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Abstract

Background: As a core component of harm reduction strategies to address the opioid crisis, several countries have instituted publicly-funded programs to distribute naloxone for lay administration in the community. The effectiveness in reducing mortality from opioid overdose has been demonstrated in multiple systematic reviews. However, the economic impact of community naloxone distribution programs is not fully understood.

Objectives: To conduct a review of economic evaluations of community distribution of naloxone, assessing for quality and applicability to diverse contexts and settings.

Data Sources: The search strategy was performed on MEDLINE, Embase, and EconLit databases.

Study Eligibility Criteria and Interventions: Search criteria were developed based on two themes: (1) papers involving naloxone or narcan, and (2) any form of economic evaluation. A focused search of the grey literature was also conducted. Studies exploring the intervention of community distribution of naloxone were selected.

Study Appraisal and Synthesis Methods: Data extraction was done using the BMJ Guidelines for Economic Submissions, assigning quality based on the impact of the missing or unclear components on the strength of the conclusions.

Results: A total of nine articles matched our inclusion criteria: one cost-effectiveness analysis, eight cost-utility analyses, and one cost-benefit analysis. Overall the quality of the studies was good (six of high quality, two of moderate quality, and one of low quality). All studies concluded that community distribution of naloxone was cost-effective, with an incremental cost-utility ratio range of $111 to $58,738 USD (2020) per quality-adjusted life year gained.

Limitations: Our search strategy was developed iteratively, rather than following an a priori design. Additionally, our search was limited to English terms.

Conclusions and Implications of Key Findings: Based on this review, community distribution of naloxone is a worthwhile investment, and should be considered by other countries dealing with the opioid epidemic.

Declarations

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Availability of data and material: The authors confirm that the data supporting the findings of this study are available within the article or its supplementary materials.

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Introduction

The World Health Organization estimates that approximately 115,000 people died of opioid overdose globally in 2017 [1]. Common opioids include morphine, hydromorphone, oxycodone, heroin and fentanyl [2]. Opioids are used medically for pain relief and anesthesia, but can be highly addictive. Opioid overdose can lead to acute respiratory and nervous system depression, leading to death [3]. Several countries, particularly within Europe and North America are facing an opioid crisis, experiencing steep increases in opioid-related deaths. In the United States of America (USA), the number of deaths due to opioid overdose increased by 120% between 2010 and 2018 [1]. Moreover, the COVID-19 pandemic has exacerbated the opioid crisis. In Canada, the number of opioid-related overdose deaths increased by over 50% from April to June 2020, in comparison to January to March 2020 or in comparison to April to June 2019 [4]. In the USA, the highest number of overdose deaths ever recorded in a 12 month time frame occurred during the COVID-19 pandemic, with some jurisdictions seeing an increase of up to 98% [5].

In response to this crisis, many affected countries have recognized the importance of not only prevention and treatment, but also harm reduction. As part of a harm reduction strategy, several countries are now distributing naloxone kits to laypeople throughout the community through local pharmacies, community organizations, and public health organizations [6]. Naloxone is a drug used to temporarily reverse an overdose. It can be delivered intramuscularly, either via syringe or auto-injector, or intranasally [7]. Naloxone can often be found in emergency rooms and carried by emergency medical services (EMS). Yet, providing additional naloxone kits to the community enables people to intervene if they see someone suffering from an opioid overdose, allowing more time to receive definitive treatment at a hospital. Community distribution can take many forms, including free and easy access to naloxone kits via pharmacies, or active distribution to high-risk populations through outreach programs [6]. The first take-home naloxone programs began in the 1990s in select communities, as part of grassroots initiatives, in the USA, Italy, Germany and the United Kingdom (UK) [8]. Programs remained small and confined to specific localities until after 2010. Currently, publicly-funded take-home naloxone programs and widespread distribution of naloxone kits exist in Canada, Australia, Italy, the UK, Ukraine, Estonia, Norway, Sweden and Denmark, as well as

in some states in the USA [1, 8]. Some jurisdictions provide naloxone to anyone who requests a kit, while others provide free kits only to those at-risk of experiencing or witnessing an overdose [1, 8].

Community distribution of naloxone has been shown repeatedly to be an effective tool in reducing opioid harms [9, 10]. A systematic review of cohort studies found that laypeople can be adequately trained to properly administer naloxone, and that bystanders will intervene in suspected overdoses to provide naloxone and call EMS for transport to hospital for definitive medical treatment [9]. Also, a systematic review of observational studies found that community distribution of naloxone kits was consistently associated with decreased mortality from opioid overdose [10].

Nevertheless, effectiveness alone is often insufficient to justify publicly funding an intervention or drug in a public healthcare system. Governments want to know that an intervention is not only effective, but also worthwhile in comparison to the costs of that intervention, and often in comparison to other alternative interventions in which they could invest. It is crucial to explicitly consider the relative consequences of the alternatives to take-home naloxone and compare them with their relative costs. Though multiple systematic reviews, each including over a dozen studies, have established that naloxone is effective in reducing opioid-related mortality, the economic value of these programs is not as clearly established [11, 12, 13]. The Canadian Agency for Drugs and Technologies in Health (CADTH) performed a review and appraisal of community distribution of naloxone in 2014, but did not identify any economic evaluations at that time [11]. CADTH updated the review in 2019, but only included one cost-effectiveness study due to their specification that the comparator must be EMS or hospital administration of naloxone [12]. Mueller *et al*. (2015) similarly conducted a review of community distribution of naloxone in 2015, including cost-effectiveness of such an initiative. This review had broader inclusion criteria than CADTH, but still only two studies were identified at that time. Both Mueller *et al*. (2015) and Chao and Loshak (2019) focused mainly on effectiveness, but concluded that community distribution of naloxone was cost-effective based on the limited studies included in their reviews.

This paper synthesizes results from economic evaluations (cost-effectiveness analysis (CEA), cost-utility analysis (CUA), or cost-benefit analysis (CBA)) to determine whether community distribution of naloxone for lay administration is cost-effective. The studies are summarized and critically appraised to assess quality. Given the broader range of types of economic evaluations, specifics of the intervention, and choice of comparators, the results

of the studies are not aggregated. The applicability of findings to multiple settings and contexts is discussed. Particular attention is given to the factors that most impact cost-effectiveness.

Methods

Search Strategy

The search strategy was performed on OVID MedLine, OVID Embase, and EconLit databases on August 10, 2020 using search criteria detailed in Appendix A. Search criteria were based on two themes: (1) papers involving naloxone or narcan, and (2) any form of economic evaluation. Search criteria were first developed for the MedLine search, and were then adapted for use in other databases. A targeted grey literature search was conducted by searching for the term "naloxone" on the websites of governmental agencies devoted to evaluations of drugs and prominent mental health organizations within the USA, as well as those of the USA's *Organization for Economic Co-operation and Development* comparator countries. The search strategy was developed in collaboration with a McMaster University Health Sciences Librarian.

Inclusion and Exclusion Criteria

Inclusion criteria required articles to contain an economic evaluation inclusive to CEA, CUA, or CBA, and include community distribution of naloxone as a component of assessment. These three types of analysis primarily differ in the way that the outcome is measured. CEAs are measured in health units such as life-years gained, CUAs are measured in health-related preferences such as quality adjusted life years (QALY), and CBAs are measured in dollars. Additionally, they answer different efficiency questions, CEAs and CUAs answers whether the intervention is worthwhile and the lowest-cost method of achieving it (i.e. cost-effectiveness efficiency), and CBAs answer whether there would be a net benefit to society (i.e. allocative efficiency). As well, both targeted distribution to at-risk groups within the community and expanded distribution to all laypeople were included. Both trial- and model-based analyses were included. Conversely, articles were excluded if: 1) Economic evaluation was not performed (e.g., cost listings without economic evaluation); 2) The primary intervention being studied was in-hospital or EMS naloxone distribution; or, 3) The primary intervention being studied was a non-naloxone drug for the treatment of opioid use disorder or alcohol use disorder (e.g., buprenorphine-naloxone, naltrexone, and

nalmefene). As well, systematic reviews were excluded from data extraction, but were used to identify any further articles that met inclusion criteria.

Review of Articles

Two investigators independently appraised titles and abstracts for relevance and inclusion and exclusion criteria satisfaction. Disagreements were discussed and resolved by consensus of three investigators. Identified systematic reviews were assessed by one reviewer to further identify relevant articles, however none were found.

Data Extraction and Critical Appraisal

Data extraction and quality assessment were conducted by two investigators. Data extraction sheets, attached in Appendix B, were developed following the BMJ Guidelines for Submissions of Economic Evaluations to ensure study quality and assess risk of bias [14]. This tool was chosen due to its ability to assess both trial- and model-based economic evaluations, and its comprehensive list of assessment items [15]. Additionally, Drummond *et al*. created an updated tool in 2015, however as it was deemed to be comparable, the previous version was utilized [16]. Extraction focused on identifying the research question, economic importance, intervention, comparator, primary outcome, form of economic evaluation, model details (currency, inflation and discounting), sensitivity analysis, outcome of economic evaluation, and results (incremental cost-effectiveness ratio [ICER], incremental cost-utility ratio [ICUR], and/or incremental cost-benefit ratio [ICBR]). For comparability purposes, all currency was converted to 2020 United States dollars (USD) [17, 18, 19]. Unless otherwise noted, all dollars reported hereafter represent 2020 USD. Level of quality was subjectively assigned as low, moderate, or high, based on the impact of the missing or unclear elements identified by the guidelines on the strength of the conclusions.

Results

Summary of Identified Studies

The search strategy identified a total of 977 articles to review across the three databases (see PRISMA diagram in Figure 1). No additional studies were found through the grey literature search. Of the 977 articles, 959 were excluded because they failed to meet the inclusion criteria or met the exclusion criteria. Eighteen studies remained for full-text review. Six narrative reviews were identified and excluded, as they did not present or assess

economic evaluations or considerations. One article was excluded because it provided a cost listing for a take-home naloxone program, without economic evaluation. One article was excluded as it was a minor correction to another article already included, and the correction did not change the findings of the original article. One article was excluded because it was an abstract from a conference presentation of a separate study of which no further information could be found, even after the corresponding author was contacted. A total of nine studies were included in the review. A listing of all articles that were assessed in the full-text review can be found in Appendix C, with an explanation for their exclusion.

