Annals of Internal Medicine | ORIGINAL RESEARCH

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 $53 (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. www.annals.org
For author affiliations, see end of text.

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

See also:

Print

Editorial comment. 65
Summary for Patients. I-30

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 (0.05 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 (0.800 to 0.940)	References 1 and 5
Absolute reduction for second overdose	0.015 (0.000 to 0.020)	References 1 and 5
Additional reduction for subsequent overdoses	0.015 (0.000 to 0.020)	References 1 and 5
Relative increase in survival with EMS	1.089 (1.020 to 1.158)	Reference 28 and 29
Relative increase in survival with naloxone	1.089 (1.020 to 1.158)	References 7, 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 0.60)	References 12, 29, 32, and 33
Annual relative reduction in risk for first overdose§	0.933 (0.9 to 1.0)	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 0.113)	Reference 38
Costs, $‖		
Biannual naloxone kit (2 doses plus distribution costs)	25 (12 to 75)	References 39 and 40
EMS visit	1790 (714 to 2500)	Reference 41
EMS transport to hospital	301 (271 to 331)	Reference 41
Emergency department care if transported	885 (707 to 1061)	Reference 42
Annual heroin user cost to society¶	3368 (1023 to 4041)	References 14 and 49
Utilities‖		
Heroin user	0.80 (0.73 to 0.90)	References 43–45
Relative increase in utility for heroin user in recovery	1.07 (1.00 to 1.13)	References 43 and 46

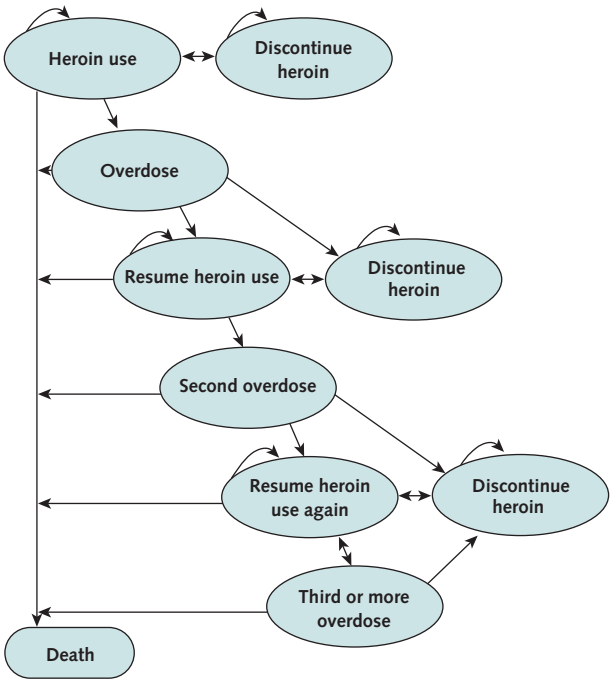
EMS = emergency medical services.
* **Appendix Table 1** (available at www.annals.org) provides the detailed rationale and additional sources for selection of point estimates and ranges.
† Summary value based on parameters listed in next 4 rows.
‡ Parameter used in sensitivity analyses to adjust for possible effects of social networks on the probability of naloxone being present at an overdose.
§ Parameter is exponentiated to 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 "tunnel 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 (Copass 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.

Role of the Funding Source

The National Institute of Allergy and Infectious Diseases had no role in the conception, design, conduct, or analysis of this study or in the decision to submit the manuscript for publication.

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, %		Number Needed to Treat*	Increased QALYs of Naloxone	Increased Costs of Naloxone, $	ICER of Naloxone, $
	5 y	Lifetime				
Base case (deterministic)	10.6	6.5	164	0.109	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	8.5	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	422
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	0.109	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	0.109	−70	Dominant
SA8: Likelihood of transport to hospital after lay naloxone halved	10.6	6.5	164	0.109	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	165	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.

