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Cost-Effectiveness of Take-Home Naloxone for the Prevention of Overdose Fatalities among Heroin Users in the United Kingdom

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ABSTRACT

Background: Heroin overdose is a major cause of premature death. Naloxone is an opioid antagonist that is effective for the reversal of heroin overdose in emergency situations and can be used by non-medical responders. **Objective:** Our aim was to assess the cost-effectiveness of distributing naloxone to adults at risk of heroin overdose for use by nonmedical responders compared with no naloxone distribution in a European healthcare setting (United Kingdom). **Methods:** A Markov model with an integrated decision tree was developed based on an existing model, using UK data where available. We evaluated an intramuscular naloxone distribution reaching 30% of heroin users. Costs and effects were evaluated over a lifetime and discounted at 3.5%. The results were assessed using deterministic and probabilistic sensitivity analyses. **Results:** The model estimated that distribution of intramuscular naloxone, would decrease overdose deaths by around 6.6%. In a population of 200,000 heroin users this equates to the prevention of 2,500 premature deaths at an incremental cost per quality-adjusted life year (QALY) gained of £899. The sensitivity analyses confirmed the

robustness of the results. **Conclusions:** Our evaluation suggests that the distribution of take-home naloxone decreased overdose deaths by around 6.6% and was cost-effective with an incremental cost per QALY gained well below a £20,000 willingness-to-pay threshold set by UK decision-makers. The model code has been made available to aid future research. Further study is warranted on the impact of different formulations of naloxone on cost-effectiveness and the impact take-home naloxone has on the wider society.

Keywords: cost-effectiveness, death, drug overdose, economic model, heroin addiction, naloxone, preventative measures, quality-adjusted life-years.

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Introduction

Heroin use carries a high risk of respiratory depression and overdose death, which accounts for substantial mortality in Europe, and has recently increased in some regions in Europe [1,2]. Naloxone, an opioid antagonist, has been shown to decrease overdose-related mortality when used by nonmedical responders in emergency situations, in combination with training and education [3–6]. European drug agencies [7] and the World Health Organization [8] recommend that take-home naloxone be more widely available. Prefilled formulations of naloxone for intramuscular administration have been the predominant form used in take-home naloxone programs across Europe [7,9]; an intranasal form has, however, been used in recent programs in Norway and Denmark (prefilled syringe with nasal adaptor kit) [10,11].

To date, no studies have assessed the cost-effective of take-home naloxone in Europe. Two studies in the United States

[12,13], one of which was later adapted to Russia [14], modeled the costs and benefits of distributing intramuscular naloxone to heroin users for use by nonmedical responders. In both cases, naloxone was considered to be robustly cost-effective. Given the recent rise of drug-related mortality in some countries across Europe and the call for the increase in availability of take-home naloxone programs, it will be critical for decision makers to understand the pharmacoeconomic implications of implementing new programs or expanding existing ones.

There is a need for an economic assessment of take-home naloxone in the European setting from a public health system perspective. The main objective of this study was to replicate the US economic model developed by Coffin and Sullivan [12] and adapt it to the United Kingdom to assess the cost-effectiveness of distributing naloxone to adults at risk of heroin overdose for use by nonmedical responders (i.e., heroin users, family, friends, and carers). We chose the United Kingdom because of its high and increasing

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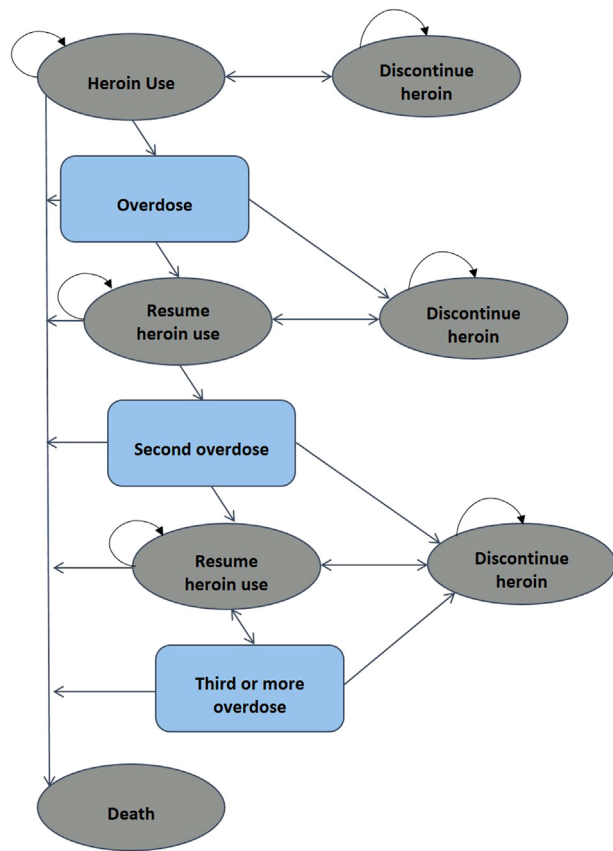


