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Original article

Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal in Russian cities

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Abstract

Objective:

To evaluate the cost-effectiveness of distributing naloxone to illicit opioid users for lay overdose reversal in Russian cities.

Method:

This study adapted an integrated Markov and decision analytic model to Russian cities. The model took a lifetime, societal perspective, relied on published literature, and was calibrated to epidemiologic findings.

Results:

For each 20% of heroin users reached with naloxone distribution, the model predicted a 13.4% reduction in overdose deaths in the first 5 years and 7.6% over a lifetime; on probabilistic analysis, one death would be prevented for every 89 naloxone kits distributed (95% CI = 32–260). Naloxone distribution was cost-effective in all deterministic and probabilistic sensitivity analyses and cost-saving if resulting in a reduction in overdose events. Naloxone distribution increased costs by US\$13 (95% CI = US\$3–US\$32) and QALYs by 0.137 (95% CI = 0.022–0.389) for an incremental cost of US\$94 per QALY gained (95% CI = US\$40–US\$325). In a worst-case scenario where overdose was rarely witnessed and naloxone was rarely used, minimally effective, and expensive, the incremental cost was US\$1987 per QALY gained. If national expenditures on drug-related HIV, tuberculosis, and criminal justice were applied to heroin users, the incremental cost was US\$928 per QALY gained.

Conclusions:

Naloxone distribution to heroin users for lay overdose reversal is highly likely to reduce overdose deaths in target communities and is robustly cost-effective, even within the constraints of this conservative model.

Introduction

Heroin overdose accounts for about half of mortality among heroin users worldwide¹, but is believed to be an even greater driver of morbidity and mortality amongst heroin users in the Russian Federation². Neither agonist maintenance therapy^{3,4} nor supervised injection facilities⁵, which have both been associated with reduced overdose death, are authorized in Russia⁶. Moreover, emergency medical services (EMS) are limited in scope and availability in many areas of Russia, and uncommonly utilized due in part to legal and cost concerns². Distribution of the opioid antagonist, naloxone, for lay administration in the event of overdose has emerged both within Russia and around the world as a promising approach to directly addressing opioid overdose^{6–8}. Naloxone is a safe,

effective, short-acting opioid antagonist for intravenous, intramuscular, subcutaneous, or intra-nasal administration to reverse opioid overdose. Naloxone is traditionally carried by EMS in localities where opioid overdose is encountered and earlier administration of naloxone is associated with fewer overdose-related complications⁹. Naloxone distribution is targeted at opioid users or anyone, including family members, who might witness an opioid overdose and includes brief education about overdose risks and management. Naloxone 'kits' in Russia are generally wallet-sized packets containing two administrations of naloxone, syringes, and a brochure.

Naloxone distribution programs have been shown to train drug users to respond effectively to overdose¹⁰, result in frequent successful opioid overdose reversals^{11–13}, and be associated with a decline in overdose mortality in communities^{14–16}. Nonetheless, heroin users who survive overdose frequently suffer future overdoses¹⁷ and policy-makers may be concerned about the overall societal cost of heroin use¹⁷. To address these concerns, and other distinct circumstances in Russia, we adapted a mathematical model of naloxone distribution originally designed for the US to Russian cities.

Methods

Model

A detailed description of the model development following methods guidance from Stout *et al.*¹⁸ can be found in the appendix of the original paper¹⁹. Briefly, we constructed a Markov model with an integrated decision analytic model (see Figure 1) in Microsoft Excel 2010TM to estimate the impact of distributing naloxone to heroin users on costs and utility with annual transitions and standard background mortality. The model takes a societal perspective over a lifetime horizon. Input parameters and ranges can be found in Table 1; instantaneous rates were transformed to probabilities²⁰. Heroin users entered the model in 'Heroin use' and could discontinue and relapse^{21,22}, overdose, or die for other reasons⁸. The overdose event was modeled separately and developed with the add-in TreePlanTM (Decision Toolworks, San Francisco, CA). The model produced three cycles of overdose, given the well-documented elevation in risk of overdose among persons who have previously overdosed¹⁷.