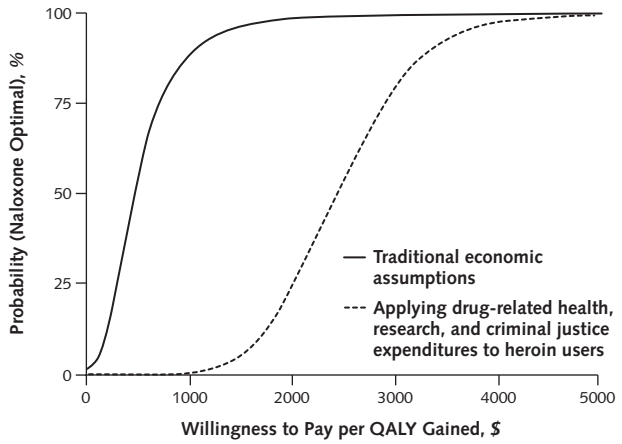
cohort and active heroin users over the lifetime in all simulations. With naloxone distribution, the model forecast a 1.7% increase in the proportion of persons discontinuing heroin use over the lifetime of the cohort and, due to the survival of high-risk heroin users, a 1.3% increase in the absolute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

From the San Francisco Department of Public Health, San Francisco, California, and University of Washington, Seattle, Washington.

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.

Grant Support: By grant 5T32AI007140-33 from the National Institute of Allergy and Infectious Diseases at the National Institutes of Health.

Potential Conflicts of Interest: None disclosed. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-1737.

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.

Requests for Single Reprints: Phillip O. Coffin, MD, San Francisco Department of Public Health, 25 Van Ness Avenue, Suite 500, San Francisco, CA 94102; e-mail, pcoffin@gmail.com.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Sporer KA.** Acute heroin overdose. Ann Intern Med. 1999;130:584-90. [PMID: 10189329]
2. **Centers for Disease Control and Prevention (CDC).** Vital signs: overdoses of prescription opioid pain relievers—United States, 1999–2008. MMWR Morb Mortal Wkly Rep. 2011;60:1487-92. [PMID: 22048730]
3. **Centers for Disease Control and Prevention (CDC).** Community-based opioid overdose prevention programs providing naloxone—United States, 2010. MMWR Morb Mortal Wkly Rep. 2012;61:101-5. [PMID: 22337174]
4. **Walley AY.** Bystander overdose education and naloxone distribution in Massachusetts. Presented at Role of Naloxone in Opioid Overdose Fatality Prevention (Public Workshop), 12 April 2012, Silver Spring, Maryland. Accessed at www.fda.gov/downloads/Drugs/NewsEvents/UCM300869.pdf on 8 May 2012.
5. **Sporer KA, Kral AH.** Prescription naloxone: a novel approach to heroin overdose prevention. Ann Emerg Med. 2007;49:172-7. [PMID: 17141138]
6. **Green TC, Heimer R, Grau LE.** Distinguishing signs of opioid overdose and indication for naloxone: an evaluation of six overdose training and naloxone distribution programs in the United States. Addiction. 2008;103:979-89. [PMID: 18422830]
7. **Doe-Simkins M, Walley AY, Epstein A, Moyer P.** Saved by the nose: bystander-administered intranasal naloxone hydrochloride for opioid overdose. Am J Public Health. 2009;99:788-91. [PMID: 19363214]
8. **Piper TM, Stancliff S, Rudenstine S, Sherman S, Nandi V, Clear A, et al.** Evaluation of a naloxone distribution and administration program in New York City. Subst Use Misuse. 2008;43:858-70. [PMID: 18570021]
9. **Enteen L, Bauer J, McLean R, Wheeler E, Huriaux E, Kral AH, et al.** Overdose prevention and naloxone prescription for opioid users in San Francisco. J Urban Health. 2010;87:931-41. [PMID: 20967505]
10. **Maxwell S, Bigg D, Stanczykiewicz K, Carlberg-Racich S.** Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths. J Addict Dis. 2006;25:89-96. [PMID: 16956873]
11. **Paone D, Heller D, Olson C, Kerker B.** Illicit drug use in New York City. NYC Vital Signs. New York: New York City Department of Mental Health and Hygeine; 2010.
12. **Coffin PO, Tracy M, Bucciarelli A, Ompad D, Vlahov D, Galea S.** Identifying injection drug users at risk of nonfatal overdose. Acad Emerg Med. 2007;14:616-23. [PMID: 17554010]
13. **Lee CP, Chertow GM, Zenios SA.** An empiric estimate of the value of life: updating the renal dialysis cost-effectiveness standard. Value Health. 2009;12:80-7. [PMID: 19911442]
14. **Substance Abuse and Mental Health Services Administration.** Results from the 2009 National Survey on Drug Use and Health: Volume 1. Summary of National Findings. Office of Applied Studies, NSDUH Series H-38A, HHS Publication SMA 10-4586. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2010.
15. **Evans JL, Hahn JA, Lum PJ, Stein ES, Page K.** Predictors of injection drug use cessation and relapse in a prospective cohort of young injection drug users in San Francisco, CA (UFO Study). Drug Alcohol Depend. 2009;101:152-7. [PMID: 19181458]
16. **Bassett IV, Walensky RP.** Integrating HIV screening into routine health care in resource-limited settings. Clin Infect Dis. 2010;50 Suppl 3:S77-84. [PMID: 20397960]
17. **Darke S, Ross J, Hall W.** Overdose among heroin users in Sydney, Australia: I. Prevalence and correlates of non-fatal overdose. Addiction. 1996;91:405-11. [PMID: 8867202]