Fig. 1 – Markov model of heroin use, discontinuation, overdose, and death. Adapted from Coffin and Sullivan [12].

heroin-related mortality rate [1,15], the introduction of new government regulations in 2015 making naloxone exempt from prescription-only medicine requirements [16], and policy imperatives aimed at widening use [17]. Because current health economic models in the area are not widely available, a secondary objective of this study was to make a version of our model publicly available in R language, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) [18]. This version is available as a supplementary file with an associated “readme” instruction file. It allows researchers to investigate further the costs and benefits of interventions aimed at reducing overdose deaths and also aids health care decision makers with resource allocation decisions by presenting fully transparent and adaptable calculations.

Methods

Model Structure

A Markov model [19] with an integrated decision tree was developed to estimate the costs and outcomes of distributing take-home naloxone to adults at risk of heroin overdose. The model was a replication of the Coffin and Sullivan model [12] and adaptations were made to both structure and content to make it relevant for the UK health care system. The model had a lifetime horizon (default value set at 64 years), a health care perspective, 1-year cycles and it included standard background mortality [20].

The Markov model tracked heroin users through four health states (Fig. 1). Heroin users were to enter the model in “heroin use” and could discontinue heroin use, resume heroin use, or die for other reasons (all-cause death). Heroin users could also have

an overdose (fatal or nonfatal), which was modeled separately using a decision tree (Fig. 2). The decision tree produces three cycles of overdose, with the final cycle for the third and all subsequent overdose events. The decision tree models the potential pathway of a patient through an overdose event for intramuscular naloxone distribution versus no naloxone distribution. An overdose could be witnessed or not witnessed, and of those witnessed, naloxone may or may not be administered when available. Furthermore, in overdoses that are witnessed, an ambulance may or may not be called. At the terminus of each arm, the patient may either live or die. The probabilities at each stage differ depending on whether the overdose is witnessed, naloxone is available, naloxone is used, and whether an ambulance is called.

First, a replication of the Coffin and Sullivan model was developed using the same structure and parameter inputs for all clinical and cost variables as published in the original article [12]. The accuracy of the model was assessed by comparing the clinical and cost-effectiveness outcomes with those provided by Coffin and Sullivan (personal communication, June, 2016). We were confident that we had replicated the original model as closely as possible with differences in incremental costs, quality-adjusted life-years (QALYs) and cost-effectiveness ratio being no more than \$5, 0.01, and \$23, respectively. This variance resulted from rounding effects and uncertainty regarding inputs not reported or referenced in the Coffin and Sullivan article, for example, standard background mortality rates.

Second, the replicated model was adapted to the UK health care system, which included structure and content changes. A targeted literature review was conducted to identify UK-specific input parameters, when available. Key terms were used to search MEDLINE and online search engines (search terms included heroin, opioid, drug-related mortality, overdose, and naloxone). No date limit was applied to the searches. The baseline model was adjusted to begin at 22 years, which reflects the average age of onset of heroin use in Europe [21], and age-specific background mortality for the United Kingdom was used [22]. The input parameters and ranges are presented in Table 1, with detailed rationale for parameter selection given in Appendix Table 1 in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2018.07.014>. The model was built in Microsoft Excel 2016 and subsequently reproduced in R version 3.3.2 [18] and validated against the Excel version.

Markov Model Transitions

Annual transition probabilities outlined in the Coffin and Sullivan model were based on epidemiological evidence derived from North America, Australia, and Europe [12]. It was assumed that these estimates were relevant for the United Kingdom. The estimates are based on evidence demonstrating that 50% of users relapse over 5 years resulting in a medium duration of heroin use of 15 years, 33% to 70% of users overdose over a lifetime, and the principal risk factor for overdose is previous overdose and therefore risk increases with each overdose [12].

Decision-Tree Parameters

Decision-tree input parameters were adapted to align with the availability and structure of UK health care services and were sourced from UK studies when available. The proportion of heroin users reached by the naloxone take-home program was assumed to be 30%. This was based on the target coverage for the Scottish naloxone take-home program aiming to reach one-third of injecting heroin users [23]. The proportion of witnessed overdoses was assumed to be 85%, on the basis of a UK study demonstrating that 85% of heroin users in treatment had a