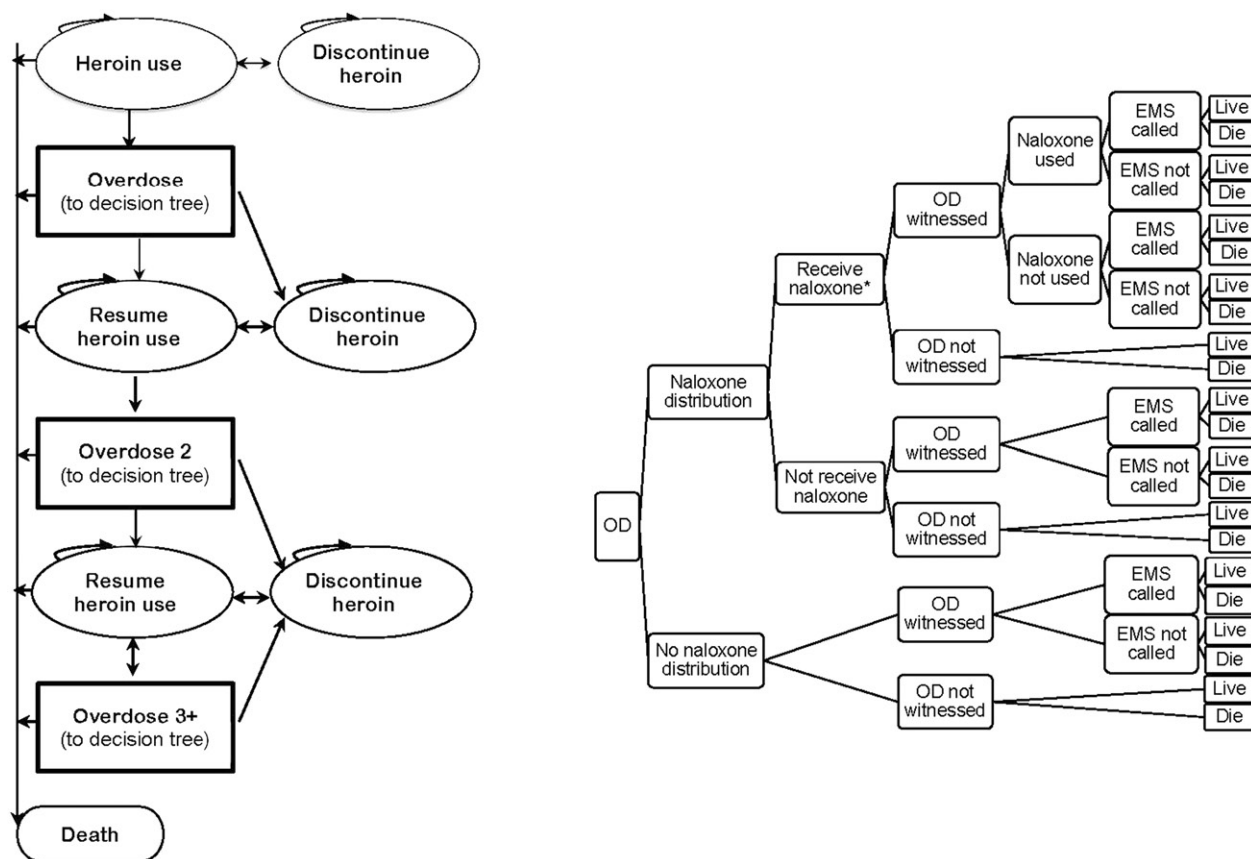


Figure 1. Model of naloxone distribution to heroin. EMS = emergency medical services. OD = overdose. Markov model with annual cycles and unlisted background mortality. Outcome of overdose events determined by decision analytic tree on right of figure. *Receive naloxone is adjusted in sensitivity analyses by the social network modifier.

Table 1. Naloxone distribution model parameters.