18. **Davidson PJ, Ochoa KC, Hahn JA, Evans JL, Moss AR.** Witnessing heroin-related overdoses: the experiences of young injectors in San Francisco. Addiction. 2002;97:1511-6. [PMID: 12472634]
19. **Davidson PJ, McLean RL, Kral AH, Gleghorn AA, Edlin BR, Moss AR.** Fatal heroin-related overdose in San Francisco, 1997-2000: a case for targeted intervention. J Urban Health. 2003;80:261-73. [PMID: 12791802]
20. **Wagner KD, Valente TW, Casanova M, Partovi SM, Mendenhall BM, Hundley JH, et al.** Evaluation of an overdose prevention and response training programme for injection drug users in the Skid Row area of Los Angeles, CA. Int J Drug Policy. 2010;21:186-93. [PMID: 19268564]
21. **Darke S, Ross J, Hall W.** Overdose among heroin users in Sydney, Australia: II. responses to overdose. Addiction. 1996;91:413-7. [PMID: 8867203]
22. **Tracy M, Piper TM, Ompad D, Bucciarelli A, Coffin PO, Vlahov D, et al.** Circumstances of witnessed drug overdose in New York City: implications for intervention. Drug Alcohol Depend. 2005;79:181-90. [PMID: 16002027]
23. **Bohnert AS, Tracy M, Galea S.** Characteristics of drug users who witness many overdoses: implications for overdose prevention. Drug Alcohol Depend. 2012;120:168-73. [PMID: 21839588]
24. **Coffin PO.** Overdose and femoral injection among Seattle-area injection drug users. In: National Institute on Drug Abuse, ed. Epidemiologic Trends in Drug Abuse, Proceedings of the Community Epidemiology Work Group. Rockville, MD: National Institute on Drug Abuse; 2011.
25. **Sporer KA, Firestone J, Isaacs SM.** Out-of-hospital treatment of opioid overdoses in an urban setting. Acad Emerg Med. 1996;3:660-7. [PMID: 8816181]
26. **Vilke GM, Sloane C, Smith AM, Chan TC.** Assessment for deaths in out-of-hospital heroin overdose patients treated with naloxone who refuse transport. Acad Emerg Med. 2003;10:893-6. [PMID: 12896894]
27. **Rudolph SS, Jehu G, Nielsen SL, Nielsen K, Siersma V, Rasmussen LS.** Prehospital treatment of opioid overdose in Copenhagen—is it safe to discharge on-scene? Resuscitation. 2011;82:1414-8. [PMID: 21745532]
28. **Wampler DA, Molina DK, McManus J, Laws P, Manifold CA.** No deaths associated with patient refusal of transport after naloxone-reversed opioid overdose. Prehosp Emerg Care. 2011;15:320-4. [PMID: 21612385]
29. **Stoové MA, Dietze PM, Jolley D.** Overdose deaths following previous non-fatal heroin overdose: record linkage of ambulance attendance and death registry data. Drug Alcohol Rev. 2009;28:347-52. [PMID: 19594787]
30. **Strang J, Manning V, Mayet S, Best D, Titherington E, Santana L, et al.** Overdose training and take-home naloxone for opiate users: prospective cohort study of impact on knowledge and attitudes and subsequent management of overdoses. Addiction. 2008;103:1648-57. [PMID: 18821875]
31. **Tobin KE, Sherman SG, Beilenson P, Welsh C, Latkin CA.** Evaluation of the Staying Alive programme: training injection drug users to properly administer naloxone and save lives. Int J Drug Policy. 2009;20:131-6. [PMID: 18434126]
32. **Darke S, Mills KL, Ross J, Teesson M.** Rates and correlates of mortality amongst heroin users: findings from the Australian Treatment Outcome Study (ATOS), 2001-2009. Drug Alcohol Depend. 2011;115:190-5. [PMID: 21130585]
33. **Darke S, Williamson A, Ross J, Mills KL, Havard A, Teesson M.** Patterns of nonfatal heroin overdose over a 3-year period: findings from the Australian Treatment Outcome Study. J Urban Health. 2007;84:283-91. [PMID: 17265131]
34. **Teesson M, Mills K, Ross J, Darke S, Williamson A, Havard A.** The impact of treatment on 3 years' outcome for heroin dependence: findings from the Australian Treatment Outcome Study (ATOS). Addiction. 2008;103:80-8. [PMID: 17995994]
35. **Huo D, Bailey SL, Ouellet LJ.** Cessation of injection drug use and change in injection frequency: the Chicago Needle Exchange Evaluation Study. Addiction. 2006;101:1606-13. [PMID: 17034440]
36. **Bruneau J, Brogly SB, Tyndall MW, Lamothe F, Franco EL.** Intensity of drug injection as a determinant of sustained injection cessation among chronic drug users: the interface with social factors and service utilization. Addiction. 2004;99:727-37. [PMID: 15139871]
37. **Hser YI.** Drug use careers: recovery and mortality. In: Substance Use by Older Adults: Estimates of Future Impact on the Treatment System. OAS Analytic Series A-21, DHHS Publication (SMA) 03-3763. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2002.