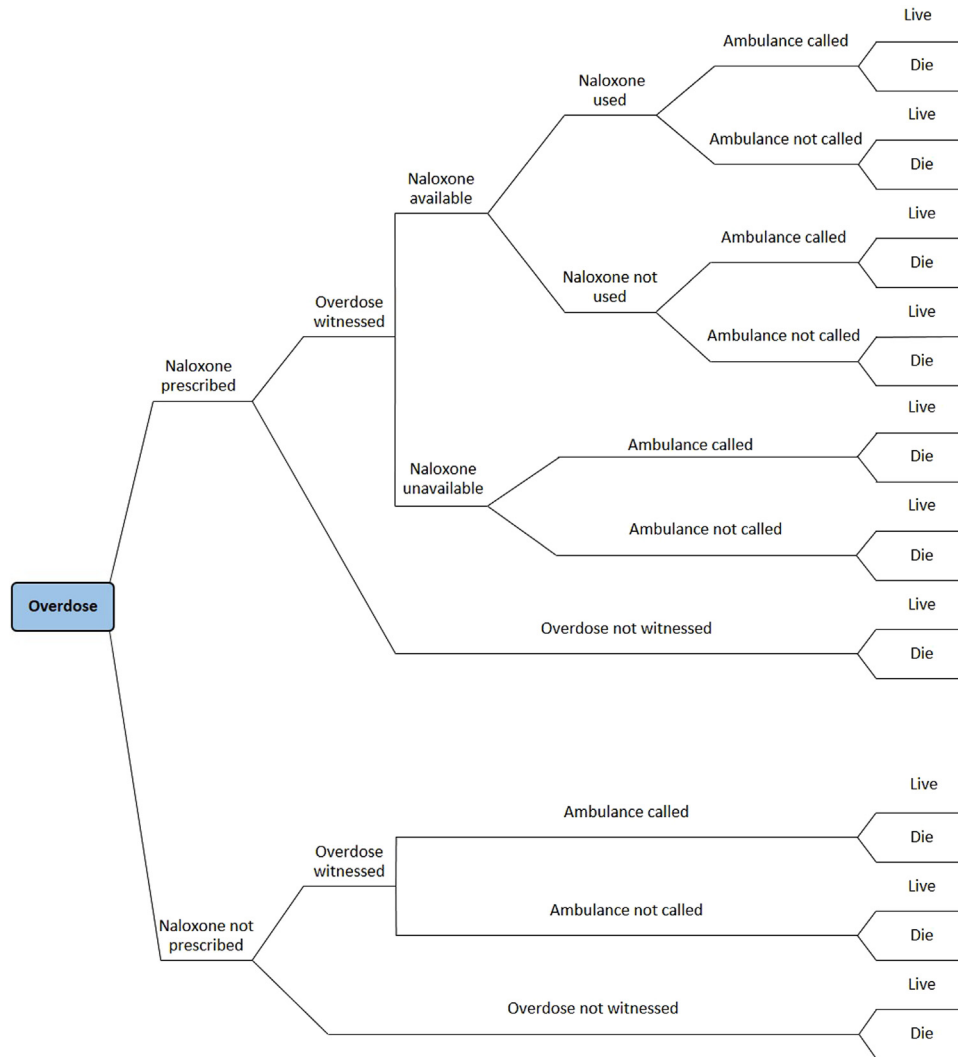


Fig. 2 – Decision tree for the overdose health state. Adapted from Coffin and Sullivan [12].

witnessed overdose [24]. The Coffin and Sullivan model outlined one estimate for “the proportion in possession of naloxone at an overdose who attempt to use it to attempt reversal” [12]. Nevertheless, this estimate is made up of the proportion of witnessed overdoses when naloxone is available (i.e., has not been lost or is not with the victim at the time of the overdose) and the proportion of witnesses with naloxone who attempt to use it. The model was adapted to include both these input parameters independently to improve model accuracy. The model assumed that 75% of users would have their naloxone kit available at the time of an overdose and in 90% of cases there would be an attempt to use it. These were based on information from several UK studies and the Scottish and Welsh take-home programs [24–29]. As in the original Coffin and Sullivan model [12], the same value was used in the sensitivity analysis for the social network modifier, which accounted for variations in the likelihood that users would take heroin in the presence of others who had been reached by the naloxone take-home program.

The likelihood of calling an ambulance and being taken to hospital was structured in a slightly different way compared with the original model aligning with data availability and UK policy guidelines on transport to hospital after an overdose. The likelihood of calling an ambulance is based on a survey from the Welsh naloxone take-home program [29]. The likelihood of being taken to

accident and emergency was assumed to be 100% following UK guidelines stating all patients suffering an opioid overdose should be transported to further care [30]. Established estimates of overdose mortality, recurrent overdoses, and the increase in survival after the use of naloxone or calling an ambulance were based on estimates used in the Coffin and Sullivan model [12,14] and UK estimates [9,23,27,31] when available.

Costs

Naloxone costs were based on the British National Formulary list price for Prenoxad® (Martindale Pharmaceuticals Ltd., Buckinghamshire, United Kingdom), an intramuscular injection (1 mg/ml, 2 ml prefilled syringe), which is licensed for use in the community [32]. Naloxone costs were incurred after each overdose when naloxone was administered biannually among active heroin users to account for naloxone going out of date (shelf life of Prenoxad is 3 years) and for losses. Distribution costs of £8 were assumed per naloxone prescription, on the basis of those estimated by Coffin and Sullivan [12]. Naloxone take-home programs included distribution of naloxone in combination with training users, and their family, friends, and carers, on how to administer the product in the event of an overdose [31,33]. Training costs were not included in the original Coffin and Sullivan model [12].

