HTH-HRE HEARING

TESTIMONY

SCR124 / SR87

NEIL ABERCROMBIE
GOVERNOR OF HAWAII

LORETTA J. FUDDY, A.C.S.W., M.P.H.
DIRECTOR OF HEALTH

STATE OF HAWAII
DEPARTMENT OF HEALTH
P.O. Box 3378
HONOLULU, HAWAII 96801-3378

In reply, please refer to:
File:

Senate Committee on Health and

Senate Committee on Higher Education

SCR 124, REQUESTING THE DEPARTMENT OF HEALTH AND THE JOHN A. BURNS SCHOOL OF MEDICINE TO CONDUCT A STUDY ON STATES WITH GOOD SAMARITAN LAWS AND THEIR IMPACT ON DECREASING DRUG OVERDOSE DEATHS.

Testimony of Loretta J. Fuddy, A.C.S.W., M.P.H.
Director of Health

Monday, March 25, 2013, 2:20pm

Department's Position: The Department of Health supports the intent of SCR124 but recommends that efforts be directed to amending SB 394, SD1.

Fiscal Implications: None

Purpose and Justification: Poisoning is a serious public health problem across the nation and in Hawaii. As noted in "Injuries in Hawai`i, 2007-2011," there has been an increasing trend in poisonings. In 2011, there were 120 fatalities, 204 hospitalizations and 860 Emergency Department visits, surpassing car crashes, drowning, pedestrian fatalities and homicides as a leading cause of injury mortality. If all intents were considered for 2011, overdose was the leading cause of injury-related death in Hawai`i with a total of 191 fatalities. It is clear that poisonings are a serious public health problem in Hawai`i.

This measure seeks to study Good Samaritan laws from other states to determine whether there were improved outcomes from poisoning episodes by encouraging those who may be affected by an overdose, or those around the victim, to seek medical attention by calling 911. It has been noted that the

fear of arrest or prosecution may cause unnecessary deaths and bad outcomes that might have been avoided if appropriate help was sought sooner. Since Good Samaritan laws have been passed in twelve other states as an effective harm reduction strategy, the Department recommends that efforts be directed to addressing the amendments proposed in SB394, SD1 rather than the proposed study. A Good Samaritan law that is appropriate to Hawaii's environment will help to ensure that medical amnesty is effectively utilized as a lifesaving measure for individuals at risk for overdose.

We defer to other agencies in regards to the impact this might have on law enforcement.

Thank you for the opportunity to testify.

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www.chowproject.org

Committee on Health
Senator Josh Green, Chair
Senator Rosalyn H. Baker, Vice Chair

Monday, March 25th, 2013
Conference Room 22, 2:20 PM

RE: STRONG SUPPORT FOR SCR 124 – Good Samaritan policies

Dear Chair Green, Vice Chair Baker and members of the committee,

My name is Heather Lusk, and I am writing on behalf of the CHOW Project to respectfully urge you to support SCR 124, which will review the effectiveness of Good Samaritan policies in decreasing mortality due to drug overdoses.

Unintentional drug overdoses are on the rise in Hawaii
According to the Hawaii Department of Health (DOH), overdose was the second leading cause of unintentional injury-related deaths in the State in 2011 and has been on the rise over the past five years. While Oahu continues to have the largest number of fatal overdoses, Maui saw almost twice the amount of fatal overdoses in 2011 compared to 2010. This mirrors fatal overdoses on the U.S. continent where 100 people die everyday from overdose and it is the leading cause of accidental death, however Hawaii has a higher than average rate of overdoses (13.3 per 100,000 compared with 9.7 nationwide). These overdoses care be prevented with a comprehensive approach including education, prescription drug monitoring and training people how to prevent and respond appropriately to overdoses.

SCR 124 will save lives
The number one reason cited among CHOW participants and in other research for not calling 911 in response to an overdose is fear of arrest for drug possession. SB 394 will give amnesty for drug possession, but will not protect people from arrest or prosecution for other offenses, such as drug trafficking. At least twelve other states have similar so called "good samaritan" legislation and over 90 college campuses have policies which provide protection from prosecution for witnesses who call 911. This bill prioritizes saving lives over drug possession.

The Community Health Outreach Work (CHOW) Project is dedicated to serving individuals, families and communities adversely affected by drug use, especially people who inject drugs, through a participant-centered harm reduction approach. CHOW works to reduce drug-related harms such as but not limited to HIV, hepatitis B/C and overdose. CHOW supports the optimal health and well-being of people affected by drug use throughout the State of Hawaii. CHOW has operated the statewide syringe exchange program for the past twenty years. In 2010, CHOW surveyed participants about their experience with overdose and more than half of CHOW's participants had witnessed an overdose in the

past two years. Unfortunately, we have lost more than one participant to overdose when 911 was not called out of fear. However, this issue does not only affect our participants. According to DOH, most of the overdoses 2004-2008 were from legitimately prescribed opiates.

Thank you for taking the time to read my testimony and please support saving lives by supporting SCR 124.

Sincerely,

Heather Lusk
Executive Director
CHOW Project
hlusk@chowproject.org

COMMUNITY ALLIANCE ON PRISONS

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COMMITTEE ON HEALTH
Sen. Josh Green, Chair
Sen. Rosalyn Baker, Vice Chair

COMMITTEE ON HIGHER EDUCATION
Sen. Brian Taniguchi, Chair
Sen. Gilbert Kahele, Vice Chair

Monday, March 25, 2013
2:20 p.m.
Room 229

STRONG SUPPORT FOR SCR 124/SR 87 – Study on States with Good Samaritan Laws

Aloha Chairs Green & Taniguchi, Vice Chair Baker & Kahele and Members of the Committees!

My name is Kat Brady and I am the Coordinator of Community Alliance on Prisons, community initiative promoting smart justice policies for more than a decade. This testimony is respectfully offered on behalf of the 5,800 Hawai`i individuals living behind bars, always mindful that approximately 1,500 individuals are serving their sentences abroad, thousands of miles away from their loved ones, their homes and, for the disproportionate number of incarcerated Native Hawaiians, far from their ancestral lands.

SCR 124/SR 87 requests the Department of Health and the John A. Burns School of Medicine to conduct a study on states with Good Samaritan laws and their impact on decreasing drug overdose deaths.

Community Alliance on Prisons supports this measure. As a coalition, we support policies that reduce harm and promote the aloha spirit. We are Hawai`i: we care for and about each other and policies that can save lives are important to all of us.

The statistics relating to overdose deaths in Hawai`i are alarming and studying states such as California, Colorado, Florida, New York, and Washington and how they addressed their problems with Good Samaritan laws will put many skeptical minds at rest. This is not a 'get out of jail free' card. It is about compassion. It is about encouraging people to do the right thing in emergency situations where time is of the essence.

We love the collaboration between DOH and JABSOM and look forward to reading the professional report about this pressing issue.

Overdose deaths are preventable. The majority of drug-related overdoses occur in the presence of others and there is usually time to intervene by calling 911, performing CPR, or with an opiate blocker such as Naloxone.

Unintentional drug overdoses are on the rise[1]. More than 100 people die of accidental drug overdose each day in the U.S. and drug overdose rates have more than tripled since 1990.

Fatal overdose was the leading cause of injury-related death in Hawai`i in 2011.

Overdose is on the rise in Hawaii with 183 deaths in 2011[2]. The increase in unintentional drug poisonings has made this the third leading cause of fatal injuries among Hawai`i residents over the last five years

Hawaii's overdose rate in 2011 is much higher than national average - 13.3 per 100,000 persons. Half of the participants in Hawaii's syringe exchange program witnessed an overdose in the past two years[3].

We are Hawai`i – we care for and about each other. SCR 124/SR 87 supports aloha and our way of life.

Mahalo for this opportunity to testify.

[1] Centers for Disease Control and Prevention http://www.cdc.gov/homeandrecreationalsafety/rxbrief/
[2] Hawaii State Department of Health, Injury Prevention and Control Program
[3] CHOW Project 2011 Evaluation Report

Committee on Health
Senator Josh Green, Chair
Senator Rosalyn H. Baker, Vice Chair

Monday, March 25th, 2013
Conference Room 22, 2:20 PM

RE: STRONG SUPPORT FOR SCR 124 – Good Samaritan policies

Dear Chair Green, Vice Chair Baker and members of the committee,

My name is Jean L. Mooney and I am writing you in regards to the strong support I have for SCR 124 (review of Good Samaritan Policies). I am a recovering drug addict with 7+ years clean and the position I would like you to understand is that I have seen many overdoses in the years I was addicted to heroin and other drugs. Too many times I have seen other addicts **leave the scene** of an overdose **for fear or legal repercussions.** This is not acceptable; we are dealing with a human life here.

Although drug addicts are often looked upon as the scourge of our society, they are somebody's child, son, daughter, niece. Until someone close to a person has overdosed, it often means nothing; you can't put a face to the addict who is gone.

I urge you to take a stand on these Good Samaritan policies, because human life is precious and it is not right to leave someone dying because of fear of arrest or incarceration. In reality, the Good Samaritan who stays at the scene of an overdose, no matter if they are an addict or not, should not be punished for saving a human life.

Thank you for your time and consideration of my testimony; I implore you all to do the right thing and help to save lives of the individuals in our community, who are unable to help themselves. Thank you.

Sincerely,

Jean L. Mooney
1665 Piikoi Street #1
Honolulu, HI 96822
(808) 450-7089

Aloha Chair Green, Vice Chair Baker, and members of the Committee.

My name is Ronald Schaeffer and I am writing in strong support of SB 394 and to urge passage of the bill, which grants limited amnesty or immunity from prosecution, a Good Samaritan bill, for individuals who witness an accidental drug overdose and call for medical help.

As noted in Section 1 of the proposed bill, accidental drug overdoses more than doubled between 2000 and 2006 and caused more deaths nationally among persons aged thirty-five to fifty-four than did motor vehicle accidents; it was the second leading cause of death for people ages fifteen to thirty-four. There were more deaths from prescription drug overdoses nation-wide and in Hawaii than from all illegal drugs combined. Every one of these people who died was someone's mother, father, son, daughter, spouse, or friend. Every one of them was loved and cared for by someone, and every one of them counts as a person in their own right regardless of their ill-advised or illegal actions. Your support and passage of SB 394 can help prevent some of these accidental overdose deaths and save lives that might otherwise be lost.

A very common reason why people die of accidental drug overdoses, from both legal prescription drugs and from illegally used drugs, is that witnesses to such an overdose are afraid that if they have drugs or drug paraphernalia in their possession and they call for help they will be arrested and prosecuted, so they don't call. In fact, such witnesses often leave the scene completely and the overdose victim gets no timely medical help whatsoever, and dies as a result. Passage of SB 394 will help increase the likelihood that drug overdose victims will get timely and appropriate medical care. It will help to save the lives of loved ones which otherwise would needlessly be cut short. What it won't do is cause drug use to increase or reward the inappropriate or illegal use of drugs.

As a Registered Nurse with almost twenty years of experience in emergency and trauma care, mostly in major medical centers, and as one who has seen an uncountable number of such drug overdoses, many of them fatal because medical care was either summoned too late or not at all, I can attest that passage of SB 394 will go a long way toward saving lives. I urge you all to do the right thing as loving, caring, compassionate human beings and pass SB 394 so that fewer people will die needlessly from accidental drug overdoses. The one who is saved could be one of your own!

Sincerely

Ronald P. Schaeffer, R.N. (retired)

From: mailinglist@capitol.hawaii.gov
To: HTHTestimony
Cc: shannonkona@gmail.com
Subject: *Submitted testimony for SCR124 on Mar 25, 2013 14:20PM*
Date: Saturday, March 23, 2013 11:39:05 PM

SCR124
Submitted on: 3/23/2013
Testimony for HTH/HRE on Mar 25, 2013 14:20PM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Shannon Rudolph	Individual	Support	No

Comments:

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From: mailinglist@capitol.hawaii.gov
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Subject: Submitted testimony for SCR124 on Mar 25, 2013 14:20PM
Date: Friday, March 22, 2013 3:31:18 PM

SCR124
Submitted on: 3/22/2013
Testimony for HTH/HRE on Mar 25, 2013 14:20PM in Conference Room 229

Submitted By	Organization	Testifier Position	Present at Hearing
Stacy Lenze	Individual	Support	No

Comments: Good Afternoon, I am writing in strong support of SCR124. According to the DOH, overdose was the number one cause of injury related death in the state in 2011. Every second day, someone in the state died needlessly. I believe we should be doing everything in our power to help those who are unable to help themselves. As was cogently stated elsewhere, a dead addict cannot recover. Thank you for your consideration. -Stacy Lenze

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

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Committee on Health
Senator Josh Green, Chair
Senator Rosalyn H. Baker, Vice Chair

Monday, March 25th, 2013
Conference Room 22, 2:20 PM

RE: STRONG SUPPORT FOR SCR 124 – Good Samaritan policies

Dear Chair Green, Vice Chair Baker and members of the committee,

My name is Thaddeus Pham, and I am writing to respectfully urge you to support SCR 124, which will review the effectiveness of Good Samaritan policies in decreasing mortality due to drug overdoses.

Unintentional drug overdoses are on the rise in Hawaii
According to the Hawaii Department of Health (DOH), overdose was the second leading cause of unintentional injury-related deaths in the State in 2011 and has been on the rise over the past five years. While Oahu continues to have the largest number of fatal overdoses, Maui saw almost twice the amount of fatal overdoses in 2011 compared to 2010. This mirrors fatal overdoses on the U.S. continent where 100 people die everyday from overdose and it is the leading cause of accidental death, however Hawaii has a higher than average rate of overdoses (13.3 per 100,000 compared with 9.7 nationwide). These overdoses care be prevented with a comprehensive approach including education, prescription drug monitoring and training people how to prevent and respond appropriately to overdoses.