The included studies consisted of one CEA, eight CUAs, and one CBA (10 analyses from nine studies - one study conducted both a CBA and a CEA). Studies covered a variety of settings, including the USA (n=5), Canada (n=1), Russia (n=1), Scotland (n=1), and the UK (n=1), where five were focused at the national level and four on specific cities. Articles were published from 2013 to 2020, and all declared funding except for two, where there were no conflicts of interest to disclose. All studies included community distribution of naloxone for lay administration as a component of their intervention, though some articles differed on specific populations targeted. Seven studies looked at users or hypothetical users, one study looked at non-users, and one study looked at counties with at least five opioid overdose deaths each year. Eight studies used the comparator of no distribution, where one used an additional comparator of pre-exposure prophylaxis, and one study compared a combination of distribution to laypeople, police and fire, and EMS. All studies used a Markov and/or decision-analytic model, apart from one study which was trial-based. Five studies used a societal perspective, three studies used a health care perspective, and one study used both a societal and a health care perspective. Six studies used a lifetime time horizon, one study used a 20-year time horizon, and two studies did not specify a time horizon. After analysis, all studies found positive benefits related to health, where community distribution of naloxone was able to either prevent or reduce the amount of overdose-related deaths.

A summary of the results from the data extraction are found in Table 1.

Cost-Utility Analyses

The study by Townsend *et al.* (2020) observed that community distribution of naloxone was only worthwhile if the kits cost less than $2,200 (USD 2017; $2,335 USD 2020), and was the most worthwhile when community distribution was combined with high EMS distribution, and low police officer and firefighter

distribution; returning an ICUR of $12,880 to $15,950 (USD 2017; $13,669 to $16,927 USD 2020) per QALY gained [20]. In a sensitivity analysis, they considered ranges for the price of naloxone,, the percentage of people that intervened in overdose, a hypothetical moral hazard, and the rates of distribution [20]. Although the rate of distribution had the largest impact, none of the variables changed the conclusion [20]. This study did not report justification for the form of economic evaluation, the details of the method of synthesis or meta-analysis of estimates, or the quantities of resources separately reported from their unit cost. This study was classified as high quality.

The study by Langham *et al.* (2018) found that the intervention increased overdoses by 2.7%, reduced overdose death by 6.6% and increased lifetime QALYs by 0.164, with an ICUR of £899 (GBP 2016; $1,334 USD 2020) per QALY gained [21]. They determined naloxone distribution to be worthwhile, assuming a £20,000 (GBP 2016; $29,672 USD 2020) willingness-to-pay threshold [21]. In their sensitivity analysis, they considered ranges for the price of naloxone, additional societal costs, rates of distribution, and witness to overdose [21]. However, none of the variables had a substantive impact and thus, did not change the conclusion [21]. This study clearly reported all elements with the exception of the rationale for the comparison intervention, justification for the form of economic evaluation, the quantities of resources or unit cost, or justification for the variables in the sensitivity analysis. Overall, this study was classified as high quality.

In the study by Cipriano and Zaric (2018) community distribution of naloxone was only worthwhile if the frequency of overdose was more than once every two years. An ICUR of <$50,000 (CAD 2017; <$40,295 USD 2020) per QALY gained was returned at a level of 2.7 overdose per year, and $100,000 (CAD 2017; $80,591 USD 2020) per QALY gained for 1.3 overdose per year [22]. Results were largely sensitive to the number of overdoses per year while also considering intensity of substance use disorder, mortality rate, and number of overdoses per year [22]. This study was classified as high quality with only the details of statistical test and confidence intervals for scholastic data, justification for the form of economic evaluation, and the rationale for the comparator not reported.

After running the model for 20 years, the intervention in the study by Uyei *et al*. (2017) reduced overdose deaths by 6% but saw an increase in HIV deaths [23]. They concluded that naloxone distribution was worthwhile, with an ICUR of $323 (USD 2015; $354 USD 2020) per QALY gained, and recommended that the program be funded [23]. In their sensitivity analysis, they considered ranges for the price of naloxone, survival rates, and the percentage of people that intervene in overdose [23]. No variables had a substantial impact, therefore did not change

the conclusion [23]. This study was determined to be high quality, missing the elements of a justification for the form of economic evaluation and quantities of resources reported separately from their unit costs.

The study by Coffin and Sullivan (2013a) found that the intervention prevented 6.5% of overdose deaths, with an ICUR of $14,000 (USD 2012; $20,020 USD 2020) per QALY gained [24]. All in all, naloxone distribution was worthwhile, with funding being recommended [24]. In their sensitivity analysis, they considered ranges for the price of naloxone, rates of bystander response, and justice system rates [24]. Bystander response rate made the largest impact on the ICUR, but did not change the conclusion [24]. This study was found to be of high quality with elements of study viewpoints and justification, rationale for comparator, justification of form of economic evaluation, quantities of resources reported separately from unit costs, and justification of discount rate not included.

The study by Coffin and Sullivan (2013b) built off their previous research by using the same model and variables in the sensitivity analysis. They found that the intervention reduced overdose deaths by 13.4% in the first five years, and 7.6% over a lifetime, with an ICUR of $94 (USD 2010; $112 USD 2020) per QALY gained [25]. Again, they found that naloxone distribution was worthwhile and recommended funding the program [25]. In the sensitivity analysis, bystander response rate again made the largest impact on the ICUR, however did not change the conclusion [25]. This study was found to be of high quality, only missing elements of study viewpoints and justification, rationale for choosing comparator, justification of form of economic evaluation, and quantities of resources reported separately from unit costs.

Results of the study by Acharya *et al*. (2020) showed that intervention modestly reduced overdose deaths, with an ICUR of $56,699 to $76,929 (USD 2018; $58,738 to $79,695 USD 2020) per QALY gained [26]. Thus, naloxone distribution was worthwhile, assuming a $100,000 (USD 2018; $103,596 USD 2020) willingness-to-pay threshold [26]. In the sensitivity analysis, the researchers considered the price of naloxone, naloxone effectiveness, the proportion of overdoses witnessed, the probability of EMS intervention, overdose risk based on specific opioid, and overdose survival rates [26][26]. Naloxone effectiveness and the proportion of overdoses witnessed had the largest impact on biannual distribution but did not change the conclusion [26]. This study quality was assessed as moderate due to the lack of clear reporting of the viewpoints of the analysis, the rationale for choosing the alternative program or intervention, the justification of the form of economic evaluation, the quantities of resources, and price data.

The study by Bird *et al.* (2015) resulted in a 3.5% decrease in overdose deaths, and had an ICUR of £560 to £16,900 (GBP 2015; $1,079 to $25,073 USD 2020) per QALY gained [27]. Thus, naloxone distribution was worthwhile, where continued funding was recommended [27]. This study performed a sensitivity analysis on averted overdose numbers [27]. This study did not report the economic importance of the research question, justification for the form of economic evaluation, details of currency price adjustment for inflation or currency conversion, time horizon of costs and benefits, justification of the discount rate, incremental analysis, the approach to sensitivity analysis, or justification of variables chosen for sensitivity analysis were not clearly reported. These missing elements resulted in a moderate quality rating.

Cost-Benefit and Cost-Effectiveness Study

In their study, Naumann *et al.* (2019) deemed community distribution of naloxone to be a good investment. They found that over the course of three years, 352 overdose deaths were prevented, leading to an ICBR of $1:$2,742 (USD 2019; $1:$2,790 USD 2020) [28]. This study based the sensitivity analysis solely on the price of naloxone [28]. They also performed a CEA and deemed community distribution of naloxone to be cost-effective [28]. The ICER was $1,605 (USD 2019; $1,633 USD 2020) per death avoided from opioid overdose [28]. This study was found to be of low quality as the rationale for choosing the comparison intervention, justification for the form of economic evaluation, details of the method of synthesis or meta-analysis of estimates, details of currency price adjustments for inflation or currency conversion, the choice of model used and its key parameters, the time horizon of costs and benefits, a discount rate, an explanation for not discounting costs, or the approach to sensitivity analysis were not clearly reported.

Discussion

We conducted a systematic review of economic analyses of community distribution of naloxone in order to better understand the economic impact of these programs. In total, nine articles were found to meet the inclusion criteria, including one CEA, eight CUAs, and one CBA. All economic evaluations identified by this review concluded that community distribution of naloxone was a worthwhile investment across all settings and populations considering the set willingness-to-pay threshold within each study. CUAs, in particular, found ICURs ranging from $111 to $58,738 USD (2020) per QALY gained, with only one study finding an ICUR above a $60,000 USD willingness-to-pay threshold, taking into account sensitivity analyses.

Application of Findings

Importantly, the study that was based on a trial [27] re-affirmed previous findings that community distribution of naloxone for lay administration was effective in reducing deaths due to opioid overdose. In terms of quality, there was a wide range across the studies, as assessed by the BMJ Guidelines for Submission of Economic Evaluations; six were deemed high quality, two were moderate quality and one was deemed to be of low quality. Many articles were missing key information to understand the assumptions behind their models or analysis of trials. As well, a large range of ICUR was returned across all analyses. Nevertheless, consistency in results across studies in varying contexts and methodologies presents strong evidence towards concluding that community naloxone distribution was a cost-effective approach to overdose prevention and the opioid crisis.

The majority of studies were from the USA, with single studies from Canada, Russia, Scotland and the UK also included. Populations across and within these settings differ greatly in many factors, such as: demographics, health care accessibility, drug use behaviour, and cultural contexts. Although all studies indicated that community naloxone distribution was cost-effective, a more representative sample of global programs or a more comprehensive localized set of data can increase external validity. In particular, the applicability of these findings to low-income settings is less certain, Several studies utilized modelling to run economic evaluations. Although reliable region specific sources of data contributed to building the models of the need for, use of, and impact of naloxone distribution, such models do not always catch the contextual and environmental nuances of a given environment. A greater proportion of primary data collection and evaluation of implemented programs will strengthen the quality of data used and potential conclusions.

One of the most important limitations in many of the studies was narrow sensitivity analyses. For example, the study by Naumann *et al.* (2019) considered only the price of naloxone within their sensitivity analysis. Yet, in the studies that considered a greater number of variables, the factors that made the largest impact on the ICUR were the rates of opioid overdose, the willingness of bystanders to intervene in witnessed overdoses, and the percentage of the target population that could be reached with the intervention. Thus, in considering whether or not to implement a program for community distribution of naloxone, these factors should be assessed. If the rate of opioid overdose is low and/or bystanders are not willing to intervene; the program will likely become less cost-effective.

Another area of recurrent concern for many of the included studies was the choice of comparator. All but two studies used no intervention as the comparator. Further, half of the studies did not explicitly justify the choice of comparator. Many settings that may be considering implementing or funding community distribution of naloxone may already have some harm reduction programs in place. In this case, the funding body may wish to know specifically whether adding naloxone distribution to their current program is cost-effective. Only the study by Uyei *et al.* (2017) compared community naloxone distribution to syringe exchange programs. This study also incorporated addiction treatment and availability of pre-exposure prophylaxis for HIV into their analysis [23]. Thus, this study represents a significant contribution to understanding how varying components of a harm reduction strategy may work together, and which are most cost-effective.