38. **Pollini RA, McCall L, Mehta SH, Vlahov D, Strathdee SA.** Non-fatal overdose and subsequent drug treatment among injection drug users. Drug Alcohol Depend. 2006;83:104-10. [PMID: 16310322]
39. **Leavitt SB.** Intranasal naloxone for at-home opioid rescue. Pract Pain Manag. 2010;10.
40. **Yokell MA, Green TC, Bowman S, McKenzie M, Rich JD.** Opioid overdose prevention and naloxone distribution in Rhode Island. Med Health R I. 2011;94:240-2. [PMID: 21913619]
41. **Larimer ME, Malone DK, Garner MD, Atkins DC, Burlingham B, Lonczak HS, et al.** Health care and public service use and costs before and after provision of housing for chronically homeless persons with severe alcohol problems. JAMA. 2009;301:1349-57. [PMID: 19336710]
42. **Centers for Disease Control and Prevention.** Web-based Injury Statistics Query and Reporting System (WISQARS). Atlanta: Centers for Disease Control and Prevention; 2005. Accessed at www.cdc.gov/ncipc/wisqars on 5 May 2012.
43. **Pyne JM, Tripathi S, French M, McCollister K, Rapp RC, Booth BM.** Longitudinal association of preference-weighted health-related quality of life measures and substance use disorder outcomes. Addiction. 2011;106:507-15. [PMID: 21205046]
44. **Nosyk B, Sun H, Guh DP, Oviedo-Joekes E, Marsh DC, Brissette S, et al.** The quality of eight health status measures were compared for chronic opioid dependence. J Clin Epidemiol. 2010;63:1132-44. [PMID: 20236799]
45. **Zaric GS, Barnett PG, Brandeau ML.** HIV transmission and the cost-effectiveness of methadone maintenance. Am J Public Health. 2000;90:1100-11. [PMID: 10897189]
46. **Vanagas G, Padaiga Z, Bagdonas E.** Cost-utility analysis of methadone maintenance treatment in Lithuania. Medicina (Kaunas). 2010;46:286-92. [PMID: 20571298]
47. **Galea S, Worthington N, Piper TM, Nandi VV, Curtis M, Rosenthal DM.** Provision of naloxone to injection drug users as an overdose prevention strategy: early evidence from a pilot study in New York City. Addict Behav. 2006;31:907-12. [PMID: 16139434]
48. **Wu LT, Woody GE, Yang C, Mannelli P, Blazer DG.** Differences in onset and abuse/dependence episodes between prescription opioids and heroin: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Subst Abuse Rehabil. 2011;2011:77-88. [PMID: 21686045]
49. **Office of National Drug Control Policy.** The Economic Costs of Drug Abuse in the United States, 1992-2002. Publication 207303. Washington, DC: Executive Office of the President of the United States; 2004.
50. **Briggs A, Claxton K, Sculpher M.** Decision Modelling for Health Economic Evaluation. Oxford, United Kingdom: Oxford Univ Pr; 2006.
51. **Jenkins LM, Banta-Green CJ, Maynard C, Kingston S, Hanrahan M, Merrill JO, et al.** Risk factors for nonfatal overdose at Seattle-area syringe exchanges. J Urban Health. 2011;88:118-28. [PMID: 21246299]
52. **Ochoa KC, Davidson PJ, Evans JL, Hahn JA, Page-Shafer K, Moss AR.** Heroin overdose among young injection drug users in San Francisco. Drug Alcohol Depend. 2005;80:297-302. [PMID: 15961257]
53. **Gossop M, Griffiths P, Powis B, Williamson S, Strang J.** Frequency of non-fatal heroin overdose: survey of heroin users recruited in non-clinical settings. BMJ. 1996;313:402. [PMID: 8761230]
54. **Hakansson A, Schlyter F, Berglund M.** Factors associated with history of non-fatal overdose among opioid users in the Swedish criminal justice system. Drug Alcohol Depend. 2008;94:48-55. [PMID: 18082338]
55. **Bohnert AS, Tracy M, Galea S.** Circumstances and witness characteristics associated with overdose fatality. Ann Emerg Med. 2009;54:618-24. [PMID: 19540622]
56. **Hser YI, Hoffman V, Grella CE, Anglin MD.** A 33-year follow-up of narcotics addicts. Arch Gen Psychiatry. 2001;58:503-8. [PMID: 11343531]
57. **Vlahov D, Wang C, Ompad D, Fuller CM, Caceres W, Ouellet L, et al; Collaborative Injection Drug User Study.** Mortality risk among recent-onset injection drug users in five U.S. cities. Subst Use Misuse. 2008;43:413-28. [PMID: 18365941]
58. **Coffin PO, Galea S, Ahern J, Leon AC, Vlahov D, Tardiff K.** Opiates, cocaine and alcohol combinations in accidental drug overdose deaths in New York City, 1990-98. Addiction. 2003;98:739-47. [PMID: 12780362]
59. **Zador D, Sunjic S, Darke S.** Heroin-related deaths in New South Wales, 1992: toxicological findings and circumstances. Med J Aust. 1996;164:204-7. [PMID: 8604187]
60. **Vlahov D, Anthony JC, Munoz A, Margolick J, Nelson KE, Celentano DD, et al.** The ALIVE study, a longitudinal study of HIV-1 infection in intravenous drug users: description of methods and characteristics of participants. NIDA Res Monogr. 1991;109:75-100. [PMID: 1661376]