Parameter	Base-case (Range)	References
<i>Proportions</i>		
Join probability that naloxone is used ^a	0.153 (0.004–0.668)	Calculated
Proportion of heroin users prescribed naloxone	0.20 (0.05–0.50)	19
Proportion of witnesses with naloxone who use it	0.8 (0.5–0.9)	69
Proportion of overdoses witnessed	0.9 (0.32–0.99)	23,44,70,71
Social network modifier ^b	1.0 (0.5–1.5)	Assumption
Proportion call EMS		2,72
First-time overdose	0.2 (0.1–0.3)	
Subsequent overdoses	0.15 (0.075–0.225)	
Proportion call EMS after naloxone		45,72
First-time overdose	0.2 (0.1–0.3)	
Subsequent overdoses	0.15 (0.075–0.225)	
Proportion survive overdose		
Unwitnessed	0.900 (0.800–0.940)	1,8,23,24
Witnessed	0.930 (0.900–0.960)	1,8,23,24
Reduction in survival for second overdose	0.015	Calibrated
Reduction in survival for subsequent overdoses	0.03	Calibrated
Relative increase in survival with EMS	1.0 (0.9–1.158)	23,24,73
Relative increase in survival with naloxone administration	1.089 (1.02–1.158)	11,12,41,69,74,75
<i>Annual transitions</i>		
Heroin use to non-overdose death (in excess of background mortality)	0.0750 (0.0025–0.0125)	8
Heroin use to overdose		2,17,23,38,40,41
First overdose	0.16 (0.09–0.27)	
Second overdose	0.22 (0.05–0.30)	
Subsequent overdoses	0.34 (0.27–0.60)	
Annual relative reduction in risk of first overdose ^c	0.93305 (0.9–1.0)	40,76
Heroin use to discontinuation of heroin use	0.05646 (0.01–0.1)	21,22
Discontinuation of heroin use to heroin use	0.35 (0.056–0.4)	32,33,35
Annual relative reduction in risk of relapse ^c	0.93305 (0.9–1.0)	36
Overdose to discontinuation of heroin use	0.05646 (0.01–0.1)	21,22
<i>Costs</i>		
Naloxone kit (2 doses + distribution costs)	\$8 (\$4–\$25)	Warsaw Pharmaceutical, Annual Reports
EMS and hospital care	\$235 (\$161–\$282)	50,51
Reduced cost after lay naloxone (less transport)	\$0 (0–\$152)	Assumption
Annual heroin user cost to society ^d	\$832 (\$584–\$1080)	57,58,60,61
<i>Utilities</i>		
Heroin user	0.65 (0.52–0.78)	52–54,77
Relative increase in utility for heroin user in recovery	1.08 (1.00–1.16)	53,78

EMS, emergency medical services.

^aSummary value based on indented parameters listed below.

^bParameter used in sensitivity analyses to estimate possible effects of social network characteristics on the probability of naloxone being present at an overdose.

^cParameter is exponentiated to the years elapsed and multiplied by its reference parameter to reduce likelihood of the event over time.

^dSet at \$0 for baseline analysis and used for secondary analysis.

Adaptation of model

Adaptation of the model included both structural changes and identification of parameters specific to Russia. With regard to structure, we adjusted the starting age to 18 years, the average age of initiating heroin use in Russia²³, and calculated age-specific background mortality from 2010 Russian Federation mortality tables. In addition, we reduced the role of EMS in managing overdose such that EMS had no impact on survival, and increased the role of witnesses in managing overdose such that any overdose that was witnessed had a higher likelihood of survival regardless of interventions employed. These changes

were based on research in Russia suggesting that, in contrast to the US¹⁹, survival with EMS care is similar or possibly lower (0.90) than survival for those who do not receive EMS care (0.93)²³ (perhaps due to delayed or unavailable EMS care, although the absence of naloxone in many ambulances may be another cause²). Given the high rate of witnessing overdose, we assumed that witnessed overdoses had a higher rate of survival than unwitnessed events. EMS thus affected only cost in the adapted model.

We adjusted several parameters to account for different epidemiologic findings, availability of healthcare

Table 2. Key epidemiologic parameters for model calibration.

Parameter	Literature estimate (source)	Model forecast
Annual rate of overdose	9–53% ²	17.7%
Proportion ever experiencing an overdose	75% ²²	77.0%
Proportion of overdoses resulting in death	9.3% ²³	9.3%
Likelihood of survival witnessed	90.7% ²³	90.9%
Likelihood of survival with emergency medical services	90% ²²	90.9%
Likelihood of survival with naloxone	96–100% ^{10,11,40,67,71–73}	98.0%
Likelihood of distributed naloxone being used to reverse an overdose	9–40% ^{10,14,62}	15.3%
Annual rate of overdose death	2.3% ^{22,77}	1.7%
Median age of overdose death	35 years ^{23,24}	36 years
Median duration of heroin use	Unknown in Russia; 10–11 years in the US ^{25,61}	31 years
Annual rate of death from all causes	1.5–2.5% ^{8,78–82}	2.7% (0.4–2.0% over initial 40 cycles of model)