SCR 124 will save lives
The number one reason cited among CHOW participants and in

other research for not calling 911 in response to an overdose is fear of arrest for drug possession. SB 394 will give amnesty for drug possession, but will not protect people from arrest or prosecution for other offenses, such as drug trafficking. At least twelve other states have similar so called "good samaritan" legislation and over 90 college campuses have policies which provide protection from prosecution for witnesses who call 911. This bill prioritizes saving lives over drug possession.

Thank you for taking the time to read my testimony and please support saving lives by supporting SCR 124.

Sincerely,

Thaddeus Pham
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Written Testimony Presented Before the
Senate Committees on Health and Higher Education

March 25, 2013 1420 Hrs. (Monday)
by
William F. Haning, III, M.D., FASAM, DFAPA

SCR 124 - REQUESTING THE DOH AND JABSOM TO CONDUCT A STUDY ON STATES WITH GOOD SAMARITAN LAWS AND THEIR IMPACT ON DECREASING DRUG OVERDOSE DEATHS

Senator Josh Green,

Senator Rosalyn H. Baker,

Senator Brian T. Taniguchi,

Senator Gilbert Kahele,

...and honored Committee Members:

Thank you for the opportunity to comment on this Resolution, which proposes research that would inform future legislation. I write as a private person independent of my role with the university; but also as a member of the Board of the American Society of Addiction Medicine, representing 14 Western states, as the Interim President of the Hawaii Society of Addiction Medicine, among other roles relating to the care of community members with substance use disorders – variously, "addiction," "abuse," or "dependence". It is important to note that in a previous career I served as an emergency medicine physician from 1976-1989, and was Medical Director of OCCC from 1982-1984. I have a strong interest in the questions posed by this resolution.

My intentions are stated simply, in two bullets:

1. In support of the resolution, to note that initiatives under this heading have been passed by 10 states. They generally take either or both of two forms:
    a. Protection against prosecution for the person reporting someone in need of immediate medical attention, in conjunction with drug overdose.

b. Availability for administration or self-administration of reversal agents ("antidotes") that are highly effective and carry little risk of harm if diverted or used improperly

2. In emphasis of the resolution's practicality, to provide a sampling of the availability of such information for paid access, review, and inclusion in the decision-making process. I will attach here three sample articles describing the effectiveness of intervention. I also insert in this text, the web link to the Drug Policy Alliance, a private nonprofit agency whose materials and whose role as a clearinghouse I have found useful.

https://docs.google.com/folder/d/0B1pSUthdnbgCZnBhZWZQei1XVkE/edit?usp=sharing

I am available to the Committee at their convenience to provide any desired input on this important subject. The beneficiaries of this resolution, in anticipation of future legislation, are our children, our siblings, sometimes our parents; and certainly the entire population of individuals whose deaths from drug overdose deprives us of those relationships, and of ultimately contributory citizens and residents. As a metaphor, please consider other illnesses of neglect, such as diabetic coma, for which we would not hesitate in creating interventions that would improve survival.

Thank you for the opportunity to testify on this matter.

William F. Haning, III, MD, DFAPA, FASAM
2133 Brown Way, Honolulu, HI 96822
haning@prodigy.net, telephone (808) 220-2685

911 Good Samaritan Laws: Preventing Overdose Deaths, Saving Lives

We are the Drug Policy Alliance.

Overdose Deaths: A Growing National Epidemic

Overdoses nationwide nearly tripled between 1999 and 2009.[1] In 2009 (the latest year data is available), more than 30,000 people people died from accidental drug overdose, resulting in more deaths than either HIV/AIDS or homicide.[2] Significant federal funding is directed toward preventing HIV/AIDS and homicide, but virtually no federal dollars are designated for overdose prevention.

Overdose deaths are almost as common as car crash fatalities. Overdose is second only to motor-vehicle accidents as a leading cause of injury-related death in the U.S.[6] And in sixteen states, overdose leads car crashes.[7] Considering how often the media reports on a fatality in a traffic accident, it is alarming that overdose is occurring at similarly high rates.

Nationally, more overdose deaths are caused by prescription drugs *than all illegal drugs combined.*[4] Legal prescription opiates, such as Oxycontin and Vicodin, are driving the increase in overdose deaths nationally. Since 2002, prescription opiate overdose deaths have outnumbered both heroin and cocaine overdose deaths.[5] Middle-aged Americans are the hardest hit by the overdose crisis. More people aged 35 to 54 died of drug overdose than in motor-vehicle accidents.[8] Additionally, drug overdose is the number two injury-related killer among young adults ages 15-34.[9]

The tragedy is that many of these deaths could have been prevented.

Good Samaritan 911 Laws: A Practical Solution That Can Save Lives

The chance of surviving an overdose, like that of surviving a heart attack, depends greatly on how fast one receives medical assistance. Witnesses to heart attacks rarely think twice about calling 911, but witnesses to an overdose often hesitate to call for help or, in many cases, simply don't make the call. The most common reason people cite for not calling 911 is fear of police involvement. People using drugs illegally often fear arrest, even in cases where they need professional medical assistance for a friend or family member. The best way to encourage overdose witnesses to seek medical help is to exempt them from criminal prosecution, an approach often referred to as 911 Good Samaritan immunity laws.

Risk of criminal prosecution or civil litigation can deter medical professionals, drug users and bystanders from aiding overdose victims. Well-crafted legislation can provide simple protections to alleviate these fears, improve emergency overdose responses, and save lives.

Multiple studies show that most deaths actually occur one to three hours after the victim has initially ingested or injected drugs.[11] The time that elapses before an overdose becomes a fatality presents a vital opportunity to intervene and seek medical help. However, "...It has been estimated that only between 10 percent and 56 percent of individuals who witness a drug overdose call for emergency medical services, with most of those doing so only after other attempts to revive the overdose victim (e.g., inflicting pain or applying ice) have proved unsuccessful."[12]

Furthermore, severe penalties for possession and use of illicit drugs, including state laws that impose criminal

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charges on individuals who provide drugs to someone who subsequently dies of an overdose, only intensify the fear that prevents many witnesses from seeking emergency medical help.

Good Samaritan immunity laws provide protection from prosecution for witnesses who call 911. Laws encouraging overdose witnesses and victims to seek medical attention may also be accompanied by training for law enforcement, EMS and other emergency and public safety personnel.

Such legislation does not protect people from arrest for other offenses, such as selling or trafficking drugs. This policy protects only the caller and overdose victim from arrest and prosecution for simple drug possession, possession of paraphernalia, and/or being under the influence.

The policy prioritizes saving lives over arrests for possession.

A Growing National Movement to Prevent Overdose Fatalities

In State Legislatures: In 2007, New Mexico was the first state in the nation to pass 911 Good Samaritan legislation. Since then, nine more states – California, Colorado, Connecticut, Florida, Illinois, Massachusetts, New York, Rhode Island and Washington – as well as the District of Columbia, have passed such laws.

The US Conference of Mayors: In 2008, the United States Conference of Mayors unanimously adopted a resolution supporting 911 Good Samaritan policies that could save thousands of lives by encouraging medical intervention for drug overdoses before they become fatal.

On College Campuses: Today, 911 Good Samaritan policies are in effect on over 90 college campus throughout the county.

[1] CDC WONDER Compressed Mortality File, ICD-10 Groups: X40-X44

[2] U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Web-based Injury Statistics Query and Reporting System (WISQARS), "20 Leading Causes of Death, United States, 2006, All Races, Both Sexes"

[3] CDC WONDER Compressed Mortality File, ICD-9 Groups: E850-E858

[4] Paulozzi, LJ, Budnitz, DS, Xi, Y. Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Safety 2006; 15: 618-627.

[5] Ibid.

[6] U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, WONDER – Compressed Mortality – Underlying Cause of Death, ICD-10 codes X40-44

[7] States with more overdose deaths than car crash deaths in 2006 are: Massachusetts, New Hampshire, Rhode Island, Connecticut, New York, New Jersey, Maryland, Pennsylvania, Ohio, Michigan, Illinois, Colorado, Utah, Nevada, Oregon and Washington. Source: Stobbe M, "CDC: Drug deaths outpace crashes in more states," The Associated Press, September 30, 2009

[8] U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report (MMWR), "QuickStats: Motor-Vehicle Traffic and Poisoning Death Rates, by Age - United States, 2005-2006," July 17, 2009, 58(27); 753

[9] U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Web-based Injury Statistics Query and Reporting System (WISQARS), "20 Leading Causes of Death, United States, 2006, All Races, Both Sexes"

[10] Strang, J. Kelleher, M. Best, D. Mayet, S. Manning, V. "Preventing opiate overdose deaths with emergency naloxone: medico-legal consideration of new potential providers and contexts." Submitted to BritishMedical Journal 3 (16 September 2005).

[11] Davidson, Peter J. et al. "Witnessing heroin-related overdoses: the experiences of young injectors in San Francisco," *Addiction* 97 (December 2002): 1511.

[12] Tracy, Melissa, et. al. "Circumstances of witnessed drug overdose in New York City: implications for intervention," *Drug and Alcohol Dependence* 79 (2005): 181-182.

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Cost-Effectiveness of Distributing Naloxone to Heroin Users for Lay Overdose Reversal

Phillip O. Coffin, MD, and Sean D. Sullivan, PhD

Background: Opioid overdose is a leading cause of accidental death in the United States.

Objective: To estimate the cost-effectiveness of distributing naloxone, an opioid antagonist, to heroin users for use at witnessed overdoses.

Design: Integrated Markov and decision analytic model using deterministic and probabilistic analyses and incorporating recurrent overdoses and a secondary analysis assuming heroin users are a net cost to society.

Data Sources: Published literature calibrated to epidemiologic data.

Target Population: Hypothetical 21-year-old novice U.S. heroin user and more experienced users with scenario analyses.

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: Naloxone distribution for lay administration.

Outcome Measures: Overdose deaths prevented and incremental cost-effectiveness ratio (ICER).

Results of Base-Case Analysis: In the probabilistic analysis, 6% of overdose deaths were prevented with naloxone distribution; 1 death was prevented for every 227 naloxone kits distributed (95% CI, 71 to 716). Naloxone distribution increased costs by $58 (CI, $3 to $156) and quality-adjusted life-years by 0.119 (CI, 0.017 to 0.378) for an ICER of $438 (CI, $48 to $1706).

Results of Sensitivity Analysis: Naloxone distribution was cost-effective in all deterministic and probabilistic sensitivity and scenario analyses, and it was cost-saving if it resulted in fewer overdoses or emergency medical service activations. In a "worst-case scenario" where overdose was rarely witnessed and naloxone was rarely used, minimally effective, and expensive, the ICER was $14 000. If national drug-related expenditures were applied to heroin users, the ICER was $2429.

Limitation: Limited sources of controlled data resulted in wide CIs.

Conclusion: Naloxone distribution to heroin users is likely to reduce overdose deaths and is cost effective, even under markedly conservative assumptions.

Primary Funding Source: National Institute of Allergy and Infectious Diseases.

Ann Intern Med. 2013;158:1-9. For author affiliations, see end of text. www.annals.org

Opioid overdose, a major source of morbidity and mortality worldwide, accounts for half of the mortality among heroin users (1) and is a leading cause of death among adults in the United States (2). Naloxone is a safe, effective, short-acting opioid antagonist for intravenous, intramuscular, subcutaneous, or intranasal administration by medical personnel and—since the late 1990s—laypersons to reverse opioid overdose. (3). Naloxone distribution is endorsed by the American Medical Association, generally integrated into preexisting services, and targeted at anyone at risk for witnessing or having an opioid overdose. Naloxone "kits" are usually wallet-sized packets containing 2 doses of naloxone and other items, including syringes, brochures, simple rescue breathing masks, and brief educational materials about overdose risks and management. As of 2010, a total of 188 U.S. programs distributing naloxone reported training 53 032 persons and recording 10 171 reversals (3).

Distribution of naloxone to laypersons for administration during a witnessed opioid overdose seems to effectively reduce both community-level overdose death rates (4) and the likelihood of death from an overdose (5). Drug users can be readily trained to respond effectively to overdose (6), naloxone programs report frequent successful reversal of opioid overdoses (7–9), and localities report substantial decreases in overdose deaths when naloxone distribution is initiated (10, 11). Naloxone distribution may be highly cost-effective because the medication is inexpensive and its use may result in a life saved, but such phenomena as the recurrent nature of overdose (12) add complexity to an economic evaluation of naloxone distribution. Our aim was to assess the expected outcomes and cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal compared with no intervention.

METHODS

We developed a cost-effectiveness analysis comparing distribution of naloxone to 20% of heroin users with no distribution. We calculated absolute and relative overdose death rates with and without naloxone distribution. We expressed cost-effectiveness findings in terms of costs, quality-adjusted life-years (QALYs), and incremental costs per QALY gained. An incremental cost of less than

Context

Programs that provide heroin users with naloxone for use during overdoses have increased over the past decade.

Contribution

In a model, naloxone reduced the rate of overdose death and was cost-effective over a wide range of assumptions. It was cost-saving in some simulations.

Caution

Hospitalization costs were assumed to be the same for naloxone recipients as for overdose survivors who did not receive naloxone. Possible additional benefits of naloxone distribution, such as reductions in drug use and other risk behaviors due to peer education, were not included.

Implication

Administration of naloxone during heroin overdoses may be a useful public health intervention.

—*The Editors*

$50 000 per QALY gained is traditionally considered cost-effective by policymakers (13).

A Markov model with an integrated decision analytic model built in Microsoft Excel 2010 (Microsoft, Redmond, Washington) estimated costs and QALYs from a societal perspective, with annual transitions, standard background mortality, and 3% annual discounting. Our baseline model began at age 21 years, the average age of initiating heroin use in the United States (14). Because the median duration of heroin use is at least 10 years (15), we ran our model separately to ages 31 and 41 years without naloxone, then initiated the model with the intervention to evaluate naloxone for mid- and late-career heroin users. Input parameters and ranges can be found in **Table 1**, with detailed rationales for parameter selection in **Appendix Table 1** (available at www.annals.org); instantaneous rates were transformed to probabilities (50). Literature review to identify parameter values included searches of the MEDLINE database by using such keywords as "(heroin or opioid* or opiate*) overdose" and "naloxone," as well as individual keyword searches for parameters unrelated to overdose and identification of additional sources from conference abstract books, online searches, and prior knowledge. We calibrated our model to be consistent with conservative estimates of overdose, mortality, naloxone use, and drug use cessation from epidemiologic studies (3, 7, 8, 10, 12, 17, 20, 21, 28–32, 47, 48, 51–61) by following methods guidance from Stout and colleagues (62) (see the **Appendix** and **Appendix Table 2**, available at www.annals.org).

