose deaths usually fall within these parameters. Thus the study sample is a near census of the population of overdose decedents in NYC during this time period. Detailed toxicological results enabled this study to stratify deaths by drug type, and limit the sample to those deaths where heroin was involved. The dataset has detailed geographic information, including the address of the location of where the overdose occurred. This granular-level data allows for geocoding and exact calculation of distance from location of overdose to location of nearest naloxone dispensing location in Hypothesis 3.

To account for differences in neighborhoods as well as co-occurring time trends, a few additional data sources were used. HIV infection rates came from NYC DOHMH surveillance. Numbers of individuals admitted for drug detoxification and numbers of individuals utilizing methadone maintenance came from the Office of Alcoholism and Substance Abuse Services, the body responsible for licensing drug treatment in New York State. The number of individuals utilizing buprenorphine maintenance treatment came from the Bureau of Narcotics Enforcement.

Concomitant use of alcohol or central nervous system depressants with heroin was approximated using NYC DOHMH overdose mortality surveillance data. Opioid analgesic misuse was also approximated using this dataset. Harm reduction participation was approximated using a state reporting system which collects the number of unique individuals accessing syringe exchange in NYC.

Heroin use prevalence was estimated by using a proxy measure, the proportion of hospital discharges that are opioid-related out of the total number of hospital discharges. This information came from the Statewide Planning and Research Cooperative System (SPARCS), a NY statewide data system which all Article 28 facilities are required to report to, and contains patient-level data on all hospital discharges as well as International Classification of Diseases (ICD)-9 codes. ZIP codes of patient residence are available from SPARCS. Additionally, neighborhoods were characterized using several neighborhood-level variables available from the US Census, including: proportion of the neighborhood population that identifies as white and non-white, proportion over age 60, proportion female, proportion of single-person households, and persons per acre.

Information on the underlying NYC population for each neighborhood came from the 2000 and 2010 US census. Linear interpolated intercensal population estimates based on census data were used for years 2001 – 2009.⁴⁸

Chapter 2: Implementation of Opioid Overdose Prevention and Heroin-related Overdose Mortality in New York City: Interrupted Times Series Analysis

2.1. Introduction

In the United States, overdose is the leading cause of death from injuries, recently surpassing traffic accidents in the number of deaths annually.¹ New York City (NYC) in particular, experiences a substantial overdose mortality burden. In NYC, “accidental drug poisoning death” or overdose is the third leading cause of premature death.² In 2013, accidental overdoses killed 788 people in NYC, more than traffic accidents.³ Over half of NYC drug overdose fatalities involved heroin.⁴

In contrast to national trends where overdose mortality rates have steadily increased over the last decades,⁵ rates in NYC have mainly decreased in recent years, from a high of 13.3 per 100,000 in 2006 to a low of 8.2 per 100,000 in 2010 and to 11.6 per 100,000 in 2013.⁴ This trend is especially pronounced among overdose deaths involving heroin, which decreased from 6.1 per 100,000 in 2006 to 3.1 per 100,000 in 2010. However, these rates increased again to 5.7 in 2011 (Figure 2.1).⁴

Accidental heroin overdoses can be prevented. In addition to training individuals who use heroin on practices to avoid accidental overdose, an opioid antagonist that reverses the effects of opioids, naloxone, is available for layperson administration. In NYC, since an overdose prevention program (OPP) was codified in state law in 2006,⁶ over 55,000 doses of naloxone

have been dispensed to trained community members as a first-aid response to opioid overdose (unpublished data, NYC Department of Health and Mental Hygiene).

The OPP initiative draws on the theoretical frameworks of the Health Belief Model⁷ and Social Cognitive Theory.^{8,9} Overdose prevention trainings last from ten minutes to three hours and are located in a variety of settings, including syringe access programs, drug treatment programs and other community-based organizations (CBOs), as well as on street corners where drug users congregate. Individuals are trained using a New York state-standardized curriculum in the risk factors for opioid overdose, how to recognize an overdose, and the proper response when witnessing an overdose, including calling 911, performing rescue breathing, and administering naloxone. Trainings are usually facilitated by health educators or other CBO staff. After the training, naloxone is prescribed and dispensed by a physician assistant, nurse practitioner, or medical doctor in the form of an “overdose rescue kit,” for use by the recipient should they witness an overdose in the future.¹⁰ In New York City, the OPP initiative has primarily targeted heroin users and their social networks, and the largest proportion of naloxone has been distributed through programs serving these populations (unpublished data, NYC Department of Health and Mental Hygiene). Overdose prevention trainings have been described in more detail elsewhere.¹¹

While studies of OPPs have demonstrated feasibility and acceptability,¹²⁻¹⁶ increase in overdose knowledge and response skills,¹⁷⁻²³ none to date have shown population-level effects on overdose mortality in NYC. The decrease in heroin-related mortality experienced in NYC since 2006 could be associated with the rise in overdose prevention programming, but it may have been

associated with other concurrent trends that impacted individuals at risk of overdose during this time period. Perhaps fewer people used heroin, decreasing the pool of individuals at risk for heroin-related overdose. Heroin users may have experienced increased utilization of medication-assisted therapy, including buprenorphine and methadone, both shown to be protective against opioid overdose.²⁴⁻²⁹ Loss of tolerance is a documented risk factor for overdose³⁰; perhaps fewer heroin users entered opioid detoxification programs which induces loss of tolerance. The expansion of harm reduction programming and specifically overdose risk reduction messaging could have decreased prevalence of both fatal and non-fatal overdose among heroin users.

This study aims to test the hypothesis that implementation of NYC's OPP was causally associated with the decrease in rate of heroin-related overdose mortality. Using interrupted time series analysis with segmented negative binomial regression models, we will be able to describe the effect of the overdose prevention program on heroin-related mortality over time.

2.2. Methods

2.2.1. Study Design

Observational data from NYC's overdose surveillance records were analyzed to determine the effect of NYC's OPP on heroin-related mortality using interrupted time series (ITS) analysis with segmented negative binomial regression models. ITS designs are frequently used when an intervention was applied at a clear point in time, and several data points were collected on the outcome of interest both before and after the intervention was implemented. When randomization is not possible, which is often the case in ecologic studies, ITS "is the strongest,

quasi-experimental design to evaluate longitudinal effects of...time-delimited interventions.”³¹

In ITS, the level and trend of the outcome prior to the intervention can serve as a comparison to the level and trend of the outcome after the intervention was implemented.³¹ Studies have found that ITS using pre-intervention data as controls found comparable average effect measures to that of a cluster-randomized controlled trial.^{32,33}

In this study, we used an ITS design with segmented negative binomial regression models to compare levels and trends of heroin-related overdose mortality after implementation of NYC’s OPP to levels and trends prior to implementation.

2.2.2. Data Collection and Measures

Independent Variable: The NYC Overdose Prevention Program

OPP was treated as a dummy variable, with zero representing the phase prior to passage of New York State’s OPP law (Jan 1, 2000 – June 30, 2006) and one representing the phase after (July 1, 2006 – December 31, 2012). While the OPP initiative rolled out slowly and increased incrementally after 2006, this changepoint ensured the earliest possible implementation was included for the most conservative estimate of effect. Effect estimates were similar when the changepoint was moved six months and one year forward.

Dependent Variables: Unintentional Heroin-related and Opioid Analgesic-related Overdose Deaths

Outcome data from a NYC Department of Health and Mental Hygiene (DOHMH) surveillance database of unintentional drug poisoning deaths were available from January 1, 2000 to

December 31, 2012, and comprised of two linked data sources: death certificates and medical examiner records. The outcome of interest, unintentional drug poisoning death, is defined where the death certificate recorded (i) the manner of death as “accidental;” and (ii) the codes for underlying causes of death as “poisoning by a psychoactive substance (excluding alcohol or tobacco)” (ICD-10 codes X40-X44) or a “mental or behavioral disorder due to a psychoactive substance” (ICD-10 codes F11-16, F18-19). Overdose fatalities with a manner of death listed as homicide, intentional, or undetermined were excluded.

OPPs have predominantly been located within agencies that serve heroin users, such as syringe exchange programs. The outcome of interest is overdose fatality with toxicology results positive for heroin in order to focus on those individuals who would have been targeted by OPP (decedents may have positive toxicology for other drugs as well). Drugs and drug metabolites are abstracted from toxicology reports of medical examiner files, and include alcohol, benzodiazepines, cocaine, methadone, heroin, and opioid analgesics. To test for effects due to unmeasured confounders, unintentional overdose fatalities with toxicology positive for opioid analgesics were considered as a negative control outcome. The sample excludes non-NYC residents and individuals under age 18, as they were presumed not to have received the intervention.

Covariates

Drug detoxification, resulting in decreased tolerance, is a documented risk factor for opioid overdose.^{30,34-36} The annual number of unique NYC residents discharged from drug detoxification programs, from the state agency responsible for licensing and regulating such

programs, the NYS Office of Alcoholism and Substance Abuse Services, was used to estimate the number of individuals discharged semiannually. Three types of detoxification services - medically monitored withdrawal, supervised inpatient withdrawal, and medically managed detoxification - were combined into a summary detoxification variable.

A protective effect on overdose mortality could have been introduced by syringe exchange programs, which provide heroin users with overdose prevention education. The number of individuals who received such education was estimated by summing the number of unique individuals who received services in NYC syringe exchange programs for each six-month period, using a database managed by the state agency responsible for regulating syringe exchange, the NYS Department of Health - AIDS Institute. These data were unavailable for the first five six-month intervals of the study period; missing values were imputed using the linear trend at point.

Because changes in heroin-related overdose mortality could reflect changes in the background prevalence of heroin use, we adjusted for this by using a proxy, the number of individuals discharged from NYC hospitals for opioid-related diagnoses, excluding detoxification and drug rehabilitation discharges. This data is collected by the NY Statewide Planning and Research Cooperative System, a comprehensive data system which collects information on discharges from all NYS hospitals. The number of unique individuals discharged from NYC hospitals was summed for each six-month period.

A total of 26 time periods from January 1, 2000 to December 31, 2012 (13 periods each in the pre-OPP and post-OPP phases) comprised the units of analysis.

2.2.3. Procedures and Statistical Analysis

Age-adjusted mortality rates were calculated for the pre- and post-implementation phases using NYC DOHMH population estimates, modified from US Census Bureau intercensal population estimates 2000-2012. A rate difference and a percentage change were calculated to compare heroin-related overdose mortality pre- and post-implementation of the OPP.

For interrupted time series analysis, segmented negative binomial regression was used. Six-month periods were the smallest time period for which covariate data was available. The outcome was the number of heroin deaths per period. Cases of overdose deaths were sorted based on date of death, and a sum of the number of cases was calculated for each six-month period. Linear trends over the study period were accounted for by using a time variable, increasing in integer increments for each period. The changepoint, introduction of OPP, was accounted for by using a dummy variable, expressed as zero for each six-month period from January 1, 2000 through June 30, 2006, and as one for each six-month period from July 1, 2006 through December 31, 2012. A third variable accounted for change in trend after implementation of OPP, and allows for estimation of the rate of change in average number of overdose deaths per six-month period after implementation of OPP, with all periods prior to implementation coded as zero, and periods after implementation starting with one for the first period (July 1 - December 31, 2006) and increasing in integer increments for each period after. (See Appendix II for model specifications.)

Both visual inspection of time series plots and the literature suggested no seasonal variation in heroin-related overdose death, so no term representing seasonality was included in the model.³⁷

The interpolated annual NYC population at risk (defined as individuals ages 15-85) was included as an offset term. Residual autocorrelation and white noise tests performed on the outcome variable determined first order autoregressive covariance structure was needed to account for correlation between repeated measures. A negative binomial distribution was used to account for excess dispersion. Negative binomial segmented regression models were estimated using the GLIMMIX procedure and non-automated backward elimination was performed to identify the model with best fit by comparing -2 residual log pseudo-likelihood.

Because the census of NYC heroin-related overdose deaths 2000-2012 was included in analysis and cases were not sampled, inferential statistics to detect findings due to random chance in sampling was not necessary. Any change in mortality was interpreted as a true change. P-values are presented, nonetheless, in order to interpret the study findings as a theoretical sample of a hypothetically infinite population, and generalize to a larger geographic area (outside of NYC) and a broader time period (prior to 2000 and after 2012).

Sensitivity Analyses

To account for time trends over the study period that may have contributed to changes in overdose risk, sensitivity analyses adjusted for covariates. Covariates were chosen based on the overdose risk literature. All covariates that may have been associated with the outcome and exposure were plotted against time and visually inspected. Because potential confounders in segmented regression are limited to those variables that changed at the same time as the intervention, covariates were included in analysis if they changed at the time that OPP was introduced.³¹

The following covariates were not included in sensitivity analysis as they did not change at the time that OPP was introduced: HIV/AIDS prevalence, which increases risk,^{38,39} and medication assisted treatment, which decreases risk for opioid OD.^{34,40,41} During this time period, while methadone maintenance utilization decreased, buprenorphine utilization increased. The two variables were combined to form an overall medication assisted treatment (MAT) variable. See Appendix III for time plots of these variables. Other variables that were theoretically presumed to be associated with the exposure and the outcome were not included in analysis because data was unavailable: prevalence of polydrug use, specifically mixing heroin with alcohol or central nervous system depressants,^{30,37,42,43} and prevalence of release from jail or prison.^{44,45}

Covariates that met confounding criteria were drug detoxification, overdose prevention education, and opioid-related hospitalizations, representing a proxy for prevalence of opioid use in the population. They were tested for multicollinearity using variance inflation factors, and added to the segmented regression models.

Additional sensitivity analyses were performed to ensure that the model was detecting true effects of the interventions by removing outliers from the most parsimonious model, by adding lag effects, and by moving the changepoint forward one and two time periods.

Negative Control Outcome

To determine whether OPP effects were specific to heroin-related overdose or were due to an unmeasured spurious factor, the analyses were repeated with opioid analgesic-related overdose as a negative control outcome.⁴⁶ Negative control outcomes can be used to detect confounding

and other threats to causal inference in observational studies, where randomization is not possible. Because naloxone effectively counteracts overdoses due to opioid analgesics in the same manner that it counteracts overdoses due to heroin, it is assumed to be subject to the same sources of bias. The OPP in NYC, however, did not target opioid analgesic users; therefore it is hypothesized that the OPP had no effect on opioid analgesic-related overdose deaths during the study period. Using opioid analgesic-related overdose as a negative control outcome, we assume that the causal pathways to heroin OD and opioid analgesic OD would be identical with the exception of the OPP. If the relationship between the intervention and heroin-related overdose deaths were due to an uncontrolled confounder, we would expect the same pattern to be observed among opioid analgesic-related overdose deaths.

Analyses were performed using SAS (v9.2).

2.3. Results

A total of 3,906 NYC residents died of unintentional heroin-related poisoning deaths during the study period. In the phase prior to implementation of OPP (January 2000 - June 2006), a total of 2,142 deaths occurred, or an average of 165 deaths per six-month period (age-adjusted mortality rate (AAR) 4.9 per 100,000). (See Table 2.1.) Following implementation of OPP (July 2006 - December 2012), a total of 1,764 deaths occurred, or an average of 136 deaths per six-month period (AAR 3.8 per 100,000). A demographic summary of heroin-related overdose decedents by pre-OPP and post-OPP phase is found in Table 2.2.

Results of a saturated segmented regression model with backward elimination showed that the term representing the change in trend following implementation of the intervention did not significantly contribute to the model. To maximize parsimony and retain statistical power, this variable was removed from the model. Therefore, the slope was not allowed to change from pre-intervention to post-intervention periods. This means that the OPP, while it may be associated with a change in the level of heroin-related overdose deaths per period, was not statistically significantly associated with a change in the rate of decrease in overdose deaths.

The parsimonious unadjusted model (Appendix II) showed that prior to the implementation of OPP, in the years 2000-2006, the trend in heroin-related overdose mortality was level ($RR=1.00$, $p=0.7592$). Immediately following implementation of the intervention, there was a 16% reduction in heroin-related overdose mortality rate ($RR\ 0.84$; $p=0.2664$). While not statistically significant, this suggests that each six-month period following implementation of OPP would see on average a 16% lower heroin-related overdose mortality rate compared with the pre-OPP phase (Table 2.3).

2.3.1. Sensitivity Analyses

Since all covariate combinations were collinear, each covariate was added separately to perform three sensitivity analyses (Appendix II for models and Appendix IV for plot of covariates against time). After adjusting for drug detoxification (sensitivity analysis 1), the level of heroin-related overdose mortality rates decreased by 13% after implementation of OPP ($RR=0.87$, $p=0.3748$). Adjusting for OD prevention education (sensitivity analysis 2) resulted in a 15% decrease in the level of heroin-related overdose mortality rate after OPP implementation ($RR=0.85$, $p=0.3254$)

After adjusting for opioid-related hospitalizations (sensitivity analysis 3), representing a proxy for prevalence of opioid use in the population, the level of heroin-related overdose mortality rate decreased by 14% (RR=0.86, $p=0.3512$) (Table 2.3).

Results did not differ when outliers were removed, when lag periods were introduced, or when the changepoint was moved.

2.3.2. Negative Control Outcome

When similar models were applied to the negative control outcome, opioid analgesic-related overdose deaths, the intervention seemed to have an effect in the opposite direction.

Implementation of OPP was associated with a 6% increase in opioid analgesic-related mortality rate (RR 1.06, $p=0.7007$) (Table 2.4). If a decrease in heroin-related overdose was due to confounding or other sources of bias, not the OPP, we would expect opioid analgesic-related overdose to decrease as well. The opposite finding suggests that the effects of OPP on heroin-related overdose death were specific to the OPP intervention and not due to uncontrolled confounders.

2.4. Discussion

The 6.5 years following implementation of NYC's OPP saw an average decrease of 29 heroin-related overdose deaths per six-month period, compared to the 6.5 years preceding implementation of the program. Aggregated age-adjusted mortality rates decreased by 22.4%, from 4.9 per 100,000 in the 6.5 years before OPP implementation to 3.8 per 100,000 in the 6.5 years after implementation.

We found, using segmented negative binomial regression, that implementation of NYC's OPP law in 2006 was associated with a 16% reduction in the level of heroin-related overdose mortality, though this finding was not statistically significant. Sensitivity analyses suggest that, after adjusting for time-varying covariates, the effect of the intervention weakened, from 15% to 13%, though all analyses showed non-significant protective findings.

While results were not statistically significant, because this study included the universe of heroin-related overdose deaths rather than a sample of cases, significance testing to determine the likelihood of a change due to chance is of limited interpretability. Instead, any change in mortality in NYC during this time period should be considered a true change, not one occurring due to chance. Inferential statistics presented here may be used, however, when conceptualizing NYC during this time period as a sample of a broader population over a larger time period, and interpreted to mean that the decreases observed may be due to chance.

When we modeled the negative outcome control, opioid analgesic-related overdose deaths, we found non-significant associations in the opposite direction, suggesting that OPP implementation was associated with the decrease in heroin-related overdose deaths independent of other co-occurring time trends.

The results of this study are similar to those found in Massachusetts, where an 18% decrease in opioid-related overdose mortality was found in communities with heavily implemented overdose prevention interventions.⁴⁷ Unlike the Massachusetts study, our study was unable to stratify by intervention implementation level; all NYC neighborhoods, including those with no OPP, were

included in the analysis. This may have biased results towards the null, and contributed to the statistical non-significance. Future studies could remove the neighborhoods without OPP and evaluate the effect of the intervention in low-implementing and high-implementation neighborhoods separately.