services, and costs. Given the small studies upon which several parameters were based, the model was calibrated to parallel findings from epidemiologic studies from Russia where available and international sites if no other sources were available (see Table 2)^{17,23–31}. Studies have demonstrated high rates of discontinuing heroin use in Russia, but rarely for more than 6 months³², and few IDUs in a St Petersburg study were able to abstain for over a year³³ in a setting with no legal agonist maintenance services and very limited availability of other treatment services³⁴; thus we assumed that relapse to heroin use would be much higher than US-based estimates of 50% relapse over 5 years³⁵. We assumed that 35% would relapse each year, although we maintained an age-based reduction in the risk of relapse³⁶, resulting in a median duration of heroin use among survivors of 31 years (much longer than the US median of 15 years of use³¹). Although a US-based study found high rates of enrollment in treatment after overdose³⁷, we did not incorporate an increased likelihood of abstinence after overdose into the baseline model due to limited treatment availability in Russia.

We assumed an annual rate of 16% for first-time overdose that declined with age such that the risk was halved at 14 years of heroin use³⁸. This rate was higher than the baseline rate for the US model in order to match epidemiologic data suggesting higher rates of overdose and overdose death (see Table 2); one possible explanation for a differential rate of first-time overdose would be the risks associated with frequent use of home-made opioids in Russia³⁹. The risks of a second and further overdoses were carried from the original model³⁸. The increasing risk of overdose^{40,41}, as well as the declining risk of a first-time overdose³⁸, were literature estimates, but were also necessary to approximate epidemiologic findings that 10–25% of heroin users overdose each year^{17,27,28,42,43}, yet only approximately two-thirds of Russian heroin users report ever overdosing^{23,24}.

Based on Russian data, overdoses were estimated to be witnessed 90% of the time²³, with a lower limit of 32% based on a study of fatal overdoses in San Francisco⁴⁴. In sensitivity analysis, a social network modifier accounted for variations in the likelihood that heroin users would use with others who had been reached by the naloxone distribution program. The use of EMS is low in Russia (ranging from 13–16%²³) and, based on the only published study, we assumed no change in the likelihood of calling EMS if naloxone was administered⁴⁵.

The estimated risk of an overdose resulting in death in Russia is 9.3%²⁴, yet the mean age of overdose death is generally in the fourth decade of life^{24,30,46}, suggesting that overdoses are more likely to be fatal in later years of opioid use. First-time overdoses, thus, had a mortality rate of 7% when witnessed and 10% when unwitnessed, with an absolute 1.5% increase in the risk of death for the second overdose, and 3% for all subsequent overdoses, resulting in an annual risk of mortality from overdose among active heroin users of ~0.6% in the early years of use, peaking at 1.9% after 30 years of use. As the mechanism for increased risk of death with recurrent overdoses is not well understood, we applied the same increased risk of death with recurrent overdoses to those receiving naloxone by calculating a relative risk reduction in mortality from these interventions.

Costs

Costs were converted to US dollars, valued at 2010 levels, and discounted 5% per annum, in accordance with methods guidance⁴⁷. Naloxone, most commonly distributed as two doses, is remarkably inexpensive in Eurasia, ranging from US\$0.61–US\$0.89 per 0.4 mg vial in 2010. The total cost of running a naloxone distribution program in Russia ranges from ~US\$9000 to distribute 2000 vials to 304 clients in Chapayevsk⁴⁸ to US\$12,700 to distribute 4745 vials to 656 clients in Naberezhnye Chelny⁴⁹; for an

average annual total cost of US\$4 per vial of naloxone distributed and US\$24 per client served. As naloxone expires after 24 months, we estimated a total cost of US\$8 per kit (two vials) distributed every 2 years, with additional replacement kits after each overdose.

The baseline total cost of EMS was estimated based on costs in Moscow, the most expensive city in Russia, as US\$235, including ambulance (5000 RUR/US\$161)⁵⁰ and emergency room care (2300 RUR/US\$74)⁵¹. The lower limit included only ambulance costs. Because witnesses in Russia are much less likely to call EMS, we assumed that all cases receiving EMS care were severe enough to warrant transport to the emergency room.