Markov Model

Figure 1 illustrates the model health states and possible transitions between states. We ran our model for 64 years, by which time most persons in the population had died. We calculated total costs and QALYs for each option by calculating the time spent in each health state and the associated cost and quality-of-life weight.

The cohort entered the model in "heroin use" and could discontinue use (35, 36), have an overdose (fatal or nonfatal), or die for other reasons (5). The risk for relapse to heroin use was based on a study that showed that 50% of users relapse over 5 years (37), with an age-based reduction in the risk for relapse such that it was half as likely after 10 years, resulting in a median duration of heroin use of 15 years (48). On the basis of a study that showed that 20% of persons who inject drugs enroll in treatment within 30 days of an overdose (38), we assumed a modest relative 10% increase in the likelihood of discontinuing heroin use after an overdose, with a range from half the baseline rate of discontinuation to double the rate.

The principal risk factor for heroin overdose is a prior heroin overdose (12). Approximately 10% to 25% of heroin users overdose annually (12, 51–53, 63), and 33% to 70% overdose over a lifetime of use (17, 54, 63, 64), consistent with evidence that the risk for a first-time overdose decreases with time spent using drugs (33). Those who have overdosed have a 4- to 5-fold higher risk for overdosing in the future and an elevated risk for dying of overdose, with some evidence that the risk is cumulative (29, 32). Because the mean age of overdose death is in the fourth decade of life (58, 59), these findings required us to assume a relatively low annual rate of first-time overdose that decreased with age such that the risk was halved after 10 years (33). The risk for repeat overdose increased after the first overdose and again after the second overdose (33). To provide conservative estimates of the effect of naloxone, we calibrated the model to mirror low-end population estimates of the annual rate of overdose (12%) and overdose death (1.0%) (1, 12, 51, 52, 63).

Decision Analytic Model

Upon transition to any stage of overdose, a decision analytic model processed the overdose (**Appendix Figure 1**, available at www.annals.org). In the absence of naloxone distribution, overdose could be witnessed or not witnessed and, if witnessed, emergency medical services (EMS) could be called or not called, resulting in probabilities that the event would produce survival or death. In the presence of naloxone distribution, the overdose could happen to a heroin user reached by the distribution program, a naloxone kit could be available, and the decision to use it could be made. The joint probability of distributed naloxone being used in a given year was 13.6% (0.4% to 63.1% in the sensitivity analysis); this value was the product of the proportion of heroin users reached by the distribution program, the likelihood that a recipient of a naloxone kit would be present at the overdose, the likelihood that the overdose would be witnessed, and the likelihood that a witness would administer the medication (20). We calculated the likelihood of contacting EMS on the basis of drug

Table 1. Naloxone Distribution Model Parameters*

Parameter	Base Case (Range)	Source
Proportions		
Joint probability that distributed naloxone is used each year	0.136 (0.004 to 0.631)	Calculated
Proportion of heroin users prescribed naloxone	0.20 (0.09 to 0.60)	Reference 16; Heller D (Personal communication)
Proportion of overdoses witnessed	0.85 (0.32 to 0.94)	References 17–19
Proportion in possession of naloxone at an overdose who use it to attempt reversal	0.8 (0.5 to 0.9)	Reference 20
Social network modifier†	1.0 (0.5 to 1.5)	Assumption
Proportion who call EMS		
First-time overdose	0.6 (0.3 to 0.8)	References 21–23
Subsequent overdoses	0.4 (0.2 to 0.6)	References 21–23
Relative likelihood of EMS being called if naloxone used	1.0 (0.8 to 1.2)	Reference 24
Likelihood of transport to hospital	0.90 (0.81 to 0.99)	Reference 25
Relative likelihood of transport to hospital after lay naloxone	1.0 (0.5 to 1.0)	References 26 and 27
Proportion who survive overdose		
No medical assistance or lay naloxone†	0.899 (0.779 to 0.940)	Calculated
First overdose	0.918 (0.893 to 0.943)	References 1 and 5
Absolute reduction for second overdose	0.015 (0.000 to 0.029)	References 1 and 5
Additional reduction for subsequent overdoses	0.015 (0.000 to 0.029)	References 1 and 5
Relative increase in survival with EMS	1.089 (1.029 to 1.150)	Reference 28 and 29
Relative increase in survival with naloxone	1.089 (1.029 to 1.150)	References 3, 8, 20, and 29–31
Annual transition rates		
Heroin use to nonoverdose death (in excess of background mortality)	0.0075 (0.0025 to 0.0125)	Reference 5
Heroin use to overdose		
First overdose	0.09 (0.02 to 0.12)	References 12, 29, 32, and 33
Second overdose	0.22 (0.05 to 0.30)	References 12, 29, 32, and 33
Subsequent overdoses	0.34 (0.27 to 0.42)	References 12, 29, 32, and 33
Annual relative reduction in risk for first overdose§	0.933 (0.3 to 1.2)	References 32 and 34
Heroin use to discontinuation of heroin use	0.06 (0.01 to 0.10)	References 35 and 36
Discontinuation of heroin use to heroin use	0.070 (0.056 to 0.084)	Reference 37
Annual relative reduction in risk for relapse§	0.933 (0.900 to 1.000)	Reference 15
Overdose to discontinuation of heroin use	0.062 (0.028 to 0.112)	Reference 38
Costs, $‖		
Biannual naloxone kit (2 doses plus distribution costs)	25 (12 to 75)	References 39 and 40
EMS visit	1790 (716 to 2500)	Reference 41
EMS transport to hospital	301 (271 to 331)	Reference 41
Emergency department care if transported	805 (362 to 1361)	Reference 42
Annual heroin user cost to society¶	3 868 (1078 to 4041)	References 14 and 43
Utilities		
Heroin user	0.83 (0.73 to 0.93)	References 43–45
Relative increase in utility for heroin user in recovery	1.07 (1.00 to 1.13)	References 43 and 46

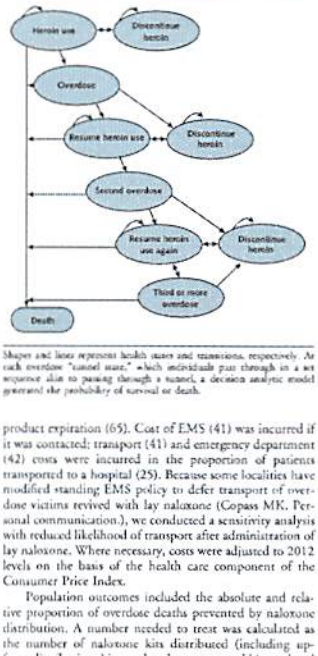
EMS = emergency medical services.
* Appendix Table 1 (available at www.annals.org) provides the detailed rationale and additional sources for selection of point estimates and ranges.
† Summary value based on parameters listed in next 4 rows.
‡ Parameter used in sensitivity analyses to adjust for possible effects of social networks on the probability of naloxone being present at an overdose.
§ Parameter is exponentiated so the years elapsed and multiplied by its reference parameter to reduce the likelihood of the event over time.
‖ 3% annual discounting.
¶ Set at $0 for baseline analysis and used for secondary analysis.

user surveys (22), including surveys evaluating EMS contact by witnesses who administered naloxone (24) or had witnessed more than 1 overdose (23). We used an established estimate of overdose mortality (5) that was increased for recurrent overdose and modified if EMS was contacted or naloxone was administered, resulting in an annual risk for overdose death of approximately 0.2% in the early years of use and peaking at 1.13% after 25 years of use. On the basis of the narrow range of results from several small studies (7, 8, 20, 28–31), we assumed similar likelihood of survival with EMS or naloxone and applied the higher likelihood of survival if both interventions were used.

Costs and Outcomes

Naloxone is obtained through contractual agreements in the United States, with programs traditionally paying approximately $6 per dose, $15 per kit of injectable naloxone (40), and $30 per kit of intranasal naloxone (39). Most programs dispense injectable naloxone, 0.4 mg/mL, and incorporate distribution into preexisting programmatic activities. We estimated a baseline cost of $25 per kit ($12 for naloxone, $3 for other components, and $10 for staff time and other distribution costs). Kit costs were incurred after each overdose in which naloxone was administered and biannually among active heroin users to account for

Figure 1. Markov model of heroin use, overdose, discontinuation, and death.



Shapes and lines represent health states and transitions, respectively. At each overdose "control state," which individuals pass through in a set sequence akin to passing through a tunnel, a decision analytic model generated the probability of survival or death.

product expiration (65). Cost of EMS (41) was incurred if it was contacted; transport (41) and emergency department (42) costs were incurred in the proportion of patients transported to a hospital (25). Because some localities have modified standing EMS policy to defer transport of overdose victims revived with lay naloxone (Gopass MK, Personal communication.), we conducted a sensitivity analysis with reduced likelihood of transport after administration of lay naloxone. Where necessary, costs were adjusted to 2012 levels on the basis of the health care component of the Consumer Price Index.

Population outcomes included the absolute and relative proportion of overdose deaths prevented by naloxone distribution. A number needed to treat was calculated as the number of naloxone kits distributed (including upfront distribution, biannual replacements, and kits replaced after an overdose) divided by the number of overdose deaths prevented. Cost-effectiveness outcomes were defined as QALYs, with a quality-of-life weight (utility, where 0 = dead and 1 = perfect health) during heroin use and recovery based on a survey of individuals not currently in treatment for substance use disorders (43).

Uncertainty

Our model accounted for uncertainty around point estimates with both deterministic methods (adjusting point estimates to predetermined extremes) and probabilistic methods (randomly selecting all parameter values simultaneously on the basis of predetermined distributions). For the probabilistic analysis, we established a probability distribution for each parameter on the basis of the point estimate (truncated normal for proportions and utilities, β for transition rates, and log-normal for costs) and ran the model 10 000 times with randomly selected values from each parameter. We calculated mean costs and QALYs by averaging across the simulations and determined 95% CIs by selecting the 2.5th and 97.5th percentile values. We also adjusted the probabilistic results to incremental net benefits [$\mu_{\text{Naloxone}} - \mu_{\text{No naloxone}}$, where μ = (willingness to pay × QALYs) − cost] and presented a cost-effectiveness acceptability curve per Fenwick and colleagues (66). To address a concern that preserving the lives of heroin users could result in excessive health care and criminal justice costs being incurred by survivors, we estimated an alternate scenario that included an annual cost applied to active heroin users. We adjusted this cost to 2012 levels by using the Consumer Price Index, based on an estimate of health care and criminal justice expenditures related to drug abuse produced by the U.S. Office of National Drug Control Policy (49), the proportion of illicit drug users that used heroin (0.9%) (14), and a conservative estimate of 200 000 heroin users in the United States (14).

Finally, we conducted deterministic sensitivity analyses on all parameters to test the robustness of our point estimates and ranges. To account for uncertainty in variables related to naloxone use and effectiveness, we developed deterministic scenarios in which we adjusted multiple parameters to extreme settings simultaneously.

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RESULTS

Population Outcomes

In the deterministic analysis, naloxone distribution prevented 6.5% of all overdose deaths for each 20% of heroin users reached by the program (**Table 2**). One overdose death would be prevented for every 164 naloxone kits distributed (that is, the number needed to treat was 164). Although the relative effect on overdose mortality was greater for younger heroin users (**Appendix Figure 2**, available at www.annals.org), the lower risk for death for that population resulted in a number needed to treat of 412 for heroin users younger than 26 years. In the probabilistic analysis, naloxone distribution prevented 6.1% of overdose deaths (95% CI, 0.7% to 19.5%), with a number needed to treat of 227 (CI, 71 to 716). Naloxone distribution resulted in a reduced rate of overdose death in the full

Table 2. Sensitivity Analyses

Parameter	Overdose Deaths Averted, %: 5 y	Overdose Deaths Averted, %: Lifetime	Number Needed to Treat*	Increased QALYs of Naloxone	Increased Costs of Naloxone, $	ICER of Naloxone, $
Base case (deterministic)	10.6	6.5	164	0.105	46	421
Base case (probabilistic)	8.5	6.1	227	0.119	53	438
Sensitivity analyses (deterministic)						
Mean age of targeted heroin users						
SA1: 31 y	9.5	6.3	163	0.114	44	386
SA2: 41 y	8.1	6.3	123	0.091	39	432
Intervention characteristics						
SA3: Distribution of naloxone to 5% of heroin users	2.7	1.6	166	0.027	11	427
SA4: Distribution of naloxone to 60% of heroin users	32.0	20.4	159	0.334	140	418
SA5: Tripled cost of naloxone distribution	10.6	6.5	164	0.105	106	977
SA6: Efficacy of naloxone reduced to a 2% relative survival benefit	2.4	1.4	739	0.024	34	1385
SA7: EMS activation after naloxone halved	10.6	6.5	164	0.105	−70	Dominant
SA8: Likelihood of transport to hospital after lay naloxone halved	10.6	6.5	164	0.105	2	23
Heroin use characteristics						
SA9: Risk for first overdose halved	10.7	6.6	302	0.063	40	625
SA10: Risk for first overdose doubled	10.6	6.5	99	0.167	53	323
SA11: Rate of discontinuing heroin use halved	10.6	6.1	166	0.129	61	470
SA12: Rate of discontinuing heroin use after overdose doubled	10.7	6.9	176	0.101	41	411
SA13: Likelihood overdose is witnessed halved	3.6	2.6	326	0.051	31	612
SA14: Social network modifier halved	5.3	3.2	301	0.054	36	661
SA15: Social network modifier increased 50%	16.0	9.9	119	0.164	56	341
SA16: No improved quality of life for abstinence	10.6	6.5	164	0.105	46	435
Worst-case scenario						
SA17: Naloxone expensive, marginally efficacious, and rarely carried and overdoses rarely witnessed	0.4	0.3	2781	0.006	80	14 000
Best-case scenario						
SA18: Upper limit of joint probability naloxone used	65.5	42.1	95	0.649	208	321
Structural sensitivity analyses						
SA19: Lower limit of overdose risk in setting of naloxone	32.0	31.2	36	0.423	−297	Dominant
SA20: Addition of a fourth stage of overdose risk†	10.6	4.9	133	0.178	52	290

EMS = emergency medical services; ICER = incremental cost-effectiveness ratio [incremental cost per QALY gained, equal to (lifetime costs with naloxone − lifetime costs without naloxone)/(lifetime QALYs with naloxone − lifetime QALYs without naloxone)]; QALY = quality-adjusted life-year; SA = scenario analysis.
* Number of naloxone kits distributed to prevent 1 death.
† Sets the risk for third overdose to 0.28 and subsequent overdoses to 0.34.