This study has several additional limitations. This study categorized the intervention dichotomously, assuming the exposure was homogenous over the post-implementation time period. It did not account for increases in the scale-up of the intervention over time. By placing the changepoint at the earliest possible time that the intervention began, immediately after passage of the Opioid Overdose Prevention law, we included the early months of the intervention, when dissemination was small, which would conservatively bias the results towards the null. The intervention was also piloted at a small scale prior to July 2006, which could have resulted in misclassification, biasing the findings towards the null. Future analyses could introduce a second changepoint, creating an additional phase, to account for the early growth years of 2004 to 2007 or 2008, and isolate change in level and trend in heroin-related overdose deaths from the early implementation phase to the later implementation phase.

The limited number of observations meant that we may have had insufficient statistical power to detect statistically significant findings. Direct adjustments for some factors associated with opioid overdose were not possible due to unavailable data, including re-entry from jail or prison, the prevalence of mixing opioids with alcohol or central nervous system depressants, purity of the heroin supply, and buprenorphine utilization. In particular, adjusting for the increase in buprenorphine utilization alone, which was not possible because data was not available prior to

2008, could have contributed to the decrease in heroin-related mortality, as has been shown in Baltimore.⁴⁸ Not including this variable could have biased findings away from the null.

Baltimore, however, had much more robust uptake of buprenorphine (7,500 unique patients by 2009, compared to 4,000 in NYC), despite a much smaller overall population, and so we would expect the effect of buprenorphine on heroin-related overdose in NYC to be smaller.

Furthermore, because both buprenorphine and methadone act as opioid agonists and confer a protective effect on opioid overdose risk, the effect on overdose mortality should not be influenced by combining buprenorphine utilization with methadone utilization. Future analysis, analyzing the effects of buprenorphine and methadone separately, could test this assumption.

Adjustments for detoxification, HIV/AIDS prevalence, medication assisted treatment, and harm reduction education were considered and included where indicated. Detoxification admissions included detoxification for all substances, and were not limited to opioids only. Therefore, trends in opioid-specific detoxifications may have been obscured. Adjustment for prevalence of heroin use was not possible, and so analysis was performed using a proxy, opioid-related hospitalizations, which may be imperfect, particularly as opioid analgesic-related hospitalizations may have increased, which would bias the estimate away from the null. If heroin use prevalence was changing at a consistent rate, however, this would be accounted for in the baseline trend variable in the segmented regression model.

It is possible that the use of opioid analgesic overdose as a negative control outcome could have been biased toward the null if opioid analgesic users had received the OPP intervention, resulting in a more conservative effect estimate. While other mortality datasets were unavailable, future

analyses could replicate this study using an alternate negative control outcome such as motor vehicle accidents.

This is the first study to demonstrate population-level effects of the overdose prevention program in NYC through the use of an interrupted time series design with segmented regression, a multivariable method that accounts for secular trends and is one of the strongest quasi-experimental methods for assessing the longitudinal effects of an intervention at the ecologic level.^{31,32} Because this method estimates pre-intervention trends in the outcome, we can distinguish between changes in the outcome that are due to the introduction of the changepoint and continuing trends over time. In particular, while we know that heroin-related overdose decedents are aging over time and increasingly involving opioid analgesics and benzodiazepines, all of which may contribute to increased overdose mortality, these trends are continuous over time, not abrupt, and are accounted for in the pre-intervention trend using segmented regression. If they were not fully accounted for, i.e. if the rate of change increased in the post-intervention phase, the OPPs intervention effects would be greater than estimated.

Using the universe of heroin-related overdose in NYC during over 13 years, this study is also the first to demonstrate population-level effects accounting for changes in detoxification, OD prevention education at syringe exchange programs, and prevalence of heroin use, as measured by opioid-related hospitalization. A key strength is this study's ability to limit cases of opioid overdose to those with toxicology results positive for heroin, through access to linked death certificates and medical examiner records, to more accurately capture the population targeted by the intervention. Last, the use of a negative outcome control offers the ability to detect

confounding and other incorrect sources causal inference,⁴⁶ and suggests that the decrease in heroin-related overdose deaths was not due to unmeasured confounders.

This study suggests that the passage of New York's 2006 Opioid Overdose Prevention Program law resulted in a decrease in heroin-related overdose mortality in NYC. The decrease in overdose deaths was striking, reducing the rate of heroin-related deaths by more than 22%, though effects dissipated somewhat in multivariable segmented regression analysis. If we assume that high-implementing neighborhoods in NYC are similar to high-implementing Massachusetts communities, we would infer that the intervention's effects seen in this study are underestimated. By expanding OPP and creating more high-implementing neighborhoods, we may expect to see more lives saved in NYC. Future research could strengthen this finding by evaluating just those neighborhoods targeted by the intervention to assess whether a dose-response relationship exists.

Table 2.1. Summary of Pre- and Post-intervention Heroin-related Overdose Deaths, New York City, 2000-2012

	Pre-intervention (Jan 2000-Jun 2006)	Post-intervention (Jul 2006-Dec 2012)
Total number of ODs in NYC	2142	1764
Average number of ODs per 6-month period	165	136
Difference in average	-29	NA
Percentage change in counts	-17.58%	NA
Age-adjusted OD mortality rate ¹	4.9	3.8
Rate difference	-1.1	NA
Percentage change in age-adjusted rate	-22.4%	NA

¹Rates are calculated using intercensal New York City population denominators updated July 2013 and averaged across years.

Abbreviations:

OD = overdose

Table 2.2. Unintentional Heroin-related Overdose Deaths, New York City, Pre- (January 2000 - June 2006) and Post-implementation (July 2006 - December 2012) of Overdose Prevention

Program

	Pre-Implementation of Opioid Overdose Prevention			Post-Implementation of Opioid Overdose Prevention			Rate Change (Post-Pre)
	N	%	AAR ¹	N	%	AAR ¹	AAR ¹
Total	2142	100%	4.9	1764	100%	3.8	-1.1
Gender							
Male	1716	80%	8.2	1365	77%	6.2	-2.0
Female	426	20%	1.9	399	23%	1.7	-0.2
Race/Ethnicity							
Black	479	22%	4.5	353	20%	3.2	-1.3
White	679	32%	5.9	569	32%	4.6	-1.3
Hispanic	898	42%	5.8	805	46%	5.2	-0.6
Other	86	4%	X	37	2%	X	X
Age, Years ²							
15 to 24	116	5%	1.5	95	5%	1.2	-0.3
25 to 34	348	16%	3.7	336	19%	3.4	-0.3
35 to 44	775	36%	8.9	416	24%	5.1	-3.8
45 to 54	700	33%	9.5	606	34%	7.9	-1.6
55 to 64	168	8%	3.2	285	16%	4.6	1.4
65 to 84	24	1%	0.5	25	1%	0.4	-0.1
Missing	11	1%	X	1	0%	X	X
Borough of residence							
Manhattan	501	23%	5.5	322	18%	3.5	-2.0
Bronx	500	23%	7.3	503	29%	7.0	-0.3
Brooklyn	657	31%	5.1	496	28%	3.6	-1.5
Queens	362	17%	2.9	306	17%	2.4	-0.5
Staten Island	122	6%	4.9	137	8%	5.4	0.5
Borough of overdose							
Manhattan	526	25%	5.8	315	18%	3.4	-2.4
Bronx	476	22%	6.9	448	25%	6.2	-0.7
Brooklyn	640	30%	4.9	477	27%	3.5	-1.4
Queens	319	15%	2.6	265	15%	2.1	-0.5

Staten Island	104	5%	4.2	119	7%	4.6	0.4
Other ³	77	4%	X	140	8%	X	X
Borough of death							
Manhattan	551	26%	6.1	360	20%	3.9	-2.2
Bronx	498	23%	7.3	488	28%	6.8	-0.5
Brooklyn	666	31%	5.1	509	29%	3.7	-1.4
Queens	323	15%	2.6	280	16%	2.2	-0.4
Staten Island	104	5%	4.2	127	7%	5.0	0.8
Neighborhood poverty ⁴							
Low (<10% below poverty)	157	7%	3.1	140	8%	2.7	-0.4
Medium (10 to <20%)	663	31%	3.4	559	32%	2.8	-0.6
High (20 to <30%)	428	20%	5.0	350	20%	3.9	-1.1
Very high (≥30%)	869	41%	8.1	700	40%	6.2	-1.9
Missing	25	1%	X	15	1%	X	X
Other drugs on board							
Methadone	524	24%	1.2	445	25%	1.0	-0.2
Opioid analgesics	194	9%	0.4	368	21%	0.8	0.4
Benzodiazepines	445	21%	1.0	681	39%	1.5	0.5
Alcohol	1093	51%	2.5	776	44%	1.7	-0.8

¹Rates are calculated using intercensal New York City population denominators updated July 2013. Rates are age-adjusted using New York City population Census 2000, and averaged across years.

²Age standardized rates are presented. Unknown age are not included in the percent of total calculation.

³Includes locations outside of NYC and decedents with unknown overdose location

⁴Neighborhood poverty (based on UHF) defined as percent of residents with incomes below 100% of the Federal Poverty Level per American Community Survey Census 2000.

Abbreviations:

AAR = age-adjusted rate

Table 2.3. Parameter Estimates, Standard Errors and *P*-values from Segmented Negative Binomial (NB) Regression Models Predicting Heroin-related Overdose Mortality in NYC

	Coefficient	RR	SE	t-statistic	P-value	Neg 2 Res Log Pseudo-Likelihood
Heroin-related OD: Segmented NB regression model ¹						-0.37
Intercept B_0	-1.6779	-	0.0850	-19.74	<.0001	
Baseline trend B_1	-0.0031	1.00	0.0099	-0.31	0.7592	
Level change after OPP B_2	-0.1691	0.84	0.1484	-1.14	0.2664	
Sensitivity analyses						
1. Heroin-related OD: Segmented NB regression model adjusting for detoxification ²						15.57
Intercept B_0	-0.5151	-	1.8106	-0.28	0.7787	
Baseline trend B_1	-0.0119	0.99	0.0169	-0.70	0.4902	
Level change after OPP B_2	-0.1413	0.87	0.1559	-0.91	0.3748	
Detoxification B_3	-0.0001	1.00	0.0001	-0.64	0.5270	
2. Heroin-related OD: Segmented NB regression model adjusting for OD prevention education ³						17.46
Intercept B_0	-1.7119	-	0.2762	-6.20	<.0001	
Baseline trend B_1	-0.0046	1.00	0.0156	-0.30	0.7707	
Level change after OPP B_2	-0.1621	0.85	0.1612	-1.01	0.3254	
OD prevention education B_3	0.0000	1.00	0.0001	0.13	0.8979	
3. Heroin-related OD: Segmented NB regression model adjusting for opioid-related hospitalization ⁴						15.11
Intercept B_0	-2.5517	-	1.0993	-2.32	0.0299	
Baseline trend B_1	-0.0102	0.99	0.0135	-0.76	0.4549	
Level change after OPP B_2	-0.1451	0.86	0.1523	-0.95	0.3512	
Opioid-related hospitalization B_3	0.0001	1.00	0.0002	0.80	0.4334	

¹ $\text{Log}(E(Y)) = \beta_0 + \beta_1 \text{Time} + \beta_2(\text{OPP})_i + \log(\text{population})$

² $\text{Log}(E(Y)) = \beta_0 + \beta_1 \text{Time} + \beta_2(\text{OPP})_i + \beta_3(\text{Detox})_i + \log(\text{population})$

³ $\text{Log}(E(Y)) = \beta_0 + \beta_1 \text{Time} + \beta_2(\text{OPP})_i + \beta_3(\text{OD prevention education})_i + \log(\text{population})$

⁴ $\text{Log}(E(Y)) = \beta_0 + \beta_1 \text{Time} + \beta_2(\text{OPP})_i + \beta_3(\text{Hospitalization})_i + \log(\text{population})$

Abbreviations:

RR = risk ratio

SE = standard error

Neg = negative

Res = residual

OPP = overdose prevention program

OD = overdose

NB = negative binomial

Table 2.4. Comparison of Results Using Negative Control Outcome

	Coefficient	RR	SE	t-statistic	P-value
a. Heroin-related OD death: Unadjusted segmented NB regression model					
Intercept B_0	-1.6779	0.19	0.0850	-19.74	<.0001
Baseline trend B_1	-0.0031	1.00	0.0099	-0.31	0.7592
Level change after OPP B_2	-0.1691	0.84	0.1484	-1.14	0.2664
b. Opioid analgesic-related OD death: Unadjusted NB segmented regression model					
Intercept B_0	-3.5235	0.03	0.0978	-36.04	<.0001
Baseline trend B_1	0.04886	1.05	0.0097	5.01	<.0001
Level change after OPP B_2	0.0577	1.06	0.1482	0.39	0.7007

Abbreviations:

RR = risk ratio

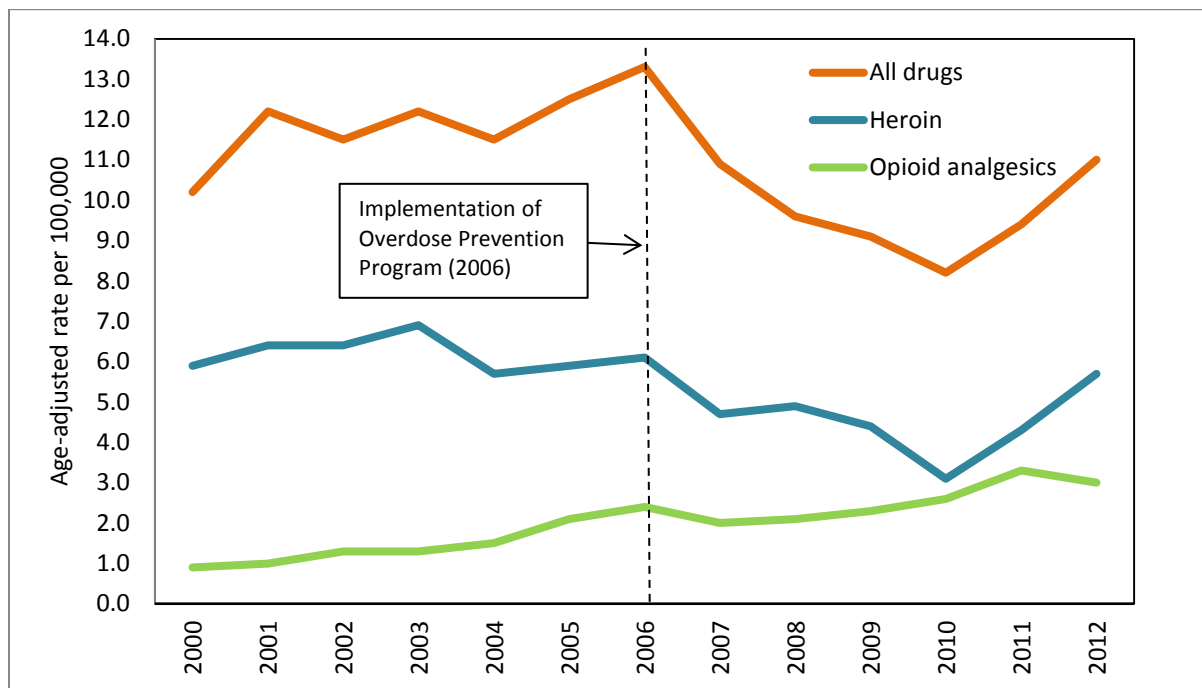
SE = standard error

OPP = overdose prevention program

OD = overdose

NB = negative binomial

Figure 2.1. Age-adjusted Rates* of All Drugs, Heroin-related, and Opioid Analgesic-related Unintentional Overdose Deaths, New York City, 2000-2012



*Age-adjusted rates per 100,000 population

Chapter 3: Spatial Patterns of Heroin-related Overdose, Pre- and Post-Implementation of New York City's Overdose Prevention Program

3.1. Introduction

In the United States (US), overdose is the leading cause of death from injuries, recently surpassing traffic accidents.¹ New York City (NYC) in particular experiences a substantial overdose mortality burden, where, “accidental drug poisoning death” or overdose (OD) is the third leading cause of premature death, killing 788 people in 2013.^{2,3} Accidental ODs now kill more New Yorkers than traffic accidents.²

Despite the substantial mortality burden from overdose, in the years after 2006, unintended OD mortality rates rose across the US, but decreased in NYC from an age-adjusted rate of 13.1 per 100,000 population in 2006 to 10.1 per 100,000 in 2012.⁴ However, this trend was limited to heroin-related deaths in NYC which decreased from a high of 6.8 per 100,000 population in 2003 to a low of 3.1 per 100,000 in 2010⁴ (Figure 3.1). Overdose deaths involving opioid analgesics increased both nationally¹ and in NYC.³ While research suggests that the rise in opioid analgesic-related OD mortality is due to the increase in opioid analgesic prescribing,^{5,6} no studies have determined the cause of NYC's decrease in heroin-related OD. It is possible that this pattern is at least partially due to NYC's policies related to OD prevention.

In 2006, New York State passed a law⁷ which made layperson administration of naloxone, an opioid antagonist, a legal, first-aid response to opioid OD in community settings. Since then, non-medically trained community members, including drug users and their friends and family

members, have received training in OD prevention and two doses of naloxone which come in an ‘overdose rescue kit.’ These interventions have traditionally been located at programs that primarily serve heroin users, such as syringe exchange programs. Overdose prevention trainings have been described in more detail elsewhere.⁸

Despite the lack of data supporting evidence-based strategies to reduce OD mortality at the population level,⁹ recent research indicates that New York State’s new law may have had an impact. For example, research has documented that heroin users are able to recognize opioid OD and administer naloxone properly,¹⁰⁻¹³ and program evaluations have described the number of naloxone doses dispensed and, to a lesser degree, the number of OD reversals reported within a subgroup of the trained population.^{8,12,14-23} One study has shown a negative linear association between naloxone and OD mortality at the population level, comparing Massachusetts communities with overdose prevention programs to communities without.²⁴ However, there has been no comprehensive evaluation of the impact of this initiative on heroin-related OD mortality in NYC since 2006. Rigorous exploration of the effect of NYC’s OD prevention initiative on OD mortality could greatly contribute to the fields of injury prevention and substance use, enabling policy makers and stakeholders to use evidence-based strategies to address the growing OD epidemic nationally and in NYC.

This study used observational data to assess changes in geospatial patterns of heroin-related OD mortality in NYC from the seven years preceding the implementation of the overdose prevention program (2000-2006) to the six years following implementation of the OPP (2007-2012), and to compare these changes in neighborhoods that experienced the intervention with neighborhoods

that did not experience the intervention. Three types of analyses were conducted: exploratory mapping to visually inspect the relationship between reductions in OD mortality and naloxone distribution; cluster scanning, which identifies neighborhoods at elevated risk; and regression modeling to test the association between naloxone dispensing and OD mortality changes, controlling for covariates. By viewing NYC in the years 2007-2012 as a quasi-experiment, in which some neighborhoods hosted the OD prevention initiative and others did not, we can test the hypothesis that decreases in heroin-related OD were associated with the initiative.

3.2. Methods

3.2.1. Data Collection and Measures

Unintentional Heroin-related Overdose Deaths

Data on heroin-related OD came from a NYC surveillance database of unintentional drug poisoning deaths comprised of two data sources: death certificates and medical examiner records, which are linked at the NYC Department of Health and Mental Hygiene. The unintentional drug poisoning death case definition was met if (i) the manner of death was “accidental;” and (ii) the codes for underlying causes of death included “poisoning by a psychoactive substance (excluding alcohol or tobacco)” (ICD-10 codes X40-X44) or a “mental or behavioral disorder due to a psychoactive substance” (ICD-10 codes F11-16, F18-19), as recorded in the death certificate.