Quality-adjusted life years

Quality-adjusted life years (QALYs) were discounted at 5% per annum. The estimate of baseline quality-of-life for this analysis was taken from a study of health-related quality-of-life (HRQoL) among persons with depression in Russia, for which the control group utility was 0.814 by the EuroQol questionnaire (EQ-5D)⁵². This value was adjusted with a multiplier of the relative utility among injection drug users^{53,54}, with a conservative estimate of increased quality-of-life during recovery⁵⁴.

Analysis

We conducted deterministic and probabilistic analyses of health outcomes (overdose and overdose death rates) and cost-effectiveness (additional cost per QALY gained over the life of the model).

We conducted one-way deterministic sensitivity analyses on all variables and several analyses to evaluate specific scenarios. To evaluate cohorts of heroin users averaging 28 and 38 years of age, we ran the no naloxone model to that age to determine the proportion of the population in each 'stage' of heroin use, assuming all heroin users were active users; we then adjusted background mortality and ran the model. To account for the potential cost of outreach efforts, we conducted an analysis increasing the cost of naloxone kits by 50% for each additional 10% of heroin users reached by the program. We also developed 'worst-case' and 'best-case' scenarios involving extremes of multiple parameters to address uncertainty in the utilization and effects of distributed naloxone. Finally, we ran a probabilistic analysis of 10,000 Monte Carlo simulations; all model parameters were simultaneously varied across ranges defined in Table 1 with distributions considered normal for proportions and utilities, log-normal for costs, and beta for transition states. We generated confidence intervals from the probabilistic simulations, defined as those values above and below the 2.5% and 97.5% ranges of results. In addition, results were converted

to incremental net benefits ($\mu_{\text{Naloxone}} - \mu_{\text{No-naloxone}}$, where $\mu = [(\text{Willingness to pay}) \times \text{QALYs}] - \text{Cost}$), and a cost-effectiveness acceptability curve was developed⁵⁵.

We applied the 'cost' of heroin use to the utility estimate, in accord with standard economic analyses. However, to address potential concerns among policy-makers that heroin users are too expensive to warrant efforts to improve survival, we developed an alternate cost-effectiveness acceptability curve assuming that heroin users are a net cost to society in addition to their reduced utility and irrespective of any productivity. In the US model, we estimated a 2011 annual cost of US\$1000 per heroin user for healthcare and research costs and US\$3300 if criminal justice costs were included⁵⁶. There is no central estimate in Russia, thus we utilized estimated expenditures on HIV and tuberculosis as a surrogate for healthcare costs. Of the estimated 1.8 million IDUs in Russia, ~37% are living with HIV, and this risk factor accounted for 62% of new HIV cases in 2009⁵⁷. There were 980,000 persons living with HIV in Russia⁵⁸ and an estimated US\$777 million was spent on HIV services in 2008⁵⁸. The actual proportion of HIV monies spent on IDUs, sex workers, and men-who-have-sex-with-men is estimated to be only 4.4%⁵⁹, amounting to a maximum HIV-related expenditure of US\$19 per heroin user annually. Under the extreme assumption that all IDUs use opioids and receive proportionate HIV funding, heroin in Russia cost ~US\$267 per user annually in HIV-related expenditures. With regard to tuberculosis, 4–14% of patients with tuberculosis in St Petersburg were drug-dependent⁶⁰, and an estimated US\$1.2 billion was spent on tuberculosis in RF in 2010⁶¹, thus tuberculosis expenditures constitute up to US\$93 per IDU annually. To mirror US estimates, we assumed that criminal justice costs were twice the maximum expenditures on HIV and tuberculosis (\$720), resulting in an estimate of US\$832 per annum based on current expenditures and an upper limit of US\$1080 per annum, assuming maximal expenditures based on need.