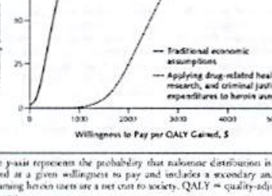
cohort and active heroin users over the lifetime in all simulations. With naloxone distribution, the model forecast a 1.7% increase in the proportion of persons discontinuing heroin use over the lifetime of the cohort and, due to the survival of high-risk heroin users, a 1.3% increase in the absolute number of overdoses.

Cost-Effectiveness

Naloxone distribution was cost-effective in our base-case and all sensitivity analyses, with incremental costs per QALY gained much less than $50 000 (**Table 2** and **Appendix Figure 3**, available at www.annals.org; see **Appendix Table 3**, available at www.annals.org, for detailed results of selected analyses). Cost-effectiveness was similar at starting ages of 21, 31, and 41 years; the greater QALY gains of younger persons were roughly matched by higher costs. In scenarios where naloxone administration reduced reliance on EMS, naloxone distribution was cost-saving and dominated (that is, less costly and more effective than) the no-distribution comparison. Cost-effectiveness was somewhat sensitive to the efficacy of lay-administered naloxone and the cost of naloxone but was relatively insensitive to the breadth of naloxone distribution, rates of overdose and other drug-related death, rates of abstinence and relapse, utilities, or the absolute cost of medical services. Naloxone was no longer cost-effective if the relative increase in survival was less than 0.05%, if 1 distributed kit cost more than $4480, or if average emergency care costs (as a proxy for downstream health costs) exceeded $1.1 million. A worst-case scenario, in which the likelihood of an overdose being witnessed, the effectiveness of naloxone, and the likelihood of naloxone being used were minimized and the cost of naloxone was maximized, resulted in an incremental cost of $14 000 per QALY gained. A best-case scenario, in which naloxone distribution reduced the risk for overdose, was dominant.

Results from our probabilistic cost-effectiveness analysis were similar to those of the deterministic analysis. Naloxone distribution increased lifetime costs by $53 (CI, $3 to $156) and QALYs by 0.119 (CI, 0.017 to 0.378) for an incremental cost of $438 per QALY gained (CI, $48 to $1706) (**Figure 2**). If we assumed that heroin users are a net cost to society beyond the scope of any other health

Figure 2. Cost-effectiveness acceptability curve for naloxone distribution under traditional assumptions and applying national drug-related expenditures to heroin users.



The y-axis represents the probability that naloxone distribution is preferred at a given willingness to pay and includes a secondary analysis assuming heroin users are a net cost to society. QALY = quality-adjusted life-year.

conditions, naloxone resulted in an incremental cost of $2429 per QALY gained (CI, $1305 to $3986).

Discussion

Naloxone distribution to heroin users would be expected to reduce mortality and be cost-effective even under markedly conservative assumptions of use, effectiveness, and cost. Although the absence of randomized trial data on naloxone distribution and reliance on epidemiologic data increase the uncertainty of results, there are few or no scenarios in which naloxone would not be expected to increase QALYs at a cost much less than the standard threshold for cost-effective health care interventions. Ecological data, in fact, suggest that naloxone distribution may have far greater benefits than those forecast in this model: Reductions in community-level overdose mortality from 37% to 90% have been seen concordant with expanded naloxone distribution in Massachusetts (7), New York City (11), Chicago (10), San Francisco (9, 67, 68), and Scotland (69). Such a result is approached in this model only by maximizing the likelihood of naloxone use or by assuming that naloxone distribution reduces the risk for any overdose. Preliminary data showing that naloxone distribution is associated with empowerment and reduced HIV risk behaviors (70, 71) suggest that future research is needed to test these hypotheses.

Data on repeat overdoses were necessary to calibrate this model to epidemiologic data showing frequent overdoses among young users but a later peak age of overdose death. Although repeat overdoses were not a primary outcome, the model predicted that they were responsible for 61% of overdose deaths in the first 10 years and 85% of lifetime overdose deaths, suggesting that active heroin users later in their careers are likely to have had no overdoses or multiple overdoses, with few having had only 1 (consistent with results from the Australian Treatment Outcome Study [33]). This intriguing result blunts the relative benefit of naloxone distribution because those who survive an overdose are likely to have future overdoses. Although a targeted program that distributes naloxone only to those who have overdosed at least once (for example, individuals recruited from an emergency department) may reduce intervention costs, benefits would be offset by failure to prevent early death among the youngest heroin users and, possibly, by failure to reach those more likely to carry naloxone because of their attention to health behaviors. Ultimately, naloxone distribution is likely to have similar cost-effectiveness regardless of the age or duration of heroin use of the target population.

Drug users face substantial stigma and are often considered to be of low value to society. To address this, we conducted a scenario analysis considering heroin users as a net cost to society. We do not advocate "taxing" drug users for survival in economic models because such an approach may serve to codify the aforementioned stigma. Nonetheless, we believe that addressing this concern was vital to evaluating an intervention with such potential public health value. Naloxone distribution remained cost-effective even under such assumptions.

The results presented in this paper should aid future efforts to evaluate the effect of naloxone distribution on overdose mortality. The effect of an intervention on immediate mortality should be greatest in the early years of implementation because survivors reversed by naloxone may be at higher risk for repeat overdose and death. Moreover, the actual number of deaths prevented may be small and difficult to attribute to a specific intervention. For example, our model forecasts that a trial reaching 10% of a population of 10 000 heroin users would prevent just 2 of 30 to 40 deaths per year. In contrast, similar coverage in New York City, where approximately 900 overdose deaths occur each year, might prevent around 50 deaths per year. Adequately powering a study of lay naloxone may therefore require distribution to a population at higher risk for overdose death (for example, at the time of release from prison) or a large-scale, multisite initiative.

We did not consider the population of opioid analgesic users because of unavailable data or substantial uncertainty for several important parameters (for example, risk for first-time or subsequent overdose, likelihood of having a witnessed overdose, or EMS use) and differences in the development and cost of clinic- versus street-based distribution programs (72). Nonetheless, naloxone distribution targeting opioid analgesic users has been associated with similar reductions in mortality (for example, a 38% reduction in overdose deaths in Wilkes County, North Carolina [72]), suggesting similar health benefits.

Our study has limitations. Because we designed this model to bias against the hypothesis that naloxone distribution would be cost-effective, the results may underestimate the benefits. Some parameters had high degrees of uncertainty, including the potential reach of a naloxone distribution program and the effectiveness of lay-administered naloxone in decreasing mortality, which we addressed with sensitivity and probabilistic analyses. We also incorporated a parameter that modified the likelihood of naloxone being available at an overdose to account for distinct patterns of socialization among heroin users (drug users in some communities use in groups, whereas others are more isolated). We did not consider possible ancillary benefits of naloxone distribution, such as reduced drug use and risk behaviors, that have been associated with training drug users to act as peer educators (73). In addition, although our study found that less EMS contact reduces the cost of naloxone distribution, there may be ancillary benefits from EMS not accounted for in this model. We also assumed that the number of severe overdoses resulting in prolonged hospitalization, but not death, would be similar between persons receiving naloxone and those receiving standard care. Finally, the model relied on epidemiologic data to represent an average of the many individual and environmental factors that may influence overdose rates, including polydrug use, incarceration, abstinence-based and agonist-maintenance treatments, population-level trends of drug use, changes in heroin supply, and shifts in policing. This is, to our knowledge, the first attempt to apply the tools of mathematical modeling to opioid overdose; as the field of overdose research matures, models that incorporate such parameters may better predict the effect of overdose interventions, particularly for smaller localities that may be more sensitive to such changes.

In summary, this analysis of naloxone distribution to heroin users for lay overdose reversal suggests that the intervention would increase QALYs and be highly cost-effective, even under markedly conservative assumptions. Controlled trials that more precisely define the utilization and relative benefit of lay naloxone distribution would help refine future modeling.

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Disclaimer: The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Reproducible Research Statement: *Study protocol:* Not applicable. *Statistical code:* Mathematical operations available from Dr. Coffin (e-mail, pcoffin@gmail.com). *Data set:* Input parameters and sources provided in the text and Appendix.

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Appendix: Calibration of the Model

We developed a deterministic model calibrated in an iterative 4-stage process to selected epidemiologic data points. The process we used during each major stage of model development is described below, and the data used to support development and calibration are provided in **Appendix Table 2**.

Model Structure and Data Ascertainment

We developed a Markov model that included the scenarios "heroin use," "discontinuation of use," "overdose," and "death." We also developed the decision analytic component to determine the overdose outcome. We searched the literature for parameter values to populate the model by using keywords defined in the main text. Most searches were done through the MEDLINE database, although data from published abstracts were also used, as was information from 2 personal communications. We selected point estimates on the basis of the quality of the study for ascertaining the parameter, the reliability of the point estimate in multiple studies, the applicability of the result to the United States, and the reasonableness of the parameter for the model. For example, if studies reported a narrow range of values for the parameter, we selected the midpoint of that range as the point estimate; where a wide range of values was reported, but most values were at 1 extreme, we selected a point estimate from the dominant portion of the range, preferably from a U.S.-based study; if 1 estimate was available, we used it if it seemed to be a reasonable assessment of the parameter; and if no estimate was available in the literature, we consulted outside experts.

Target Data, Search Algorithm, and Goodness of Fit

We evaluated the fit of the model to other epidemiologic findings on the basis of point estimates. The targets were selected on the basis of our background in the field of overdose and values identified through a literature search similar to that noted previously for parameter sources. Target data span approximately 20 years of epidemiologic studies among heroin users and injection drug users, with an emphasis on U.S.-based research. We used a trial-and-error search algorithm and attempted to fit all targets simultaneously through a visual inspection of results. We accounted for uncertainty in the target data by providing ranges from multiple studies and accepted the model as a good fit if it was within the range provided (preferably within the lower portion of the range for targets with a wide range) or within 10% for targets based on a single point estimate. In some cases, sources used to determine parameters were also used to evaluate the model; this was considered acceptable because many sources were epidemiologic studies that included results not used to determine parameters and because this multistage model generated mean parameter values that were often distinct from the predetermined point estimate.

One-Stage Model

The first goal was to produce a model that predicted that 33% to 70% of heroin users would ever have an overdose, that the annual rate of overdose would be 10% to 25%, and that the peak age of overdose mortality would be in the fourth decade of life. In addition, nonfatal overdose is known to be inversely associated with age. A single-stage model of overdose predicted that too many heroin users would have an overdose and overdose death would thus occur too early in the model, whereas the risk for dying from an overdose was much lower than literature estimates. Moreover, because several studies have shown that overdose begets overdose, a primary goal of the model was to determine how repeat events affected the cost-effectiveness of naloxone distribution.

Two-Stage Model

We added a second stage of overdose to the model. This required us to identify a parameter value for the risk for first-time overdose compared with that for repeat overdose. This adjustment generated a closer approximation of the median age of overdose death but still had too few overdoses resulting in death and too few overdose deaths annually. Furthermore, the model now generated too much mortality among young heroin users. At this stage, we also adjusted the structure of the overdose to parameters estimating the likelihood that naloxone at the scene of an overdose would be used for reversal.

Three-Stage Model

We extended the model to a third stage of overdose on the basis of the same data source that allowed the initial expansion. This generated predictions that, overall, were much more consistent with the targets. The proportion ever having an overdose was now closer to the midrange of our estimate, the proportion of overdoses resulting in death was now within range, and the median age of overdose death was now in the latter part of the fourth decade. Although the annual rate of overdose death was higher, it was now too high. On the basis of the lifetime and annual rates of overdose and median age of overdose death, this model seemed structurally acceptable and we thus decided to stop adding further levels of overdose (a further stage of overdose is evaluated in Table 2). However, the annual rates of overdose and all-cause mortality, overdose mortality, and mortality among young heroin users were all at the upper range of literature estimates.

Final Model

To reduce the overall risk for death, particularly that occurring in early years, we searched for data to support increasing the risk for death from repeat overdose. Because several studies supported this claim, we generated a new parameter reducing the risk for survival for the second and subsequent overdoses. Through trial and error, we established this to be an absolute 1.5% reduction in likelihood of survival for the second overdose and a 3.0% reduction for subsequent overdoses, applied to all overdoses before any intervention. We considered also decreasing the likelihood that an overdose would be witnessed for subsequent overdose under the hypothesis that persons having repeat overdoses would have increasing social isolation, but we could not find any data to support this hypothesis. The adjustment forced us also to adjust the likelihood of survival from a first-time overdose, which was increased to 91.8%, and allowed us to increase the risk for a first-time overdose from 6% to 9%, which is closer to literature estimates. These changes, however, increased the likelihood of ever overdosing to 68%, which is too close to the upper limit of literature estimates for our conservative model; thus, on the basis of studies suggesting a decreasing risk for overdose over time for those who never overdosed, we incorporated an additional variable to reduce the likelihood of overdose each year for those who never overdosed, such that overdose risk was halved after 10 years of using heroin without ever having an overdose. Finally, because this model resulted in most surviving heroin users continuing to use throughout their lives, we incorporated an additional parameter reducing the likelihood of relapse to heroin use after each year of abstinence, such that after 10 years of abstinence the risk for relapse was halved. This model was deemed acceptable because all values were within the range of target values or within 10% of a point estimate and, to err on the side of a conservative model, the annual rate of overdose, proportion of overdoses resulting in death, and likelihood that distributed naloxone would be used to reverse an overdose were in the lower range of the available estimates.