61. **Evans JL, Tsui JI, Hahn JA, Davidson PJ, Lum PJ, Page K.** Mortality among young injection drug users in San Francisco: a 10-year follow-up of the UFO study. Am J Epidemiol. 2012;175:302-8. [PMID: 22227793]
62. **Stout NK, Knudsen AB, Kong CY, McMahon PM, Gazelle GS.** Calibration methods used in cancer simulation models and suggested reporting guidelines. Pharmacoeconomics. 2009;27:533-45. [PMID: 19663525]
63. **Milloy MJ, Kerr T, Mathias R, Zhang R, Montaner JS, Tyndall M, et al.** Non-fatal overdose among a cohort of active injection drug users recruited from a supervised injection facility. Am J Drug Alcohol Abuse. 2008;34:499-509. [PMID: 18584579]
64. **Havens JR, Oser CB, Knudsen HK, Lofwall M, Stoops WW, Walsh SL, et al.** Individual and network factors associated with non-fatal overdose among rural Appalachian drug users. Drug Alcohol Depend. 2011;115:107-12. [PMID: 21126831]
65. **Lenton SR, Hargreaves KM.** Should we conduct a trial of distributing naloxone to heroin users for peer administration to prevent fatal overdose? Med J Aust. 2000;173:260-3. [PMID: 11130352]
66. **Fenwick E, Claxton K, Sculpher M.** Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ. 2001;10:779-87. [PMID: 11747057]
67. **Hart A.** Annual Report: Fiscal Year 2009-2010. San Francisco: City & County of San Francisco, Office of the Chief Medical Examiner; 2011:148.
68. **Hart A.** Annual Report: July 2002 to June 2003. San Francisco: City & County of San Francisco, Office of the Chief Medical Examiner; 2004:30.
69. **McAuley A, Best D, Taylor A, Hunter C, Robertson R.** From evidence to policy: The Scottish national naloxone programme. Drugs (Abingdon Engl). 2012;19:309-19.
70. **Lankenau SE, Wagner KD, Silva K, Kecojevic A, Iverson E, McNeely M, et al.** Injection Drug Users Trained by Overdose Prevention Programs: Responses to Witnessed Overdoses. J Community Health. 2012. [PMID: 22847602]
71. **Coffin PO, Coffin LM, Fitzpatrick T, Murphy S.** Drug overdose, lay naloxone, and HIV risk behaviors among persons who inject drugs [Abstract MOPE218]. Presented at XIX International AIDS Conference, Washington, DC, 22–27 July 2012.
72. **Albert S, Brason FW 2nd, Sanford CK, Dasgupta N, Graham J, Lovette B.** Project Lazarus: community-based overdose prevention in rural North Carolina. Pain Med. 2011;12 Suppl 2:S77-85. [PMID: 21668761]
73. **Mackesy-Amiti ME, Ouellet LJ, Golub ET, Hudson S, Hagan H, Garfein RS.** Predictors and correlates of reduced frequency or cessation of injection drug use during a randomized HIV prevention intervention trial. Addiction. 2011; 106:601-8. [PMID: 21182555]