Model validation

Details regarding calibration of the original model can be found in the appendix of the original paper¹⁹. A similar process was undertaken to calibrate the model to be concordant with epidemiologic findings from Russia (Table 2). The final model predicted that just over 50% of heroin users would continue to use after 31 years, substantially longer than US estimates that heroin use continues for an average of 15 years^{26,62} due to limited treatment availability. The model predicted an average rate of overdose of 17.7% per year, higher than US estimates^{17,27,28}, but a low estimate based on data from Russia²³, with the greatest number of overdoses occurring

early in a heroin user's career. The model predicted an average all-cause mortality rate of 2.7% per year, increasing with age among active users. The model predicted an average rate of overdose death among active heroin users of 1.7%, somewhat low compared to literature estimates in excess of 2% per annum². The model matched the literature estimate of a witnessed overdose resulting in death in Russia of 9.3%²³. The predicted median age of overdose death was 36 years, consistent with findings that young heroin users overdose frequently, but the median age of overdose death is in the fourth decade of life^{23,29}. The model predicted that, among overdose deaths, an average of ~17% received medical attention, consistent with estimates from other countries that one-fifth of overdose deaths received EMS care³⁰. The model predicted a 14.4% chance of a naloxone kit being used for overdose reversal, consistent with passively collected program reports from clients returning to obtain another naloxone kit (i.e., number of kits used to reverse overdose/total number of kits dispensed)^{11,15,63}. Forty years after beginning heroin use, 52% of the initial cohort had died and 30% had discontinued use.

Results

Population outcomes

On deterministic analysis, naloxone distribution prevented 7.6% of overdose deaths for each 20% of the heroin using population reached by the program (see Table 3 and Figure 2). We estimate that one overdose death was prevented for every 54 naloxone kits distributed (i.e., 'number needed to treat' = 54). On probabilistic analysis, naloxone distribution prevented 7.2% of overdose deaths (95% CI = 1.1–29.5%), with a number needed to treat of 89 (95% CI = 32–260). Naloxone distribution resulted in a reduced rate of overdose death among the full cohort and among active heroin users over the lifetime in all simulations, with a 2.5% increase in recovered heroin users and 3.5% increase in the number of overdoses.

Cost-effectiveness

Naloxone distribution was cost-effective in our base-case and all sensitivity analyses, with an incremental cost of US\$71 per QALY gained (Table 3 and Supplementary Figure). Cost-effectiveness was insensitive to the age of targeted users. Cost-effectiveness was somewhat sensitive to the efficacy of lay-administered naloxone at preventing overdose death and the cost of naloxone, but was relatively insensitive to other parameters. If naloxone kit costs increase with expanded coverage, the incremental cost per QALY gained would modestly increase. Naloxone was dominant only if resulting in fewer overdose events

through a hypothetical behavior change mechanism⁶⁴. A worst-case scenario, in which the likelihood of an overdose being witnessed, the efficacy of naloxone, and the likelihood of naloxone being carried at an overdose were minimized and the cost of naloxone was tripled, resulted in an incremental cost of US\$2605 per QALY gained.

Results from the probabilistic sensitivity analysis were similar to the base case findings. Naloxone distribution increased cost by US\$13 (95% CI = US\$3–US\$32) and QALYs by 0.137 (95% CI = 0.022–0.389) for an incremental cost of US\$94 per QALY gained (95% CI = US\$40–US\$325) (Figure 3). If we assumed that heroin users are a net cost to society beyond the scope of any other health conditions, naloxone resulted in an incremental cost of US\$1000 per QALY gained (95% CI = US\$644–US\$1450; US\$928 on deterministic analysis). See Supplementary Table for absolute outcomes of selected analyses.

Discussion

We set out to investigate the cost-effectiveness of naloxone distribution in Russian cities by adapting a previously published model and using Russian data as available. Naloxone distribution is likely to reduce opioid overdose mortality in Russia at minimal cost, even under conservative assumptions. Naloxone remained cost-effective if lay administration at a witnessed overdose produced essentially any improvement in survival. However, the reductions estimated in this model were substantially less than real-world reductions in community-level overdose mortality observed concordant with expanded naloxone distribution in several regions^{11,13,15,16,65}. This difference suggests that the true impact of naloxone may be in excess of our baseline model.

These results are largely consistent with the US analysis, although naloxone distribution may produce greater benefit at a lower cost in Russia. Overdose in Russia is believed to be more frequent, more often witnessed (possibly due to more common family and group living among drug users⁶⁶), and less likely to receive medical attention, resulting in an environment in which lay administered naloxone can have a dramatic impact on mortality. The costs of naloxone distribution, EMS care, and healthcare for drug users is much lower in Russia than the US, resulting in a comparatively greater cost-effectiveness, although making naloxone distribution less likely to result in a cost saving from reduced emergency medical care. Overall, these results suggest that naloxone distribution, while generally cost-effective, is even more likely to result in health benefits in regions where heroin users have less access to medical services.