Strengths and Limitations

In comparison to previous reviews, this review includes the latest findings and has the broadest inclusion criteria. In fact, a review by CADTH in 2014 did not identify any studies on this topic, which demonstrated the need for further research [11]. A later systematic review of this topic still only included 2 studies [13]. In contrast, we were able to include nine studies, as more research on this area has been done in recent years, in order to provide a greater understanding of the economic impact of community distribution of naloxone in a variety of contexts. The broad inclusion criteria has meant that direct comparison of studies was more difficult and a meta-analysis was not possible. Nevertheless, the fact that all studies concluded that community distribution of naloxone was economically worthwhile is notable. This allows readers to consider which of these studies would be most applicable and adaptable to their contexts.

In assessing our review using the AMSTAR 2 tool [29], which can be seen in Appendix D, one noticeable difference is that we did not use an a priori design. Instead, our review protocol, including our search strategy, was developed iteratively. However, our final search strategy was reviewed with a health sciences librarian. Additionally, the search was limited to English terms, which may have missed other studies, particularly within the grey literature.

Future Directions

This review demonstrates that there remains a need for further economic evaluations of community distribution of naloxone programs across broader populations and contexts. Future evaluations can be improved by

choosing a more context-relevant comparator and by expanding the variables considered in the sensitivity analyses. In particular, both programs that targeted groups at risk of experiencing or witnessing an overdose and programs that distributed naloxone to any interested layperson were included in this review, where one of the studies compared those two distribution strategies. Thus, this review demonstrates the importance of incremental analysis of varying strategies in future evaluations, in order to best inform policy and program decisions.

Additionally, several studies discussed briefly the costs and outcomes that may be relevant from a societal perspective, but none performed a full analysis. The inclusion of more productivity and justice system considerations would be informative. Further, the low availability of economic evaluations of community naloxone distribution programs indicate the importance of including an economic evaluation and an overall evaluation process as a component of all naloxone distribution programs from the planning and implementation stages. In order to have high-quality measures to serve as control and comparators from pre- and post-implementation stages, an economic evaluation could be incorporated in the implementation of naloxone programs. An increased sample size of evaluations of community naloxone distribution programs would aid in gathering a robust base of data across contexts and inform future implementation of programs. Lastly, all studies were from high- or middle-income countries, thus results are not generalizable to low-income countries, where health care systems are not financially stable. Further research into naloxone availability and distribution across assorted settings is recommended.

Conclusion

In sum, all studies found community distribution of naloxone to be cost-effective. Findings from this review can help inform and advocate for further implementation of naloxone distribution programs in areas where opioid overdose is a prominent concern. Though safe injection sites and EMS are often equipped with naloxone, people who use opioids may prefer to use drugs in isolation or among other users. The findings of this review are relevant to policymakers who implement guidelines and programs for overdose response. The findings from this review demonstrate that in many settings, community distribution of naloxone for lay administration is likely a worthwhile investment. Based on these findings, countries that are currently providing publicly-funded take-home naloxone programs should continue to do so, and perhaps explore how those programs may be expanded. Countries and jurisdictions that are not yet funding community distribution of naloxone should consider similar programs

based on an assessment of their rate of opioid overdose, willingness of bystanders to intervene in an overdose, and ability to reach the target population.

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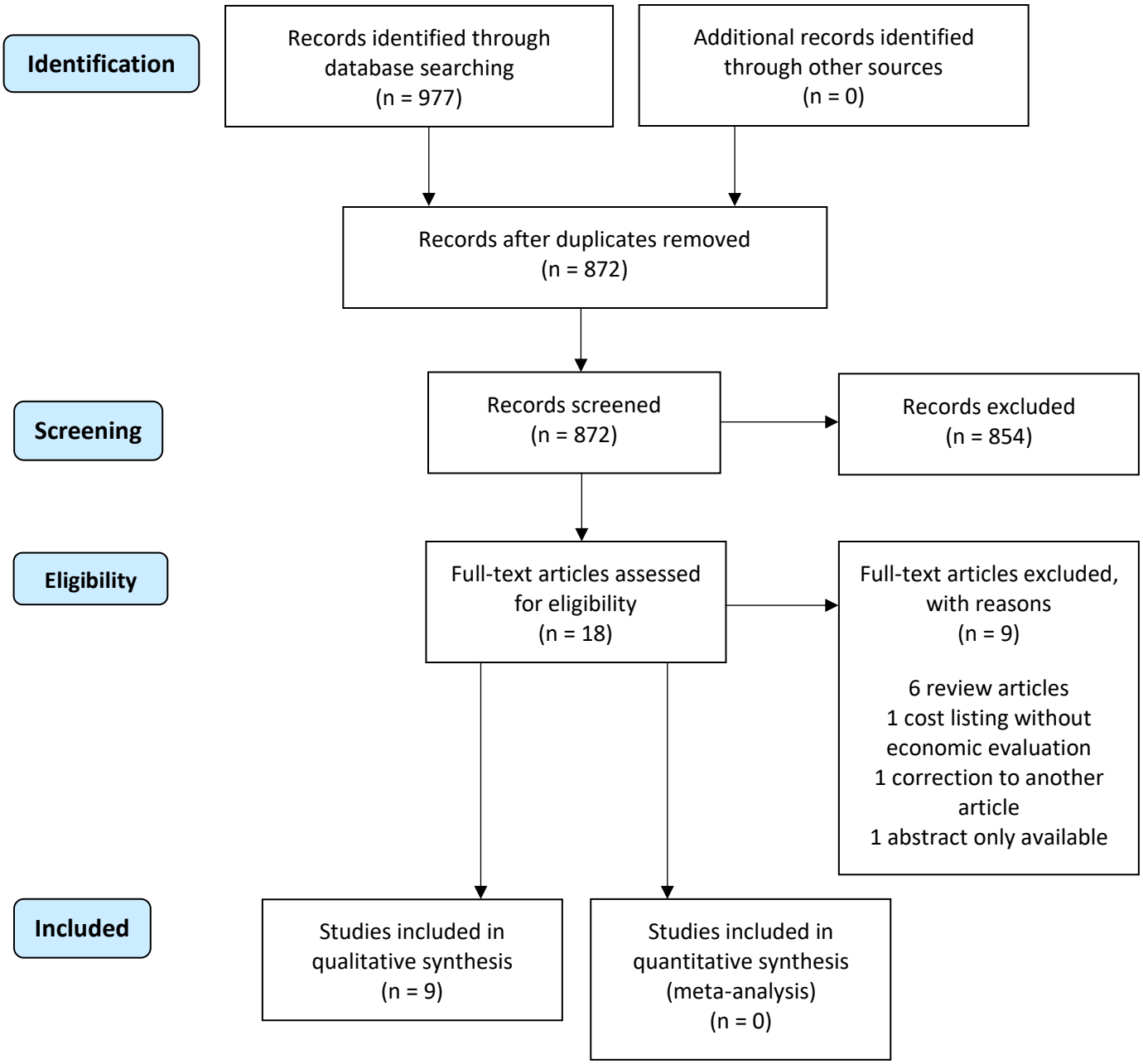

Figure 1. PRISMA diagram [30] outlining review of articles from database search. 197 articles were returned from MEDLINE, 780 from Embase, and zero from EconLit.

Table 1. Summary of included studies [20, 21, 22, 23, 24, 25, 26, 27, 28]

Study	Setting	Population	Intervention	Comparator	Model	Time Horizon of Cost	Effects	ICBR/ICUR/ICER	Sensitivity Analysis	Conclusion	Quality	Limitations
Townsend et al (2020)	United States	Hypothetical individuals with OUD who enter the model at 35	Community distribution of naloxone to community, fire/policy, and EMS	Eight strategies that encompass all combinations of low and high distribution to laypeople, police and fire, and EMS	Decision-analytic	Lifetime	Intervention reduced overdose deaths	ICUR: $12,880 - $15,950/ QALY	Considered: - Price of naloxone - Rates of distribution - Percentage of people that intervene in overdose - Hypothetical moral hazard Rate of distribution made the largest impact; did not change conclusion	Naloxone distribution is a good investment and worthwhile, assuming <$2,200 per kit	High	Did not report: - Justification for form of economic evaluation, - Details of synthesis of estimates - Quantities of resources
Langham et al (2018)	United Kingdom	Adults (≥22 years) at risk of heroin overdose	Community distribution of naloxone for lay administration	No distribution	Markov model with an integrated decision tree	Lifetime (default value set to 64 years)	Intervention increased overdoses by 2.7%, reduced overdose deaths by 6.6%, and increased lifetime QALYs by 0.164	ICUR: £899.00/ QALY	Considered: - Price of naloxone - Additional societal costs - Rates of distribution - Witness to overdose No substantive impact; did not change conclusion	Naloxone distribution is worthwhile, assuming a $20,000 willingness-to-pay threshold	High	Did not report: - Rationale for comparison intervention - Justification for form of economic evaluation - Quantities of resources - Justification for variables chosen for sensitivity analysis
Cipriano & Zaric (2018)	Toronto, Canada	High-school students	Community distribution of naloxone in Toronto District School Board high schools	Other treatment and harm reduction plans in Toronto (status quo)	Decision-analytic model	Lifetime	Intervention reduced overdose deaths by 40%	ICUR: <$50,000/ QALY if 2.7 overdose/yr; $100,000/QALY if 1.3 overdose/yr	Considered: - # of overdoses per year - Intensity of substance use disorder - Mortality rate Number of overdoses per year had the	Naloxone distribution is worthwhile, assuming the frequency of overdose is more than 2.7 overdoses per year	High	Did not report: - Details of statistical test - Justification for form of economic evaluation - Rationale for comparison intervention

									largest impact, with naloxone no longer a worthwhile investment under 1.3 overdoses per year			
Uyei et al (2017)	Connecticut, United States	HIV-negative people who inject drugs and were not on PrEP	Community distribution of naloxone for lay administration	No additional intervention, naloxone distribution plus linkage to addiction treatment, naloxone distribution plus PrEP, naloxone distribution plus linkage to addiction treatment and PrEP	Decision-analytic Markov	20 years	Intervention reduced overdose deaths by 6%, but increased HIV deaths	ICUR: $323/QALY	Considered: - Price of naloxone - Survival rates - Percentage of people that intervene in overdose No substantial impact; did not change conclusion	Naloxone distribution is worthwhile, recommend funding	High	Did not report: - Justification for form of economic evaluation - Quantities of resources
Coffin. & Sullivan (2013a)	United States	Hypothetical 21-year old novice U.S. heroin users and more experienced users	Community distribution of naloxone for lay administration to those at high risk of opioid overdose	No distribution	Integrated Markov and decision analytic	Lifetime	Intervention prevented 6.5% of overdose deaths	ICUR: $14,000/ QALY	Considered: - Price of naloxone - Rate of bystander response - Justice system rates Bystander response rate made largest impact on ICER; did not change conclusion	Naloxone distribution is worthwhile; recommend funding	High	Did not report: - Study viewpoints - Rationale for comparison intervention - Justification for form of economic evaluation - Quantities of resources - Justification of discount rate
Coffin & Sullivan (2013b)	Russia	Heroin users, starting at the age of 18	Community distribution of naloxone for lay administration to those at high risk of	No distribution	Integrated Markov and decision analytic	Lifetime	Intervention reduced overdose deaths by 13.4% in the first five years and	ICUR: $94/QALY	Considered: - Price of naloxone - Rate of bystander response - Justice system rates	Naloxone distribution is worthwhile; recommend funding	High	Did not report: - Study viewpoints - Rationale for comparison intervention - Justification for form of