OPPs have predominantly been located within agencies that serve heroin users, such as syringe exchange programs. Individuals who used heroin were assumed to have been targeted by NYC’s overdose prevention program (OPP). Unintentional OD deaths were included in analysis if

toxicology results were positive for heroin or its metabolites, either alone or in addition to other drugs. Drugs and drug metabolites were abstracted from toxicology reports of medical examiner files and include alcohol, benzodiazepines, cocaine, methadone, heroin, and opioid analgesics. The sample excluded non-NYC residents and homicides, intentional, and undetermined manners of death.

Unintentional heroin-related OD deaths of NYC residents from January 1, 2000 to December 31, 2012 were aggregated by neighborhood and by time period. Pre-implementation of OPP included years 2000-2006, post-implementation of OPP included years 2007-2012. (While the OPP law was passed in July 2006, data on the exposure were available beginning in 2007, so the post-implementation time period was set at January 2007.) The dataset included measures for the location of OD, location of death, and location of decedent residence. This analysis used location of OD as that was the site where the intervention could have been performed and is the most precise data point; had naloxone been available at that location, the fatality could have been averted.

The NYC Overdose Prevention Program (OPP)

Measures of the locations and volume of NYC overdose prevention trainings were operationalized using the locations and number of naloxone doses dispensed. Dispensing locations were collected by contacting Program Directors or Clinical Directors at registered OPPs that had received naloxone shipments from 2007-2012. Contacts at each program were asked to identify site locations where naloxone doses were distributed in that time period and to approximate the percentage of distribution for each site. In most cases, records of distribution

locations were available to determine exact proportions of distribution (n=38, or 83% of programs); in others, a crude estimation by OPP leadership was used (n=5, 11% of programs). If the number of persons trained was provided instead of doses distributed, it was assumed that every person received two doses. The proportions determined from this information were applied to the total number of doses ordered by each program, which was available from NYC's two suppliers, NYC Department of Health and Mental Hygiene and NY State Department of Health-AIDS Institute. If no information from the program was available, all of the doses were assumed to be dispensed at the location for which the program registered with the State Department of Health, usually the program headquarters (n=3, or 7% of programs).

Geographic Area and Neighborhood Characteristics

Neighborhoods were defined as neighborhood tabulation areas (NTAs), which are aggregations of census tracts with a minimum 15,000 population. This delineation allows a sufficient number of neighborhoods for comparisons (NYC has 195 NTAs), while maintaining homogeneity within each neighborhood.

Age, race, gender, population density, and proportion of single-person households were measured at the neighborhood level and were used to account for differences between neighborhoods that may confound the relationship between the exposure and the outcome. Age was operationalized as the percent of the neighborhood population age 60 or over, and was included because studies suggest that OD risk decreases after middle age.^{1,3,25-27} While studies that assess the relationship between race and OD risk are inconclusive,²⁵⁻²⁸ because neighborhood poverty has been found to be associated with overdose^{3,29} and was unavailable at

the NTA level, race was included as a proxy for socioeconomic status. Race was defined as the percent of the neighborhood population that identifies as non-Hispanic white. Men die of heroin OD at nearly four times the rate of that for women,^{3,28,30} so gender was included as the percent of the neighborhood population female. Population density and household composition were each included based on theory, despite lack of published evidence: because witnesses must be present in order to use naloxone, we assume neighborhoods with more dense populations and neighborhoods with fewer single-person households are more able to benefit from naloxone programs. Population density was defined as the number of persons per acre. Household composition was defined as the percent of individuals who live in single-person households. These data were obtained from publicly available data via NYC's Department of City Planning.³¹ Data on drug using prevalence or drug-related morbidity were not available at the NTA level.

3.2.2. Procedures and Statistical Analysis

Mapping Exposure and Outcome Variables

Locations of the overdoses and interventions were geocoded using the NYC Department of Health and Mental Hygiene's geoprocessor GeoPortal. This allowed for geo-visualization of patterns and the application of spatial statistical methods for evaluating associations with the intervention. Locations of OD returned a 19% un-match rate. Un-matched records were manually corrected, and those decedents for whom no street address was available for location of OD were removed from the analysis (n=344). Locations of interventions returned no un-matches.

Overdose location data were imported to ArcGIS® geographic information software (v10.0), and the total number of ODs was summed for each neighborhood tabulation area. Neighborhoods

were assigned an outcome value, the number of heroin-related OD deaths that occurred in that area, and mortality rates were calculated using the population over age 18 in each NTA from the US Census 2010. Data were stratified into two periods: pre-intervention (2000-2006) and post-intervention (2007-2012), and median number and median rate of ODs per NTA were calculated for each period. The median number and rate were divided by the number of years in each period. Choropleth maps of the outcome were created to visualize the spatial distribution.

Overdose prevention programs were implemented more heavily in some neighborhoods of NYC and less heavily or not at all in others, as programs tended to be sited in areas of highest need where injection drug users lived or congregated and where drug OD rates were elevated. If all NYC neighborhoods are analyzed as a whole, the effects of the intervention would be diluted by those neighborhoods that did not have the intervention. To address this, naloxone doses were summed for each neighborhood and divided by the neighborhood population at risk, defined as residents over age 18. The mean rate and range of doses dispensed per neighborhood population were calculated. Mean number and rate of doses per neighborhood population were divided by 6, the number of years over which the doses were dispensed, in order to estimate a naloxone dose rate for each neighborhood per year.

Cluster Detection

Geospatial clusters of ODs were detected using a spatial scan statistic,³² as encoded in the SaTScan software (v9.3).³³ This method evaluates many possible clusters, each centered on a NTA and varying in size (number of contiguous NTAs), where the maximum cluster size was set to 50% of the underlying population. For each potential cluster with risk that is elevated relative

to everywhere in NYC outside of the cluster, the null hypothesis is tested whereby the elevated cluster is assumed to have risen from random chance alone.

Unpopulated neighborhoods such as parks, cemeteries and airports (7 neighborhoods total) were removed, which resulted in the removal of 22 OD cases (17 in the pre-OPP period and 5 in the post-OPP period).

Clusters with elevated risk were then identified and mapped if there was no more than a 10% chance of incorrectly rejecting the null hypothesis that the elevated risk was from random variation ($p < 0.10$).

Regression Modelling

Exposure and outcome variables were plotted and visually inspected for normality. Rates of naloxone doses dispensed by neighborhood population were not normally distributed, so the rate of naloxone doses per thousand population plus a constant (1) was log-transformed. One outlier, a neighborhood in midtown Manhattan which housed the state's overdose prevention technical assistance provider and served as a central naloxone warehouse for other programs, was removed from analysis.

In order to accommodate a large number of neighborhoods with no overdose prevention programs, naloxone was treated as an ordinal variable with four strata. Neighborhoods with no naloxone doses dispensed formed one stratum and the remaining neighborhoods were allocated into three strata with an equal number of neighborhoods in order to maximize statistical power

and guarantee sufficient observations within each strata: low (<5.1 doses per thousand residents or log dose rate <1.8), medium (6.8 to 20.2 doses per thousand residents or log dose rate 2.1-3.1), and high naloxone penetration (>21.9 doses per thousand residents, or log dose rate >3.1). This approach allows for detection of a dose-response relationship between the intervention and its effects. A similar approach was used by Walley and colleagues.²⁴

The number of ODs and OD rates were calculated for each naloxone penetration category, and rate differences were calculated to compare pre-intervention to post-intervention periods within each penetration category. Analysis of variance was used to compare rate differences between each penetration category, with neighborhoods with no naloxone serving as the reference group. The null hypothesis was that the mean OD rate difference for each neighborhood penetration strata was equal.

The analysis was repeated controlling for neighborhood characteristics using linear regression. Neighborhood-level predictor variables included proportion of the population over age 60, female, white non-Hispanic, single-person households, and persons per acre.

As a sensitivity analysis, to test for a dose-response association solely among the neighborhoods with any naloxone while controlling for key neighborhood characteristics, ordinary least squares regression was performed using the log of naloxone doses as a continuous predictor, and the difference in OD death from pre- to post-OPP as the continuous outcome.

All multivariable regression analyses used backward elimination to reject covariables that were not significantly associated with the difference in OD mortality rate (t -statistic $p>0.05$). Since our units of observation, NTAs, are spatially contiguous polygons, the model was tested for residual spatial autocorrelation using global Moran's I statistic. Model residuals were not spatially autocorrelated (Moran's I $p=0.8293$), so standard multivariable regression was used. Regression analyses were performed using SAS (9.2).

3.3. Results

In the study period (2000-2012), there were a total of 3,562 unintentional heroin-related OD deaths in NYC: 2,182 OD deaths in the years prior to OPP (2000-2006) and 1,380 in the years after implementation of OPP (2007-2012).

On average, neighborhoods experienced 1.14 heroin-related OD deaths per year in the years prior to implementation of OPP and 1.00 heroin-related OD death per year in the years following implementation of OPP (Table 3.1).

3.3.1. Mapping Exposure and Outcome Variables

Maps of heroin-related OD by neighborhood are shown in Appendix V.

In the six years immediately following implementation of OPP, a total of 57,097 naloxone doses were dispensed in NYC, or an average of 8,157 doses per year, from 152 dispensing locations. One-third of NYC neighborhoods (64 NTAs or 34%) hosted at least one naloxone dispensing location, with neighborhoods ranging from one to 12 dispensing sites. The mean number of

naloxone doses dispensed over seven years by neighborhood was 300 (range 0 to 6,635), or an average of 50 doses per year (Table 3.2). For a map of naloxone doses dispensed by neighborhood, see Figure 3.2.

3.3.2. Cluster Detection

Spatial scans detected 7 clusters of heroin-related OD prior to OPP, three of which were statistically significant ($p < 0.10$). These clusters were located in the South Bronx/Northern Manhattan, Central and Downtown Brooklyn/Lower East Side Manhattan, and East Brooklyn. After implementation of OPP, 5 clusters were detected, three of which were statistically significant ($p < 0.10$): South Bronx, Lower East Side Manhattan, and Central Brooklyn (Appendix VI). All three clusters shrank in size from pre- to post-OPP, and the northern Manhattan neighborhoods, which had substantial naloxone coverage, disappeared from the cluster altogether. The cluster relative risk in Central Brooklyn, an area with fairly little naloxone coverage, did not change from pre- to post-OPP (RR=1.9, 2.0, respectively).

3.3.3. Regression Modeling

Two-thirds of neighborhoods had no naloxone dispensed ($n=124$). The remaining neighborhoods were stratified into tertiles of 21 neighborhoods each (low, medium, high naloxone penetration, each containing 11% of all NYC neighborhoods).

Neighborhood groups experienced mean OD rates between 3.6 and 9.5 per 1,000 population in the pre-OPP period and between 2.8 and 6.4 in the post-OPP period (Table 3.3). All four strata

saw decreases in OD mortality from pre- to post-OPP, with high penetration neighborhoods experiencing the largest rate decrease.

Differences in rate of OD from pre- to post-OPP increased in magnitude with a dose-response relationship from low to high naloxone penetration level (-0.7, -1.6, -3.1 ODs per person-year per neighborhood), though neighborhoods with no naloxone also experienced a decrease in OD mortality which was similar to that experienced by neighborhoods with low naloxone penetration (-0.8 OD per person-year per neighborhood). The difference in rate between high penetration neighborhoods and no naloxone neighborhoods was statistically significant ($p < 0.0001$) in an unadjusted regression model.

After controlling for neighborhood characteristics (proportion of the population age 60 and over, female, white non-Hispanic, population density, and proportion of single-person households), only population density remained statistically significant ($p = 0.0094$) and was retained in the multivariable model. The association between high naloxone penetration neighborhoods and no naloxone neighborhoods remained significant after controlling for population density ($p = 0.0007$). Low and medium naloxone penetration neighborhoods did not experience OD rate changes significantly different from neighborhoods with no naloxone ($p = 0.5106$ and $p = 0.2386$, respectively).

Sensitivity analysis, limiting the sample to the 63 neighborhoods with any naloxone distribution and treating the predictor as a continuous variable, also found that the only statistically significant neighborhood covariate was population density ($p = 0.0027$). All other neighborhood

covariates were dropped from the multivariable model. Naloxone dose rate was statistically significantly associated with OD rate difference ($p=0.0003$), after controlling for population density (Table 3.4). For every increase of 10 doses per 1,000 neighborhood population, the expected rate difference is -2.6, after controlling for population density. See Appendix VII for specification of the multivariable models.

3.4. Discussion

When comparing decreases in OD mortality from the years prior to NYC's overdose prevention program to the years following its implementation, we detect a statistically significant difference between high naloxone penetration neighborhoods and those neighborhoods with no naloxone. Neighborhoods that had high naloxone penetration experienced a nearly four-fold decrease in OD deaths (3.1 per 100,000 rate difference) over neighborhoods with no naloxone (0.8 per 100,000). Medium and low naloxone penetration neighborhoods did not demonstrate changes in OD mortality significantly different from neighborhoods without naloxone. When neighborhoods without naloxone were removed from the analysis and the number of naloxone doses dispensed per neighborhood population was treated as a continuous variable, a significant dose-response relationship was seen between naloxone and change in OD mortality, after controlling for neighborhood characteristics. For every 10 doses of naloxone distributed per 1,000 residents, we would expect to see two to three lives saved.

While we would expect several of the covariates, such as gender, age, and living alone, to be significant predictors of OD risk at the individual level, it is not surprising that they are insignificant at the neighborhood level because neighborhoods did not demonstrate large

variation. Population density was shown to be significantly associated with OD mortality change; more densely populated neighborhoods saw steeper decreases in OD mortality. We suspect that this is because ODs are more likely to be witnessed and responded to in more densely populated neighborhoods. Given the shifting OD epidemic to more wealthy and suburban communities that are presumably less densely populated, this finding poses important questions for policymakers and program coordinators.

This study's findings replicate those found in Massachusetts, where a dose-response relationship between naloxone implementation and OD mortality was demonstrated at the community level.²⁴ This study builds on the Massachusetts findings by replicating the study in a much more densely-populated jurisdiction and comparing neighborhoods located closer to each other than the communities studied in Massachusetts. Furthermore, it isolates the population targeted by the intervention by solely examining heroin-related OD.

We were surprised to find that OD mortality decreased in neighborhoods with no naloxone distribution, though to a smaller degree than neighborhoods with medium and high levels of naloxone penetration. This decrease could be due to a number of unmeasured factors, such as decreased prevalence of heroin use or decreased heroin purity, or increased access to substance use disorder treatment. Unfortunately, these measures were not available at the neighborhood level. Other drug use trend data were unavailable at the neighborhood level, including age of the heroin user and concomitant use of substances such as benzodiazepines and opioid analgesics with heroin. Citywide data, however, suggest an increase in age, concomitant drug use and perhaps heroin use prevalence, which would each lead to an increase in overdose mortality,

resulting in a conservative estimate of the OPP's effect. Similarly, poverty measures were unavailable at the neighborhood level. While race was included as a proxy for poverty, there may be residual confounding. Future analyses could strengthen the findings by incorporating drug-using characteristics and poverty measures into neighborhood-level ecologic analyses.

This analysis used location of overdose as its main outcome on the basis that this location is the most precise point at which the intervention could have been used to avert overdose mortality. It is possible, however, that if a person lived closer to the OPP, they may have been more likely to receive the intervention, even if they are using heroin and at risk of overdose further from the program. In future analyses, the location of residence could be used as the main outcome to assess this hypothesis and compare findings to those presented here.

Diffusion of the intervention outside of the neighborhoods in which they were housed may also have contributed to the small decreases in OD mortality in the neighborhoods with no naloxone. A limitation of this study is that we do not know the degree to which this may have occurred. Given the tightly spaced neighborhoods of NYC and its efficient public transportation system making it easy to travel from one neighborhood to another, it is possible that individuals received naloxone in one neighborhood and used it to prevent OD fatality in another. We suspect that this occurrence, however, is minimal because previous studies have shown that individuals who access syringe exchange programs, the majority of OPP participants during the study period, live within a ten-minute walk from the program on average,³⁴ and the majority of ODs occur in the home.³⁵ If we assume that diffusion occurred to some degree, the results would bias towards the null, underestimating the association between the intervention and OD mortality. Future

analyses could account for the ways in which drugs and drug use move throughout the city geospatially, on the assumption that naloxone would move similarly, including subway lines, airports and train stations, and gang activity.

This study used the number of doses shipped to each program from the suppliers. We do not know how many doses of naloxone were actually dispensed to individuals at each program. It is likely that programs did not dispense all of the naloxone that they were shipped. Thus, the associations found were a conservative estimate, if in fact a smaller number of doses were associated with the decrease in OD mortality.

While the exposure is measured as naloxone doses dispensed, in fact individuals receive overdose prevention training with naloxone. Training curriculum includes information on ways to reduce risk of opioid OD. The association found in these analyses must be jointly attributed to both the naloxone doses and the educational intervention, since it is not possible to separate the effects of the two. Therefore, we cannot determine which aspect(s) of the intervention is the “active ingredient” associated with decreased OD mortality.

Last, all analyses were performed at the ecologic level using observational data. While evidence suggests program effectiveness, we cannot conclude that the relationship between the overdose prevention program and overdose mortality is causal.

Given the paucity of evidence-based strategies to reduce overdose mortality at the population level, this study contributes important information in favor of public health policies and

resources that support community-based overdose prevention programs and naloxone distribution among non-medically trained bystanders. While NYC is unlike other jurisdictions in some ways, given that similar results were found in Massachusetts communities, this suggests these findings may be generalizable to other settings experiencing similar overdose epidemics.

Overdose mortality rates continue to rise nationally and remain the third largest premature killer in NYC. Because of this substantial burden, providing at-risk individuals with evidence-based tools is ever more critical. Naloxone and overdose prevention education for individuals at-risk of overdose as well as their family members and friends may be one important tool in curtailing overdose mortality.