Current Author Addresses: Dr. Coffin: San Francisco Department of Public Health, 25 Van Ness Avenue, Suite 500, San Francisco, CA 94102.
Dr. Sullivan: Pharmaceutical Outcomes Research and Policy Program, University of Washington, 1959 NE Pacific Street, Box 357630, Seattle, WA 98195-7630.

Author Contributions: Conception and design: P.O. Coffin, S.D. Sullivan.
Analysis and interpretation of the data: P.O. Coffin, S.D. Sullivan.
Drafting of the article: P.O. Coffin.
Critical revision of the article for important intellectual content: P.O. Coffin, S.D. Sullivan.
Final approval of the article: P.O. Coffin, S.D. Sullivan.
Provision of study materials or patients: P.O. Coffin.
Statistical expertise: P.O. Coffin, S.D. Sullivan.
Obtaining of funding: P.O. Coffin.
Administrative, technical, or logistic support: P.O. Coffin.
Collection and assembly of data: P.O. Coffin.

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).

Continued on following page

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		
First overdose	0.09 (0.02 to 0.12)	To account for the high rate of overdose among young heroin users and the established finding that less than 75% 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).
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, $*		
Biannual 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, this 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 charge in the cost estimate of the numerator is not generally done). 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) (49), 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%.

Continued on following page

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.

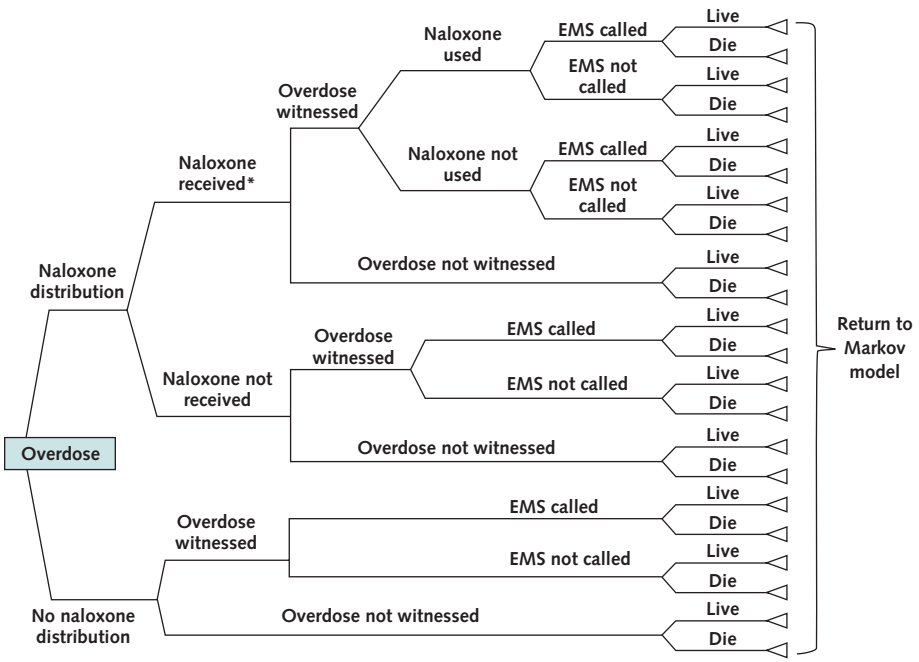
EMS = emergency medical services; SF-6D = Short Form-6D.
* 3% annual discounting.