			opioid overdose				7.6% over a lifetime		Bystander response rate made largest impact on ICER; did not change conclusion			economic evaluation - Quantities of resources
Acharya et al (2020)	United States	High risk prescription opioid users	Naloxone distribution to all high-risk RxO users either one-time or biannually	Baseline naloxone distribution strategy based on existing naloxone dispensing rates	Markov model with monthly cycle length and attached decision tree	Lifetime	Intervention modestly reduced overdose deaths	ICUR: $56,699-$76,929/QALY	Considered: - Price of Naloxone - Naloxone effectiveness - Proportion of overdoses witnessed - Probability of EMS intervention - Overdose survival rates Naloxone effectiveness and proportion of overdoses witnessed had the largest impact on biannual distribution; did not change conclusion	Naloxone distribution is worthwhile, assuming a $100,000 willingness-to-pay threshold	Moderate	Did not report: - Study viewpoints - Rationale for comparison intervention - Justification for form of economic evaluation, - Quantities of resources
Bird et al (2015)	Scotland	Those at highest risk of ORD, who might be expected to benefit the most from NNP	Community distribution of naloxone to individuals at risk of opioid overdose, following prison release	Same group, prior to intervention	N/A	N/A	Intervention prevented 42 overdose deaths (3.5% decrease)	ICUR: £560-£16,900/ QALY	Considered: - Averted overdose numbers No substantive impact; did not change conclusion	Naloxone distribution is worthwhile; recommend continued funding	Moderate	Did not report: - Economic importance of the research question - Justification for form of economic evaluation - Price adjustment for inflation or currency conversion

												- Time horizon of costs and benefits - Justification of the discount rate - Incremental analysis - Approach to sensitivity analysis - Justification for variables chosen for sensitivity analysis
Naumann et al (2019)	North Carolina, United States	North Carolina counties with at least five opioid overdose deaths each year in the period immediately preceding implementation	Community distribution of naloxone for lay administration	No distribution	Trial-based	N/A	Intervention prevented 352 overdoses over 3 years	ICBR: $2742 benefit/dollar spent ICER: $1605/death avoided	Considered: - Price of naloxone No substantive impact; did not change conclusion	Naloxone is cost-effective; recommend funding	Low	Did not report: - Justification of comparison intervention - Justification for form of economic evaluation - Details of synthesis of estimates - Price adjustment for inflation or currency conversion - Model details - Time horizon of costs and benefits - Discount rate - Approach to sensitivity analysis

Appendix A: Search strategy, written as in OVID

1. exp Naloxone/ or narcan.mp. or naloxone.mp. or Evzio.mp.
2. exp “costs and cost analysis”/ or cost effectiveness.mp. or cost utility.mp. or cost benefit.mp. or economic analysis.mp. or economic evaluation.mp. or cost.mp.
3. 1 and 2

Appendix B.

Study Details		
Title	Cost-effectiveness analysis of alternative naloxone distribution strategies: First responder and lay distribution in the United States	
Author	Townsend T, Blostein F, Doan T, Madson-Olson S, Galecki P, Hutton DW	
Year of publication	2020	
Publication type	International Journal of Drug Policy	
Funding	None declared	
Setting	United States	
Type of intervention	8 different naloxone distribution strategies (different mixes of EMS, fire, police, or laypeople)	
Study design		
1. The research question is stated	Yes	"To evaluate the cost-effectiveness of increased naloxone distribution to laypeople, police and firefighters, emergency medical services personnel, and combinations of these groups."
2. The economic importance of the research question is stated	Yes	"Prior studies have not examined whether the cost-effectiveness of naloxone distribution varies by the group targeted."
3. The viewpoint(s) of the analysis are clearly stated and justified	Yes	"With the rapid evolution of the opioid crisis, the cost-effectiveness of naloxone distribution to all target groups may be shifting. Given these changing circumstances, the variation in advantages and disadvantages across strategies, the scarcity of resources available to address the crisis, and the rising cost of naloxone, a cost-effectiveness analysis of each distribution, both independently and in combination, is needed."
4. The rationale for choosing the alternative programs or interventions compared is stated	Yes	There are potential advantages and disadvantages of distribution to each of these groups.
5. The alternatives being compared are clearly described	Yes	Eight strategies that encompass all combinations of low and high distribution to laypeople, police and fire, and EMS: low levels of distribution to all groups, high distribution to all groups, and all other combinations of high and low distribution to the three groups.
6. The form of economic evaluation used is stated	Yes	Stated as cost-effectiveness analysis but upon further review is more appropriately classified as a cost-utility analysis.
7. The choice of form of economic evaluation is justified in relation to the questions being addressed	No	
Data collection		
8. The source(s) of effectiveness estimates are stated	Yes	Nationally representative data and synthesis of one-off studies.
9. Details of the design and results of effectiveness study are given (if based on a single study)	Not Appropriate	

10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	No	
11. The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	Strategy ranking, determined by net monetary benefit; cost-effectiveness, expressed in incremental costs per QALY gained.
12. Methods to value health states and other benefits are stated	Yes	Number of fatal overdoses.
13. Details of the subject from whom valuations were obtained are given	Yes	Hypothetical individuals with opioid use disorder who enter the model at 35 years of age.
14. Productivity changes (if included) are reported separately	Yes	In Table 3.
15. The relevance of productivity changes to the study question is discussed	Yes	"The increased overall costs of naloxone distribution, training, and the societal health and criminal justice costs of individuals with OUD living longer were considerably smaller than the productivity gained by averting deaths - the productivity losses averted by keeping a person alive longer far out-weighed the societal costs of doing so (e.g., added costs to the criminal justice and health care systems)."
16. Quantities of resources are reported separately from their unit costs	No	
17. Methods for the estimation of quantities and unit costs are described	Yes	Rationales for quantities and costs are described in Appendix Table 2.
18. Currency and price data are recorded	Yes	USD currency. Price data recorded in Appendix Table 2.
19. Details of currency of price adjustments for inflation or currency conversion are given	Yes	Consumer Price Index used to adjust costs to 2017 USD.
20. Details of any model used are given	Yes	Decision-analytic model.
21. The choice of model used and the key parameters on which it is based are justified	Yes	Attached in appendix Table 2.
Analysis and interpretation of results		
22. Time horizon of costs and benefits is stated	Yes	Lifetime horizon
23. The discount rate(s) is stated	Yes	3%
24. The choice of rate(s) is justified	Yes	Referenced Sanders et al.
25. An explanation is given if costs or benefits are not discounted	Not Appropriate	
26. Details of statistical tests and confidence intervals are given for stochastic data	Yes	"In a probabilistic sensitivity analysis, we simultaneously varied all parameters in 10,000 iterations of a Monte Carlo simulation"

27. The approach to sensitivity analysis is given	Yes	"We conducted a tornado analysis to examine the effects of varying each parameter individually on model outcomes. For a set of particularly uncertain or potentially influential parameters, we conducted threshold analyses to examine whether any value of the parameter would change the model's conclusion."
28. The choice of variables for sensitivity analysis is justified	Yes	"Mortality parameters enabled examination of the impact of increasing use of highly potent fentanyl-like products on cost-effectiveness, as this shift may result in greater mortality at traditional naloxone doses, and/or entail higher costs when multiple doses are required. Rising naloxone prices, the effectiveness of subsequent doses of naloxone when multiple doses are administered, and hypothetical moral hazard."
29. The ranges over which the variables are varied is stated	Yes	Attached in appendix Table 2.
30. Relevant alternatives are compared	Yes	Attached in appendix Table 2.
31. Incremental analysis is reported	Yes	Low laypeople, low fire police, high EMS = $12,000/QALY gained; high laypeople, low fire police, high EMS = $12,880/QALY gained; high laypeople, high fire police, high EMS = $15,950/QALY gained
32. Major outcomes are presented in a disaggregated as well as aggregated form	Yes	Aggregated: "High levels of distribution to all three groups maximized net monetary benefit and minimized the number of overdose deaths, while low levels of distribution to all groups entailed the reverse outcomes." Disaggregated: "every strategy was cost-saving compared its next-best alternative, and cost savings were greatest in the maximum distribution strategy because it minimized death. The second highest-ranking strategy involved high distribution to laypeople and EMS, but low distribution to police and fire. The third highest-ranking strategy involved high distribution to laypeople and police and fire, but low distribution to EMS."
33. The answer to the study question is given	Yes	"In both the societal and health sector analyses, high distribution to all three target groups minimized overdose deaths and maximized net monetary benefit, a measure that takes into account both costs and health gains."
34. Conclusions follow from the data reported	Yes	"Our findings support increased naloxone distribution to laypeople likely to experience or witness overdose, police and fire, and EMS. When resource constraints limit a community's ability to increase distribution to all three groups, distribution to laypeople and EMS should be prioritized."
35. Conclusions are accompanied by the appropriate caveats	Yes	"Incomplete and imperfect data produce uncertainty in the parameter estimates in our model. Community-level heterogeneity may necessitate different distribution approaches in different communities. We defined 'high lay distribution' such that, 75% of overdose events, either the victim or a witness would have at some point obtained naloxone. However, we are unable to estimate the proportion of target lay-people who should receive naloxone in order to ensure that, at 75% of overdose events, someone has naloxone"

Study Details		
Title	Cost-effectiveness of take-home naloxone for the prevention of overdose fatalities among heroin users in the United Kingdom	
Author	Sue Langham, Antony Wright, James Kenworthy, Richard Grieve, William C.N. Dunlop	
Year of publication	2018	
Publication type	Value in Health	
Funding	Mundi-pharma International Ltd.	
Setting	United Kingdom	
Type of intervention	IM naloxone distribution to non-medical adults at risk of heroin overdose	
Study design		
1. The research question is stated	Yes	"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)."
2. The economic importance of the research question is stated	Yes	"There is a need for an economic assessment of take-time naloxone in the European setting from a public health perspective."
3. The viewpoint(s) of the analysis are clearly stated and justified	Yes	The United Kingdom was chosen because of its high and increasing heroin-related mortality rate, the introduction of new government regulations in 2015 making naloxone exempt from prescription-only medicine requirements, and policy imperatives aimed at widening use.
4. The rationale for choosing the alternative programs or interventions compared is stated	No	
5. The alternatives being compared are clearly described	Yes	No naloxone distribution.
6. The form of economic evaluation used is stated	Yes	Stated as cost-effectiveness analysis but upon further review is more appropriately classified as a cost-utility analysis.
7. The choice of form of economic evaluation is justified in relation to the questions being addressed	No	
Data collection		
8. The source(s) of effectiveness estimates are stated	Yes	Epidemiological evidence derived from North America, Australia, and Europe, using UK-specific input parameters when available. It was assumed that these estimates were relevant for the United Kingdom.
9. Details of the design and results of effectiveness study are given (if based on a single study)	Not Appropriate	
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Yes	"The estimates were 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 principle risk factor for overdose is previous overdose, therefore risk increases with each overdose."