Appendix Table 1. Point Estimate and Range of Naloxone Distribution Model Parameters, With Justification

Parameter	Base Case (Range)	Justification
Proportions		
Joint probability that distributed naloxone is used each year	0.136 (0.004 to 0.631)	This parameter is calculated from parameters in the next 4 rows. It was targeted to approximate the findings of epidemiologic studies suggesting that 9% to 40% of dispensed naloxone is used to reverse an overdose (3, 7, 10, 47).
Proportion of heroin users prescribed naloxone	0.20 (0.05 to 0.50)	This parameter is based on a review of HIV testing rollout in resource-limited settings that showed 5% to 60% coverage (16), author experience with naloxone distribution programs, and estimate of 20% coverage of naloxone distribution provided by the naloxone coordinator at the New York City Department of Mental Health and Hygiene (Heller D. Personal communication.)
Proportion of overdoses witnessed	0.85 (0.32 to 0.94)	Overdoses are generally believed to be witnessed in most cases, although there is 1 study of fatal overdose that shows a lower rate of witnessed overdose (32%), supporting the hypothesis that bystanders are important to reducing overdose mortality (17–19). The range included the witnessed rate for fatal overdoses as a lower limit and a relative increase of 10% as an upper limit. Because the likelihood of an overdose being witnessed may vary by how socially isolated a group of heroin users is, the parameter "relative likelihood that naloxone will be present at an overdose event" was adjusted in sensitivity analyses.
Proportion in possession of naloxone at an overdose who use it to attempt reversal	0.8 (0.5 to 0.9)	This parameter, which is based on a cohort study, represents the likelihood that an overdose witness who has naloxone will use it (20).
Social network modifier	1.0 (0.5 to 1.5)	This is an assumption that is set to reflect other data points. The point estimate for this parameter relies on the other parameters, and the range allows for a broader range of error in the related variables (that is, if heroin users in a given community are more or less likely to use in groups, this variable would be higher or lower, respectively). For example, heroin users in the Haight-Ashbury district of San Francisco, California, tend to be younger and to use in groups, whereas those in the Tenderloin district of San Francisco tend to be older and may have higher degrees of social isolation (19). This modifier could hypothetically be set to 1.5 for the Haight-Ashbury district and 0.5 for the Tenderloin district.
Proportion who call EMS		
First-time overdose	0.6 (0.3 to 0.8)	The likelihood of calling EMS varies by locality, with ranges from 20% to 60%, and increasing data suggest that those who witness multiple overdoses are less likely to call EMS at a subsequent overdose, consistent with the hypothesis that EMS is used as a last resort rather than a first-line response (21–23).
Subsequent overdoses	0.4 (0.2 to 0.6)	
Relative likelihood of EMS call if naloxone is used	1.0 (0.8 to 1.2)	The only data on which to base this estimate are from a small survey comparing drug users who used naloxone with those who did not in their most recent witnessed overdose (23, 24). A wide range was selected to illustrate the degree of confidence in the point estimate.
Likelihood of transport to hospital	0.9 (0.81 to 0.99)	Most jurisdictions require that all overdose victims be transported to the hospital for evaluation, resulting in a fairly high rate of transport (25). Relative range was estimated as ±10%.
Relative likelihood of transport to hospital after lay naloxone	1.0 (0.5 to 1.0)	Two large studies have shown the safety of paramedics not transporting overdose victims to the hospital after they have been revived with naloxone (26, 27), and some localities have changed EMS policy to defer transport of overdose victims revived with lay naloxone (Copass M. Personal communication.) Thus, in the sensitivity analysis, we allowed less transport to the hospital after lay naloxone administration.
Proportion who survive overdose		
No medical assistance or lay naloxone	0.899 (0.784 to 0.940)	This is the product of the model run with each stage of overdose set at the point estimate, with a range based on each stage of overdose risk set to lower and upper limits; the point estimate is consistent with literature estimates (5).
First-time overdose	0.918 (0.800 to 0.940)	Parameters were selected on the basis of the commonly accepted belief that 90% of overdoses result in survival without EMS care or lay naloxone (1, 5). To account for high rates of nonfatal overdose at younger ages but a median age of overdose death in the fourth decade of life, we adjusted the likelihood of survival lower for each overdose while maintaining the resulting average likelihood of survival of approximately 90.0% among those not receiving EMS or naloxone.
Absolute reduction for second overdose	0.015 (0.000 to 0.020)	
Additional reduction for subsequent overdoses	0.015 (0.000 to 0.020)	
Relative increase in survival with EMS	1.089 (1.020 to 1.158)	Most opioid overdoses are easily treated medically, but EMS activation is often delayed. In 1 study of overdoses that required naloxone administration (a small subset of opioid overdoses), 93.2% survived (28). On the basis of this and several studies of overdoses reversed with lay naloxone (7, 8, 20, 29–31), we assumed an equivalent likelihood of survival of approximately 98% at baseline. The parameter was presented as a relative likelihood to account for the varying baseline likelihood of survival and adjustments during sensitivity analysis. The absolute value is 0.978 (range, 0.784 to 1.000).
Relative increase in survival with naloxone	1.089 (1.020 to 1.158)	This parameter is based on several small studies of lay naloxone administration, as well as unpublished data, showing that 96% to 100% of cases result in survival (7, 8, 20, 29–31). Because these data were self-reported, a wide relative risk of ±63% was selected. The absolute value is 0.978 (range, 0.784 to 1.000).

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Appendix Table 1—Continued

Parameter	Base Case (Range)	Justification
Annual transition rates		
Heroin use to nonoverdose death (in excess of background mortality)	0.0075 (0.0025 to 0.0125)	Heroin users are at excess risk for death in addition to overdose (5).
Heroin use to overdose		To account for the high rate of overdose among young heroin users and the established finding that less than 25% of users ever overdose, we adjusted annual overdose rates on the basis of several studies showing a higher risk for overdose among those who have overdosed previously (12, 29, 32, 33).
First overdose	0.09 (0.02 to 0.12)	
Second overdose	0.22 (0.05 to 0.30)	
Subsequent overdoses	0.34 (0.27 to 0.60)	
Annual relative reduction in risk for first overdose	0.933 (0.900 to 1.000)	An additional approach used to calibrate the model to extant epidemiologic findings was to decrease the likelihood of a first-time overdose such that for those who had never overdosed, risk for first-time overdose was half after 10 y of use (32, 34); this does not affect the likelihood of repeat overdoses. The parameter was exponentiated to the years elapsed and the result multiplied by its reference parameter to reduce the likelihood of the event over time.
Heroin use to discontinuation of heroin use	0.06 (0.01 to 0.10)	The rate of discontinuing heroin use was taken from large prospective cohorts (35, 36).
Discontinuation of heroin use to heroin use	0.070 (0.056 to 0.084)	The risk for relapse to heroin use was based on a study showing 50% relapse over 5 y (37), with an age-based reduction in risk for relapse such that relapse was half as likely after 10 y (15), resulting in an average duration of heroin use of 10 to 12 y (35, 36, 48).
Annual relative reduction in risk for relapse	0.933 (0.900 to 1.000)	This parameter acted as the age-based reduction in the risk for relapse (15). The parameter was exponentiated to the preceding number of model cycles and the result multiplied by its reference parameter to reduce the likelihood of the event over time.
Overdose to discontinuation of heroin use	0.062 (0.028 to 0.113)	The only study examining rates of discontinuing drug use after overdose found that 26% of injection drug users sought substance abuse treatment within 30 d of an overdose event, 75% of whom enrolled, suggesting an increase in discontinuation of heroin use related to the overdose event (38). We thus assumed a relative 10% increase in the likelihood of discontinuing heroin use after an overdose, ranging on sensitivity analysis from half to double the rate of discontinuation if there was not an overdose (38).
Costs, $*		
Biennial naloxone kit (2 doses plus distribution costs)	25 (12 to 75)	U.S. naloxone distribution programs pay approximately $6 per dose of naloxone, $15 per kit of injectable naloxone (40), and at least $25 per kit of intranasal naloxone (39). Most programs dispense injectable naloxone, 0.4 mg/mL, and incorporate distribution into preexisting programmatic activities. We estimated a total cost of $25 per kit ($12 for naloxone, $3 for other components, and $10 for overhead), with a range from $12 for naloxone alone to $75 for intranasal naloxone plus expenses for a dedicated naloxone distribution program. We did not use wholesale acquisition costs because naloxone is rarely distributed to retailers and most transactions are contractual.
EMS visit	1790 (714 to 2500)	The cost of EMS was estimated from a recent cost-effectiveness evaluation (41).
EMS transport to hospital	301 (271 to 331)	The transport cost was taken from the same source (41) but modeled separately because the likelihood of transport to the hospital may vary.
Emergency department care if transported	885 (707 to 1061)	The baseline value used here is the cost of emergency department care treatment and release, without hospitalization, based on the Centers for Disease Control and Prevention Web-based Injury Statistics Query and Reporting System (42). In contrast to the Thomson Reuters database, the source includes contracted physician payments. We adjusted the value from 2005 to 2012 costs on the basis of the health care portion of the Consumer Price Index and estimated a relative range of ±20% for the sensitivity analysis.
Average annual societal cost of heroin user for secondary analysis (set to $0 for baseline)	3368 (1023 to 4041)	Our baseline model did not include this cost parameter because doing so would violate principles of cost-effectiveness analysis (the reduced "value" of a heroin user's life is accounted for in the utility estimate for the denominator of the equation; including a change in the cost estimate of the numerator is not generally condoned). However, we did incorporate such a hypothetical cost into a subanalysis because of the concerns of some policymakers that saving the lives of heroin users may lead to higher cost outlays, thereby reducing the cost-effectiveness from a societal perspective. To estimate the annual societal cost of the average heroin user (a difficult task), we used an estimate produced by the U.S. Office of National Drug Control Policy, based on U.S. health care and criminal justice expenditures related to drug abuse ($52 243 million) (48), multiplied by the proportion of illicit drug users who used heroin (0.9%) (14), divided by a low estimate of the number of heroin users in the United States (200 000) (14), and adjusted from 2002 to 2012 costs on the basis of the health care costs portion of the Consumer Price Index, resulting in a final per annum cost of $3368 per active heroin user. The lower limit was $1023, including only health care costs, and the upper limit was 20%.

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Appendix Table 1—Continued

Parameter	Base Case (Range)	Justification
Utilities*		
Heroin user	0.80 (0.73 to 0.90)	Recent estimates of utility for substance abuse come from treatment seekers who are more likely to perceive drug use as negatively affecting their quality of life, and the mean age for both studies is substantially older than the beginning age of the model (43, 44). The latter study, involving clients at a midwestern U.S. substance abuse treatment intake center, included a 6-mo follow-up survey that may have captured those not actively seeking treatment and documented a utility of 0.80 by SF-6D methodology and a 6.5% improvement for those who achieved interim abstinence (43–45).
Relative increase in utility for heroin user in recovery	1.07 (1.00 to 1.13)	To be consistent and conservative, we used the 6.5% improvement in utility from the above study, although the SF-6D methodology has been found to be poorly responsive to changes in drug use (44) and a study of opioid maintenance therapy found a relative improvement of 16% in utility for a heroin user (46). Utility was coded to never exceed 1.0 when values were set to upper extremes simultaneously.

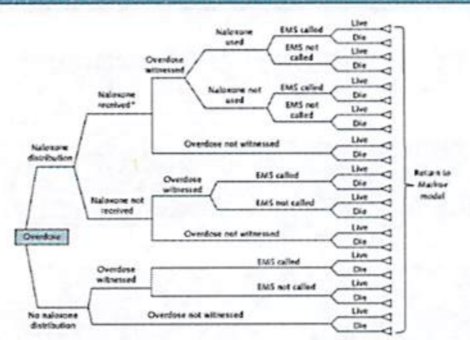
EMS = emergency medical services; SF-6D = Short Form 6D.
* 3% annual discounting.

Appendix Table 2. Targets and Cost-Effectiveness Results for Model Calibration*

Parameter	Literature Estimate	Reference	1-Stage Model	2-Stage Model	3-Stage Model	Final Model
Annual rate of overdose among active users, %	10 to 25	12, 51–53, 63	55†	19	21	12
Proportion ever having an overdose	33 to 70	17, 54, 63, 64	78	78	52	50
Proportion of overdoses resulting in death	3 to 15	21, 55	1.1	1.5	6	4
Likelihood of overdose survival without assistance, %	90	5	90†	90†	90†	90.0
Likelihood of overdose survival with EMS or naloxone, %	96 to 100	7, 8, 20, 28–31	98†	98†	98†	97.8
Annual rate of overdose death among active users, %	1.0	1	0.2	0.4	1.3	1.0
Annual rate of all-cause death among active users, %	1.5 to 2.5	5, 56, 57	2.6	4.0	3.6	1.97
Among those aged <30 y, %	0.91		0.9	1.4	1.4	0.98
Median age of overdose death, y	31 to 40	32, 56, 59, 61	26	32	38	38
Likelihood of distributed naloxone being used to reverse an overdose, %	9 to 40	3, 7, 10, 49	4	13.6	13.6	13.6
Median duration of heroin use, y	10 to 15	40, 60	2	12	11	15
Cost difference, $	–	–	63	188	43	46
QALY difference	–	–	0.271	0.780	0.109	0.109
ICER, $	–	–	232	241	394	421

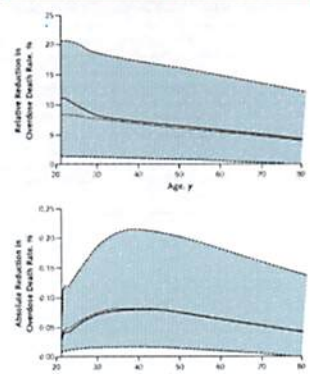
EMS = emergency medical services; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
* The Appendix provides details about the model development.
† Predetermined value.