Table 3.1. Overdose Information by Neighborhood Tabulation Area (NTA), NYC, 2000-2012

	Pre-OPP (2000-2006)	Post-OPP (2007-2012)
Total number of ODs	2182	1380
Years in period	7	6
Number of ODs/# of years in period	311.7	230.0
Median number of ODs per NTA (range)	8 (0,53)	6 (0, 34)
Median number of ODs per NTA/# of years in period	1.1	1.0
Median rate of ODs per NTA per 100,000 population 18+ (range)	3.8 (0.0, 18.8)	2.9 (0.0, 12.3)
Median rate of ODs per NTA per 100,000 population 18+/# of years in period	0.6	0.5

Abbreviations:

NTA = neighborhood tabulation area

OD = overdose

OPP = overdose prevention program

Table 3.2. Naloxone Information by Neighborhood Tabulation Area (NTA), NYC, 2007-2012

	Mean	Range
Naloxone doses dispensed per neighborhood	300	min=0, max=6,635
Naloxone doses dispensed per neighborhood/# of years	50	0, 1106
Rate of naloxone per neighborhood per 1,000 pop 18+	8.0	0.0, 153.3
Rate of naloxone per neighborhood per 1,000 pop 18+/# of years	1.3	0.0, 25.6

Abbreviations:

NTA = neighborhood tabulation area

Min = minimum

Max = maximum

Pop = population

Table 3.3. Overdose Mortality Rate in NYC, 2000-2012, Stratified by Neighborhood Naloxone Penetration Level

	No naloxone neighborhoods (n=124)			Low* penetration neighborhoods (n=21)			Medium penetration neighborhoods (n=21)			High penetration neighborhoods (n=21)		
	Pre-OPP**	Post-OPP	p-value***	Pre-OPP	Post-OPP	p-value	Pre-OPP	Post-OPP	p-value	Pre-OPP	Post-OPP	p-value
Total # of ODs	1012	672		343	257		284	171		488	263	
Mean # of ODs per neighborhood	8.2	5.4		16.3	12.2		13.5	8.1		23.2	12.5	
Mean OD rate	3.6	2.8		6.5	5.8		5.7	4.1		9.5	6.4	
Rate difference		-0.8	Ref		-0.7	0.5106		-1.6	0.2386		-3.1	0.0007
Percentage rate reduction		-22%			-11%			-28%			-33%	

* Low <5.1 doses per thousand residents (log dose rate <1.80); medium = 6.8 to 20.2 doses per thousand residents (log dose rate 2.05-3.06); high naloxone penetration >21.9 doses per thousand residents (log dose rate >3.13)

**Pre-OPP period = Jan 1, 2000 to Dec 31, 2006. Post-OPP period = Jan 1, 2007 to Dec 31, 2012

***P-values indicate significance of difference between neighborhood strata and reference (neighborhoods with no naloxone) controlling for population density

Abbreviation:

OPP = overdose prevention program

OD = overdose

Table 3.4. Multivariable Regression Results for Neighborhoods with any Naloxone Distribution*
(2007-2012)

	Univariate (crude) models			Final adjusted model		
	Parameter estimate	SE	p-value	Parameter estimate	SE	p-value
Log naloxone dose rate	-1.07	0.309	0.0009	-1.12	0.289	0.0003
Persons per acre	-0.01	0.004	0.0027	-0.02	0.007	0.0025
Proportion of population age 60+	4.18	3.072	0.175	N/A**	-	-
Proportion of population female	2.29	6.939	0.7421	N/A	-	-
Proportion of population White non-Hispanic	0.57	0.638	0.3747	N/A	-	-
Proportion of single-person households	-3.29	2.742	0.2311	N/A	-	-

*n=63 neighborhoods

**N/A = Not applicable because variable did not contribute to multivariable model

Abbreviations:

SE = standard error

Figure 3.1. Age-adjusted Rate of Unintentional Drug Poisoning Deaths by Drug Type, NYC, 2000-2012

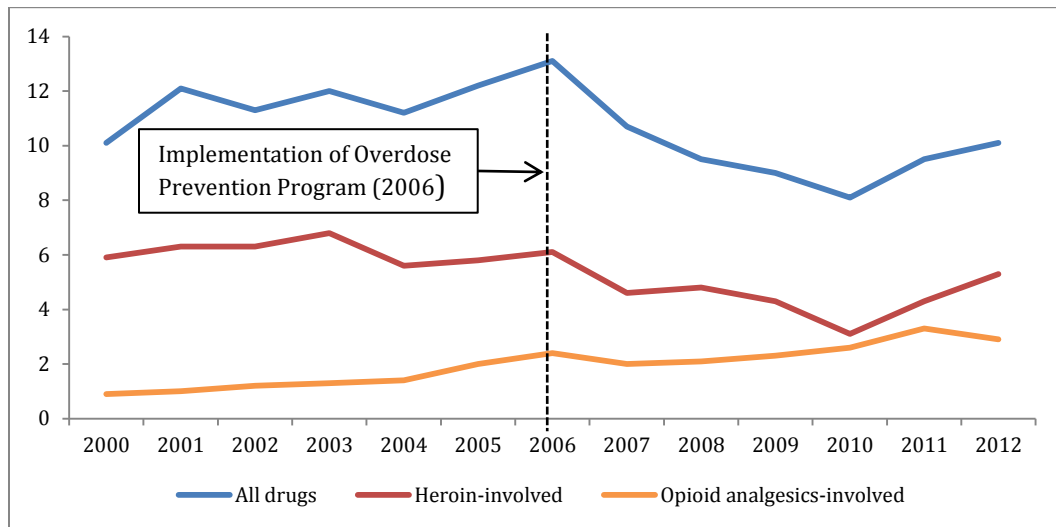
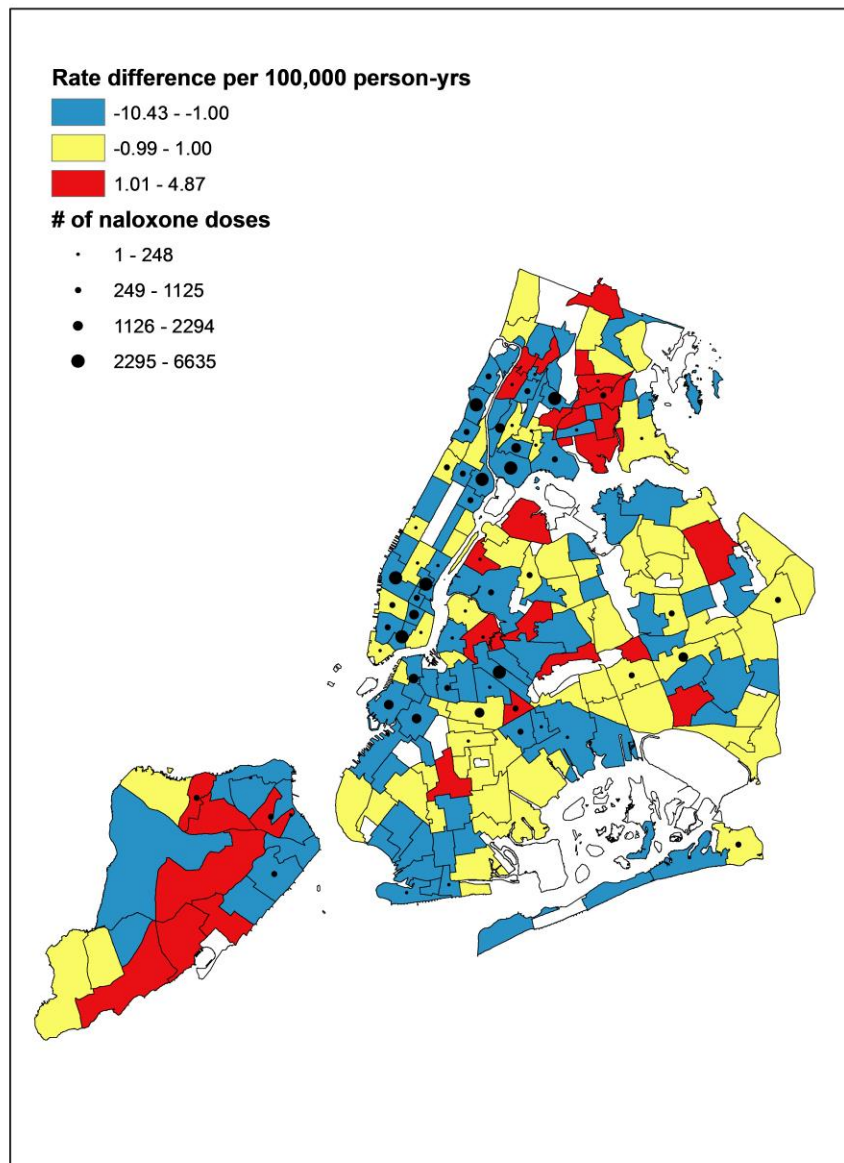


Figure 3.2. Difference in Heroin-related Overdose Mortality Rate (Post-OPP – Pre-OPP) by NYC Neighborhood Tabulation Area (NTA) and Number of Naloxone Doses Dispensed (Post-OPP)



Chapter 4: Using Spatial Methods to Evaluate Overdose Prevention in the Lower East Side, New York City, 2000–2012

4.1. Introduction

Overdose deaths in the United States (US) have nearly quadrupled since 2000, and are now the country's largest cause of injury-related death.¹ The increase in this epidemic has been seen most acutely in recent years, when the rate of heroin-related overdose rose from 1.0 per 100,000 in 2010 (n=3,036) to 2.7 in 2013 (n=8,257).¹ New York City (NYC) has experienced a similar trend. Between 2010 and 2013, the rate of heroin-related overdose deaths rose each year, from 3.1 per 100,000 in 2010 (n=209) to 6.2 in 2013 (n=420).²

With the burden of heroin-related overdose rapidly increasing, there is a critical need to design, implement, and evaluate effective interventions that decrease overdose mortality. Community-based overdose prevention education with naloxone distribution is one such intervention that has seen increasing popularity in the US. This intervention, which has been implemented in 27 states and the District of Columbia, provides training to drug users and their social networks in overdose risk factors, recognition of opioid overdose, and appropriate responses, including administering naloxone hydrochloride, an opioid antagonist that reverses the effects of an opioid overdose.³ According to a 2012 Centers for Disease Control report, overdose prevention programs (OPPs) have distributed naloxone to over 53,000 individuals and have received reports of over 10,100 overdose reversals since 1996.⁴

A New York State law passed in July 2006 made layperson administration of naloxone a legal, first-aid response to opioid overdose. Since then, non-medically trained community members in NY, including drug users and their friends and family members, can receive training in overdose prevention and two doses of naloxone which comes in an ‘overdose rescue kit.’ Overdose prevention trainings are provided by community-based organizations that serve drug users, facilitated by health educators, nurse practitioners or physician assistants, and typically last from 10 minutes to one hour. Overdose prevention trainings have been described in more detail elsewhere.⁵

Several studies have demonstrated that nonmedical bystanders trained at OPPs can appropriately respond to opioid overdose, including administering naloxone.⁶⁻¹⁴ Many of these studies, however, lack systematic follow-up methods, rely on self-reported naloxone utilization data only from those participants who return to the OPP, and suffer from small sample sizes and short follow-up periods. Despite the proliferation of OPPs in response to the rising epidemic, rigorous analyses of the population-level effectiveness of these programs are sparse. Only one study was designed to show population-level effects, and it reported that communities with comprehensive OPPs experienced decreases in overdose mortality, compared to communities without OPPs.¹⁵ No studies have delineated the geographic boundaries of the area in which these interventions are effective, though studies of other harm reduction programs have done so, suggesting the need for locally sited interventions.¹⁶⁻¹⁸ Further studies of community-based overdose prevention programs are needed to describe and evaluate the public health impact of OPPs in reducing mortality associated with opioid overdose,¹⁹ and particularly, to determine how interventions should be sited in order to maximize their effects.

In order to address this gap, this study aims to examine the public health impact of a community-based OPP in NYC's Lower East Side by testing the hypothesis that overdose risk increases with distance from the OPP location. One other study to date has used this method to test intervention effects on overdose mortality, by examining mortality risk as a function of distance.²⁰ This rationale derives from Bradford Hill's causal criterion of specificity, which states that a causal association is more likely if the association is at a specific site among a specific population.²¹

The study will use overdose mortality surveillance data, comparing mortality rates before and after the implementation of the OPP, as a more thorough and robust source of information than self-reported naloxone utilization data, which is incomplete and subject to selection bias.

Because the surveillance data is derived from the NYC Office of the Chief Medical Examiner, which is responsible for investigating all deaths of a suspicious nature, this data is believed to represent the census of all heroin-related overdose deaths in this NYC neighborhood. A study period of 13 years (2000-2012) will allow for a more stable analysis of differences between pre- and post-implementation periods, and is less likely to be subject to chance fluctuations in overdose rates year to year.²²

The Lower East Side's OPP has the longest-running overdose prevention program in the city, which began as a pilot in 2004, and has been described elsewhere.²³ This OPP serves as an opportunity to evaluate the community-level effects on an OPP's surrounding area.

The Lower East Side (LES) neighborhood in NYC is home to a population representative of New Yorkers overall. LES mortality and premature mortality rates, proportion of residents by

age, living in poverty, foreign-born, White, Hispanic, without health insurance, and proportion of people who report fair or poor health, mental illness, and serious psychological distress are similar to that of NYC overall.²⁴ The rate of drug-related deaths and drug-related hospitalizations are also similar to those of NYC as a whole.²⁴ This study's results could be used to shape policy and direct responses to opioid overdose in NYC and elsewhere.

4.2. Methods

4.2.1. Data Collection and Measures

Unintentional Heroin-related Overdose Deaths

Data were derived from a NYC surveillance database of unintentional opioid poisoning deaths from years 2000 to 2012 that comprised of two linked data sources: death certificates and medical examiner records. The outcome of interest, unintentional drug poisoning death, was defined as the death certificate recorded (i) the manner of death as “accidental;” and (ii) the codes for underlying causes of death as “poisoning by a psychoactive substance (excluding alcohol or tobacco)” (ICD-10 codes X40-X44) or a “mental or behavioral disorder due to a psychoactive substance” (ICD-10 codes F11-16, F18-19) (n=6,582).

OPPs have predominantly been located within agencies that serve heroin users, such as syringe exchange programs. Individuals who used heroin were assumed to have been targeted by NYC's overdose prevention program (OPP). For this study, we limited to heroin-related overdose deaths in order to focus on those individuals who could have been targeted by the OPP (n=4,533). Toxicology results were derived from medical examiner records, and classified into drug categories by drug metabolites. Annual NYC surveillance of unintentional overdose reports

deaths that involve alcohol, benzodiazepine, cocaine, heroin, opioid analgesic, and methadone. Decedents may have had positive toxicology for other drugs as well. Cases were excluded if they were non-NYC residents (n=627). (See Figure 4.1 for flowchart of sample selection.)

Mortality records without a location of overdose were excluded from analysis (n=344). For this analysis, the outcome was limited to individuals who overdosed in the Lower East Side neighborhood of NYC (n=130). Location of overdose was chosen as the outcome, rather than location of residence or location of death, as that was the most precise location where naloxone could have been used to reverse the overdose. The Lower East Side was defined as the aggregation of three neighborhood tabulation areas that most closely aligned with the overdose prevention program's catchment area²⁵: the East Village, Chinatown, and the Lower East Side.

The Lower East Side Overdose Prevention Program (OPP)

NYC's first overdose prevention program was sited in the Lower East Side as part of a pilot program in June 2004. The overdose prevention program is housed within a community-based non-profit harm reduction organization that primarily serves injection drug users. Administrative data from the program was used to describe the number of individuals trained and the number of reversals reported aggregated for all years (2004-2012). For the evaluation of effects, the program was treated dichotomously, with the pre-implementation phase representing years 2000-2003 and the post-implementation phase representing years 2004-2012.

4.2.2. Procedures and Statistical Analysis

Locations of the intervention, overdose deaths, and population counts were geocoded using the NYC Department of Health and Mental Hygiene's geoprocessor GeoPortal. The average annual overdose rate per 100,000 population for the neighborhood was calculated for the pre-intervention phase (2000-2003) using 2000 Census population counts, and for the post-intervention phase (2004-2012) using the 2010 Census population counts. The rate difference and percent rate reduction were calculated, and the statistical significance of the difference was tested non-parametrically using Wilcoxon signed-rank.

Street walking distance from the intervention site to each overdose location was computed using the ArcGIS™ 10.2 Network Analyst extension. Street walking distance was defined as the shortest walkable route using city streets, and represented the most accurate measure of distance for individuals who access the OPP. Mean and median distance was calculated for each phase.

Overdose mortality records were divided into pre-intervention and post-intervention phases, and summed by census tract using geographic information software. Census tracts were chosen because they were the smallest geographical unit that displayed enough detail to allow for comparison across groups. Each census tract was assigned an outcome value, the number of heroin-related overdose deaths that occurred in that tract, and mortality rates were calculated using the population in each census tract. The average distance from overdose death to the intervention site was calculated for each census tract, as well as the distance from census tract centroid to the intervention site.

To visualize trends and anomalies in the spatial distribution of the data, dot distribution maps were created for each year, and choropleth maps of the census tract rate of overdose fatalities were created for pre- and-post intervention phases, and percent rate reduction from pre- to post-intervention.

To assess overdose mortality risk as a function of distance from census tract centroid to OPP, we plotted the post-intervention overdose mortality rate against distance, and used Poisson regression to quantify the association between overdose risk and distance to intervention. Census tracts served as the unit of analysis, and we tested the predictor, distance from the intervention, as both a continuous and a categorical variable. We used log of the 2010 census tract population as an offset term to account for the underlying population at risk, and determined that *p* values were significant if equal to or greater than 0.05.

Analyses were performed using ArcGIS (10.2), SPSS (17.0), and SAS (9.2).

4.3. Results

From 2004 to 2012, the LES OPP trained and dispensed naloxone to 1,239 individuals. A total of 232 overdose reversals using naloxone were reported by the program.

Between the years of 2000 and 2012, the annual number of heroin-related overdose deaths in the Lower East Side ranged from 4 to 14. (See Appendix VIII for a bar chart of overdose number by year, and Appendix IX-XXI for dot distribution maps of overdose deaths by year.) A total of 51 heroin-related unintentional overdose deaths took place in the Lower East Side in the pre-

intervention years 2000-2003 for an average annual overdose rate of 7.7 per 100,000 population, and 79 overdoses occurred in the post-intervention years 2004-2012, with an average annual overdose rate of 5.3 per 100,000 population (Table 4.1). The overdose rate decreased by 2.3 per 100,000 population, or 44%.

Street walking distance from location of overdose to the intervention site ranged from 1,525 to 8,921 feet. The median distance was 5,231 feet in the pre-intervention phase and 5,283 feet in the post-intervention phase (mean distance was 5,092 and 5,015, respectively). For histograms of distance frequencies pre- and post-intervention, see Appendix XXII and XXIII).

In the pre-intervention phase, annual average overdose rates by census tract ranged from 0.0 to 48.2 per 100,000 population. In the post-intervention phase, rates ranged from 0.0 to 20.3. Rate differences between the two phases ranged from -48.2 to 14.3, with 19 of the 30 (63%) census tracts experiencing a decrease or no change in overdose mortality rate. The census tract where the OPP was located saw the steepest decrease in heroin-related overdose deaths, from a rate of 7.8 per 100,000 population pre-intervention to 1.31 post-intervention (rate difference=-6.5, percent rate reduction = -496%). Rate differences overall for all census tracts were not statistically significant (Wilcoxon signed-rank $p=0.150$). Maps of overdose mortality rates by census tract for the pre-OPP implementation period (2000-2003) and the post-implementation period (2004-2012) are displayed in Figure 4.2.

Plotting distances from the census tract centroids to the site of the intervention against census tract overdose mortality rates post-intervention yielded a slope with correlation coefficient 0.42 and significance $p=0.02$ (Figure 4.3).

Univariable Poisson regression was also used to assess the relationship between distance to the OPP and overdose mortality. When distance was treated as a continuous variable, the association was statistically significant ($p=0.0002$), with each increase in foot distance representing an increase in risk by 0.0002. An individual is 1.22 times more likely to die from a heroin overdose for every 1,000 feet away from the OPP. When distance was treated as an ordinal variable with four categories, the category with the furthest distance (greater than 6,000 feet) yielded the largest risk relative to the closest distance category (less than 3,000 feet) (3.26 per 100,000 population, $p=0.0003$).

4.4. Discussion

Using surveillance data, this population-based approach to measuring the effectiveness of overdose prevention programming suggests that OPPs are associated with a reduced risk of heroin-related overdose mortality. The data show that heroin-related overdose mortality in NYC's Lower East Side decreased by 44% after the establishment of an OPP, and the neighborhood immediately surrounding the OPP experienced the steepest decrease. Mapping of overdose locations revealed that few overdoses occur in the immediate vicinity of the OPP. Regression analysis showed that, using street walking distance from overdose location to the OPP, every 1,000 feet from the OPP represents a 1.2 increase in risk of heroin-related overdose.