11. The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	Incremental cost per QALY gained.
12. Methods to value health states and other benefits are stated	Yes	Number of overdoses and overdose deaths.
13. Details of the subject from whom valuations were obtained are given	Yes	Adults (≥22 years) at risk of heroin overdose.
14. Productivity changes (if included) are reported separately	Not Appropriate	
15. The relevance of productivity changes to the study question is discussed	Not Appropriate	
16. Quantities of resources are reported separately from their unit costs	No	
17. Methods for the estimation of quantities and unit costs are described	Yes	"Naloxone costs were based on the British National Formulary list price for Prenoxad®, Naloxone costs were incurred after each overdose when naloxone was administered biannually among active heroin users to account for naloxone going out of date. Distribution costs were assumed per naloxone prescription, on the basis of those estimated by Coffin and Sullivan. Training costs were estimated on the basis of a per-care contact with the drug service 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."
18. Currency and price data are recorded	Yes	GBP currency. Naloxone = £15.30 per unit; distribution = £8.50; training costs for users, family, and friends = £124 per kit for first time administration; ambulance = £233; accident and emergency visit = £278.
19. Details of currency of price adjustments for inflation or currency conversion are given	Yes	Costs adjusted to 2016 GDP
20. Details of any model used are given	Yes	Markov model with an integrated decision tree.
21. The choice of model used and the key parameters on which it is based are justified	Yes	"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. The replicated model was adapted to the UK health care system, which included structure and content changes. Key parameters are presented in Table 1, with detailed rationale for parameter selection in Appendix Table 1."
Analysis and interpretation of results		
22. Time horizon of costs and benefits is stated	Yes	Lifetime horizon (default value set at 64 years)
23. The discount rate(s) is stated	Yes	3.5%
24. The choice of rate(s) is justified	Yes	In accordance with UK guidance

25. An explanation is given if costs or benefits are not discounted	Not Appropriate	
26. Details of statistical tests and confidence intervals are given for stochastic data	Yes	"Probabilistic sensitivity analysis was 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"
27. The approach to sensitivity analysis is given	Yes	Deterministic and probabilistic sensitivity analyses
28. The choice of variables for sensitivity analysis is justified	Not Clear	
29. The ranges over which the variables are varied is stated	Yes	In Table 1.
30. Relevant alternatives are compared	Yes	In Table 2.
31. Incremental analysis is reported	Yes	£899/QALY gained
32. Major outcomes are presented in a disaggregated as well as aggregated form	Yes	Aggregated: "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." Disaggregated: "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. 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%, 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."
33. The answer to the study question is given	Yes	"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."
34. Conclusions follow from the data reported	Yes	"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 £20,000 willingness-to-pay threshold set by UK decision makers."

35. Conclusions are accompanied by the appropriate caveats	Yes	"The model uses data based on epidemiologic 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. 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. 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 so vary significantly between risk groups. The model base case does not include societal costs."

Study Details		
Title	Cost-effectiveness of naloxone kits in secondary schools	
Author	Lauren E. Cipriano & Gregory S. Zaric	
Year of publication	2018	
Publication type	Drug and Alcohol Dependence	
Funding	The David G. Burgoyne Faculty Fellowship and the J. Allyn H. Mingay Chair in Management Science	
Setting	High schools in the Toronto District School Board	
Type of intervention	Distribution of naloxone kits within the Toronto District Schools Board	
Study design		
1. The research question is stated	Yes	"To use the principles of cost-effectiveness analysis to understand the conditions under which a school-based naloxone program is a cost-effective use of resources."
2. The economic importance of the research question is stated	Yes	"High schools present a comparably low risk setting in which the value of investing in overdose prevention is unknown."
3. The viewpoint(s) of the analysis are clearly stated and justified	Yes	"We performed our cost-effectiveness analysis not because the program is costly, but because it has unclear value."
4. The rationale for choosing the alternative programs or interventions compared is stated	No	
5. The alternatives being compared are clearly described	Yes	Other treatment and harm reduction plans in Toronto - 'status quo'
6. The form of economic evaluation used is stated	Yes	Stated as cost-effectiveness analysis but upon further review is more appropriately classified as a cost-utility analysis
7. The choice of form of economic evaluation is justified in relation to the questions being addressed	No	
Data collection		
8. The source(s) of effectiveness estimates are stated	Yes	Estimated from the medical literature and Toronto-specific sources whenever possible.

9. Details of the design and results of effectiveness study are given (if based on a single study)	Not Appropriate	
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Yes	Model documentation follows CHEERS recommendations.
11. The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	Incremental cost for QALY gained and Canadian average age-specific future costs.
12. Methods to value health states and other benefits are stated	Yes	Quality-of-life weights, estimated from Statistics Canada, the Canadian Institute for Health Information (CIHI), and the Canadian Community Health Survey, and probability of a fatal opioid overdose.
13. Details of the subject from whom valuations were obtained are given	Yes	High-school students.
14. Productivity changes (if included) are reported separately	Not Appropriate	
15. The relevance of productivity changes to the study question is discussed	Not Appropriate	
16. Quantities of resources are reported separately from their unit costs	Yes	"We assumed that Toronto Public Health would train one staff member per school, an addition 10% of staff would need to be trained per year to account for retirement and staff turnover."
17. Methods for the estimation of quantities and unit costs are described	Yes	"The cost of training was based on annual teacher salaries to reflect the opportunity cost of time devoted to training. All staff would require retraining every three years. We assumed that the initial cost of naloxone was $18,000, which was the mid-point of a published estimated cost range. We assumed start-up costs would be amortized over 10 years, consistent with the amortization duration the TDSB applies to the first-time equipping of schools. We assumed that all staff would require retraining every three years, consistent with Red Cross general first-aid certification requirements. We assume that naloxone kits would need to be replaced every two years."
18. Currency and price data are recorded	Yes	Prices reported in CAD currency. Costs reported in Table 1.
19. Details of currency of price adjustments for inflation or currency conversion are given	Yes	Costs were adjusted for inflation using the Canadian Consumer Price Index
20. Details of any model used are given	Yes	Decision-analytic model
21. The choice of model used and the key parameters on which it is based are justified	Yes	Key parameters are justified by calculation, assumption, or reference. Reported in Table 1.
Analysis and interpretation of results		
22. Time horizon of costs and benefits is stated	Yes	Lifetime

23. The discount rate(s) is stated	Yes	"Future costs and health benefits discounted at 1.5%."
24. The choice of rate(s) is justified	Yes	"Consistent with the 2017 Canadian Guidelines for the Economic Evaluation of Health Technologies"
25. An explanation is given if costs or benefits are not discounted	Not Appropriate	
26. Details of statistical tests and confidence intervals are given for stochastic data	No	
27. The approach to sensitivity analysis is given	Yes	Deterministic and probabilistic sensitivity analysis
28. The choice of variables for sensitivity analysis is justified	Yes	"Values were varied significantly, including scenario analysis in which overdose survivors have the same future costs and benefits as the general population."
29. The ranges over which the variables are varied is stated	Yes	In Table 1.
30. Relevant alternatives are compared	Yes	In Table 1.
31. Incremental analysis is reported	Yes	ICER = less than $50,000 per QALY if 2.7 overdoses/year, and ICER =$100,000 per QALY if 1.3 overdoses/year
32. Major outcomes are presented in a disaggregated as well as aggregated form	Yes	Aggregated: "When the total expected number of overdoses annually across all 112 high-school in the TDSB is more than two per year, then the program would cost less than $50,000 per QALY-gained if the program reduces opioid poisoning mortality by at least 20%. If there is less than one overdose every year, it is unlikely that a school-based naloxone program will be cost-effective unless the program reduces the mortality rate by at least 40%." Disaggregated: "If the current mortality rate from opioid overdose is higher than in our base case, then a school naloxone program appears dramatically more cost-effective. However, if current care in response to an overdose at a Toronto high school results in a mortality rate less than 5%, then it is unlikely a school naloxone program will reduce mortality enough to be cost-effective even if there are more than two overdoses per year. $50,000 per QALY-gained, the probability that a school-based naloxone program is cost-effective only exceeds 50% if there are more than two overdoses per year and the program reduces mortality by more than 27% or if there is more than one overdose per year and the program reduces mortality by more than 46%."
33. The answer to the study question is given	Yes	"A school-based naloxone program is cost-effective at a willingness-to-pay of $50,000 per QALY-gained under the following conditions: if it reduces opioid poisoning mortality by at least 40% and there is at least one overdose per year, or, if it reduces mortality by at least 20% and there are at least two overdoses per year."

34. Conclusions follow from the data reported	Yes	"If the risk of an overdose in a Toronto high school is low, then other programs aimed at improving the health and wellbeing of students may be better use of limited resources. However, our analysis demonstrates that making naloxone available in TDBS schools is likely to be cost-effective if there are at least two overdoses every year."
35. Conclusions are accompanied by the appropriate caveats	Yes	"Our analysis has limitations including many simplifications. Our model only considers whether or not naloxone in high schools is cost-effective compared to the status quo--it does not consider increasing access to drug use education, harm reduction programs targeting youths, or other social programs which may effectively prevent unsafe drug use, overdose, or overdose mortality."