Table 1 – Naloxone distribution model parameters.

Input name	Base case (range)	Source
<i>Markov model annual transition parameters for UK adaptations</i>		
Heroin use to nonoverdose death (in excess of background mortality)	0.0075 (0.0025–0.0125)	[12]
Heroin use to overdose		[12]
First overdose	0.09 (0.02–0.12)	
Second overdose	0.22 (0.05–0.30)	
Subsequent overdoses	0.34 (0.27–0.60)	
Annual relative reduction in risk for first overdose	0.933 (0.900–1.000)	[12]
Heroin use to discontinuation of heroin use	0.06 (0.01–0.10)	[12]
Discontinuation of heroin use to heroin use	0.070 (0.056–0.084)	[12]
Annual relative reduction in risk for relapse	0.933 (0.900–1.000)	[12]
Overdose to discontinuation of heroin use	0.062 (0.028–0.113)	[12]
<i>Decision-tree parameters (proportions) used in the UK adaptations</i>		
Joint probability that distributed naloxone is used each year (calculated)	0.17	Calculated
Proportion of heroin users prescribed naloxone	0.30 (0.05–0.60)	[12,23]
Proportion of witnessed overdoses	0.85 (0.32–0.94)	[12,24,49]
Proportion of witnessed overdoses when naloxone is available (i.e., has not been lost or not with the victim at the time of the overdose)	0.75 (0.40–0.85)	Assumption based on References [25–28]
Proportion of witnesses with naloxone who attempt to use it	0.90 (0.77–0.99)	Assumption based on References [24,27,29]
Social network modifier	1.0 (0.5–1.5)	[12]
Proportion who call an ambulance		
Proportion who call an ambulance (no naloxone use)	0.60 (0.30–0.80)	[29]
Proportion who call an ambulance (no naloxone use) and then go to accident and emergency	1.0 (0.50–1.0)	[30]
Proportion who call an ambulance after naloxone use	0.85 (0.55–0.95)	[25]
Proportion who call an ambulance after naloxone use and then go to accident and emergency	1.0 (0.50–1.0)	[30]
Proportion who survive overdose		
Proportion who survive an unwitnessed overdose	0.90 (0.80–0.94)	[14]
Reduction in survival for second overdose	0.015 (0.000–0.020)	[12]
Reduction in survival for subsequent overdoses	0.015 (0.000–0.020)	[12]
Proportion who survived a witnessed overdose (no naloxone or ambulance)	0.918 (0.800–0.940)	[12]
Relative increase in survival during a witnessed overdose when an ambulance was called (no naloxone)	1.013 (0.980–1.035)	Assumption based on Reference [23]
Relative increase in survival during a witnessed overdose with naloxone	1.067 (1.035–1.089)	Assumption based on References [9,12,27,31]
<i>UK model costs</i>		
Intramuscular naloxone (1 mg/ml, 2 ml prefilled syringe of Prenoxad®)	£15.30 is the price for one	[32]
Distribution	£8.50	[12]
Training costs for users, family, and friends	£124 per kit for first-time administration	[34]
Ambulance	£233	[35]
Accident and emergency visit	£278	[35]
<i>Utility values</i>		
Heroin user	0.80 (0.73–0.90)	[12]
Relative increase in utility for heroin user in recovery	1.07 (1.00–1.13)	[12]

Guidance suggests that training could be run on a one-to-one basis or in a small group. Costs were estimated at £124 on the basis of a per-care contact with the drug service [34] and applied for first-time administration of naloxone. Costs for an ambulance callout and visit to accident and emergency were sourced from National Health Service reference costs [35]. Costs are presented in UK pounds, using 2016 as the costing year and discounted at 3.5%, in accordance with UK guidance [36].

Outcomes

Outcomes were expressed in terms of clinical outcomes (number of overdoses and overdose deaths) and cost-effectiveness outcomes (cost per QALY, discounted at 3.5% per annum) [36].

Absolute utility values for a heroin user not in treatment, together with a relative increase in utility for those in recovery, were assumed to be the same as those in the Coffin and Sullivan model [12].

Sensitivity Analysis

Deterministic and probabilistic sensitivity analyses were carried out to assess the robustness of the model. Univariate analysis, whereby input values are individually varied to plausible upper and lower bounds while remaining values retained their baseline, was undertaken for all input parameters. Selected results were plotted in a tornado diagram and, in addition, were documented in a tabular format.

Probabilistic sensitivity analysis was also undertaken by randomly drawing values from a distribution around each of the inputs during 10,000 simulations. Distributions were beta distribution for proportions and transition rates, gamma for costs and utility decrements, and lognormal for utility rates. The results of these simulations were used to form a scatterplot of incremental effectiveness against incremental costs of naloxone distribution versus no naloxone distribution. In addition, the results from each of these simulations were used to calculate incremental net benefits and from these a cost-effectiveness acceptability curve demonstrating the probability

of cost-effectiveness at different willingness-to-pay thresholds was created.