These findings suggest that placement of an overdose prevention program in an urban area suffering from high opioid overdose mortality rates may have a protective effect on those in the immediate surrounding neighborhood. They are consistent with the findings of other studies that have shown protective effects at the individual and population levels, and add to the literature by testing the intervention's effectiveness using a novel geospatial method. The specificity of the analysis, one of Bradford Hill's causal criteria, combined with results of other studies that demonstrate criteria such as biological gradient, plausibility, and temporality, lends evidence that the association between OPPs and reduced overdose mortality may be causal.²¹

This study also produces a new finding, that OPPs' effectiveness may have spatial limits, and that OPPs need to be sited locally, in communities where heroin use occurs, in order to confirm a protective effect.

There are several limitations in our analyses. First, because of the small sample of cases in this geographic area, rates may be unstable. For this reason, we combined multiple years of census tract data. This, however, means that trends internal to each study period were averaged. In fact, heroin-related overdose mortality decreased from 2005 to 2010 and increased from 2010 to 2012. These trends are obscured because the post-intervention phase is analyzed as an average across years.

This study did not assess the role of factors other than the OPP that may have contributed to the decrease in heroin-related overdose mortality that was demonstrated. It is possible that fewer individuals were using heroin and at risk of overdose, access to substance use disorder treatment

improved in the period after 2004, or heroin purity decreased compared to the years prior. Furthermore, while neighborhood-level data describing the demographic profile of heroin users were unavailable, citywide trends, such as the aging of the population and increasing use of opioid analgesics and benzodiazepines, would predict an increase the rate of overdose mortality. We expect that outside factors such as drug use prevalence or treatment access would have had a similar effect on all census tracts, and therefore the associations seen were due to the OPP. The fact that overdose rates decreased most substantially in the area immediately surrounding the OPP suggests that the program may have been responsible for at least some portion of the decrease in overdose mortality. However, future analyses could introduce these factors to specifically evaluate their effect on the association between the OPP and overdose mortality.

This study did not take into account the movement of people and drugs, using geospatial data such as subway lines and gang activity. We presume that these things impact the way in which naloxone moves around the community. Future analyses would include these geospatial data.

While the study suggests the OPP may be associated with decreased overdose mortality at the ecologic level, these findings do not confirm that the same association exists at the individual level. For example, direct receipt of naloxone may not improve one's chances of surviving a heroin-related overdose if the individuals around that person at the time of the overdose do not know how to use naloxone to reverse the overdose. This study is not able to confirm that those individuals that received the intervention are the individuals that averted heroin-related overdose mortality.

This study is also unable to decipher exactly what causal pathway might explain the association. The program provided overdose prevention education, such as techniques to reduce overdose risk, and naloxone, as well as many other services geared towards the reduction of harm among people who use drugs. This study is unable to differentiate between the effects of the services the program provided during the study period. However, the program was established in 1992, and the decrease in overdose mortality did not occur until many years later, which suggests that the introduction of the OPP, and not other program services, may have contributed to the decrease.

Last, we evaluated the effectiveness of OPPs using one neighborhood only, and it may be that characteristics unique to NYC's Lower East Side lessen the degree to which these findings are generalizable to other neighborhoods and cities. The demographic make-up of the Lower East Side, however, is not particularly different from the demographics of the city as a whole, so we suspect that the protective effects of OPPs may be replicated if studied in other contexts. This study supports the findings of Walley and colleagues, which also showed an ecologic effect among communities in Massachusetts.¹⁵ It also supports the studies that have reported of OPPs at the individual level.

To conclude, our study adds to the evidence supporting OPPs as an effective public health intervention, and extends these findings by suggesting the intervention, to maximize effectiveness, needs to be sited locally. Because OPPs are some of the most promising interventions to address the growing burden of overdose mortality, they may prove a crucial element to reversing the current national mortality trends. As the trend in overdose mortality

continues to rise, both in NYC and nationally, public health agencies and community-based organizations in areas with high overdose mortality rates may use these findings to support the implementation and expansion of OPPs in order to decrease the number of lives lost to opioid overdose.

Table 4.1. Overdose Mortality in the Lower East Side, NYC, 2000-2012

	Pre-intervention (2000-2003)	Post-intervention (2004-2012)
Number of years	4	9
Total # of OD's	51	79
Average annual # of OD's	12.8	8.8
LES population estimate ¹	166,379	164,937
Average annual OD rate/Pop (per 100,000)	7.7	5.3
Rate difference		-2.3
Percentage reduction		-30.6%

¹For pre-intervention, population estimates come from the 2000 Census. For post-intervention, population estimates come from the 2010 Census.

Abbreviations:

NYC = New York City

OD = overdose

LES = Lower East Side

Pop = population

Figure 4.1. Flow Chart of Case Selection Criteria

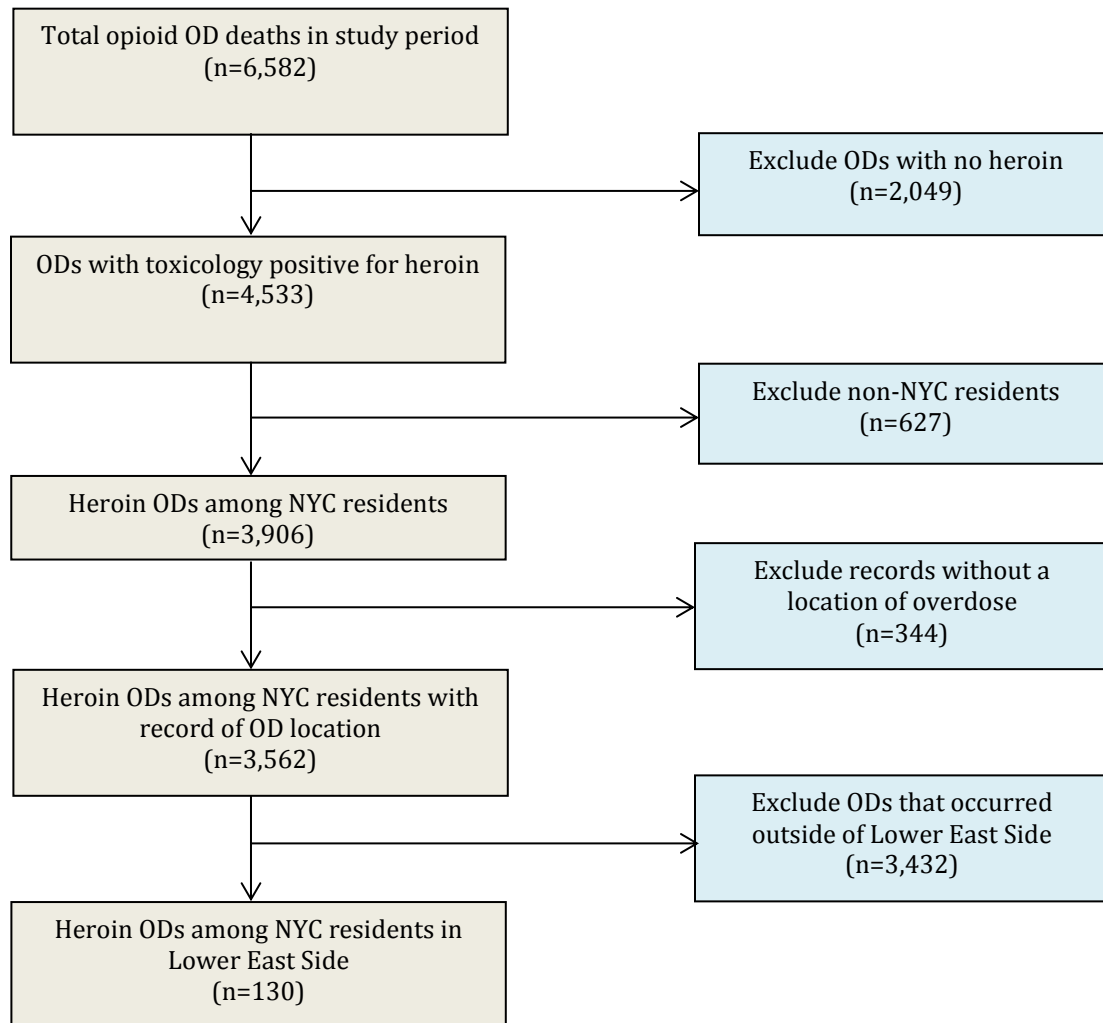


Figure 4.2. Overdose Mortality Rate by Census Tract, Lower East Side, NYC, Pre- and Post-implementation of OPP

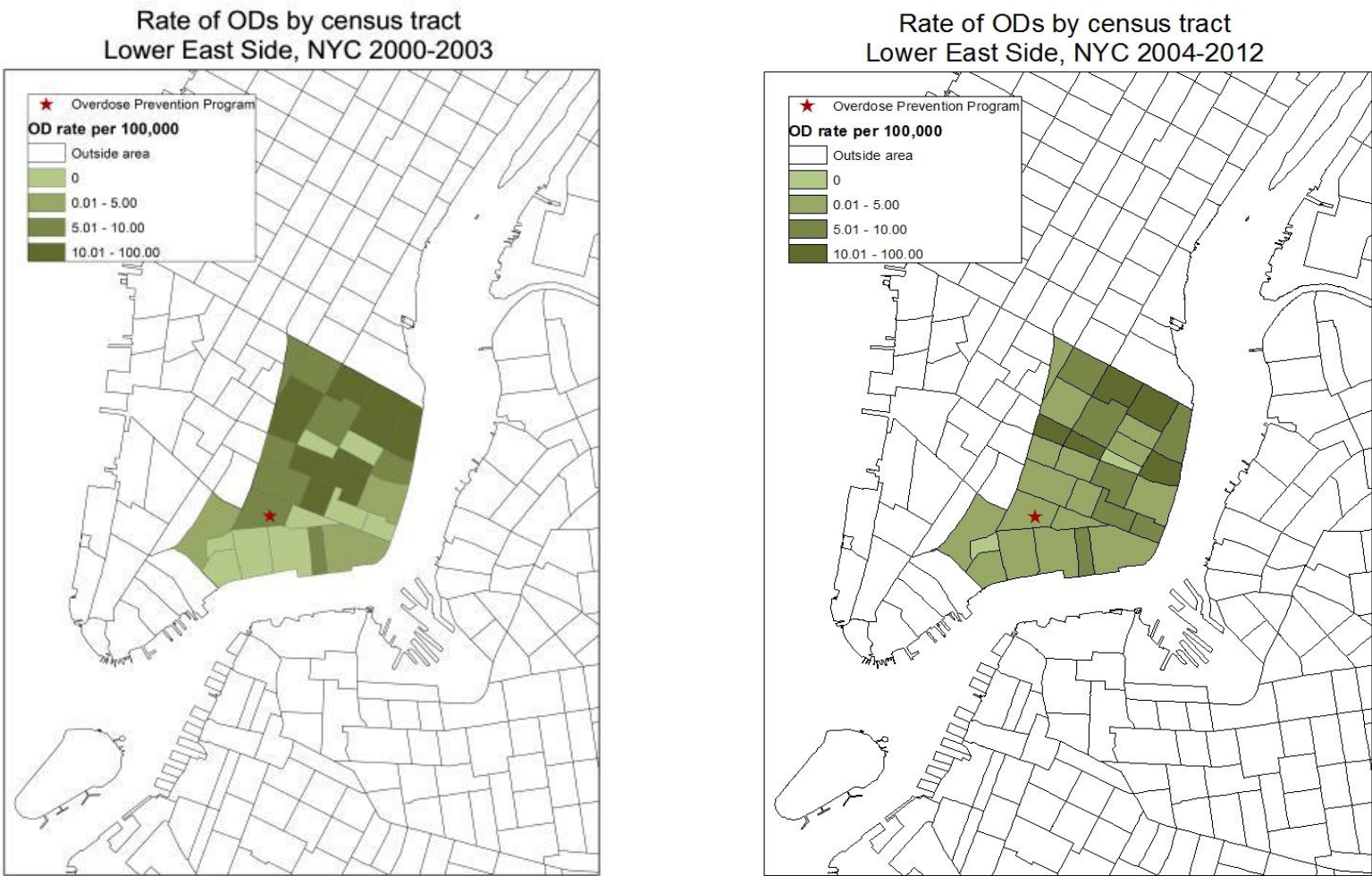
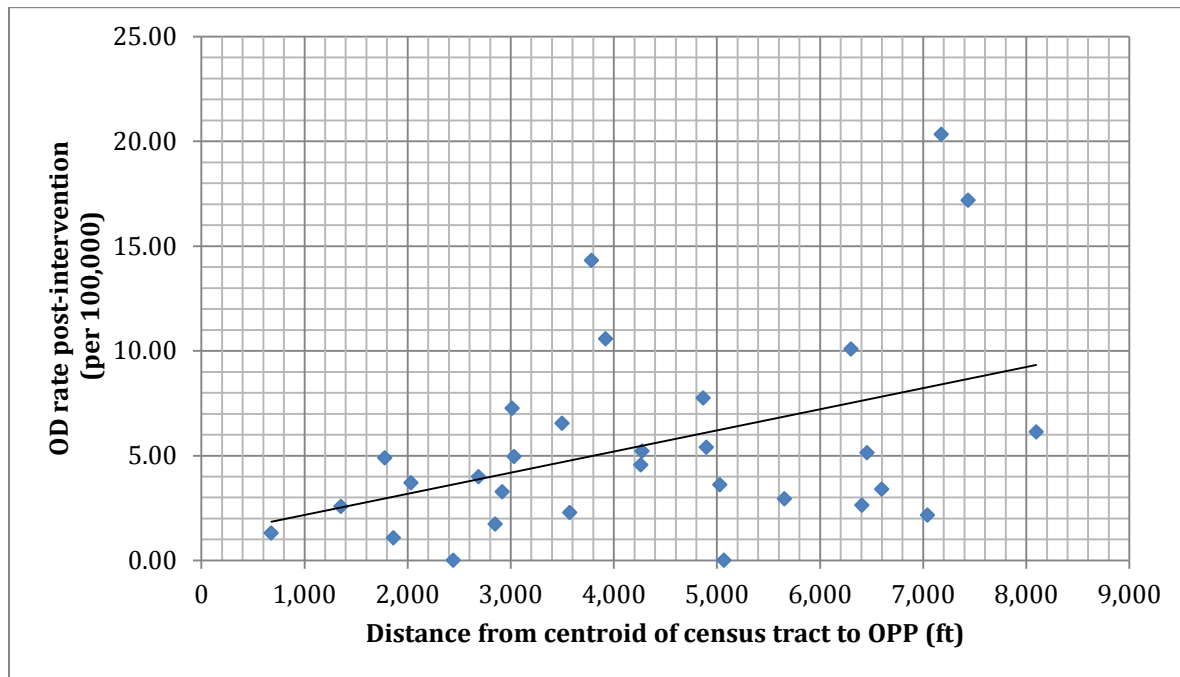


Figure 4.3. Distance between Census Tract Centroid and Intervention Site by Census Tract
Overdose Mortality Rate, Lower East Side, NYC, 2004-2012



Chapter 5: Discussion

5.1. Overview of the Dissertation

Heroin-related overdose in the United States (US)¹ and New York City (NYC)² represents a large burden of mortality, killing more individuals than traffic accidents. Despite this, there have been limited studies to date to demonstrate evidence-based interventions that successfully reduce overdose mortality.³ At the individual level, cross-sectional and small cohort studies suggest that overdose prevention programs (OPPs) can increase individual knowledge about overdose risk and train people to properly administer naloxone, an opioid antagonist that reverses the effects of heroin overdose. At the population level, only one study to date has demonstrated reductions in mortality,⁴ and none have been conducted in NYC, and which hosts one of the country's oldest and largest overdose prevention programs, dispensing over 55,000 doses of naloxone. Since the programs' implementation in 2006, rates of heroin-related overdose in NYC have decreased. However, no studies to date have determined if the decrease in heroin-related mortality is associated with the implementation of NYC's overdose prevention program.

This retrospective study aimed to test for an association between New York City's (NYC) overdose prevention program and heroin-related overdose mortality in NYC. Using 13 years of vital statistics data matched with medical examiner records (2000-2012), representing the census of heroin-related overdose mortality during this time period, I used three different analytic approaches to identify and describe the relationship between NYC's OPP and heroin-related overdose mortality. I hypothesized that the association between the intervention and reduced mortality could be demonstrated both temporally and spatially.

In Chapter 2, I specifically tested the hypothesis that *implementation of the OPP in 2006 reduced the rate of heroin-related overdose mortality, after accounting for factors other than the OPP that might explain temporal change in overdose mortality, between 2000 and 2012*. To do this, I described heroin-related overdose mortality and compared demographic characteristics of overdose decedents prior to OPP implementation with the demographic characteristics of overdose decedents post-implementation. I then used interrupted time series analysis to compare the level and trend in overdose mortality before and after the introduction of the overdose prevention program, analyzing NYC as a whole. I employed a negative control outcome to assess whether an association between the intervention and the change in level of overdose mortality may have been due to unmeasured confounding.

In Chapter 3, I tested the hypothesis that *the reduction in heroin-related overdose mortality rate between the seven years preceding the implementation of the OPP and the six years following its implementation was greater in NYC neighborhood tabulation areas in which the OPP was implemented, compared with neighborhood tabulation areas in which no OPP was implemented*. I mapped overdose prevention programs using geographic information systems, and quantified the number of naloxone doses dispensed by neighborhood. Use of a spatial scan statistic allowed me to detect geospatial clusters of heroin-related overdoses and compare neighborhoods with greater intervention penetration with neighborhoods with less intervention penetration to see if they experienced greater decreases in overdose mortality using multivariable regression.

In Chapter 4, I tested the hypothesis that *within the neighborhood of an OPP, risk of heroin-related overdose death increased with increasing distance from a naloxone dispensing site*. I

zoomed in to the Lower East Side of Manhattan, used as a model, and examined overdose mortality risk as a function of distance from the overdose prevention program at a more granular level. I calculated street walking distance from the program to each overdose mortality location. For each census tract, I calculated and mapped overdose mortality rates, and used Poisson regression to test for an association between distance from the census tract centroid and the number of overdose deaths per census tract. The main findings and interpretations of each of these analyses are summarized in the next section.

Together, these analyses, using three different statistical and geospatial techniques, help elucidate the relationship between NYC's overdose prevention program and heroin-related overdose mortality.

5.2. Summary of the Findings

5.2.1. Chapter 2

Between years 2000 and 2012, 3,906 individuals died of heroin-related overdose in NYC. In the period prior to implementation of OPP (January 2000 - June 2006), an average of 165 heroin-related overdose deaths (age-adjusted rate (AAR) 4.9 per 100,000) occurred every six months. In the years after implementation (July 2006 – December 2012), 136 deaths (AAR 3.8 per 100,000) occurred every six months on average, representing a 22% decrease in age-adjusted mortality rate.

Interrupted time series analysis (ITS) is a method commonly used to test interventions implemented at a clear point in time when data has been collected routinely prior to and after the

implementation of the evaluation. It allows for the comparison of levels and trends in an outcome, using the pre-implementation phase as a control, and has been shown to be a powerful analytic tool, demonstrating similar results to that of cluster-randomized controlled trials.⁵ Because New York State passed a law allowing for OPP implementation, allowing us to see a clear point in time that divides pre- and post-intervention phases, and because heroin-related overdose mortality surveillance exist for 6.5 years prior to the law's passage and 6.5 years after, ITS was an appropriate method to test the effects of the OPP intervention over time.