Study Details		
Title	Effects of naloxone distribution alone or in combination with addiction treatment with or without pre-exposure prophylaxis for HIV prevention in people who inject drugs: A cost-effectiveness modelling study	
Author	Jennifer Uyei, David A. Fiellin, Marianne Buchelli, Ramon Rodriguez-Santana, R. Scott Braithwaite	
Year of publication	2017	
Publication type	Lancet Public Health	
Funding	State of Connecticut Department of Public Health and the National Institute of Mental Health	
Setting	Connecticut, United States	
Type of intervention	Varying combinations of naloxone distribution, PrEP and addiction treatment	
Study design		
1. The research question is stated	Yes	"To investigate the health benefit and cost-effectiveness of the current naloxone distribution programme in Connecticut, USA, as well as three novel combination strategies that combine naloxone distribution with linkage to addiction treatment with or without PrEP."
2. The economic importance of the research question is stated	Yes	"PrEP has been shown to substantially reduce the probability of HIV infection in people who inject drugs, but the value of expanding PrEP is variable, with the cost per QALY gained in the range of $50,000-350,000 and sensitive to HIV prevalence and the cost of PrEP."
3. The viewpoint(s) of the analysis are clearly stated and justified	Yes	"Mathematical models are important to inform policy and decision making because it is difficult to tell whether the advantages of combination strategies will be attenuated when considering the downstream costs associated with treating substance use disorders, HIV, hepatitis C, and their sequelae, or amplified because of the cases of HIV and hepatitis C that are averted."
4. The rationale for choosing the alternative programs or interventions compared is stated	Yes	"The comparator of no additional intervention assumed a scenario in which none of the other four strategies were added to syringe exchange, naloxone distribution plus linkage to addiction treatment and naloxone distribution plus PrEP are untested strategies (but based on established programmes)."
5. The alternatives being compared are clearly described	Yes	No additional intervention, naloxone distribution plus linkage to addiction treatment, naloxone distribution plus PrEP,

		naloxone distribution plus linkage to addiction treatment and PrEP.
6. The form of economic evaluation used is stated	Yes	Stated as cost-effectiveness analysis but upon further review is more appropriately classified as a cost-utility analysis
7. The choice of form of economic evaluation is justified in relation to the questions being addressed	No	
Data collection		
8. The source(s) of effectiveness estimates are stated	Yes	Published sources.
9. Details of the design and results of effectiveness study are given (if based on a single study)	Not Appropriate	
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Yes	Attached in Appendix.
11. The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	QALY, total costs associated with each strategy, and incremental cost-effectiveness ratio.
12. Methods to value health states and other benefits are stated	Yes	Survival probability, life expectancy, and number and percentage of overdose deaths averted.
13. Details of the subject from whom valuations were obtained are given	Yes	HIV-negative people who inject drugs and were not on PrEP.
14. Productivity changes (if included) are reported separately	Not Appropriate	
15. The relevance of productivity changes to the study question is discussed	Not Appropriate	
16. Quantities of resources are reported separately from their unit costs	No	
17. Methods for the estimation of quantities and unit costs are described	Yes	"The naloxone kit reflects the current price that the Connecticut Department of Public Health pays per dose of naloxone. Paramedic dispatch cost included basic life support response, transport to the emergency department, and an assessment. Cost of admission to hospital after an assessment. PrEP included the cost of medication, four doctor visits, and laboratory tests. HIV antiretroviral treatment was taken from a recent study. Methadone treatment is based on findings from a study."
18. Currency and price data are recorded	Yes	USD currency. $66 for 2 doses in naloxone kit; $10 distribution cost; $3,182 paramedic dispatch cost; $15,845 admission to hospital after an assessment; $11,800 annual PreP cost per person; $32,652 annual HIV antiretroviral treatment cost per patient; $4,821 annual methadone treatment cost per person

19. Details of currency of price adjustments for inflation or currency conversion are given	Yes	All costs were converted into 2015 USD
20. Details of any model used are given	Yes	Decision-analytical Markov model
21. The choice of model used and the key parameters on which it is based are justified	Yes	"Model structure and parameters were developed and selected in consultation with programme implementation and policy experts at the Connecticut Department of Public Health and discussed with other experts in the field of addiction and HIV infection who are knowledgeable about service delivery for individuals in Connecticut who use drugs."
Analysis and interpretation of results		
22. Time horizon of costs and benefits is stated	Yes	20 years
23. The discount rate(s) is stated	Yes	3% annually
24. The choice of rate(s) is justified	Yes	Referenced previous research
25. An explanation is given if costs or benefits are not discounted	Not Appropriate	
26. Details of statistical tests and confidence intervals are given for stochastic data	Yes	"Overall model uncertainty was tested in a probabilistic sensitivity analysis, in which we drew 10,000 random values from specified probability distributions for each parameter (beta distribution for rates, probabilities, and utilities, and gamma distribution for costs)."
27. The approach to sensitivity analysis is given	Yes	One-way sensitivity analysis
28. The choice of variables for sensitivity analysis is justified	Yes	"There is ample uncertainty about their precision, and they were shown to have substantial effects on the value of some strategies."
29. The ranges over which the variables are varied is stated	Yes	Attached in Appendix.
30. Relevant alternatives are compared	Yes	Attached in Appendix.
31. Incremental analysis is reported	Yes	"In the base case analysis, compared to no additional intervention, the naloxone distribution strategy yielded an ICER of $323 per QALY."

32. Major outcomes are presented in a disaggregated as well as aggregated form	Yes	Aggregated: "when all strategies were simultaneously considered, naloxone distribution plus linkage to addiction treatment was cost saving compared with no additional intervention, naloxone distribution alone, and naloxone distribution plus PrEP." Disaggregated: "at the societal willingness-to-pay threshold of $100,000 per QALY, the preferred strategy was the combination of naloxone distribution, PrEP, and linkage to addiction treatment, whereas if lower willingness-to-pay thresholds were used, the naloxone distribution plus linkage to addiction treatment was preferable. When the annual probability of relapse increased to 18-9%, naloxone distribution plus linkage to addiction treatment was no longer cost saving compared with naloxone distribution alone, although the strategy was still cost-effective even at the highest plausible value of 85%. When the likelihood of discontinuing injection drug use because of treatment declined less than 23-7%, naloxone distribution plus linkage to addiction treatment was no longer cost saving but was still cost-effective at the lowest plausible value of 8-6%. When the likelihood of entering addiction treatment for strategies that included referral to addiction treatment was less than 5-5%, the naloxone distribution plus linkage to addiction treatment strategy remained dominant and QALYs increased while costs decreased. When the scale of strategy implementation reached 90% participation, naloxone distribution plus linkage to addiction treatment was no longer cost saving compared with no additional intervention."
33. The answer to the study question is given	Yes	"Naloxone distribution through syringe service programmes provides good value for money compared with no additional intervention. The addition of linkage to addiction treatment saves money compared with either no additional intervention or naloxone distribution alone. Combining PrEP with naloxone distribution and linkage to addiction treatment resulted in the greatest health gains and was cost-effective, with an ICER of less than $100,000 per QALY gained."
34. Conclusions follow from the data reported	Yes	"Naloxone distribution through syringe service programmes is cost-effective compared with syringe distribution alone, but when combined with linkage to addiction treatment is cost saving compared with no additional services. A strategy that combines naloxone distribution, PrEP, and linkage to addiction treatment results in greater health benefits in people who inject drugs and is also cost-effective."
35. Conclusions are accompanied by the appropriate caveats	Yes	"The combined interventions considered in the analysis have yet to be tested. We used estimates for treatment enrolment, adherence, and efficacy based on studies that tested the strategy components independently. We only analysed one model of linkage to addiction treatment. We did not simulate hepatitis C infection or downstream societal effects such as crime and incarceration. We did not consider whether possession of naloxone encourages riskier heroin use"

Study Details

Title	Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal	
Author	Phillip O. Coffin & Sean D. Sullivan	
Year of publication	2013	
Publication type	Annals of Internal Medicine	
Funding	National Institute of Allergy and Infectious Disease	
Setting	United States	
Type of intervention	Naloxone distribution for lay administration	
Study design		
1. The research question is stated	Yes	"To assess the expected outcomes and cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal compared with no intervention."
2. The economic importance of the research question is stated	Yes	"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 add complexity to an economic evaluation of naloxone distribution."
3. The viewpoint(s) of the analysis are clearly stated and justified	No	
4. The rationale for choosing the alternative programs or interventions compared is stated	No	
5. The alternatives being compared are clearly described	Yes	No naloxone distribution.
6. The form of economic evaluation used is stated	Yes	Stated as cost-effectiveness analysis but upon further review is more appropriately classified as a cost-utility analysis
7. The choice of form of economic evaluation is justified in relation to the questions being addressed	No	
Data collection		
8. The source(s) of effectiveness estimates are stated	Yes	"Published literature calibrated to epidemiologic data."
9. Details of the design and results of effectiveness study are given (if based on a single study)	Not Appropriate	
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Yes	"We calibrated our model to be consistent with conservative estimates of overdose, mortality, naloxone use, and drug use cessation from epidemiologic studies by following methods guidance from Stout and colleague. See appendix table 2."
11. The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	Incremental costs per QALY gained.
12. Methods to value health states and other benefits are stated	Yes	Overdose deaths prevented.

13. Details of the subject from whom valuations were obtained are given	Yes	"Hypothetical 21-year old novice U.S. heroin user and more experienced users."
14. Productivity changes (if included) are reported separately	Not Appropriate	
15. The relevance of productivity changes to the study question is discussed	Not Appropriate	
16. Quantities of resources are reported separately from their unit costs	No	
17. Methods for the estimation of quantities and unit costs are described	Yes	Naloxone kit - biannual to account for product expiration, $12 for naloxone, $3 for other components, $10 for overhead; EMS visit - estimated from a recent cost-effectiveness evaluation; EMS transport to hospital - estimated from a recent cost-effectiveness evaluation; Emergency department care if transported - cost of emergency department care treatment and release, without hospitalization, based on the Centres for Disease Control and Prevention Web-based Injury Statistics Query and Reporting Systems; Average annual societal cost of heroin user for secondary analysis-estimate produced by the U.S. Office of National Drug Control Policy
18. Currency and price data are recorded	Yes	USD currency. Naloxone kit = $25; EMS visit = $1,790; EMS transport to hospital = $301; Emergency department care if transported = $885; Average annual societal cost of heroin user for secondary analysis = $3,368
19. Details of currency of price adjustments for inflation or currency conversion are given	Yes	"Where necessary, costs were adjusted to 2012 levels on the basis of the health care component of the Consumer Price Index."
20. Details of any model used are given	Yes	"Markov model with an integrated decision analytic model incorporating recurrent overdoses and a secondary analysis assuming heroin users impose a net cost to society."
21. The choice of model used and the key parameters on which it is based are justified	Yes	"Markov model shows health states and possible transitions between states. Upon transition to any stage of overdose, a decision analytic model processed the overdose. Detailed rationales for parameter selection in Appendix Table 1."
Analysis and interpretation of results		
22. Time horizon of costs and benefits is stated	Yes	Lifetime
23. The discount rate(s) is stated	Yes	3% annual discounting
24. The choice of rate(s) is justified	No	
25. An explanation is given if costs or benefits are not discounted	Not Appropriate	