Scenario Analysis

A number of scenario analyses were carried out. First, the impact of increasing the costs of naloxone distribution was assessed. This included increasing the price, the distribution costs, and the training costs. Second, the impact of adding societal costs to the model was assessed, that is, making the assumption that heroin users are a net cost to society. We assessed the impact of

Table 2 – Base case, sensitivity analysis, and scenario analysis results.

Input name	Lifetime overdose deaths averted (%)	Incremental cost of naloxone distribution (£)	Incremental QALY of naloxone distribution	ICER of naloxone distribution (£)
Base case	6.6	146	0.163	899
<i>Sensitivity analyses</i>				
Proportion of heroin users prescribed naloxone increased from 30% to 60%	13.6	295	0.331	891
Proportion of heroin users prescribed naloxone decreased from 30% to 5%	1.1	24	0.027	905
Social network modifier increased from 1.0 to 1.5	10.1	167	0.246	679
Social network modifier decreased from 1.0 to 0.5	3.3	125	0.081	1,557
Proportion of witnessed overdoses increased from 85% to 94%	7.6	152	0.182	835
Proportion of witnessed overdoses decreased from 85% to 32%	2.1	118	0.057	2,047
Relative increase in survival when naloxone available decreased from 1.067 to 1.035	3.0	142	0.074	1,917
Proportion of witnesses with naloxone who attempt to use it increased from 90% to 99%	7.3	150	0.179	839
Proportion of witnesses with naloxone who attempt to use it reduced from 90% to 77%	5.7	140	0.139	1,010
Proportion of witnessed overdoses in which naloxone is available increased from 75% to 85%	7.5	152	0.185	821
Proportion of witnessed overdoses when naloxone is available reduced from 75% to 40%	3.5	127	0.086	1,475
No quality-of-life improvement for heroin user in recovery	6.6	146	0.156	935
Naloxone distribution costs increased 10-fold (from £8.50 to £85.00)	6.6	388	0.163	2,388
Rate of first overdose increased from 9% to 12%	6.6	152	0.197	772
Rate of first overdose reduced from 9% to 2%	6.7	126	0.046	2,716
<i>Scenario analyses</i>				
Naloxone price increased 10-fold (from £15.30 to £153.00)	6.6	582	0.163	3,580
Naloxone price increased 10-fold and distribution and training costs doubled	6.6	645	0.163	3,965
Addition of an annual cost to society of a heroin user and discontinued heroin user: criminal justice costs only	6.6	2,621	0.163	16,121
Addition of an annual cost to society of a heroin user and discontinued heroin user: criminal justice and victim costs	6.6	8,321	0.163	51,172
Multivariate scenario: lower thresholds for witnessed, naloxone available, naloxone used, efficacy and price of naloxone doubled	0.4	155	0.012	12,925
Multivariate scenario: higher thresholds for witnessed, naloxone available, naloxone used, efficacy and price of naloxone at base case	13.2	168	0.315	534

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

applying a societal cost to all heroin users and discontinued heroin users in the model. The societal cost applied included criminal justice and victim costs. Costs used were those reported by a UK health technology assessment of methadone and buprenorphine and inflated to 2016 prices. Original costs reported by Connock et al. [37] are provided in parentheses. For heroin users, criminal justice and victim costs were £13,592 (£8,397) and £14,395 (£8,893), respectively, and for discontinued heroin users, these were £11,390 (£7,037) and £49,900 (£30,827), respectively. Third, multivariate deterministic scenarios were developed using combined plausible upper and lower bounds for the following parameters: overdose witness rates, cost and efficacy of naloxone, and rates of carrying and use of naloxone.

Results

Clinical and Economic Outcomes

The economic model estimated that a distribution of take-home naloxone reaching 30% of heroin users would prevent 6.6% of overdose deaths at an incremental cost-effectiveness ratio of £899/QALY gained over a lifetime (Table 2).

In a population of 200,000 heroin users with no naloxone distribution, the model estimated that there would be 385,007 overdoses, of which 9.8% would result in death (37,688). Although

a 30% distribution of naloxone to adults at risk of heroin overdose for use by nonmedical responders would increase the number of overdoses by 2.7% (to 395,416) because of the increase in survival of heroin users at risk of a subsequent overdose, it would result in a decrease in the number of overdose deaths by 2,500 (to 35,188).

Results of the probabilistic analysis are presented in the next section. In terms of confidence intervals (CIs) around the observed values, a 30% distribution of intramuscular naloxone to heroin users would increase lifetime QALYs by 0.164 (95% CI, 0.021-0.514) and costs by £156 (95% CI, £33-£365) for an incremental cost per QALY gained of £952 (95% CI, £431-£3,330).