Using segmented regression, the term representing the change in trend following implementation of the intervention was not statistically significant. We therefore were able to remove this term from our analysis, which means we did not allow the slope to vary between implementation periods. Using this form of the model, the level of heroin-related overdose mortality decreased by 16% following implementation of OPP. Though this effect was not statistically significant (RR 0.84; CI 0.62, 1.15), the study included the universe of heroin-related overdose deaths rather than a sample of cases, so significance testing to determine the likelihood of a change due to chance is of limited interpretability. I interpret any change in mortality to be considered a true change, and not one occurring due to chance.

I conducted several sensitivity analyses to test the robustness of the results. Adding three different covariates that may have confounded the association between the OPP and heroin-related mortality (drug detoxification, OD prevention education, opioid-related hospitalization), each separately, resulted in a decrease in effect size by 1-3%. Results did not differ significantly

when outliers were removed, when lag periods were introduced or when the changepoint was moved.

I used a negative control outcome, opioid analgesic-related overdose mortality, to test whether the findings may have been associated not with the intervention, but with other spurious factors. This technique is particularly useful to detect confounding in observational studies when randomization is not possible. If the OPP intervention is found to have the same effect on opioid analgesic-related overdose, which should be unaffected by the intervention, that would suggest that unmeasured confounders, not the OPP, contributed to the decrease in heroin-related mortality. Using the same segmented regression model, the intervention was found to have the opposite effect. Implementation of the OPP was associated with a 6% increase in opioid-related overdose mortality, suggesting that the intervention's protective effects against heroin-related overdose were specific to the intervention and not unmeasured confounders.

While a strength of ITS is its ability to compare post-intervention levels and trends using pre-intervention levels and trends as controls, one of its limitations is that the exposure is assumed to be homogeneous over the post-implementation period. In fact, in NYC, OPPs increased in number and size between the years 2006 and 2012. ITS also requires many units of observation to be sufficiently powered. Because this analysis only had 26 6-month periods, it may have been underpowered to detect a change in trend post-intervention. Last, because this study spanned 13 years and relied on observational data, it is difficult to identify covariate measures that are consistently collected over the entire study period. As such, several covariates that ideally would have been modeled, such as buprenorphine utilization and incarceration, as they theoretically

may confound the relationship between exposure and outcome, were unable to be included in the analysis.

My findings closely replicate the findings of a similar ITS study in Massachusetts, where an 18% decrease in opioid-related overdose mortality was found in communities with heavily implemented overdose prevention programs.⁴ Given that the ITS analysis examined NYC as a whole, and not merely the parts of NYC with heavily implemented OPP, I suspect that the effect size found was subject to dilution. By limiting the analysis to the parts of NYC with OPP, in Chapter 3, I intended to get a more accurate estimate of the intervention's effects.

5.2.2. *Chapter 3*

During the years prior to OPP implementation (2000-2006), an average of 1.14 heroin-related OD deaths occurred in each neighborhood annually (median neighborhood OD rate per 100,000 population over age 18 per year = 0.55). This rate decreased to an average of 1.00 death per neighborhood per year in the years after implementation of the intervention (2007-2012, median neighborhood OD rate per 100,000 population over age 18 per year = 0.48).

Measures of the locations and volume of NYC overdose prevention trainings were operationalized using the locations from which and the number of naloxone doses dispensed. In the first six years of NYC's OPP, 57,097 naloxone doses were dispensed. In order to isolate neighborhoods with any intervention in order to more accurately measure effects, I mapped intervention locations and summed naloxone doses by neighborhood. I found that one third of NYC neighborhoods had any OPP in the six years post-OPP implementation. The mean number

of naloxone doses dispensed per neighborhood over six years was 300 (range 0 - 6,635), or 1.33 doses per 1,000 neighborhood population over age 18 per year.

Spatial scans, a method that detects potential clusters where risk is elevated relative to everywhere in NYC outside of the cluster, detected three statistically significant clusters of heroin-related ODs prior to OPP: South Bronx/Northern Manhattan, Central and Downtown Brooklyn/Lower East Side Manhattan, and East Brooklyn. After implementation of OPP, three significant clusters remained but clusters decreased in geographic size, suggesting fewer areas with heightened risk: South Bronx, Lower East Side Manhattan, and Central Brooklyn. Cluster relative risk in the neighborhood with minimal naloxone coverage (Central Brooklyn), where we would not expect to see a reduction in overdose risk, did not change: risk of overdose mortality in this area was similar in the pre-OPP period to that of the post-OPP period.

I categorized neighborhoods into four strata based on the total number of naloxone doses dispensed in that neighborhood per neighborhood resident: no naloxone, low naloxone penetration (<5.1 doses per 1,000 residents), medium naloxone penetration (6.8 to 20.2 doses per 1,000 residents), and high naloxone penetration (>21.9 doses per 1,000 residents). Examining overdose mortality revealed that all strata experienced decreases in OD mortality from pre-OPP to post-OPP. High naloxone penetration neighborhoods experienced the largest rate decrease (rate difference = -0.8 in no naloxone neighborhoods, -0.7 in low penetration neighborhoods, -1.6 in medium penetration neighborhoods, and -3.1 in high penetration neighborhoods). Neighborhoods with no naloxone experienced a decrease in OD mortality similar to that of neighborhoods with low naloxone penetration. The difference in rate between high penetration

and no naloxone neighborhoods was statistically significant ($p=0.0007$) after controlling for neighborhood population density. Other neighborhood characteristics (age, gender, race, household composition) were not significantly associated with overdose mortality rate difference.

I conducted sensitivity analyses to test whether the large amount of neighborhoods with no naloxone had impacted the outcome. Limiting the analysis to only those neighborhoods with any naloxone distribution and treating the predictor as a continuous variable confirmed the findings. The rate of naloxone doses dispensed per neighborhood population was statistically significantly associated with overdose mortality rate difference after controlling for population density ($p=0.0003$). For every increase of 10 naloxone doses per 1,000 population, we would expect to see 2.6 overdose deaths averted.

A major strength of this analysis is in its rich overdose surveillance database, which enables mapping of overdose locations within neighborhoods and allows for neighborhood comparisons. This database also allows us to limit the analysis to only those overdoses in which toxicologies were positive for heroin, as heroin users and their social networks were the primary target for OPPs. A limitation of this method, however, is that we do not know if the neighborhoods where naloxone was dispensed are the same neighborhoods where naloxone is used. Because neighborhoods are all located within a relatively small geographic area, and NYC has an accessible public transit system, diffusion of the intervention may have occurred. This could have contributed to the decrease in overdose mortality found in the neighborhoods with no naloxone dispensing locations. Another limitation of this analysis is that while the exposure was measured as naloxone does, individuals received overdose prevention education along with

naloxone. This analysis is unable to disentangle whether the effects of naloxone from those of overdose prevention education. Last, this study takes place at the neighborhood level only. It cannot determine if individuals who receive overdose prevention training and naloxone personally experience protective effects, or if this finding is solely ecologic. To answer this question, hierarchical linear modeling would be ideal. However, data on naloxone use at the individual and neighborhood level was unavailable, so this method was not possible.

5.2.3. *Chapter 4*

In the Lower East Side Manhattan, which hosted NYC's first OPP, an average of 12.75 heroin-related overdose deaths occurred annually in the years prior to the implementation of OPP (2000-2003) and 8.78 deaths in the years after implementation of OPP (2004-2012). Average annual rate per 100,000 population decreased by 30.6%, from 7.66 to 5.32.

Using a method that has been applied to evaluate a safer injection facility in Vancouver, Canada,⁶ I tested the hypothesis that mortality risk increases as distance from the intervention increases. This rationale derives from Bradford Hill's causal criterion of specificity, which states that a causal association is more likely if the association is at a specific site among a specific population.⁷ If the OPP did in fact exhibit a protective effect, we would assume that distance from the OPP to the location of OD mortalities would increase after implementation of the OPP. In fact, median street walking distance from overdose location to OPP was slightly larger after implementation of the LES OPP, 5,231 feet in the pre-intervention period compared to 5,283 feet in the post-intervention period.

Nearly two thirds of census tracts (63%) in the Lower East Side saw a decrease or no change in overdose mortality from pre-OPP to post-OPP period, with rate differences ranging from -48.2 to 14.3 per 100,000 population. The census tract where the OPP was located experienced the greatest decrease in heroin-related overdose death, from 7.8 per 100,000 in the pre-OPP period to 1.31 in the post-OPP period (rate difference -6.5, percent rate reduction -496%). Census tract overdose mortality rate in the post-OPP period was correlated with distance from the OPP, and this correlation was statistically significant ($r=0.42$, $p=0.02$). Univariable regression analysis showed that distance from the intervention, measured both as a continuous and a categorical variable, was significantly associated with overdose mortality risk. When distance was treated as a continuous variable, each increase in foot distance represented an increase in risk by 0.0002 ($p=0.0002$). An individual is 1.22 times more likely to die from a heroin overdose for every 1,000 feet away from the OPP. When distance was treated as an ordinal variable with four categories, the category with the furthest distance (greater than 6,000 feet) yielded the largest risk relative to the closest distance category (less than 3,000 feet) (3.26 per 100,000 population, $p=0.0003$).

The important contribution of this analysis is its suggestion that OPPs' effectiveness may have spatial boundaries. In order to maximize their protective effects, OPPs need to be sited locally. A limitation of this study was its small sample of cases, which necessitated the aggregating of multiple years of census tract data. As such, trends internal to each period were averaged, obscuring the fact that, in the post-OPP period, rates decreased from 2006 to 2010 and then increased from 2010 to 2012. Similar to the analyses in Chapter 3, this chapter is also limited by its inability to distinguish between the effects of overdose prevention education and naloxone,

and is also only able to show ecologic effects, which again may not represent an association at the individual level. This is the first study of its kind to measure the link between overdose risk and distance to OPP. In order to better understand this relationship, the method would need to be repeated in other neighborhoods.

5.3. Strengths and Public Health Significance

This study has a number of strengths. The study sample, using data from the NYC Office of the Chief Medical Examiner, which is responsible for investigating all deaths of a suspicious nature, comprises a near census of heroin-related overdose deaths among NYC residents during the study time period.⁸ In-depth toxicology results allows for the restriction of the sample to those overdoses positive for heroin use, which is the specific population targeted by the OPP intervention. The large sample size, nearly 4,000 individuals, enables stratification by year and by neighborhood in order to isolate and identify patterns. By studying 13 years of data, conclusions regarding differences between pre-OPP and post-OPP periods are relatively stable and less suspect to chance fluctuations in the data which occur year to year.

A key methodological strength to this study is its use of multiple innovative approaches to test for population-level effects of the overdose prevention program. Using interrupted time series allows for the assessment of the intervention's effects on the level and trend of the outcome, controlling for other time-varying trends that occurred in NYC during the study period, namely the decrease in detoxification admissions and the increase in opioid use, as measured by opioid-related hospitalizations. This method, using pre-intervention data as controls, has been found to be comparable to measures of cluster-randomized, controlled trials.⁹ Using geospatial analytic

methods, this study is able to assess the effects of the intervention at a more granular level, first by comparing neighborhoods within NYC, and then by comparing census tracts within one neighborhood. Spatial covariate information was included in order to account for neighborhood-level differences that may explain an association between the intervention and any reduction in heroin-related overdose mortality.

By triangulating findings from both time series and geospatial methods, a case can be made for the protective effects of the OPP. While the findings from time series analyses were not statistically significant, they did show an association in the direction of a protective effect. This analysis evaluated the city as a whole, and Chapter 3 found that the majority of NYC neighborhoods hosted no intervention, suggesting that time series analysis repeated just among neighborhoods with the intervention, may reach statistical significance. These findings, in conjunction with two geospatial methods finding positive associations, suggest that the association between the intervention and heroin-related overdose mortality is likely not due to chance. While this association, which uses observational data only, cannot be interpreted as a causal relationship, these findings, in conjunction with findings from other studies, may together contribute to a building body of literature suggesting the association is causal.

This is the first study to demonstrate effects of NYC's overdose prevention program, and only the second in the country to demonstrate population-level effects of the intervention more generally. This study reproduces the findings of a similar interrupted time series conducted in Massachusetts, and adds to it by introducing novel methods that confirm the associations between the intervention and overdose mortality reductions.

A final strength of this study is its relevance and timeliness amidst a growing opioid overdose epidemic, both in NYC and across the US. Increasing resources and attention are turned to identifying evidence-based interventions that cities and states can implement to address the morbidity and mortality associated with opioid use. This study's findings can be a useful contribution as jurisdictions decide which interventions to implement, where to target them, and how to allocate resources in the most cost-effective manner.

5.4. Limitations

This study used observational data and was not subject to the rigors of a randomized, controlled environment, and as such, it is subject to several limitations. As such, I cannot assert that the associations described here are causal effects, because I cannot guarantee that they are unaffected by unmeasured confounding. The overdose prevention program is a two-part intervention which always included training on overdose risk reduction as well as naloxone dispensing. Because the two components were never administered separately and could not be measured separately, the effects that were found could have been attributed to either or both of the intervention components. This suggests that overdose prevention programs, in order to maximize the chance of impacting overdose mortality, should continue to offer the pairing of risk reduction education with naloxone, until further evidence is available. Second, data on the number of naloxone doses directly dispensed to individuals were unavailable, so the number of doses provided to OPPs was used as a proxy measure (in Chapter 3) of the intervention. It is assumed that OPPs do not dispense 100% of their naloxone supply, and thus, measurement of the intervention's magnitude was likely to be over-estimated. Accordingly, any findings are conservative, and likely due to less intervention than that which was estimated. Third, the intervention was evaluated using the

location in which naloxone doses were dispensed, though they could have been utilized in other locations (in Chapters 3 and 4). (Data on location of naloxone utilization was unavailable.) This could have violated the Stable Unit Treatment Value Assumption, which assumes that the effect of the exposure on one neighborhood is independent of the exposure on other neighborhoods.¹⁰ If this assumption were violated, intervention dissemination would have presumably misclassified naloxone doses from areas of higher penetration to areas of lower penetration, resulting in a conservative effect estimate, biasing findings towards the null. Fourth, for all analyses the intervention was evaluated dichotomously (pre versus post), which does not allow for variation in the amount the intervention was implemented over time. In fact, OPPs began in 2006 and have slowly increased in number and reach over time. By averaging intervention effects across years, variation over time is lost.

Because this intervention was not randomly assigned, we cannot assume that units of analysis (years, neighborhoods, census tracts) are exchangeable, meaning one unit would have had equal risk of overdose mortality, had OPP not been implemented.¹¹ Because areas with higher overdose mortality burdens were in fact targeted for the intervention, this assumption was violated. In order to account for these differences, covariates were introduced into multivariable models (time-varying covariates in Chapter 2, neighborhood-varying characteristics in Chapter 3), but residual, unmeasured confounding could have remained. Ideally, prevalence of heroin use could be controlled for over time and at the neighborhood-level, but measures were unavailable. A proxy, opioid-related hospitalizations, was available and used at the city level in Chapter 2, but could have been an incomplete proxy. Additionally, this variable was unavailable for units of geography smaller than the city as a whole. Other covariates that may have varied over time or

by neighborhood, such as polydrug use, substance use treatment access, and poverty, if available at the neighborhood level, would have improved the rigor of these analyses.

Last, all findings are applicable at the ecologic level only. Results found at the ecologic level cannot be interpreted to apply at the individual level. It could be that individuals directly trained in overdose prevention and who receive naloxone may not themselves experience the protective effects of the intervention, but those around them do. However, when an exposure affects many individuals simultaneously, ecologic designs such as those that study neighborhood effects, are often better equipped to answer a research question than individual-level designs.¹² Analytic techniques that take advantage of multiple levels of data, including both individual and neighborhood levels such as hierarchical linear models, were not possible because joint distributions of individual and neighborhood-level data was unavailable.

5.5. Policy Recommendations and Future Research Directions

Findings from this study will allow jurisdictions to calculate the number of naloxone doses need to effectively curtail the heroin-related overdose burden, a calculation that could not have been done previously.

The effectiveness of this intervention suggests that expanded access to OPP for heroin users and those at risk of witnessing heroin overdose could further reduce overdose mortality. While this study's findings do not suggest particular means of increasing access, policymakers have suggested that access to naloxone could be expanded through a number of strategies, using both programmatic and policy levers.

(1) OPPs need to be offered to individuals with minimal barriers in a low-threshold manner, requiring little time, no or minimal identifying personal information, and no qualifications or certifications. A recent study has shown that brief education, as short as five to 10 minutes, can achieve a high level of knowledge, comfort, and facility managing opioid overdose.¹³

(2) Policies that enable OPPs to dispense naloxone in wider areas at more hours of the day and night should be implemented. These include naloxone access laws; third party prescribing laws, which allow third parties, not solely those at risk of overdose themselves but those who may witness opioid overdose, to receive a prescription for naloxone with the intent for community-based, pre-hospital administration; non-patient specific prescriptions, or “standing orders,” which allow non-clinically trained personnel to dispense naloxone under a medical director’s license; and prescriber liability protections, which protect those who prescribe, dispense, or distribute naloxone to laypersons from criminal prosecution.¹⁴

(3) For those who could benefit from naloxone but are not able to or do not choose to access overdose prevention programs, naloxone needs to be more widely available in traditional clinical settings such as primary care clinics, emergency departments, and pharmacies. Physician and pharmacist education needs to be developed and implemented more widely, naloxone needs to be covered by both public and commercial insurance carriers, and/or naloxone could be available over-the-counter at pharmacies.

(4) At this time, naloxone is available in three formulations. Two of these require somewhat complicated assembly. (The third formulation, an auto-injector, is new to the market, has limited availability, and is nearly ten times as costly as the other formulations.) In order to increase access to naloxone more broadly, formulations will need to be easy to assemble, require

little training, are easy to carry with a person at all times, and are affordable. At this time, a few products are undergoing clinical trial, but are not yet available, with the exception of the auto-injector, Evzio.®

Future analyses could test the hypotheses that, by expanding access to naloxone through the programmatic and policy initiatives above, opioid overdose mortality rates will further decrease.

Because this study is the first of its kind, future research is needed to replicate, confirm, and better understand the findings described here. Specifically, analyses that utilize interrupted time series at the neighborhood level, analyzing only those neighborhoods which hosted OPP dispensing sites, could be an important contribution. Similarly, sensitivity analyses that repeat the ITS but use other statistical methods, such as ARIMA models, could confirm the findings in Chapter 2. Other types of time series methods that analyze trends year-by-year, such as linear or joinpoint regression or age-period-cohort modeling, could supplement the comparison of two periods conducted in Chapter 2. Year-by-year analyses such as these could help us better understand the association between OPPs and overdose mortality, particularly since a limitation of the post-OPP period in my study its lack of homogeneity with respect to the exposure, and overdose mortality rates decreased and then increased within the span of the period.

In order to confirm the findings described in Chapter 3, neighborhood-level analyses could be replicated using a different geographic area, such as community districts, United Hospital Fund neighborhoods, or police precincts, to determine if the finding is specific to the definition of the neighborhood utilized.

The distance analysis performed in the Lower East Side of Manhattan in Chapter 4 could be replicated in other neighborhoods that similarly have one fairly strong OPP, in order to determine if the correlation between distance and overdose risk is particular to the LES OPP or generalizable to other OPPs. Washington Heights, in northern Manhattan, is one such neighborhood that has hosted a strong OPP and kept rigorous records, and may be a good candidate for future research.