Appendix Figure 1. Decision analytic model of an overdose in the setting of naloxone distribution to heroin users.



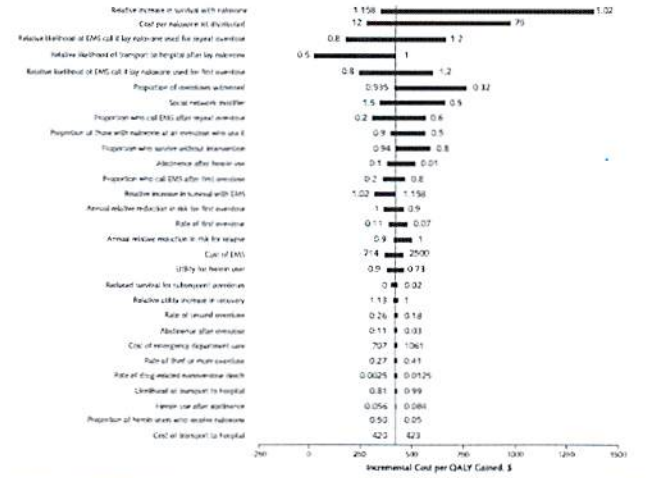
EMS = emergency medical services
* Modified by the likelihood of naloxone being present at an overdose.

Appendix Figure 2. Relative (top) and absolute (bottom) reduction in overdose death rate among active heroin users from naloxone distribution for lay overdose reversal.



Solid lines represent the results of the deterministic model from baseline parameters; other lines represent the results of the probabilistic analysis, including the mean (*dotted line*) and 95% CI (*dashed lines*). Absolute rates were adjusted by the number of active heroin users to represent the effect in a community of heroin users at various stages of drug use.

Appendix Figure 3. One-way sensitivity analyses of naloxone distribution to heroin users for lay overdose reversal.



Analyses of all model parameters based on maximum predicted ranges. EMS = emergency medical services; QALY = quality-adjusted life-year.

Appendix Table 1. Absolute Outcomes From Selected Deterministic Sensitivity Analyses

Parameter	No Naloxone	Naloxone
Population outcomes (per 200 000 heroin users)		
Baseline scenario		
Lifetime overdoses, *n*	918 509	933 759
Lifetime overdose deaths, *n*	27 406	25 613
Naloxone kits delivered, *n*	–	294 434
Worst-case scenario*		
Lifetime overdoses, *n*	886 298	886 936
Lifetime overdose deaths, *n*	31 263	31 672
Naloxone kits delivered, *n*	–	251 749
Best-case scenario†		
Lifetime overdoses, *n*	925 389	998 832
Lifetime overdose deaths, *n*	26 492	15 350
Naloxone kits delivered, *n*	–	1 096 345
Naloxone distribution reduces overdose risk‡		
Lifetime overdoses, *n*	918 509	696 868
Lifetime overdose deaths, *n*	27 406	18 835
Naloxone kits delivered, *n*	–	307 712
Individual outcomes		
Baseline scenario		
Life-years	44 625	44 996
Among those who discontinued heroin use	27 782	27 974
Undiscounted QALYs	37 144	37 419
Among those who discontinued heroin use	23 670	23 834
Discounted QALYs	19 121	19 229
Among those who discontinued heroin use	9 887	9 942
Undiscounted costs, $	2180	2217
Of naloxone, $	–	44
Discounted costs, $	1423	1429
Of naloxone, $	–	30
Incremental cost per QALY gained, $	–	421
Kits needed to prevent 1 death, *n*	–	144
Worst-case scenario		
Life-years	43 764	43 781
Among those who discontinued heroin use	27 272	27 282
Undiscounted QALYs	36 430	36 446
Among those who discontinued heroin use	23 236	23 244
Discounted QALYs	18 824	18 836
Among those who discontinued heroin use	9 736	9 739
Undiscounted costs, $	1029	1144
Of naloxone, $	–	114
Discounted costs, $	696	776
Of naloxone, $	–	79
Incremental cost per QALY gained, $	–	14 000
Kits needed to prevent 1 death, *n*	–	2781
Best-case scenario		
Life-years	44 803	46 803
Among those who discontinued heroin use	27 887	29 044
Undiscounted QALYs	37 302	38 953
Among those who discontinued heroin use	23 760	24 746
Discounted QALYs	19 182	19 831
Among those who discontinued heroin use	9 918	10 245
Undiscounted costs, $	2273	2753
Of naloxone, $	–	158

Continued

Appendix Table 1—Continued

Parameter	No Naloxone	Naloxone
Discounted costs, $	1586	1794
Of naloxone, $	–	104
Incremental cost per QALY gained, $	–	321
Kits needed to prevent 1 death, *n*	–	99
Naloxone distribution reduces overdose risk‡		
Life-years	44 625	45 358
Among those who discontinued heroin use	27 782	28 508
Undiscounted QALYs	37 144	38 249
Among those who discontinued heroin use	23 670	24 289
Discounted QALYs	19 121	19 543
Among those who discontinued heroin use	9 887	10 084
Undiscounted costs, $	2180	1935
Of naloxone, $	–	49
Discounted costs, $	1423	1196
Of naloxone, $	–	30
Incremental cost per QALY gained	–	Dominant
Kits needed to prevent 1 death, *n*	–	36

QALY = quality-adjusted life-year.

* Sets the proportion of overdoses witnessed to 0.425, social network modifier of likelihood that naloxone is present at the scene to 0.5, relative increase in survival with naloxone to 1.020, and cost of naloxone to $75.

† Sets the joint probability that naloxone is used to the maximum value by setting to the upper-limit proportion of heroin users receiving naloxone to 0.60, the proportion of overdoses witnessed to 0.935, the proportion with naloxone at an overdose who administer it to 0.9, and the social network modifier to 1.5.

‡ Sets the risk for overdose to the lower limit for all wages in the setting of naloxone distribution.

Expanded Access to Opioid Overdose Intervention: Research, Practice, and Policy Needs

Rates of fatal drug overdoses have more than doubled in the United States over the past decade to become one of the leading causes of preventable injury death. Overall drug overdose deaths increased to a record of 38 329 in 2010, outpacing deaths from motor vehicle traffic crashes nationally for 2 years running (1). Most of the increase in such deaths is related to prescription opioids and mirrors an increase in opioid prescribing (1, 2). Diversion of these medications contributes to the problem (3), and both higher opioid doses and polysubstance use are significant contributing factors (3, 4).

Many actions are needed to address the complexity of the problem. In response, the Office of National Drug Control Policy has embarked on a 4-pronged effort to address prescription drug abuse: public and clinician education, controlled substance tracking and monitoring, proper medication disposal, and law enforcement (5). The Office of National Drug Control Policy and others have also endorsed direct interventions to treat opioid overdoses as an important component of this comprehensive approach (6, 7). The article by Coffin and Sullivan in this issue (8) represents a significant step in the evolution of the science in this area: a detailed analysis of the cost-effectiveness of overdose intervention with naloxone administration for heroin abusers. The authors suggest that lay naloxone administration is likely to be highly cost-effective in this setting, a robust finding that holds up under various assumptions. Future analyses that extend their findings to the setting of prescription opioids would be welcome.

Naloxone is safe and effective for the treatment of opioid overdose (9). Its use is standard practice in emergency settings, where it is administered to patients with an opioid-induced coma or respiratory depression because of its rapid action as a μ-opioid–receptor antagonist. Despite its potential to safely, rapidly, and completely reverse an opioid overdose (7–9), the public health impact of this medication has not yet reached its full potential.

A key factor limiting widespread use of naloxone is that the only U.S. Food and Drug Administration (FDA)–approved formulation is injectable. Potential alternatives include formulations that could be delivered by an intranasal device (10) or an auto-injector, both of which show great promise but require additional research. Ultimately, approval of a naloxone formulation that could be used without a prescription would also help encourage broader use, although additional studies are needed in this area as well.

In April 2012, the FDA, the National Institute on Drug Abuse (NIDA), the Centers for Disease Control and Prevention, and the Office of the Assistant Secretary for Health jointly sponsored a public meeting on the potential for expanded access to naloxone, particularly its use outside of conventional medical settings (11). Researchers from various locations—both here and abroad—reported encouraging data on the ability of naloxone to reverse opioid overdose and emphasized the use of intranasal formulations administered in nonmedical settings. At the meeting, the FDA outlined the regulatory pathway for approval of both intranasal and auto-injector devices. The primary requirement would be to show bioequivalence of the new formulation to the existing approved injectable formulation, and additional required studies may be limited in number, of short duration, and modest in size. Switching naloxone from prescription to over-the-counter status to increase availability was also discussed; the necessary studies would center on the ability of consumers to accurately diagnose an overdose and correctly administer the medication.

Since the meeting, federal agencies have continued to address this urgent public health need through targeted educational efforts, research, and communications. For example, the NIDA is encouraging research on strategies to help prevent opioid tolerance; to develop opioid delivery systems that are less likely to be diverted; to evaluate the effectiveness of naloxone distribution among high-risk patients; and to lay the groundwork for the development of devices that deliver naloxone automatically when a preset threshold for oxygen concentration signals respiratory depression, even when patients are asleep. The FDA has continued to encourage the pharmaceutical industry to develop data on the comparability of injection and alternative formulations of naloxone (12) through discussions with naloxone manufacturers here and abroad. In addition, the Substance Abuse and Mental Health Services Administration has been developing an overdose "toolkit" to educate persons at high risk for overdose and their families (11).

However, prevention of overdose can be only 1 facet of an overall comprehensive approach to prescription drug abuse. Increases in both the number of prescriptions and the doses of opioids prescribed seem to be significant contributors to the problem (1, 2, 4, 5), suggesting that education and enhanced physician access to patient prescription records might be part of the solution. For instance, the NIDA, in partnership with the pain consortium at the National Institutes of Health, has funded "pain centers of excellence" to develop curricula to better prepare clinicians and nurses for screening and monitoring pain, including proper management of opioid medications. In July 2012, the FDA announced the approval of a Risk Evaluation and Mitigation Strategy for high-potency and extended-release opioids, which is focused on prescriber and patient education and has a goal of reducing the abuse of these powerful drugs. In addition, access to state Prescription Drug Monitoring Program data in a rapid, automated manner can inform clinicians about other controlled substances that may have been prescribed to their patients. Such information can change prescribing practices and may reduce both inadvertent and intentional medication misuse (13). Programs are currently operational in most states, but physician enrollment and utilization have been disappointing. Projects at the Substance Abuse and Mental Health Services Administration and the Office of the National Coordinator for Health Information Technology to enhance and simplify access to Prescription Drug Monitoring Program data in real-world clinical settings, such as emergency departments and primary care practices, are underway.

In parallel to these advances, there is an urgent need for continued research and practice development. The NIDA and the FDA are keen to work with public health and pharmaceutical company partners on pharmacokinetic studies of intranasal and injectable naloxone, and they welcome inquiries. Additional formative and implementation studies of naloxone distribution and overdose intervention in field settings, particularly for prescription opioid abusers, are also needed, as are studies of the ways to embed overdose intervention into a broader addiction intervention system (that is, to use overdose interventions as points of entry into drug treatment). Studies of the use of take-home naloxone for persons receiving high dosages of prescription opioids and of those abusing the drugs are warranted to determine whether such interventions reduce mortality and morbidity. In particular, studying the effectiveness of layperson-administered naloxone in reversing overdose from long-acting and extended-release opioids is essential (7, 9, 10).

We applaud Drs. Coffin and Sullivan for their important contribution to this public health effort, and we encourage much additional work that can bring such potentially life-saving interventions more firmly into the mainstream of both clinical practice and community programs for licit and illicit drug users.

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RESEARCH

Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis

OPEN ACCESS

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Abstract

Objective To evaluate the impact of state supported overdose education and nasal naloxone distribution (OEND) programs on rates of opioid related death from overdose and acute care utilization in Massachusetts.

Design Interrupted time series analysis of opioid related overdose death and acute care utilization rates from 2002 to 2009 comparing community-year strata with high and low rates of OEND implementation to those with no implementation.

Setting 19 Massachusetts communities (geographically distinct cities and towns) with at least five fatal opioid overdoses in each of the years 2004 to 2006.

Participants OEND was implemented among opioid users at risk for overdose, social service agency staff, family, and friends of opioid users.

Intervention OEND programs equipped people at risk for overdose and bystanders with nasal naloxone rescue kits and trained them how to prevent, recognize, and respond to an overdose by engaging emergency medical services, providing rescue breathing, and delivering naloxone.

Main outcome measures Adjusted rate ratios for annual deaths related to opioid overdose and utilization of acute care hospitals.

Results Among these communities, OEND programs trained 2912 potential bystanders who reported 327 rescues. Both community-year strata with 1-100 enrollments per 100 000 population (adjusted rate ratio 0.73, 95% confidence interval 0.57 to 0.91) and community-year strata with greater than 100 enrollments per 100 000 population (0.54, 0.39 to 0.76) had significantly reduced adjusted rate ratios compared with communities with no implementation. Differences in rates of acute care hospital utilization were not significant.

Conclusions Opioid overdose death rates were reduced in communities where OEND was implemented. This study provides observational evidence that by training potential bystanders to prevent, recognize, and respond to opioid overdoses, OEND is an effective intervention.