26. Details of statistical tests and confidence intervals are given for stochastic data	Yes	"For the probabilistic analysis, we established probabilistic distributions for each parameter on the basis of the point estimate (truncated normal for proportions and utilities, beta 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."
27. The approach to sensitivity analysis is given	Yes	Deterministic: "adjusting point estimates to predetermined extremes" Probabilistic: "randomly selecting all parameters values simultaneously on the basis of predetermined distributions"
28. The choice of variables for sensitivity analysis is justified	Yes	"Variables chosen to account for uncertainty in variables related to naloxone use and effectiveness"
29. The ranges over which the variables are varied is stated	Yes	In Table 1.
30. Relevant alternatives are compared	Yes	In Table 1.
31. Incremental analysis is reported	Yes	Probabilistic analysis: $438 per QALY gained Sensitivity analysis: in a worst-case scenario the ICER was $14,000 per QALY gained
32. Major outcomes are presented in a disaggregated as well as aggregated form	Yes	Aggregated: "naloxone distribution was cost-effective in the base-case analysis and all sensitivity analyses, with incremental costs per QALY gained much less than $50,000." Disaggregated: "cost-effectiveness was similar at starting ages of 21, 31, and 41. The greater QALY gains of younger persons were matched by higher costs. When naloxone administration reduced reliance on EMS, naloxone distribution was cost saving. Cost-effectiveness was sensitive to the efficacy of lay-administered naloxone and the cost of naloxone but was insensitive to the breadth of naloxone distribution, rates of overdose and other drug-related deaths, rates of abstinence and relapse, utilities, or the cost of medical services. Naloxone was no longer cost-effective if the increase in survival was less than 0.05%, if 1 distributed kit cost more than $4,480, or if emergency care costs exceeded $1.1 million."
33. The answer to the study question is given	Yes	"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."
34. Conclusions follow from the data reported	Yes	"Naloxone distribution to heroin users is likely to reduce overdose deaths and is cost-effective, even under markedly conservative assumptions"
35. Conclusions are accompanied by the appropriate caveats	Yes	"The results may underestimate the benefits. We did not consider possible ancillary benefits of naloxone distribution. We 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. The model relied on epidemiologic data to represent an average of the many individual and environmental factors that may influence overdose rates."

Study Details		
Title	Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal in Russian cities	
Author	Phillip O. Coffin & Sean D. Sullivan	
Year of publication	2013	
Publication type	Journal of Medical Economics	
Funding	Open Society Foundation	
Setting	Russian cities	
Type of intervention	Naloxone distribution for lay administration	
Study design		
1. The research question is stated	Yes	"To evaluate the cost-effectiveness of distributing naloxone to illicit opioid users for lay overdose reversal in Russian cities."
2. The economic importance of the research question is stated	Yes	"Heroin users who survive overdose frequently suffer future overdoses and policymakers may be concerned about the overall societal cost of heroin use."
3. The viewpoint(s) of the analysis are clearly stated and justified	No	
4. The rationale for choosing the alternative programs or interventions compared is stated	No	
5. The alternatives being compared are clearly described	Yes	No naloxone distribution.
6. The form of economic evaluation used is stated	Yes	Stated as cost-effectiveness analysis but upon further review is more appropriately classified as a cost-utility analysis
7. The choice of form of economic evaluation is justified in relation to the questions being addressed	No	
Data collection		
8. The source(s) of effectiveness estimates are stated	Yes	"Published literature calibrated to parallel findings from epidemiologic studies from Russia where available and international sites if no other sources were available."
9. Details of the design and results of effectiveness study are given (if based on a single study)	Not Appropriate	
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Yes	"A detailed description of the model development follows methods guidance from Stout et al."
11. The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	Incremental costs per QALY gained, incremental net benefits
12. Methods to value health states and other benefits are stated	Yes	Overdose deaths prevented.

13. Details of the subject from whom valuations were obtained are given	Yes	Heroin users, starting at the age of 18
14. Productivity changes (if included) are reported separately	Not Appropriate	
15. The relevance of productivity changes to the study question is discussed	Not Appropriate	
16. Quantities of resources are reported separately from their unit costs	No	
17. Methods for the estimation of quantities and unit costs are described	Yes	Naloxone kit - $4 per vial of naloxone distributed, $24 per client served, two vials in each kit distributed every 2 years due to naloxone expiration after 24 months; EMS - based on costs in Moscow, $161 for ambulance, $74 for emergency room care
18. Currency and price data are recorded	Yes	USD currency. Naloxone kit = $8; EMS = $235
19. Details of currency of price adjustments for inflation or currency conversion are given	Yes	Costs were converted to US dollars, valued at 2010 levels.
20. Details of any model used are given	Yes	Markov model with an integrated decision analytic model
21. The choice of model used and the key parameters on which it is based are justified	Yes	Key parameters are justified by calculation, assumption, calibration, or reference
Analysis and interpretation of results		
22. Time horizon of costs and benefits is stated	Yes	Lifetime
23. The discount rate(s) is stated	Yes	5% per annum
24. The choice of rate(s) is justified	Yes	“In accordance with methods guidance.”
25. An explanation is given if costs or benefits are not discounted	Not Appropriate	
26. Details of statistical tests and confidence intervals are given for stochastic data	Yes	“We ran a probabilistic analysis of 10,000 Monte Carlo simulations. All model parameters were simultaneously varied across ranges 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 2.5% and 97.5% ranges of results.”
27. The approach to sensitivity analysis is given	Yes	“One-way deterministic sensitivity analysis on all variables and several analyses to evaluate specific scenarios.”
28. The choice of variables for sensitivity analysis is justified	Yes	“To evaluate cohorts of heroin users averaging 28 and 38 years old, to account for the potential cost of outreach efforts, and to address uncertainty in the utilization and effects of distributed naloxone.”
29. The ranges over which the variables are varied is stated	Yes	In Table 1.

30. Relevant alternatives are compared	Yes	In Table 1.
31. Incremental analysis is reported	Yes	Base case analysis: $71 per QALY gained Probabilistic sensitivity analysis: $94 per QALY gained Sensitivity analysis: in a worst-case scenario the ICER was $2,605 per QALY gained
32. Major outcomes are presented in a disaggregated as well as aggregated form	Yes	Aggregated: "naloxone distribution was cost-effective in the base-case and all sensitivity analyses, with an incremental cost of $71 per QALY gained." Disaggregated: "Cost-effectiveness was insensitive to the age of targeted users. Cost-effectiveness was sensitive to the efficacy of lay-administered naloxone at preventing overdose death and the cost of naloxone but was insensitive to other parameters."
33. The answer to the study question is given	Yes	"Naloxone distribution is likely to reduce opioid overdose mortality in Russia at minimal cost, even under markedly conservative assumptions. Naloxone remained cost-effective if lay administration at a witnessed overdose produced essentially any improvement in survival"
34. Conclusions follow from the data reported	Yes	"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."
35. Conclusions are accompanied by the appropriate caveats	Yes	"Baseline results may under-estimate the full benefit of naloxone. Some parameters relied on data from outside of Russia. There are no estimates of quality-of-life among heroin users in Russia. We did not incorporate possible ancillary benefits of naloxone distribution. The model assumed the existence of low-threshold services for heroin users within which naloxone distribution could be embedded. The model relied on epidemiologic data to represent an average of a host of factors that may influence overdose rates"

Study Details	
Title	Cost-Effectiveness of Intranasal Naloxone Distribution to High-Risk Prescription Opioid Users
Author	Mahip Acharya, Divyan Chopra, Corey J. Hayes, Benjamin Teeter, Bradley C. Martin
Year of publication	2020
Publication type	Value in Health
Funding	None declared
Setting	United States
Type of intervention	Naloxone distribution to high-risk RxO users
Study design	

1. The research question is stated	Yes	"To estimate the number of fatal opioid overdoses averted, the cost, the effectiveness, and the cost-effectiveness of 2 pharmacist-oriented approaches to expand naloxone distribution to high-risk prescription opioid users."
2. The economic importance of the research question is stated	Yes	"The costs and cost-effectiveness of this distribution approach have not been assessed thoroughly. These are important factors to consider when implementing such programs on a large scale given the budget constraints and uncertainty around the ultimate effectiveness of this approach to reduce opioid-related death."
3. The viewpoint(s) of the analysis are clearly stated and justified	No	
4. The rationale for choosing the alternative programs or interventions compared is stated	No	
5. The alternatives being compared are clearly described	Yes	Baseline naloxone distribution strategy based on existing naloxone dispensing rates
6. The form of economic evaluation used is stated	Yes	Stated as cost-effectiveness analysis but upon further review is more appropriately classified as a cost-utility analysis
7. The choice of form of economic evaluation is justified in relation to the questions being addressed	No	
Data collection		
8. The source(s) of effectiveness estimates are stated	Yes	Probability estimates from the published literature and analyses of claims data
9. Details of the design and results of effectiveness study are given (if based on a single study)	Not Appropriate	
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Yes	Attached in Appendix Table 1.
11. The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	Incremental costs per QALY gained, ICER
12. Methods to value health states and other benefits are stated	Yes	Number of overdose deaths
13. Details of the subject from whom valuations were obtained are given	Yes	"High risk prescription opioid users: received prescription opioids at doses greater than or equal to 90 MME per day at least once a month"
14. Productivity changes (if included) are reported separately	Not applicable	
15. The relevance of productivity changes to the study question is discussed	Not applicable	

16. Quantities of resources are reported separately from their unit costs	No	
17. Methods for the estimation of quantities and unit costs are described	Yes	"The Veterans Affairs Federal Supply Schedule was used for the intranasal naloxone cost. The cost of the naloxone kit with 2 doses, for both one-time and biannual follow-up distribution. The time required by pharmacists for naloxone distribution from Doe-Simkins et al and calculated the time cost using the average hourly wage of pharmacists in 2018. For the subsequent naloxone distribution to the same individual, we applied one-third of the time cost for the first distribution. Healthcare costs were obtained from analysis of claims data and assumed for other Markov states. EMS visit, EMS transportation, and emergency department care were taken from the Coffin and Sullivan model."
18. Currency and price data are recorded	Not Clear	USD currency. No price data recorded.
19. Details of currency of price adjustments for inflation or currency conversion are given	Yes	"Inflated all costs to 2018 US dollars using the medical component of the Consumer Price Index."
20. Details of any model used are given	Yes	"Markov model with a monthly cycle length and an attached decision tree"
21. The choice of model used and the key parameters on which it is based are justified	Yes	"Models from Coffin and Sullivan and Langham et al were adapted for this study. Key parameters stated in Table 1. The parameters for age were chosen based on the age distribution of high-risk RxO users from a U.S. collection of administrative claims data. All other parameters are either referenced, a claims analysis, or an assumption."
Analysis and interpretation of results		
22. Time horizon of costs and benefits is stated	Yes	Lifetime horizon
23. The discount rate(s) is stated	Yes	3% annually
24. The choice of rate(s) is justified	Yes	References Sanders et al.
25. An explanation is given if costs or benefits are not discounted	Not Appropriate	
26. Details of statistical tests and confidence intervals are given for stochastic data	Yes	"For the probabilistic sensitivity analysis, we ran 500 samples of 100,000 individual trials. We used beta distributions for probabilities and utilities, gamma distributions for costs, and lognormal distributions for relative risks."
27. The approach to sensitivity analysis is given	Yes	"We used deterministic, probabilistic, and threshold analyses to examine the sensitivity of the findings"
28. The choice of variables for sensitivity analysis is justified	Not clear	All input parameters mentioned in Table 1. No justification reported.
29. The ranges over which the variables are varied is stated	Yes	In Table 1.
30. Relevant alternatives are compared	Yes	In Table 1.