This study only analyzed heroin-related overdoses, as that was the community of individuals targeted by OPPs in NYC originally. However, overdoses involving opioid analgesics make up an increasing proportion of all overdose deaths. It is unknown to what degree this initiative may reduce opioid analgesic-related overdose mortality at the population level. Because it is physiologically similar to heroin, the effects of opioid analgesics can similarly be reversed with naloxone, but because use patterns may be different, it is unknown if the intervention would be equally effective. For example, the effectiveness of naloxone relies on the presence of a witness to the overdose victim who can administer naloxone. No research to date has determined if opioid analgesic overdoses occur in the presence of others to the same extent that heroin overdoses do. Repeating the analyses described here, focusing on opioid analgesic-related overdose, would be a particularly valuable contribution to the literature.

This study evaluated the overdose prevention program primarily using neighborhoods as the unit of analysis. In effect, I tested the theory of neighborhood effects: can an entire neighborhood experience health benefits through a health promotion program that touches just a few of its residents?

The theory of neighborhood effects is premised on the recognition that “social influences on health operate through many different processes, one of which may be the types of areas or neighborhoods in which people live.”¹⁵ Neighborhoods and their contexts can be both pathogenic and salutogenic, putting residents at risk of morbidity and mortality while also affording residents health-promoting opportunities.

By focusing on neighborhoods, we assume that regardless of whether or not an individual has been trained in overdose prevention, that individual enjoys the protective effects if he or she lives in a neighborhood in which others have been trained.

This is the first time that the theory of neighborhood effects has been tested using the NYC overdose prevention program. The findings here suggest that interventions that are delivered to a relatively small number of individuals can have important effects on population health. High naloxone penetration neighborhoods had as few as 11 individuals trained per 1,000 residents, yet saw a 33% decrease in overdose mortality rate from pre-OPP to post-OPP.

The idea that neighborhoods can provide health conferring effects on the individuals that live in them, and that interventions that improve neighborhoods may not need to be large, expensive, or far-reaching, has important implications.

This study demonstrates a framework for using extant, observational data to assess the impact of health interventions in the real world, where randomized treatment assignment is often not possible. Nonetheless, as public health practitioners and epidemiologists, we are challenged to

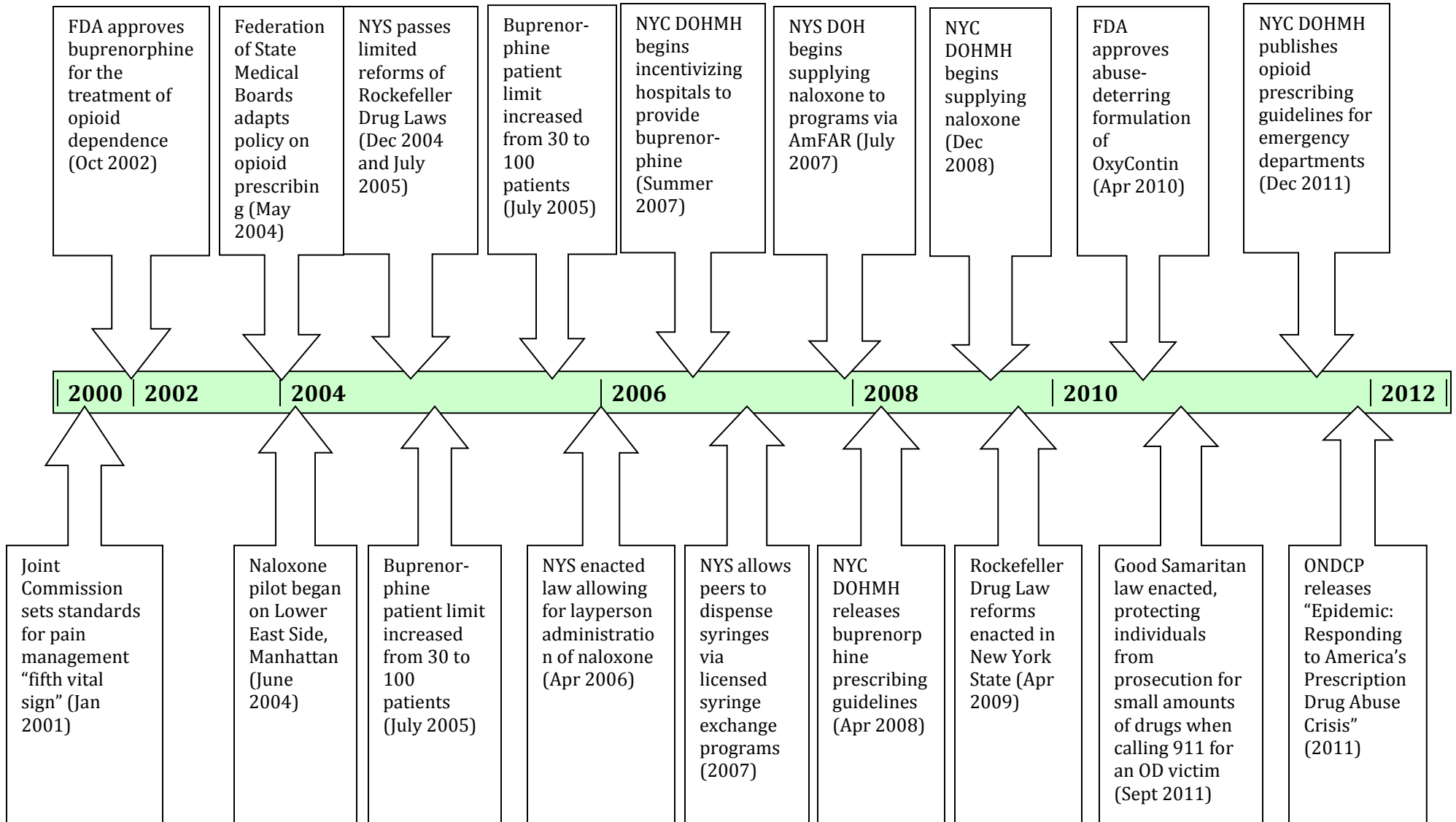
understand if and how our programs and policies are impacting the populations they affect.

What are the methods we can use, given imperfect measures, to try and understand what interventions work? In many situations in public health, we are “stuck with observational [data] to answer causal questions.”¹⁶

In this study, I used OPPs to test this framework – namely, by combining several methods, both temporal and spatial, of analyzing the effects of an intervention to try and infer causal effects. A similar framework could be applied to other community-based interventions where the impact on population health is unknown. This framework, which builds on methods such as directed acyclic graphs, instrumental variables, and propensity score matching, can add to the toolbox of epidemiologic methods for causal inference using observational data.

Appendix

Appendix I. Timeline of Key Policy Events Related to Overdose Mortality, New York City, 2000-2012



Appendix II. Interrupted Time Series Models using Segmented Negative Binomial (NB)

Regression

Saturated segmented NB regression model:

$$\text{Log}(E(Y)) = \beta_0 + \beta_1 \text{Time} + \beta_2 \text{OPP}_i + \beta_3 \text{TimePostOPP}_i + \log(\text{population})$$

Y is the independent outcome variable (number of unintentional heroin-related overdoses aggregated into 6-month periods). Linear trends over the study period were accounted for by using a time variable, expressed as one for January 1 through June 30, 2000 and increasing in integer increments for each period; β_1 is the model coefficient for the semiannual *Time* variable. The changepoint, introduction of OPP, was accounted for by using a dummy variable, *OPP*, expressed as zero for each six-month period from January 1, 2000 through June 30, 2006, and as one for each six-month period from July 1, 2006 through December 31, 2012. β_2 is the coefficient for the indicator variable for the implementation of OPP. β_3 is the model coefficient for the 6-month time periods following implementation of OPP, with all periods prior to implementation coded as zero, and starting with one for the first period of implementation (July 1- December 31, 2006) and increasing in integer increments for each period. β_k represents the effects for a set of covariates of interest (opioid-related hospitalizations (*Hosp*), drug detoxification (*Detox*), and overdose prevention education (*ODEduc*)).

Final segmented NB regression model

$$\text{Log}(E(Y)) = \beta_0 + \beta_1 \text{Time} + \beta_2 \text{OPP}_i + \log(\text{population})$$

Sensitivity analysis 1: Segmented NB regression model adjusting for detoxification

$$\text{Log}(E(Y)) = \beta_0 + \beta_1 \text{Time} + \beta_2 \text{OPP}_i + \beta_3 \text{Detox}_i + \log(\text{population})$$

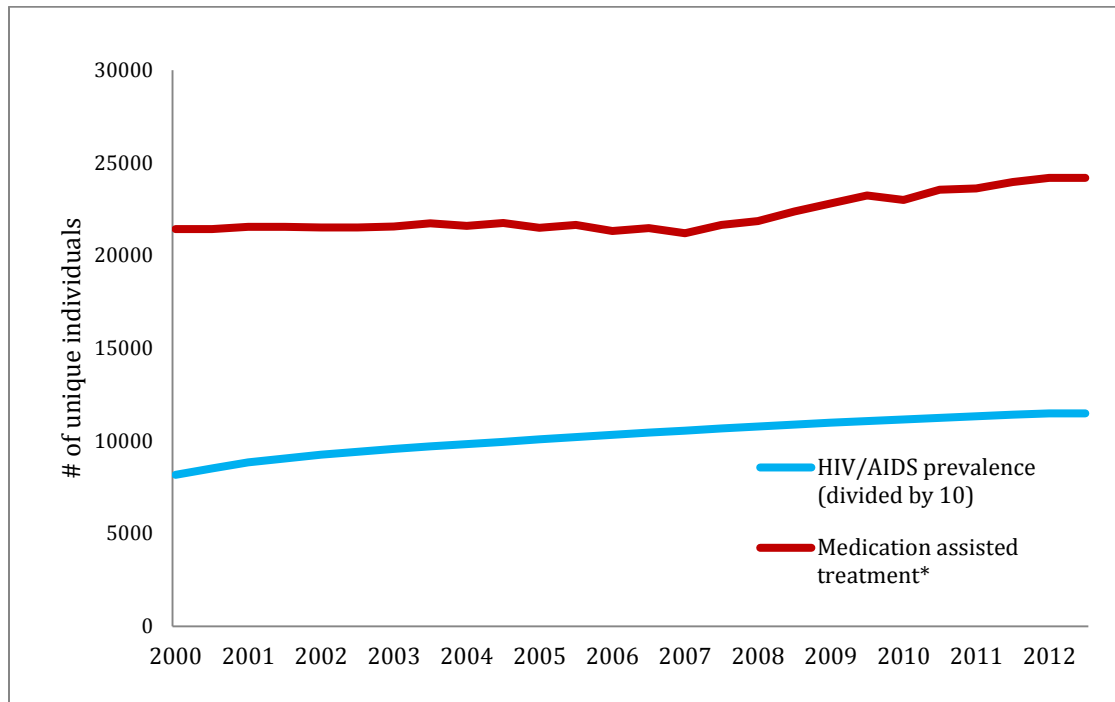
Sensitivity analysis 2: Segmented NB regression model adjusting for syringe exchange (proxy for OD prevention education)

$$\text{Log}(E(Y)) = \beta_0 + \beta_1 \text{Time} + \beta_2 \text{OPP}_i + \beta_3 \text{OD prevention education}_i + \log(\text{population})$$

Sensitivity analysis 3: Segmented NB regression model adjusting for opioid-related hospitalization (proxy for prevalence of opioid use)

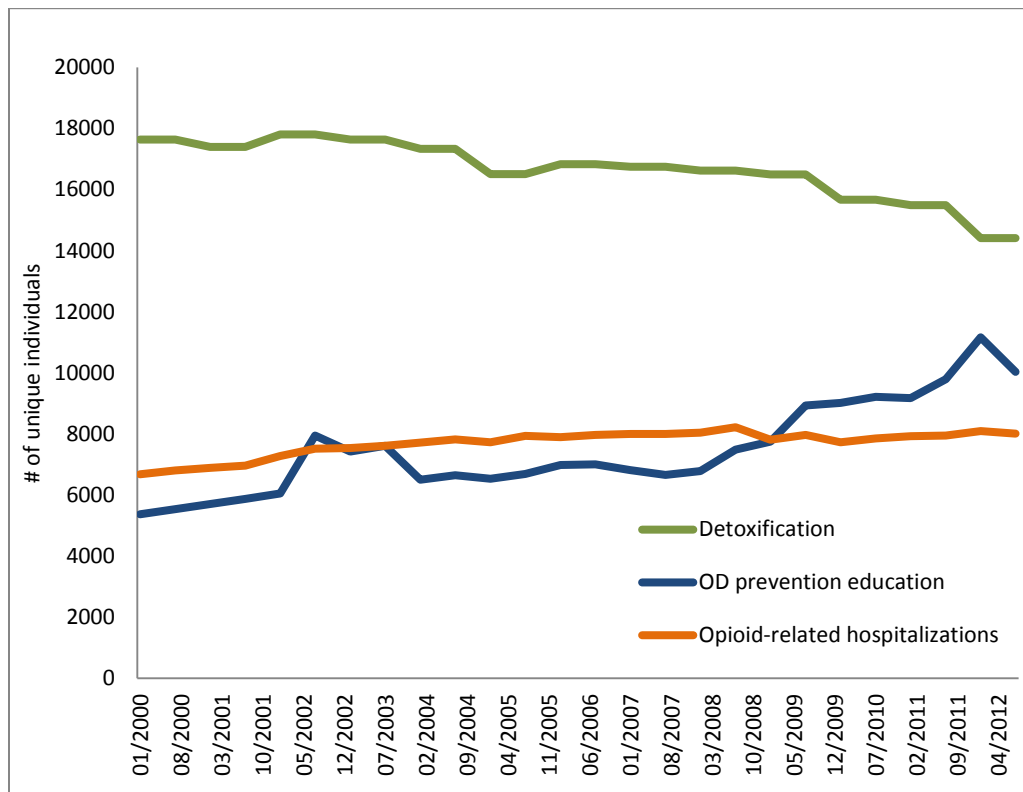
$$\text{Log}(E(Y)) = \beta_0 + \beta_1 \text{Time} + \beta_2 \text{OPP}_i + \beta_3 \text{Hospitalization}_i + \log(\text{population})$$

Appendix III. Time Plot of Unique Number of Individuals with Living with HIV/AIDS and in Medication Assisted Treatment by Year, New York City, 2000-2012

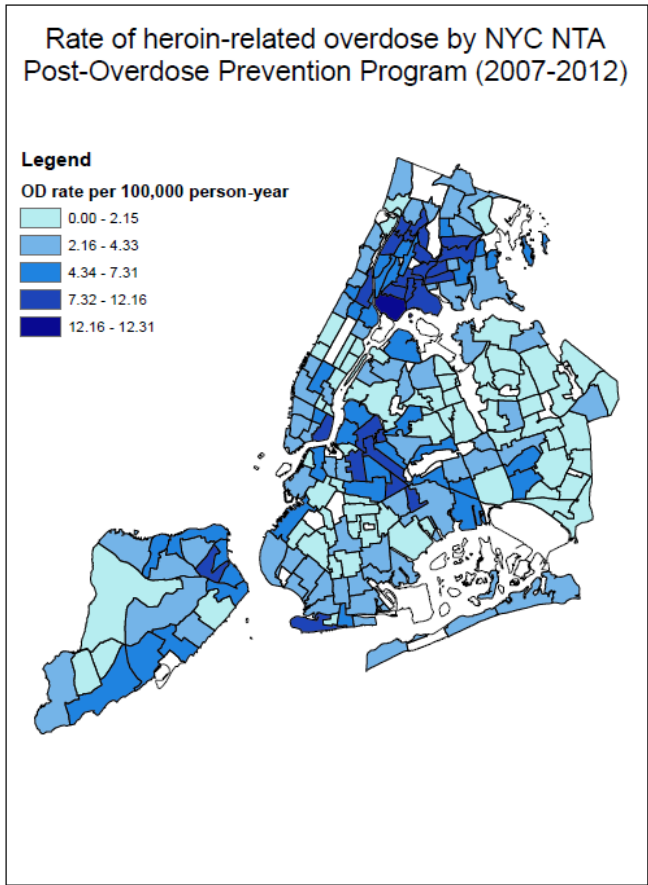
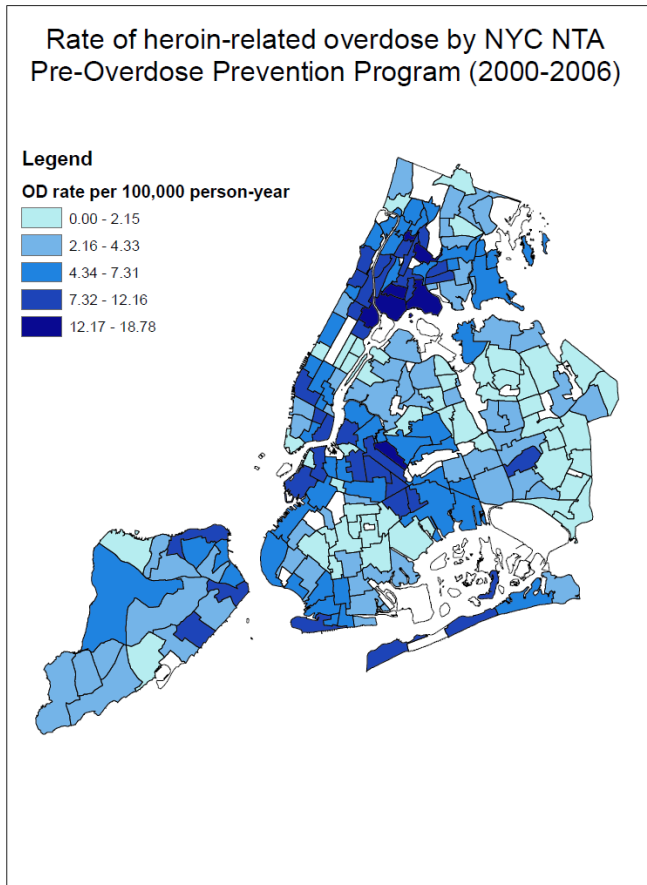


*Medication assisted treatment includes both buprenorphine and methadone maintenance.