Sensitivity Analysis

Cost effectiveness (Fig. 3; Table 2) was somewhat sensitive to rate of first overdose, proportion of witnessed overdoses, the efficacy of naloxone (in terms of impact on survival), the proportion of witnessed overdoses when naloxone was available, and the social network modifier (which reflects the likelihood that users would take heroin in the presence of others who had been reached by the naloxone take-home program). Cost-effectiveness was relatively insensitive to the remaining parameters. Incremental cost per QALY gained did not exceed more than £3,000 in any of the univariate analyses. Those that increased the incremental cost per QALY gained to more than £2,000 included reducing the rate of first overdose from 9% to 2%, increasing

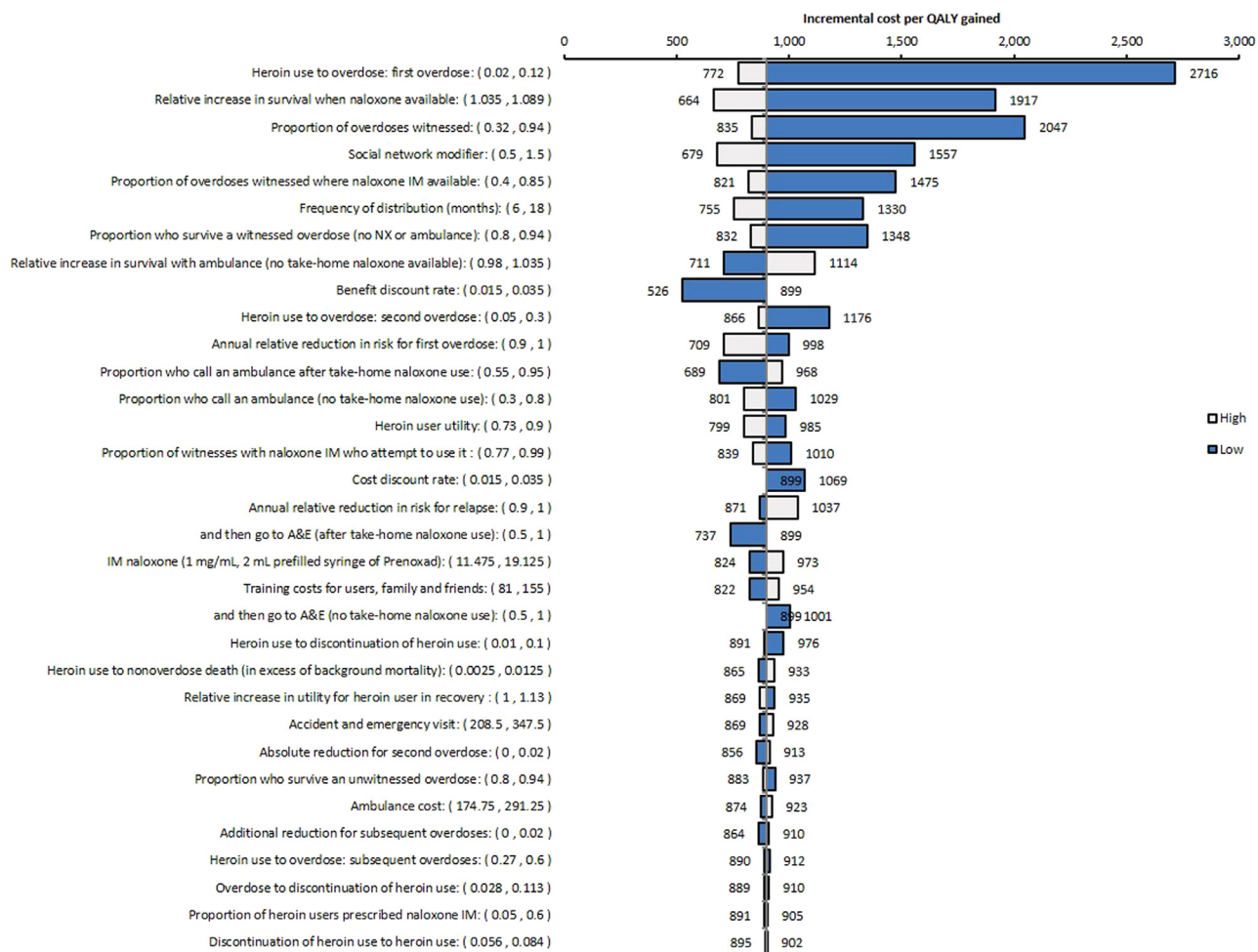


Fig. 3 – One-way sensitivity analysis of the cost-effectiveness of naloxone distribution. A&E, accident and emergency; IM, intramuscular; NX, naloxone; QALY, quality-adjusted life-year.