Introduction

Poisoning, nine out of 10 of which are related to drug overdoses,[1] has surpassed motor vehicle crashes to be the leading cause of death by injury in the United States.[2] Overdose is also a major cause of death in Canada,[3] Europe,[4] Asia,[5 6] and Australia.[7] In the United States, increases in fatal overdose since the mid-1990s have been driven by the growth in prescriptions for opioid analgesics[8] and their non-medical use.[1 9] Opioid related emergency department visits and admissions to hospital have increased over the same period.[10] In Massachusetts, since 2005, annual opioid-related overdose deaths have exceeded motor vehicle deaths.[11]

Strategies have been implemented to deal with opioid overdose. Prescription drug monitoring programs,[12] prescription drug take back days, safe opioid prescribing guidelines, and education programs seek to reduce opioid misuse and/or diversion to people who do not have prescriptions. While these strategies are promising, none has been demonstrated in clinical trials or controlled observational studies to reduce overdose rates. Methadone maintenance treatment[13 14] and supervised injection facilities[15] are strategies associated with decreased fatalities from overdose in controlled studies.

Naloxone is an opioid antagonist that reverses the effects of opioid overdose. Overdose education and naloxone distribution (OEND) programs tackle overdose by educating people at risk for overdose and bystanders in how to prevent, recognize, and respond to an overdose. Participants in the program are trained to recognize signs of overdose, seek help, rescue breathe, use naloxone, and stay with the person who is overdosing. From 1996 through 2010, over 50 000 potential bystanders were trained by OEND programs in the United States, resulting in over 10 000 opioid overdose rescues with naloxone.[16] In March 2012, the United Nations Commission on Narcotic Drugs recognized overdose as a global public health issue that warrants focus by the World Health Organization and member countries, including the use of naloxone for the prevention of opioid overdose.[17] Studies of OEND programs have demonstrated feasibility,[18 19] increased knowledge and skills,[20 21] and a concomitant reduction in fatal overdoses after initiation of OEND.[22 23] A controlled study of OEND and overdose rates has not been completed. Implementation of OEND in Massachusetts in communities with a high burden of opioid overdose created the opportunity to study the impact of OEND on opioid related fatal overdose and acute care hospital utilization rates, using high burden communities with low or no OEND implementation as concurrent controls.

Methods

We conducted an interrupted time series analysis of annual opioid related rates of overdose fatalities and utilization of acute care hospitals comparing communities and years where OEND was implemented with those where it was not. The analysis was conducted at the city/town level. Massachusetts consists of 351 geographically distinct cities and towns (referred to as communities). We included the 19 communities with five or greater opioid related unintentional or undetermined intentional fatal poisonings in each year from 2004 to 2006, which were the years immediately preceding the implementation of OEND.

The Massachusetts OEND program

In 2006-07, two community public health agencies began providing OEND.[20] The Massachusetts Department of Public Health expanded the program to four more organizations in 2007 and two more in 2009. These agencies, which provided HIV education and prevention services to substance users, provided OEND to potential overdose bystanders through trained non-medical public health workers under a standing order from the OEND medical director. Potential overdose bystanders were opioid users at risk for overdose, as well as social service agency staff, family, and friends of opioid users. Training sites included syringe access programs, HIV education drop-in centres, addiction treatment programs, emergency and primary healthcare settings, and community meetings, such as support groups for family members of opioid users.

Training curriculums were initially developed by the Harm Reduction Coalition and the Chicago Recovery Alliance,[24 25] and adapted for nasal naloxone. OEND trainers completed a four hour course, knowledge test, and two trainings of potential bystanders supervised by a master trainer. The training of program participants by OEND trainers were conducted in groups or individually, took as little as 10 minutes for enrollees with substantial pre-existing knowledge and as much as 60 minutes for groups that generated discussion or had enrollees without prior knowledge of overdose, and were tailored to the training setting. Key elements included minimizing the risk of overdose by reducing polysubstance misuse (for example, concomitant alcohol, benzodiazepine, or cocaine), accounting for reduced tolerance after abstinence, and not using alone; recognizing overdose by assessing for unresponsiveness and decreased respirations; and responding to an overdose by seeking help, providing rescue breathing, administering nasal naloxone, and staying with the person until medical personnel arrived or the person recovered. Trainings concluded with enrollees demonstrating proper assembly of the naloxone device and how naloxone should be administered. Naloxone rescue kits contained instructions, two prefilled syringes with 2 mg/2 mL naloxone hydrochloride, and two mucosal atomization devices. Two doses were included in case one dose was not sufficient or if overdose symptoms returned, because the half-life of many opioids is longer than that of naloxone.

Data collection and measures

Fatal opioid overdose rates

For the fatal opioid overdose outcome, we calculated rates of unintentional and undetermined intentional opioid related drug poisonings by community of residence using in-state occurrent deaths from the electronic database maintained by the Massachusetts Registry of Vital Records and Statistics, Massachusetts Department of Public Health. Death certificates on fatal poisonings in Massachusetts are completed through a single centralized, statewide office of the chief medical examiner, where they are required by law to be reported. Opioid related deaths were defined by ICD-10 (international classification of diseases, 10th revision) codes indicating unintentional or undetermined intentional poisoning (X40-X44, Y10-Y14) in the underlying cause of death field and an opioid specific T code of T40.0-T40.4 and/or the narcotic T code T40.6 in any of the multiple cause of death fields. The use of T40.6 to identify opioid related deaths is recommended in jurisdictions where a high proportion of deaths with this code is opioid specific.[26] An unpublished review of 2007 Massachusetts death certificate literals indicated that T40.6 had a positive predictive value of 98% for an opioid related death. Furthermore, 96.7% of unintentional or undetermined intentional deaths by poisoning in Massachusetts in 2007 received at least one ICD-10 code in the range (T36-T50.8), indicating that specific information on agent or class of agent was present on death certificates for nearly all drug related deaths.

Opioid overdose related acute care hospital utilization rates

We used the Massachusetts inpatient hospital and outpatient emergency department discharge databases administered by the Massachusetts Division of Health Care Finance and Policy to quantify acute care hospital inpatient and emergency department discharges associated with opioid poisoning by city or town of residence. Submission of external cause of injury codes (E codes) are required by state regulation on all cases with a

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Extra material supplied by the author (see http://www.bmj.com/content/346/bmj.f174?tab=related#webextra)

Map of the 19 communities in Massachusetts
coefficients for covariates in adjusted absolute and relative models of opioid overdose related unintentional deaths
coefficients for covariates in adjusted absolute and relative models of opioid related acute care utilizations
Control models of OEND implementation and ratio of opioid related overdose deaths to cancer deaths
Control models of OEND implementation and ratio of opioid related acute care utilizations to motor vehicle crash acute care utilizations

principle diagnosis of injury or poisoning, ensuring high quality data for state injury surveillance. Cases were defined as discharges having an ICD-9-CM (international classification of diseases, ninth revision, clinical modification) code of one or more of the following opioid related discharge diagnosis or E codes: 965 (.00, .01, .02, .09), E850 (.0, .1, .2). We excluded those cases receiving an E code indicating that the poisoning was the result of intentional self harm, assault, an adverse effect of a drug in therapeutic use, or legal intervention. To avoid duplicate counts with the fatality measure we excluded deaths occurring during the hospital event from this outcome.

Descriptive variables from enrollment and naloxone rescue attempt questionnaires

The Massachusetts Department of Public Health OEND program database included information from program questionnaires collected at both enrollment and whenever an enrollee requested an additional naloxone kit. The completed questionnaires were scanned by form reading software and entered into the program database. At enrollment, zip code of residence, drug use history, and overdose history were collected. We defined users as participants who reported active use or being in treatment or in recovery. Non-users were all other participants, typically social service agency staff, family, and friends of opioid users. A questionnaire was completed when a participant requested a naloxone refill because naloxone had been used during an overdose rescue. Staff were trained to define an overdose when administering the questionnaire as an episode when an individual was unresponsive and had signs of respiratory depression after using substances. We only counted events where participants reported their own overdose rescue attempts if another person administered the naloxone. Self administered naloxone was rarely reported and was not counted as a rescue attempt because a person able to self administer the drug was not considered to be unresponsive. We considered naloxone to be successfully administered if the person's unresponsiveness and respiratory depression improved. Other descriptive variables included the zip code of the place in which the overdose occurred, relationship to the person who overdosed, setting (public or private), number of naloxone doses used, whether naloxone was successful, emergency medical system involvement, rescue breathing, and staying with the person who overdosed.

Independent variables: OEND enrollment rates

To determine the cumulative enrollment rates for the 19 communities with high overdose burdens we used the community of residence based on the zip code of residence on the enrollment questionnaire. We modeled OEND implementation in two ways. Firstly, we categorized OEND implementation into three groups within each year based on the median cumulative enrollment rate (relative model). Groups included community-year strata with no implementation, those below the median (low implementers), and community-year strata with enrollment rates above the median (high implementers). Secondly, to determine if an absolute population density of enrollment was associated with overdose rates, we categorized communities in each year into three categories based on cumulative enrollment rate levels of no implementation, 1-100 per 100 000 population and >100 per 100 000 population (absolute model). In the models we used enrollment cut points of 0, 1-75, >75 and in sensitivity analyses cut points of 0, 1-150, and >150.

Covariates

To account for geographic differences in overdose risk, we adjusted our analyses for demographics. We linearly interpolated community specific data (age, sex, race or ethnicity, poverty) for each year from the community specific 2000[27] and 2010[28] US Census Bureau data.

We used data from the Massachusetts prescription drug monitoring program to adjust for opioid prescriptions to "doctor shoppers," defined as individuals who had schedule II opioid prescriptions from four or more prescribers and filled prescriptions at four or more pharmacies in a 12 month period.[12] We calculated the proportion of schedule II opioid prescriptions dispensed to doctor shoppers per total opioid prescriptions for each community-year stratum.

Inpatient medically supervised withdrawal (detox) results in a period of abstinence that can increase overdose rates,[29 30] whereas engagement in methadone treatment results in decreased rates of overdose.[14] Office based buprenorphine treatment expanded during the study period. To adjust for these three treatment services, we calculated population rates of methadone maintenance, buprenorphine maintenance, and detox events for each community-year stratum using data from the Massachusetts Department of Public Health Bureau of Substance Abuse Services treatment database. Any treatment program licensed by and contracted with the Substance Abuse Services was required to report admission and discharge information.

We accounted for linear trends over the study period by using a time variable T, expressed as 1 for the index year 2002 and increasing in integer increments for each year of the study period.

Statistical analysis

For the interrupted time series we used the annual rates of fatal opioid related overdose and acute care hospital utilization associated with non-fatal opioid overdose by community of residence for the units of analysis. The denominators were the community population based on US Census estimates. Based on the independent variable definitions, we coded individual community-year combinations with an indicator variable denoting "implementation." As in other studies of injury trends[31] and program implementation,[32] we used Poisson regression models to test our hypotheses that those community-year strata with higher implementation would have lower rates. We modeled rates directly with a log-linear statistical model by including counts as the dependent outcome and population at risk as an offset term. We controlled for community level covariates by including them in the model. All hypothesis tests used a significance level (α) of 0.05. We performed regression diagnostics, including quasi likelihood information criteria,[33] to assess goodness of fit. Based on these, we chose first order autoregressive covariance structure to account for the interdependence of repeated measures.

To determine whether our findings were specific to overdose outcomes or due to an unmeasured health system effect, such as healthcare reform, we conducted additional sensitivity analyses. We refit the adjusted Poisson fatal overdose models substituting fatal opioid overdose rates with overdose death to cancer death rate ratios for each community-year stratum using data from the Massachusetts Registry of Vital Records and Statistics. We also refit models substituting acute care utilization rates associated with non-fatal opioid related poisoning with non-fatal opioid related poisoning or non-fatal motor vehicle traffic related injury rate ratio for each community-year stratum.[34] To define cancer deaths we used ICD-10 codes

C000-C979, representing malignant neoplasms. We defined cases of non-fatal motor vehicle traffic related injury by discharge diagnoses with an ICD-9-CM code of 800-909.2, 909.4, 909.9, 910-994.9, 995.5-995.59, 995.80-995.85 and an E code, E810-E819 (.0-.9), for unintentional motor vehicle traffic crash. All analyses were done using SAS version 9.3.

Results

Table 1[1] lists the characteristics of the 19 communities in Massachusetts. These make up about 30% of the state population and contribute almost half of Massachusetts' fatal opioid overdoses and acute care hospital utilizations for non-fatal opioid overdose.

Between 18 September 2006 and 31 December 2009 in Massachusetts, 4857 individuals were enrolled in OEND and 545 naloxone rescue attempts reported. Among the 19 communities meeting the study criteria, 2912 individuals were enrolled (table 2[1]) and 327 rescue attempts made (table 3[1]). The experience of witnessing an overdose was common among both users and non-users at enrollment. Users commonly had a personal history of overdose and reported detoxification treatment and incarceration in the past year.

Of 327 rescue attempts using naloxone reported by 212 individuals, 87% (286/327) were reported by users. Most rescue attempts occurred in private settings. The rescuer and the person who overdosed were usually friends. Naloxone was successful in 98% (150/153) of the rescues attempts. For the three rescue attempts where naloxone was not successful, the people who overdosed received care from the emergency medical system and survived.

Among the 19 communities studied, none had any OEND implementation in 2002-05, 7 had some implementation in 2006 (median of 3 enrollees per 100 000 population), 14 had some in 2007 (median of 7 enrollees per 100 000), and all 19 had OEND implementation in 2008-09 (medians of 55 and 142, respectively). Figures 1[1] and 2[1] show the unadjusted rates of unintentional opioid related overdose deaths and acute acre utilizations, respectively, categorized by no, low and high implementation.

Adjusted models: OEND implementation and fatal overdose rates

Generally, opioid related death rates were reduced in those communities that implemented OEND compared with community-year strata with no OEND implementation. In the adjusted model based on absolute numbers of enrollments, both the low implementer community-year strata with 1-100 enrollments per 100 000 population (adjusted rate ratio 0.73, 95% confidence interval 0.57 to 0.91) and the high implementer community-year strata with greater than 100 enrollments per 100 000 population (0.54 0.39 to 0.76) had significantly reduced adjusted rate ratios in a dose related fashion compared with communities with no implementation (table 4[1], for full models see supplementary tables 4a and 4b). In sensitivity analyses, using alternative cut points of 75 enrollments and 150 enrollments per 100 000 population, rate ratios were similar. For the adjusted model that used the median enrollment rates, overdose death rates were reduced, but significantly so only for the low implementer group (0.71, 0.57 to 0.90).