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	15†	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 19	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	3.8	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, 58, 59, 61	29	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	48, 60	7	12	11	15
Cost difference, *$*	–	–	63	188	43	46
QALY difference	–	–	0.271	0.780	0.109	0.109
ICER, *$*	–	–	232	241	394	421

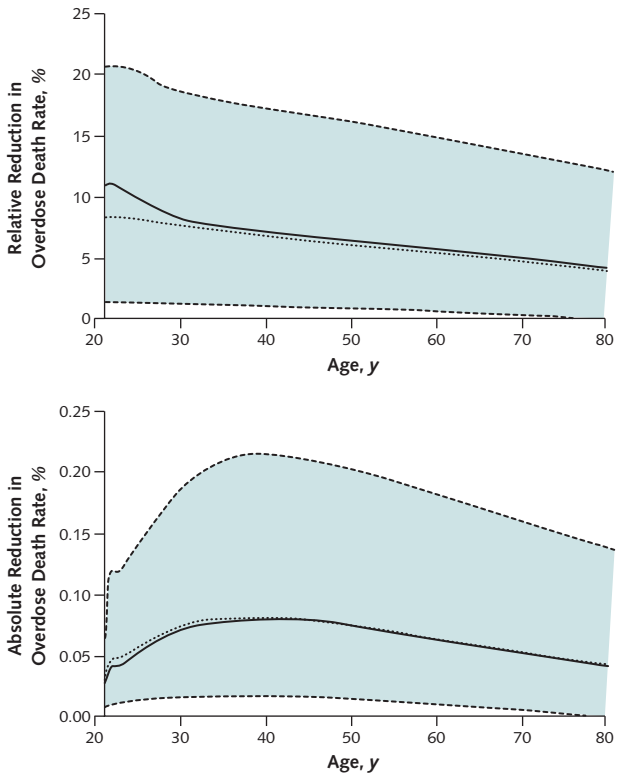
EMS = emergency medical services; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
* The **Appendix** provides details about the model development.
† Predetermined value.