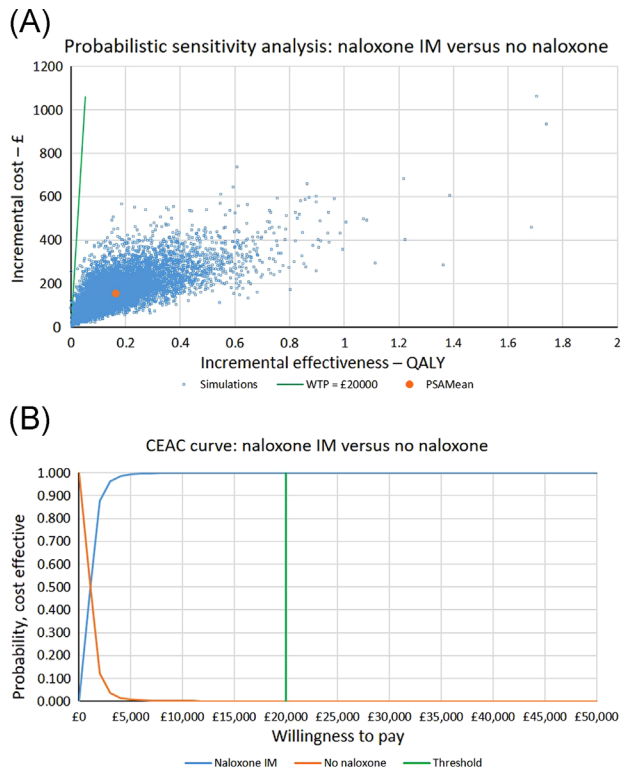


Fig. 4 – (A) Cost-effectiveness acceptability plane and (B) CEAC for IM naloxone compared with no naloxone distribution. CEAC, cost-effectiveness acceptability curve; IM, intramuscular; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; WTP, willingness to pay.

the distribution costs of naloxone 10-fold, and decreasing the proportion of witnessed overdoses from 85% to 32%.

In addition, a number of univariate analyses demonstrated further increases, over the base case, in lifetime overdose deaths averted. Analyses in which the percentage of lifetime overdose deaths averted exceeded 7% included increasing 1) the proportion of heroin users prescribed naloxone from 30% to 60%, 2) the social network modifier from 1.0 to 1.5, 3) the proportion of witnessed overdoses from 85% to 94%, 4) the proportion of witnessed overdoses when naloxone is available from 75% to 85%, and 5) the proportion of witnesses with naloxone who attempt to use it from 90% to 99%.

The cost-effectiveness acceptability plane (Fig. 4A) and the cost-effectiveness acceptability curve (Fig. 4B) demonstrate the high probability (99.8%) that naloxone distribution is cost-effective compared with no naloxone distribution at a cost per QALY threshold of less than £20,000.

Scenario Analysis

The scenario analysis results are presented in Table 2. Increasing the price of intramuscular naloxone 10-fold and doubling the distribution and training costs increased the incremental cost-effectiveness ratio to £3,965/QALY gained. The addition of annual societal costs of a heroin user and discontinued heroin user increased the incremental cost-effectiveness ratio to £16,121/QALY gained when only criminal justice costs were included and to £51,172/QALY gained when both criminal justice and victim costs were included. The multivariate deterministic scenario analysis for lower parameter bounds, using a health

care perspective and not including societal costs (cost of naloxone was doubled and the likelihood of an overdose being witnessed, naloxone being available and used, and the efficacy of naloxone was set to lower values), generated an incremental cost-effectiveness ratio of £12,925/QALY gained with an estimated 0.4% of overdose deaths being avoided.

Discussion

The main objective of this study was to replicate and adapt an economic model developed by Coffin and Sullivan [12], and use epidemiological data in the absence of clinical trials, to assess the cost-effectiveness of distributing intramuscular naloxone to adults at risk of heroin overdose for use by nonmedical responders compared with no naloxone distribution in a European setting. A naloxone take-home program in a European market, in this case the United Kingdom, targeted at 30% of heroin users, was shown to be highly cost-effective. The sensitivity analysis confirmed the robustness of the results. These results are in line with the cost-utility analyses conducted for the United States [12,13] and Russia [14], where the incremental cost-effectiveness ratio of naloxone distribution was US \$438 [12], US \$323 [13], and US \$94/QALY gained [14] compared with no naloxone distribution. The small difference in cost-effectiveness relative to the present study can be accounted for by differences both in study design and in health care systems. In terms of study design, there were differences in parameter estimates and costs included; for example, the US and Russian studies did not include the cost of training heroin users and their family, friends, and carers on naloxone use. In addition, structural adaptations were made to the current model to improve accuracy. In terms of health care systems, there were differences in the assumed availability of services. For example, in the Russian study, it was assumed that emergency services were called only in a minority of cases and that they had no impact on survival. This was in contrast to the present study, which assumed a high rate of contact with emergency services, which had a consequent positive impact on survival.