Saving the lives of heroin users may not be a priority for some policy-makers, and may in fact appear to add to state

Table 3. Sensitivity analyses.

	% OD deaths averted (5 y/lifetime)*	Number needed to treat*	Increased QALYs of naloxone	Increased costs of naloxone	ICER of naloxone
Base case (deterministic)	13.4%/7.6%	54	0.152	\$11	\$71
Base case (probabilistic)	11.3%/7.2%	89	0.137	\$13	\$94
Sensitivity analyses (deterministic)					
<i>Mean age of targeted heroin users</i>					
SA1: 28 years	11.4%/7.7%	67	0.126	\$10	\$76
SA2: 38 years	10.7%/8.0%	71	0.095	\$8	\$87
<i>Intervention characteristics</i>					
SA3: Distribution of naloxone to 5% of heroin users	3.3%/1.8%	55	0.038	\$3	\$72
SA4: Distribution of naloxone to 50% of heroin users	33.6%/20.0%	52	0.392	\$28	\$71
SA5: Tripled cost of naloxone distribution	13.4%/7.6%	54	0.152	\$30	\$199
SA6: Efficacy of naloxone reduced to a 2% relative sur- vival benefit	3.5%/1.9%	216	0.039	\$10	\$256
SA7: EMS activation after naloxone halved	13.4%/7.6%	54	0.152	\$6	\$38
<i>Heroin use characteristics</i>					
SA8: Risk of first overdose halved	13.4%/7.7%	104	0.097	\$11	\$109
SA9: Risk of first overdose doubled	13.3%/7.4%	33	0.204	\$11	\$54
SA10: Rate of discontinuing heroin use halved	13.4%/6.9%	55	0.162	\$12	\$74
SA11: Rate of discontinuing heroin use after overdose doubled	13.4%/7.9%	55	0.148	\$10	\$70
SA12: Likelihood overdose is witnessed halved	5.7%/3.1%	96	0.072	\$9	\$12
SA13: Likelihood naloxone recipient carries naloxone at a witnessed overdose halved	6.7%/3.7%	89	0.075	\$9	\$122
SA14: Likelihood naloxone recipient carries naloxone at a witnessed overdose increased 50%	20.1%/11.6%	43	0.230	\$13	\$54
SA15: No improved quality-of- life for abstinence	13.4%/7.6%	54	0.149	\$11	\$73
SA16: 20% reduction in base- line quality-of-life for heroin user	13.4%/7.6%	54	0.122	\$11	\$89
<i>Worst-case scenario</i>					
SA17 (SA5 + SA6 + SA12 + SA14): Naloxone expensive, marginally efficacious and rarely carried; overdoses rarely witnessed	0.7%/0.4%	677	0.009	\$24	\$2605
<i>Best-case scenarios</i>					
SA18: Upper limit joint prob- ability naloxone used	73.5%/48.9%	36	0.892	\$44	\$49
SA19: Lower limit OD risk in setting of naloxone	48.8%/40.4%	11	0.490	—\$36	Dominant
<i>Structural sensitivity analysis</i>					
SA20: SA4 + naloxone cost increases 50% per absolute 10% increase in coverage	33.6%/20.0%	52	0.392	\$65	\$166

OD, overdose; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; SA, sensitivity analysis; EMS, emergency medical services.

*Number of kits needed to prevent one death.