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



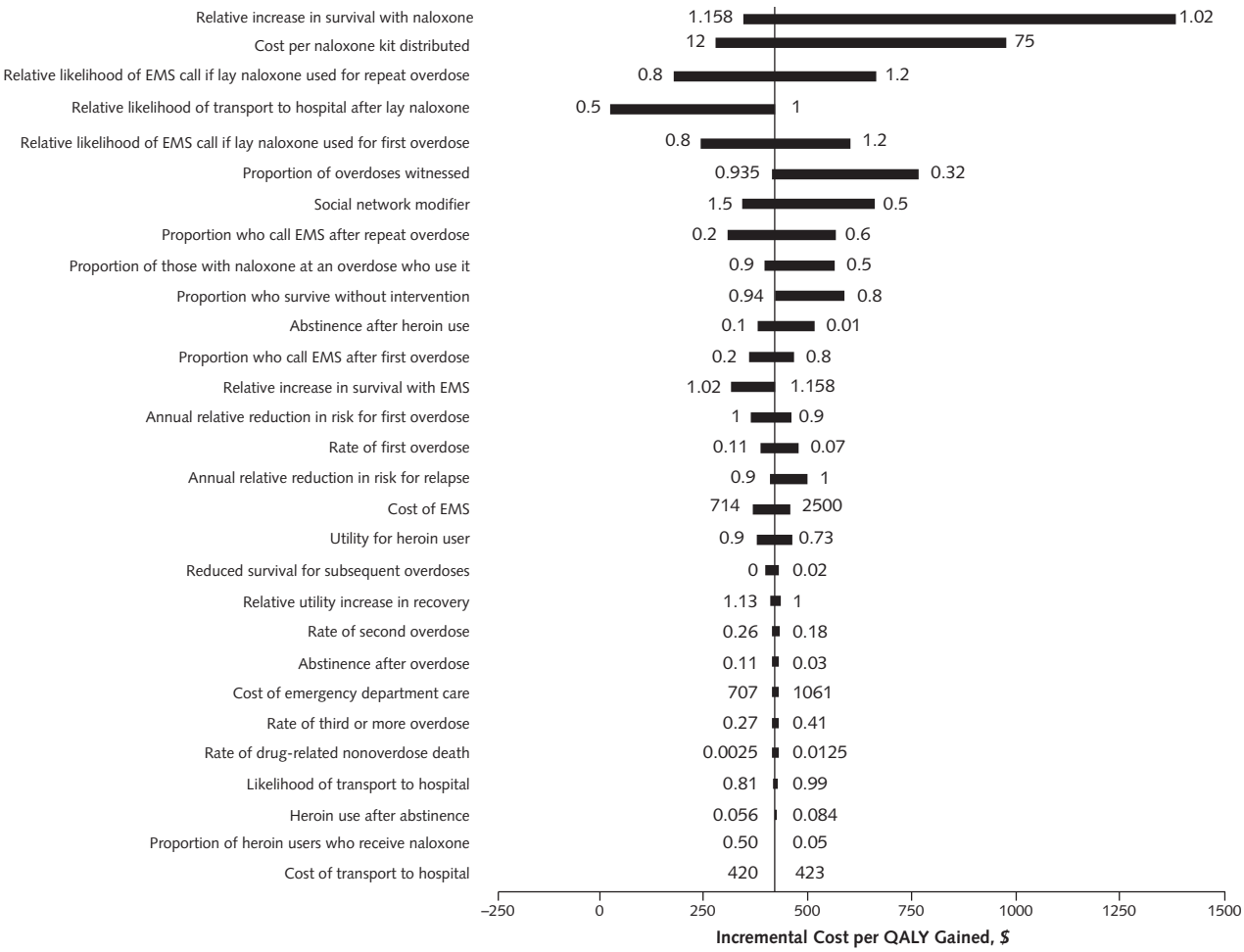
EMS = emergency medical services.
* Modified by the likelihood of naloxone being present at an overdose.

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 3. 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	930 759
Lifetime overdose deaths, *n*	27 406	25 613
Naloxone kits delivered, *n*	–	294 484
Worst-case scenario*		
Lifetime overdoses, *n*	886 298	886 936
Lifetime overdose deaths, *n*	31 763	31 672
Naloxone kits delivered, *n*	–	251 749
Best-case scenario†		
Lifetime overdoses, *n*	925 169	998 692
Lifetime overdose deaths, *n*	26 492	15 350
Naloxone kits delivered, *n*	–	1 056 341
Naloxone distribution reduces overdose risk‡		
Lifetime overdoses, *n*	918 509	698 868
Lifetime overdose deaths, *n*	27 406	18 835
Naloxone kits delivered, *n*	–	307 712
Individual outcomes		
Baseline scenario		
Life-years	44.625	44.955
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, $	2140	2217
Of naloxone, $	–	44
Discounted costs, $	1433	1479
Of naloxone, $	–	30
Incremental cost per QALY gained, $	–	421
Kits needed to prevent 1 death, *n*	–	164
Worst-case scenario		
Life-years	43.764	43.781
Among those who discontinued heroin use	27.272	27.282
Undiscounted QALYs	36.430	36.444
Among those who discontinued heroin use	23.236	23.244
Discounted QALYs	18.824	18.830
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	37.292	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, $	2373	2753
Of naloxone, $	–	158
Discounted costs, $	1586	1794
Of naloxone, $	–	106
Incremental cost per QALY gained, $	–	321
Kits needed to prevent 1 death, *n*	–	95
Naloxone distribution reduces overdose risk		
Life-years	44.625	45.958
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, $	2140	1705
Of naloxone, $	–	45
Discounted costs, $	1433	1136
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 stages in the setting of naloxone distribution.