In terms of clinical outcomes, the model predicted that naloxone distribution would decrease overdose deaths by about 6.6%. In a population of 200,000 heroin users, this equates to saving 2,500 lives over a lifetime. The sensitivity analyses demonstrated that, among other variables, increasing the distribution of take-home naloxone to heroin users and increasing the use and availability of naloxone at the time of a witnessed overdose would improve these clinical outcomes further. This has important policy implications. The analysis suggests that the implementation of new take-home naloxone programs or expanding existing ones will have a measurable positive impact on lives saved. It also suggests that focusing on those aspects of the program that may lead to an increased availability or use of naloxone at the time of an overdose death, through for example training or different types of naloxone administration, could further increase the clinical benefits.

The clinical outcomes estimated in our model are very conservative compared with reductions in overdose deaths seen in the Scottish national naloxone program that started in 2011. An early evaluation of the effectiveness of the program, the first assessment of a naloxone program at the population level, demonstrated a 36% reduction in the proportion of heroin-related overdose deaths that occurred in the 4 weeks after release from prison [5]. This study estimated that the cost per QALY gained would range from £560 to £1940; nevertheless, only prescription costs were included in the analysis. The utility of a heroin user was assumed to be 0.7 with life-years gained by overdose-related death prevention of 10 years.

Evidence from the Welsh national naloxone program and pilot programs in England suggests that 95% to 100% of heroin users who had overdoses that were witnessed, and when naloxone was available and administered, survived [9,27,31]. These evaluations were not designed to assess the reduction in overdose mortality resulting from naloxone distribution and are limited by small sample sizes. Nevertheless, an analysis conducted by the World Health Organization of 20 global take-home naloxone programs found a mortality rate in witnessed overdoses of 1.0% (0.83%–1.21%) and although there were no comparators in these studies, the report outlined that the mortality rate after overdoses has previously been estimated at 2% to 4%. Despite classifying the quality of evidence on the effectiveness of take-home naloxone as “very low,” the World Health Organization issued a strong recommendation to provide access to and training on administration of naloxone to people likely to witness a heroin overdose [8].

Only the intramuscular route of administration of naloxone is available in the United Kingdom currently. Introduction of an intranasal formulation would have added value over an intramuscular route of administration. Similar efficacy, in terms of time to reversal of overdose, has been demonstrated [38–40]. There is, however, no risk of needle-stick injury and subsequent risk of infection from blood-borne pathogens with the intranasal route of administration [41], a particular concern for nonmedical responders given the high rate of HIV and hepatitis B or C in heroin users [42,43]. It is also easier to use, requires less training, and the nose is often readily available [41]. Such benefits may increase distribution and the likelihood of use during an overdose. Furthermore, a recent study suggested that the proportion of injecting drug users prescribed intramuscular naloxone who carry it with them could be as low as 5% [44]. Injecting drug users have stated a preference for the intranasal mode of administration [45] and therefore availability of such a formulation may lead to higher carriage rates.

The second objective of this study was to enable further research on the costs and benefits of interventions aimed at reducing heroin-related overdose deaths. There has been a recent debate emphasizing the need to improve transparency in decision making. We have therefore made our model available online in R format to ensure transparency and help facilitate future research and policy recommendations [46].

This study has several limitations. First, the model uses data based on epidemiological studies in the absence of randomized controlled trials and, when data were not available for the United Kingdom, input parameters were drawn from the original Coffin and Sullivan model that contained predominantly North American data, with supporting evidence from Australia and Europe [12]. This was accounted for by carrying out extensive sensitivity analyses to test the robustness of the results.

Second, there are potential benefits of training drug users on the administration of naloxone and guidelines to follow if they witness an overdose which are not included in this analysis that could potentially lead to improved cost-effectiveness estimates for naloxone distribution. These relate to process utility. For example, in Wales the national take-home program offers all new clients tests for HIV or hepatitis B or C virus and many are trained in first aid [29]. Programs may increase the number of support services available to users and may also lead to the spread of information from trained users to nontrained users [29]. Third, the model demonstrates cost-effectiveness in a general population of heroin users; nevertheless, rates of overdose and effectiveness of take-home naloxone programs are likely to vary significantly between risk groups. For example, rates are likely to be higher in those with reduced tolerance (recently released from prison or hospital or recently completed detoxification) or using other sedating drugs (e.g., benzodiazepines) [23,47,48]. Finally, the model base case does not include societal costs. The topic of broader societal impact has substantial ethical and political implications because it relates to

the positive and negative impact a heroin user can have on society. Although we assessed the impact of adopting a societal perspective in a scenario analysis using data from previously published models, further research is required in this area to accurately represent the impact a take-home naloxone program would have on society as a whole.

Conclusions

Our evaluation suggests that the distribution of take-home naloxone decreased overdose deaths by about 6.6% and was cost-effective with an incremental cost per QALY gained well below a £20,000 willingness-to-pay threshold set by UK decision makers. The model code has been made available to aid future research. Further study is warranted on the impact of different formulations of take-home naloxone, such as intranasal, and the impact take-home naloxone has on the wider society.

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Supplemental Materials

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