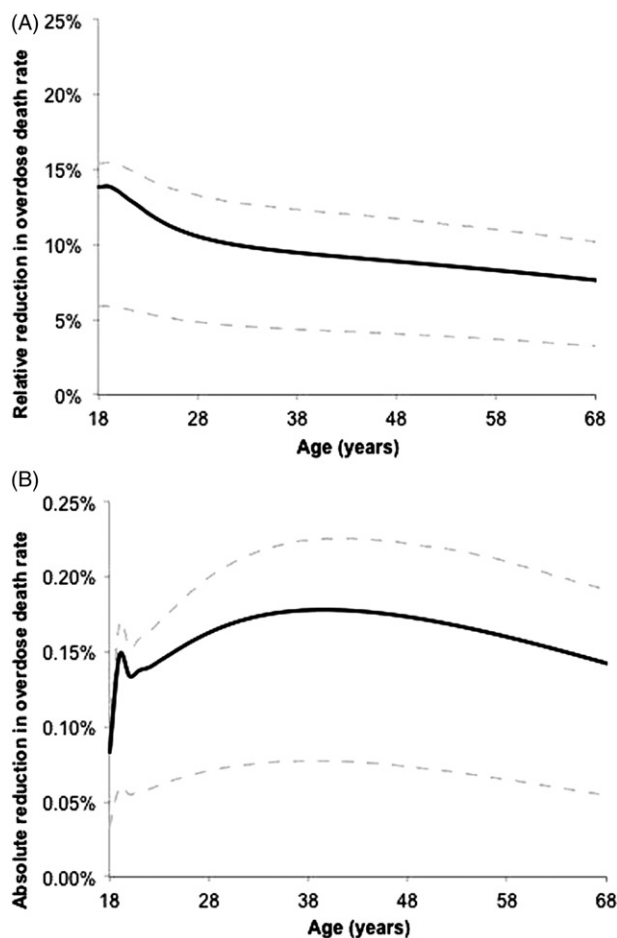


Figure 2. Reduction in overdose death rate from naloxone distribution for lay overdose reversal. Deterministic results represented by solid lines and 2.5% and 97.5% limits of the probabilistic analysis are represented by the dashed lines. Absolute rates were adjusted by the number of active heroin users to represent the effect in a community of users.

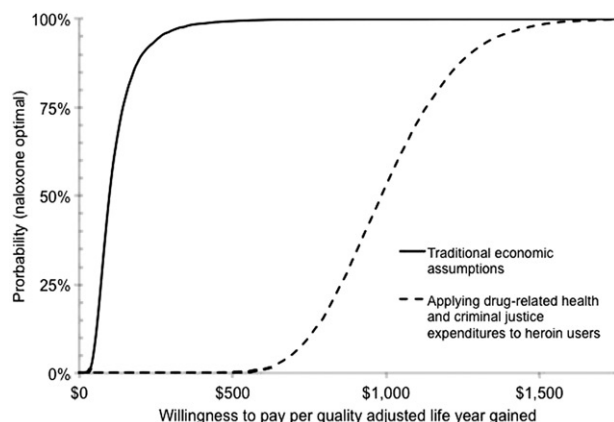


Figure 3. Cost-effectiveness acceptability curve of naloxone distribution. y-axis represents the probability that naloxone distribution is preferred at willingness to pay defined on x-axis.

expenditures in unsustainable ways. To address this, we conducted a scenario analysis considering heroin users as a net cost to society. This analysis is not consistent with

traditional economic analyses, as we 'double-charged' heroin users by reducing their utility (the denominator of the equation) and increasing their costs (the numerator). We do not advocate this approach to economic analyses for drug users as such an approach may codify the stigma of drug use. Nonetheless, naloxone distribution remained cost-effective even under such assumptions.

Limitations

Baseline results may under-estimate the full benefit of naloxone. Some parameters had high degrees of uncertainty, thus we conducted sensitivity and probabilistic analyses and provided confidence intervals. Some parameters relied on data from outside of Russia, including the estimated efficacy of administered naloxone. There are no estimates of quality-of-life among heroin users in Russia, thus we relied upon similar sources as other authors conducting cost analyses, but based our baseline estimate on the product of those estimates and an estimate of the quality-of-life of the general population of Russia. We did not incorporate possible ancillary benefits of naloxone distribution, such as reduced drug use and risk behaviors⁶⁷, but did evaluate the latter possibility in a sensitivity analysis. In addition, our model assumed the existence of low-threshold services for heroin users within which naloxone distribution could be embedded; costs may be higher for *de novo* programs, an increasing concern in Russia as drug service programs have faced major challenges⁶⁸. Finally, the model relied on epidemiologic data to represent an average of a host of factors that may influence overdose rates, such as poly-drug use, policing tactics, substance use disorder treatment program availability, and changes in heroin supply. Models incorporating such parameters, as this field of research develops, may better predict the impact of overdose interventions.

Conclusions

In summary, this analysis of naloxone distribution to heroin users for lay overdose reversal in Russia suggests that the intervention may be highly cost-effective, even under conservative assumptions.

Transparency

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