Adjusted models: OEND implementation and opioid related non-fatal acute care hospital utilizations

For non-fatal opioid overdose related acute care hospital utilizations, there was no statistically significant association between the communities based on absolute or relative enrollment rates compared with no implementation (table 5[1], for full models see supplementary tables 5a and 5b). In sensitivity analyses, rate ratios were similar then alternative cut points of 75 enrollments and 150 enrollments per 100 000 population were used.

Control models

Models in which the opioid related overdose fatality outcome were substituted for the ratio of opioid related overdose death rates over the cancer related death rates had statistically significant associations in a similar pattern to the original models. Thus the associations of OEND implementation with fatal overdose rates occurred independently of any effects related to cancer fatalities (see supplementary table 6). The similar procedure with motor vehicle crash injuries and acute care utilization models showed no association of OEND implementation on rates, independent of motor vehicle injuries (see supplementary table 7).

Discussion

Between 2006 and 2009, Massachusetts overdose education and nasal naloxone distribution (OEND) programs trained thousands of people who use opioids and their families, friends, and social service providers to prevent, recognize, and respond to overdoses, resulting in hundreds of reported rescue attempts. Compared with no implementation, both low and high implementation of OEND were associated with lower rates of opioid related deaths from overdose, when adjusted for demographics, utilization of addiction treatment, and doctor shopping (schedule II opioid prescriptions from ≥4 prescribers and filled prescriptions at ≥4 pharmacies in a 12 month period). These associations were seen independently of effects related to cancer death rates. Rates of opioid related visits to an emergency department and admission to hospital were not significantly different in communities with low or high implementation of OEND.

Strengths and limitations of the study

The major strength of this study was the interrupted time series analysis approach that capitalized on naturally occurring geographic and time controls owing to the broad but variable implementation of OEND in Massachusetts. The study included years 2002-09, yet OEND implementation began in some communities in 2006 and gradually expanded through 2009. Thus the "no implementation" comparison group included all 19 communities for 2002-05 and only those communities with no enrollment in 2006-09. The pre-implementation and post-implementation comparisons (no versus any implementation) hinged on when implementation started in an individual community. Further, we investigated effects among those communities with high and low implementation. When implementation was defined in a relative manner, based on the median implementation rate in each year, there was an association in the expected direction, but there did not seem to be an implementation dose relation with opioid related overdose death rates. Yet when implementation was defined in an absolute manner based on the cumulative number of enrollments per population, there was both an association in the expected

direction and a dose relation with death rates. A community's absolute enrollment rate had a stronger impact on overdose death rates than the relative enrollment rate. We included both a disease specific mortality and healthcare utilization outcome. We repeated the analyses with substitute outcomes that incorporated unrelated conditions to check if there was some system level effect in how deaths or acute care utilizations were coded that could account for our findings.

Using an observational approach, this study cannot prove definitively that OEND caused a reduction in opioid related overdose death rates. This study had several other limitations to the data available, which we attempted to address. Firstly, the true population of opioid users in each community was not known. To account for this we adjusted analyses for differences in demographics, use of addiction treatment, and proportion of prescriptions to doctor shoppers. Secondly, opioid overdose fatalities may have been misclassified. However, in Massachusetts the medical examiner's office is centralized, with each death certificate processed through the same system. Thirdly, visits to emergency departments and admissions to hospitals associated with opioid poisoning were defined based on administrative discharge codes. Although discharge codes are a blunt measure of cause for utilization, systematic directional misclassification has not been found in other studies.[39] Fourthly, overdoses may have occurred in clusters, which could result in the assumption that spurious events represent a trend. However, this study was conducted over eight years in 19 communities. Fifthly, we created measures of OEND implementation consistent with our conception of how OEND may impact on rates of fatal overdose and acute care utilization, but they have not been validated in other populations. We tested several levels of OEND implementation and found similar patterns of association with opioid related overdose and acute care utilization rates. Lastly, the description of reported overdose rescue attempts was limited to only those rescues reported back to programs, and thus was likely underreported.

Interpretation

This study provides observational evidence that OEND is an effective public health intervention to address increasing mortality in the opioid overdose epidemic by training potential bystanders to prevent, recognize, and respond to opioid overdoses. OEND implementation seemed to have a dose related impact, where the higher the cumulative rate of OEND implementation, the greater the reduction in death rates. While OEND programs should reduce visits to emergency departments and hospital admissions by preventing overdoses in the first place, they may also increase visits by encouraging bystanders to engage the emergency medical system, which is an explicit part of OEND curriculums. This balance of reducing and increasing the use of the emergency medical system may be why no association was found for acute care utilization.

Implications for research, policy, and practice

Some research issues follow from this study. Because OEND targets not only the overdose risk behaviours of the trainee but empowers trainees to intervene in another person's overdose, it makes a fuller impact at the community level rather than at the individual level. Therefore, an individual level prospective clinical trial is unlikely to capture the community level effect of OEND unless it uses a multisite or social network design or measures community level outcomes to account for the network effects and potential contamination between individual participants. It is also important to determine how OEND should be tailored and implemented among different populations to maximize effectiveness. In Massachusetts, similar OEND curriculums have been delivered to heroin users, prescription opioid users, patients in emergency departments, people who are incarcerated, family members, social service providers, police officers, and fire fighters.

This study provides strong support for the public health agency policy and community based organisation practice to implement and expand OEND programs as a key way to address the opioid overdose epidemic. Two features of the Massachusetts OEND programs that supported broad implementation include the use of an nasal naloxone delivery device and the use of a standing order issued by the health department, which allowed non-medical personnel to deliver OEND. These features may enable broader implementation with greater impact as more communities implement OEND.

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Contributors: AYW, AO, and HHH developed the original study design and all authors contributed to additional model development. HHH developed the definitions for fatal and non-fatal opioid overdose outcome. EQ managed the data and she and ZX and AO performed data analysis. All authors contributed to data interpretation and had full access to the de-identified dataset in the study and take responsibility for the integrity of the data and accuracy of the data analyses. AYW, MD-S, and AS-A wrote the first draft of the manuscript and all authors contributed to editing. AYW is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: AYW, ZX, EQ, MDS, AS-A, and AO had support from the Center for Disease Control and Prevention grant 1R21CE001602-01 for this study; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the institutional review boards of Boston University Medical Center (H-28736) and the Massachusetts Department of Public Health (249874-3). Because this study used de-identified data previously collected, informed consent was not required.

Data sharing: No additional data available.

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What is already known on this topic

Opioid overdose is a major, expanding cause of preventable death in many countries

Education about overdose and naloxone distribution is an innovative, community based response deployed in many settings that has not been examined in controlled studies

What this study adds

Death rates from opioid overdose were reduced in communities where overdose education and naloxone distribution was implemented compared with not implemented

This provides observational evidence that an overdose education and nasal naloxone distribution program is an effective public health intervention to address the epidemic of fatal opioid overdose

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Tables

Table 1| **Characteristics of 19 Massachusetts communities* with high opioid overdose burden. Values are percentages unless stated otherwise**

Characteristics	Communities (n=19)
2005 population, total	2 055 086
Mean	108 162
Median	87 302
Range	30 236-609 690
Age <18 years	22.4
Male	48.0
Race or ethnicity:	
Hispanic	13.8
White, non-Hispanic	63.9
Black, non-Hispanic	11.9
Other, non-Hispanic	10.1
Below poverty level	16.4
Treatment events per 100 000 people, 2009:	
Inpatient detoxification	630.3
Methadone maintenance	161.8
Stated funded buprenorphine maintenance	41.5
Opioid prescriptions to doctor shoppers†	10.9

*Geographically distinct cities and towns.
†Schedule II opioid prescriptions dispensed to doctor shoppers (individuals with schedule II opioid prescriptions from ≥4 prescribers and filled prescriptions at ≥4 pharmacies in 12 month period) per total opioid prescriptions dispensed.

Table 2| **Characteristics of potential overdose bystanders trained in overdose education and nasal naloxone distribution program in 19 Massachusetts communities*, 2006-09. Numbers are percentages (number/number in group) unless stated otherwise**

Characteristics	All enrollees (n=2912)	Users† (n=2007)	Non-users (n=905)
Mean (SD) age (years)	38.1 (12.1)	36.1 (11.1)	42.6 (13.0)
Female and male to female transgender	44.4 (1274/2870)	38.1 (751/1973)	58.3 (523/897)
Race or ethnicity:			
White, non-Hispanic	69.5 (2013/2896)	71.2 (1421/1996)	65.8 (592/900)
Hispanic	16.2 (468/2896)	17.0 (339/1996)	14.3 (129/900)
Black or African American, non-Hispanic	10.5 (305/2896)	8.7 (174/1996)	14.6 (131/900)
Other, non-Hispanic	3.8 (110/2896)	3.1 (62/1996)	5.3 (48/900)
Detox in past year	—	47.3 (950/2007)	NA
Incarceration in past year	—	27.1 (460/1695)	NA
Lifetime history of overdose	—	54.0 (976/1808)	NA
Received naloxone at last overdose	—	60.0 (503/838)	NA
Overdose witnessed ever	73.6 (2036/2767)	80.8 (1571/1944)	56.5 (465/823)
Reported at least one overdose rescue	7.3 (212/2912)	9.2 (184/2007)	3.1 (28/905)

NA=not available.
Denominators less than total number for each group are due to missing information.
*Geographically distinct cities and towns.
†Enrollees who self reported active substance misuse, currently engaged in treatment or in recovery at enrollment.

Table 1 | Overdose rescue attempts reported by bystanders trained in the overdose education and nasal naloxone distribution program in 19 Massachusetts communities*, 2006-09

Variables	% (No/No in group)		
	All enrollees (n=327)	Users† (n=286)	Non-users (n=41)
Status of person who overdosed:			
Friend	69 (216/313)	72 (200/276)	43 (16/37)
Partner or family	16 (49/313)	12 (34/276)	41 (15/37)
Stranger	10 (32/313)	9 (26/276)	16 (6/37)
Self	5 (16/313)	6 (16/276)	0 (0/37)
Overdose setting:			
Private	78 (249/317)	80 (221/277)	70 (28/40)
Public	22 (68/317)	20 (56/277)	30 (12/40)
No of doses used:			
1	48 (149/312)	48 (129/272)	50 (20/40)
2	48 (150/312)	48 (130/272)	50 (20/40)
>3	4 (13/312)	5 (13/272)	0 (0/40)
Naloxone successful	98 (150/153)	98 (130/133)	100 (20/20)
911 called or emergency personnel present	33 (106/326)	26 (75/285)	76 (31/41)
Rescue breathing performed	38 (123/327)	37 (105/286)	44 (18/41)
Stayed with victim until alert and awake or help arrived	89 (287/321)	90 (253/280)	83 (34/41)

Denominators less than total number for each group are due to missing information.
*Geographically distinct cities and towns.
†Enrollees who self reported active substance use, currently engaged in treatment or in recovery at enrollment.

Table 4 | Models of overdose education and nasal naloxone distribution implementation and unintentional opioid related overdose death rates in 19 communities* in Massachusetts, 2002-09

Cumulative enrollments per 100 000 population	Rate ratio	Adjusted rate ratio† (95% CI)	P value
Absolute model:			
No implementation	Reference	Reference	
Low implementation: 1-100 enrollments	0.80	0.73 (0.57 to 0.91)	<0.01
High implementation: >100 enrollments	0.62	0.54 (0.39 to 0.76)	<0.01
Relative model:			
No implementation	Reference	Reference	
Low implementation: <median	0.85	0.71 (0.57 to 0.90)	<0.01
High implementation: >median	1.00	0.78 (0.60 to 1.01)	0.06

*Geographically distinct cities and towns.
†Adjusted for city/town population rates of age under 18, male, race or ethnicity (Hispanic, white, black, other), below poverty level, medically supervised inpatient withdrawal treatment, methadone treatment, Bureau of Substance Abuse Services funded buprenorphine treatment, prescriptions to doctor shoppers (individuals with schedule II opioid prescriptions from ≥4 prescribers and filled prescriptions at ≥4 pharmacies in 12 month period), and year.

Table 3 | Models of overdose education and nasal naloxone distribution implementation and opioid overdose related acute care hospital utilizations in 19 communities* in Massachusetts, 2002-09

Cumulative enrollments per 100 000 population	Rate ratio	Adjusted rate ratio† (95% CI)	P value
Absolute model:			
No implementation	Reference	Reference	
Low implementation: 1-100 enrollments	1.00	0.93 (0.80 to 1.08)	0.4
High implementation: >100 enrollments	1.06	0.92 (0.75 to 1.13)	0.4
Relative model:			
No implementation	Reference	Reference	
Low implementation: <median	0.96	0.90 (0.78 to 1.07)	0.2
High implementation: >median	1.10	1.00 (0.86 to 1.16)	1.0

*Geographically distinct cities and towns.
†Adjusted for city/town population rates of age under 18, male, race or ethnicity (Hispanic, white, black, other), below poverty level, medically supervised inpatient withdrawal treatment, methadone treatment, Bureau of Substance Abuse Services funded buprenorphine treatment, prescriptions to doctor shoppers (individuals with schedule II opioid prescriptions from ≥4 prescribers and filled prescriptions at ≥4 pharmacies in 12 month period), and year.

Figures

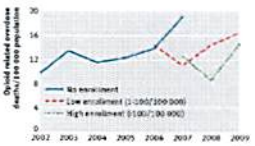

Fig 1 Unadjusted unintentional opioid related overdose death rates in 19 communities with no, low, and high enrollment in overdose education and nasal naloxone distribution program in Massachusetts, 2002-09

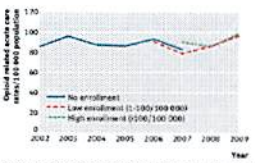

Fig 2 Unadjusted opioid related acute care hospital utilization rates in 19 communities with no, low, and high enrollment in overdose education and nasal naloxone distribution program in Massachusetts, 2002-09