Appendix IV. Time Plot of Unique Number of Individuals in Detoxification, Syringe Exchange, and Opioid-related Hospitalizations by 6-month Period, New York City, 2000-2012



Appendix V. Maps of Heroin-related Overdose Mortality by Neighborhood, NYC, 2000-2012



Change in rate of heroin-related overdose
by NYC NTA, 2000-2012
(Post-OPP - Pre-OPP)

Legend

Change in OD rate per 100,000 person-yr

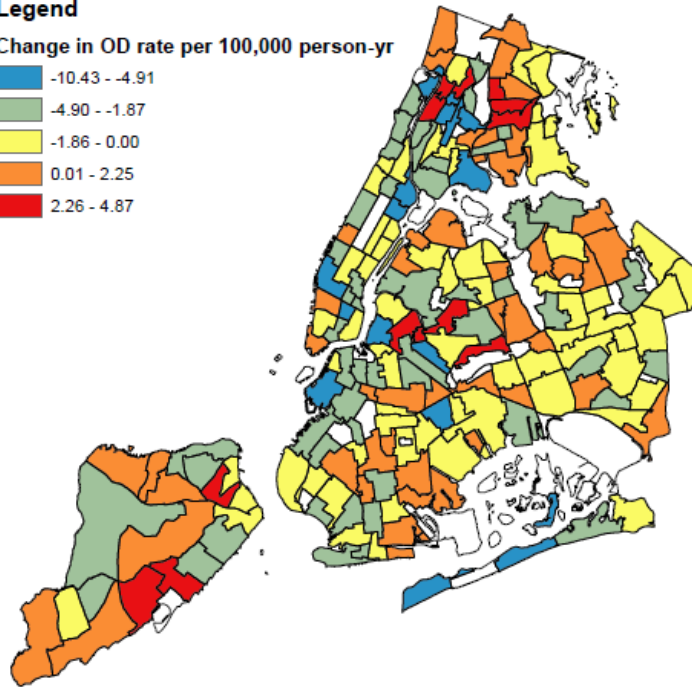
-10.43 - -4.91

-4.90 - -1.87

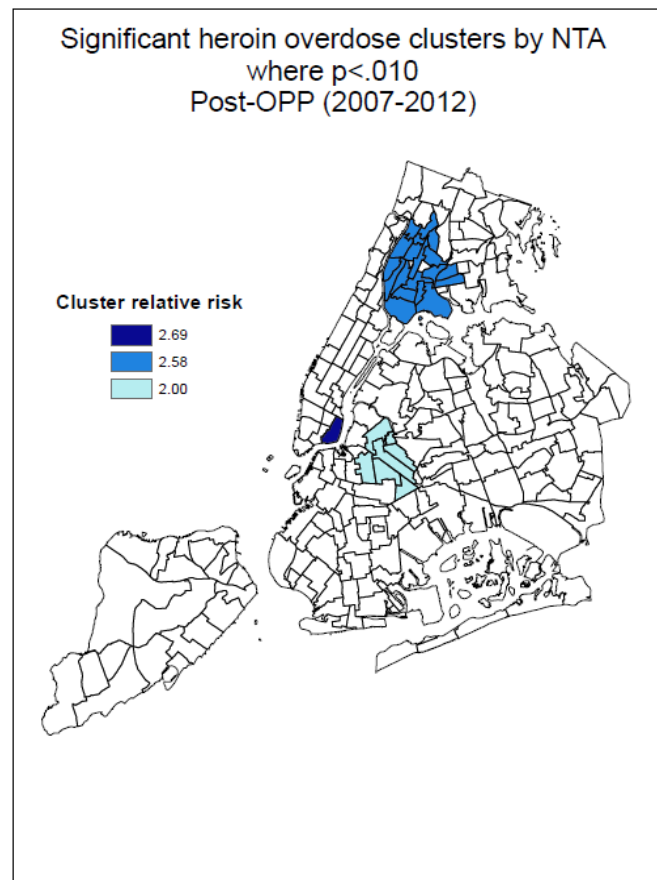
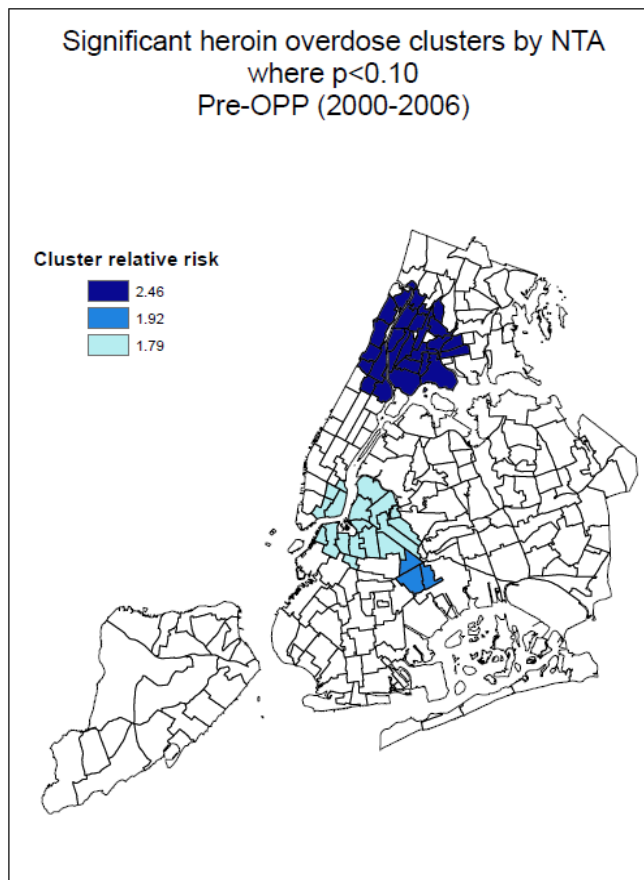
-1.86 - 0.00

0.01 - 2.25

2.26 - 4.87



Appendix VI. Overdose Mortality Cluster Detection, NYC, Pre- and Post-Implementation of
Overdose Prevention Program



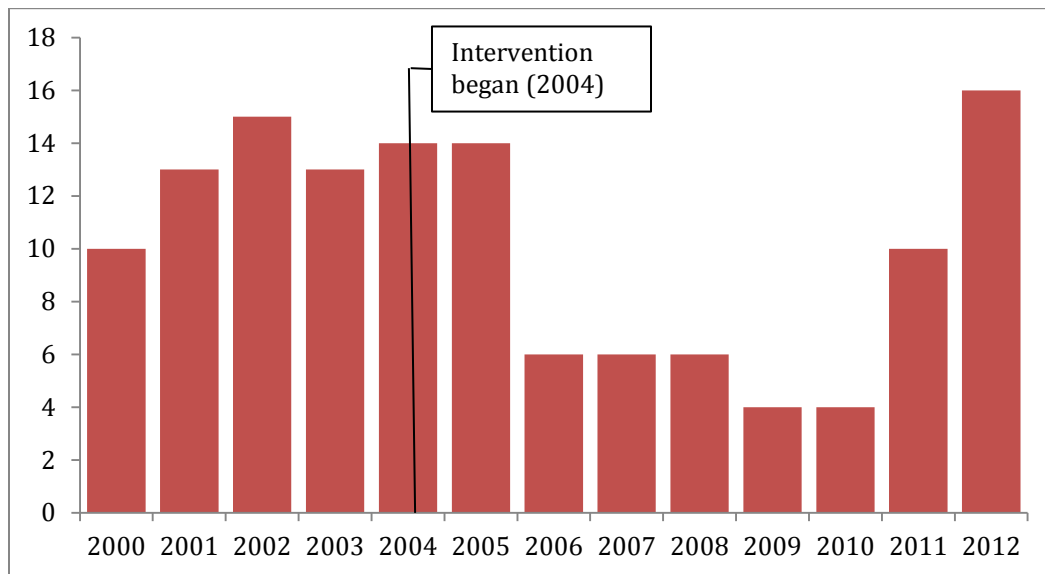
Appendix VII. Specification of Multivariable Models

Overdose rate difference

$$\begin{aligned} &= \beta_0 + \beta_1(\log dose rate_{low}) + \beta_2(\log dose rate_{medium}) \\ &+ \beta_3(\log dose rate_{high}) + \beta_4(population density) + e \end{aligned}$$

$$Overdose\ rate\ difference = \beta_0 + \beta_1(\log dose rate) + \beta_2(population density) + e$$

Appendix VIII. Number of Heroin-related Overdose Fatalities, Lower East Side, NYC, 2000-2012



Appendix IX. Map of Heroin-related Overdose Fatalities, Lower East Side, NYC, 2000

LES heroin deaths, 2000
(n=10)



Appendix X. Map of Heroin-related Overdose Fatalities, Lower East Side, NYC, 2001

LES heroin deaths, 2001
(n=13)



Appendix XI. Map of Heroin-related Overdose Fatalities, Lower East Side, NYC, 2002

LES heroin deaths, 2002
(n=15)



Appendix XII. Map of Heroin-related Overdose Fatalities, Lower East Side, NYC, 2003

LES heroin deaths, 2003
(n=13)



Appendix XIII. Map of Heroin-related Overdose Fatalities, Lower East Side, NYC, 2004

LES heroin deaths, 2004
(n=13)



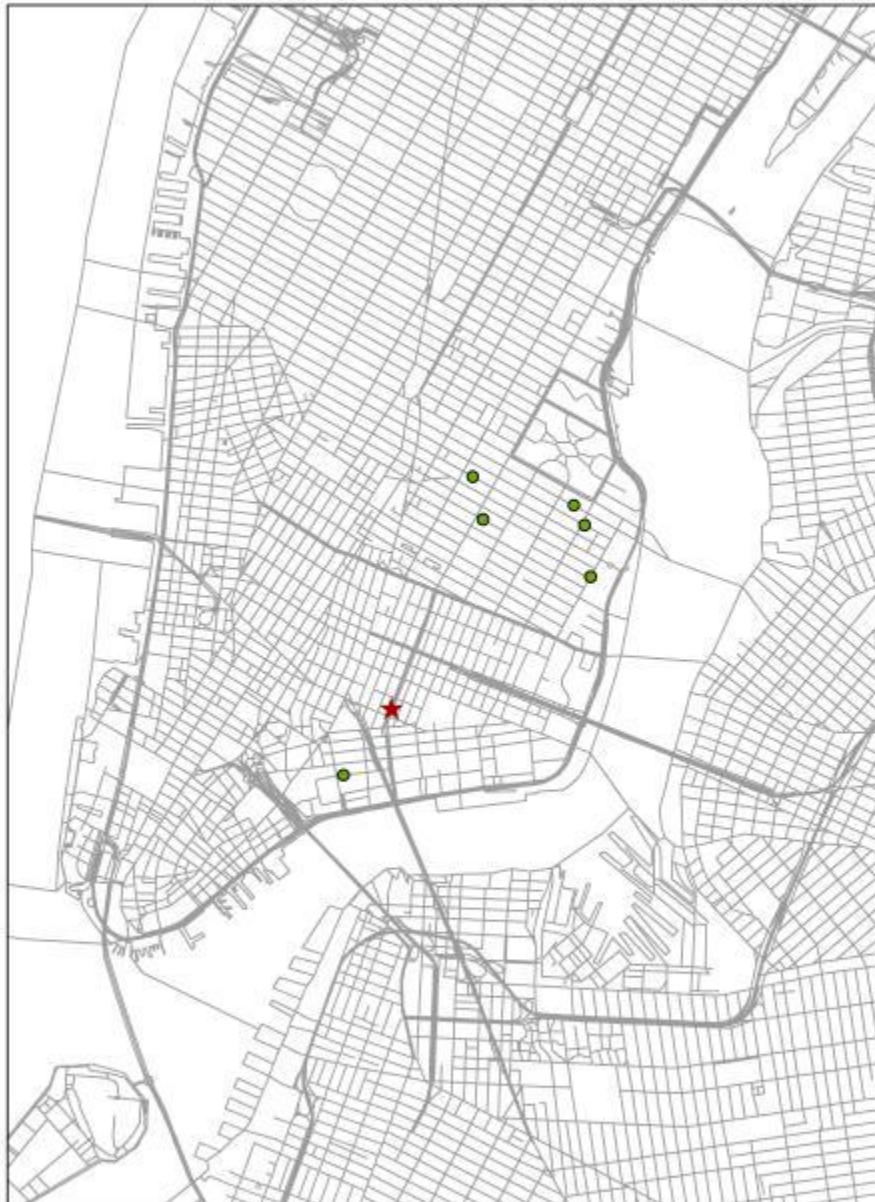
Appendix XIV. Map of Heroin-related Overdose Fatalities, Lower East Side, NYC, 2005

LES heroin deaths, 2005
(n=14)



Appendix XV. Map of Heroin-related Overdose Fatalities, Lower East Side, NYC, 2006

LES heroin deaths, 2006
(n=6)



Appendix XVI. Map of Heroin-related Overdose Fatalities, Lower East Side, NYC, 2007

LES heroin deaths, 2007
(n=6)



LES heroin deaths, 2008
(n=6)



Appendix XVIII. Map of Heroin-related Overdose Fatalities, Lower East Side, NYC, 2009

LES heroin deaths, 2009
(n=4)



Appendix XIX. Map of Heroin-related Overdose Fatalities, Lower East Side, NYC, 2010

LES heroin deaths, 2010
(n=4)



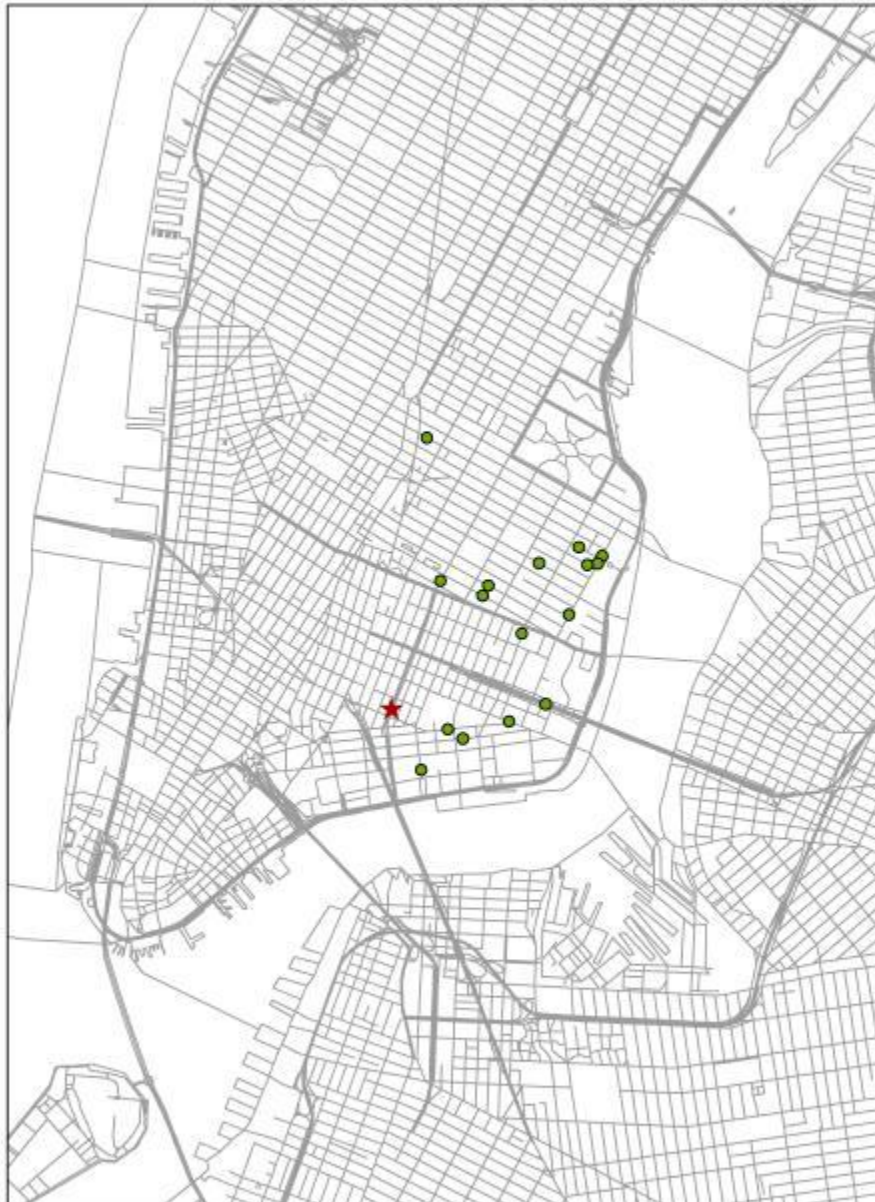
Appendix XX. Map of Heroin-related Overdose Fatalities, Lower East Side, NYC, 2011

LES heroin deaths, 2011
(n=10)

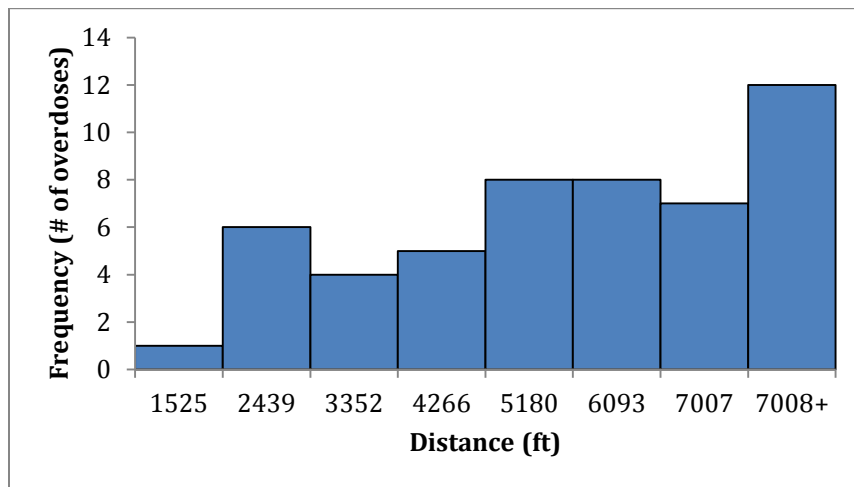


Appendix XXI. Map of Heroin-related Overdose Fatalities, Lower East Side, NYC, 2012

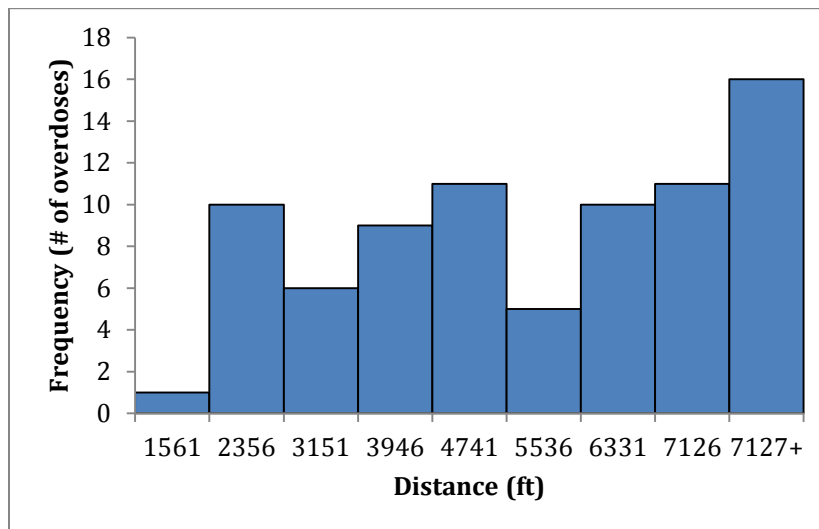
LES heroin deaths, 2012
(n=16)



Appendix XXII. Histogram of Frequency of Overdose Deaths by Street Walking Distance from Location of Overdose to Intervention Site, Lower East Side, NYC, 2000-2003



Appendix XXIII. Histogram of Frequency of Overdose Deaths by Street Walking Distance from Location of Overdose to Intervention Site, Lower East Side, NYC, 2004-2012



Appendix XXIV. List of Abbreviations

AAR = age-adjusted rate
AIDS = acquired immunodeficiency syndrome
CBO = community-based organization
CI = confidence interval
Detox = detoxification
DOHMH = Department of Health and Mental Hygiene
ESDA = exploratory spatial data analysis
FDA = Food and Drug Administration
Ft = feet
HCV = hepatitis C virus
HIV = human immunodeficiency virus
ICD = International Classification of Diseases
ITS = interrupted time series
LES = Lower East Side
LESHRC = Lower East Side Harm Reduction Center
MAT = medication assisted treatment
Max = maximum
Min = minimum
N/A = not applicable
NTA = neighborhood tabulation area
NYC = New York City
NYS = New York State
OD = overdose
ONDCP = Office of National Drug Control Policy
OPP = overdose prevention program
Pop = population
RR = risk ratio
SE = standard error
SES = socioeconomic status
SPARCS = Statewide Planning and Research Cooperative System
US = United States

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