31. Incremental analysis is reported	Yes	"One-time distribution compared with baseline naloxone distribution = $56,699 per QALY; biannual distribution compared with one-time naloxone distribution = $84,799 per QALY; biannual distribution compared with baseline naloxone distribution = $76,929 per QALY."
32. Major outcomes are presented in a disaggregated as well as aggregated form	Yes	Aggregated: "probabilistic sensitivity analyses showed that the one-time and biannual distribution in the base case were cost-effective 29% and 50% of the time, respectively, at willingness-to-pay of $100,000 per QALY." Disaggregated: "biannual distribution was cost-effective in 32% and 52% of the iterations at $50,000 per QALY and $150,000 per QALY, respectively. One-time distribution was cost-effective in 31% and 29% of the iterations at $50,000 per QALY and $150,000 per QALY, respectively."
33. The answer to the study question is given	Yes	"A pharmacy-based distribution model of intranasal naloxone to high-risk RxO users would likely be an effective strategy for preventing a modest number of fatal opioid overdoses and would also be cost-effective."
34. Conclusions follow from the data reported	Yes	"Both one-time and biannual follow-up distribution of naloxone would likely lead to modest reductions in opioid overdose deaths, with substantially more deaths averted using the biannual distribution strategy. Both one-time and biannual distribution strategies were found to be cost-effective at a willingness-to-pay threshold of $100,000 per QALY compared with baseline distribution. The probability sensitivity analysis indicated that the biannual distribution approach would be cost-effective at $100,000 per QALY around 50% of the time."
35. Conclusions are accompanied by the appropriate caveats	Yes	"We assumed that the transitions between high-risk, low-risk, and no RxO use were unaffected by overdose. Our probabilities to model transitions between RxO states were obtained using data between 2012 and 2015. We did not account for refusal to accept naloxone by RxO users at the pharmacies or account for disposal of naloxone once distributed. We applied a higher utility for discontinuation of RxO health states on the grounds that the discontinuation was a result of improvement in underlying pathophysiology of pain. We did not consider methadone or suboxone treatment for the no opioid use after an illicit opioid use state. We did not account for the fact that fentanyl overdoses may require higher doses of naloxone. We modeled the distribution of the intranasal formulation of naloxone and did not consider a less expensive IM distribution strategy. We did not include training cost to pharmacists in our model."

Study Details	
Title	Effectiveness of Scotland's National Naloxone Programme for reducing opioid-related deaths: a before (2006-10) versus after (2011-13) comparison
Author	Sheila M. Bird, Andrew McAuley, Samantha Perry & Carole Hunter
Year of publication	2015
Publication type	Society for the Study of Addiction
Funding	Medical Research Council
Setting	Scotland, in community settings and all prisons

Type of intervention	Brief training and standardized naloxone supply became available to individuals at risk of opioid overdose	
Study design		
1. The research question is stated	Yes	"To assess the effectiveness for Scotland's National Naloxone Program (NNP) by comparison between 2006-10 (before) and 2011-13 (after) and to assess cost-effectiveness."
2. The economic importance of the research question is stated	No	
3. The viewpoint(s) of the analysis are clearly stated and justified	Yes	"Evidence of naloxone's effectiveness in reducing fatalities from opioid overdose was rated as weak by the World Health Organization and has been insufficient for policy change in America. Scotland's NNP makes it uniquely placed to address these important limitations on empirical knowledge about naloxone's effectiveness at a population level."
4. The rationale for choosing the alternative programs or interventions compared is stated	Yes	Before/after effects of the National Naloxone Policy implementation.
5. The alternatives being compared are clearly described	Yes	Before the implementation of the NNP.
6. The form of economic evaluation used is stated	Yes	Stated as cost-effectiveness analysis but upon further review is more appropriately classified as a cost-utility analysis
7. The choice of form of economic evaluation is justified in relation to the questions being addressed	No	
Data collection		
8. The source(s) of effectiveness estimates are stated	Yes	National Records of Scotland
9. Details of the design and results of effectiveness study are given (if based on a single study)	Not Appropriate	
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Not Appropriate	
11. The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	"Prescription-cost per QALY gained (if the life-years gained by ORD prevention are 1 or 10 years)."
12. Methods to value health states and other benefits are stated	Yes	Percentage of ORDs with a 4-week antecedent of prison release, proportion of ORDs with a 4-week antecedent of prison release or hospital discharge.
13. Details of the subject from whom valuations were obtained are given	Yes	"Those at highest risk of ORD, who might be expected to benefit the most from NNP."
14. Productivity changes (if included) are reported separately	Not Appropriate	
15. The relevance of productivity changes to the study question is discussed	Not Appropriate	

16. Quantities of resources are reported separately from their unit costs	Yes	Number of Naloxone kits issued = 11,898 from 2011-2013
17. Methods for the estimation of quantities and unit costs are described	Not Appropriate	"Naloxone at a prescription cost (currently) of less than £225,000" - trial based so cost not estimated
18. Currency and price data are recorded	Yes	GBP currency. Prescription price of naloxone = £225 000
19. Details of currency of price adjustments for inflation or currency conversion are given	No	
20. Details of any model used are given	Not Appropriate	
21. The choice of model used and the key parameters on which it is based are justified	Not Appropriate	
Analysis and interpretation of results		
22. Time horizon of costs and benefits is stated	No	
23. The discount rate(s) is stated	Yes	"3% per annum if 10 life-years were gained"
24. The choice of rate(s) is justified	No	
25. An explanation is given if costs or benefits are not discounted	Not Appropriate	
26. Details of statistical tests and confidence intervals are given for stochastic data	Yes	"Chi-squared with one degree of freedom, applying quality-of-life as 0.7 for those at risk of ORD, discounting future life-years by 3% per annum, returns 95% CIs for prescription-cost per QALY gained if the life-years gained by ORD prevention are 1 or 10 years."
27. The approach to sensitivity analysis is given	No	
28. The choice of variables for sensitivity analysis is justified	Not clear	Varied on averted overdose number. Not justified.
29. The ranges over which the variables are varied is stated	Not Appropriate	
30. Relevant alternatives are compared	Not Appropriate	
31. Incremental analysis is reported	No	
32. Major outcomes are presented in a disaggregated as well as aggregated form	Yes	Aggregated: "when 12,000 naloxone kits were issued at current prescription cost of £225,000 prescription cost per QALY gained are £4,900-$16,900 for one year and £560-£1,940 for 10 years." Disaggregated: "Nearly 12 000 naloxone kits were distributed during 2011–13, Scotland's NNP may have prevented 42 prison release ORDs at a prescription cost of less than £225,000. 95% CIs for the prescription cost per QALY gained

		are £4900–16 900 and £560–1940 (with 3% per annum discounting if 10 life-years were gained, QALYs would be 6.1).”
33. The answer to the study question is given	Yes	“Prescription cost per QALY gained are £4,900-£16,900 for one year and £560-£1,940 for 10 years.”
34. Conclusions follow from the data reported	Yes	“With 2 years of Scotland's National Naloxone Programme to follow, the current data suggest at least 20% and best estimate of 36% reduction in prison release ORDs, which may be due directly to the programme.”
35. Conclusions are accompanied by the appropriate caveats	Yes	“The beneficiary of community- issued naloxone is typically not the person for whom it was prescribed: NNP’s beneficiaries are therefore not individually identifiable. Only one-third of naloxone-on-release kits are used on the ex-prisoner for whom the kit was prescribed, NNP’s effectiveness in respect of prison release ORDs could be an overestimation of its generalized effectiveness.”

Study Details		
Title	Impact of a community-based naloxone distribution program on opioid overdose death rates	
Author	Rebecca B. Naumann, Cristine Piette Durrance, Shabbar I. Ranapurwala, Anna E. Austin, Scott Proescholdbell, Robert Childs, Stephen W. Marshall, Susan Kansagra, Meghan E. Shanagan	
Year of publication	2019	
Funding	National Center for Injury Prevention and Control at the Centers for Disease Control and Prevention	
Publication type	Drug and Alcohol Dependence	
Setting	North Carolina, United States	
Type of intervention	Community distribution of naloxone kits (following legal policy change), prioritizing people at high risk of opioid overdose; includes training to those who receive kit; both IM and intra-nasal	
Study design		
1. The research question is stated	Yes	“To evaluate the North Carolina community-based naloxone distribution program by estimating the association between naloxone distribution rates and OOD rates and conducting a cost-benefit and cost-effectiveness analysis of the naloxone distribution program.”
2. The economic importance of the research question is stated	Yes	“No research has been conducted during the most recent ‘wave’ of the opioid crisis and there has been little research examining the cost-benefit or cost-effectiveness of such programs.”
3. The viewpoint(s) of the analysis are clearly stated and justified	Yes	“Early evidence, outside of North Carolina, indicates that naloxone distribution programs may be associated with decreases in OOD rates. However, most studies that have evaluated community-based naloxone programs have largely focused on process measures of program impact.”
4. The rationale for choosing the alternative programs or interventions compared is stated	No	
5. The alternatives being compared are clearly described	Yes	No naloxone distribution.

6. The form of economic evaluation used is stated	Yes	Cost-benefit analysis and cost-effectiveness analysis
7. The choice of form of economic evaluation is justified in relation to the questions being addressed	No	
Data collection		
8. The source(s) of effectiveness estimates are stated	Yes	"Annual counts of naloxone kits distributed by the NCHRC by county from August 2013 through December 2016 and mortality data obtained from the NC Vital Statistics Office for 2000-2016."
9. Details of the design and results of effectiveness study are given (if based on a single study)	Not Appropriate	
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	No	
11. The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	"Monetized using a conservative value of life.", cost per death avoided for every dollar invested in naloxone distribution.
12. Methods to value health states and other benefits are stated	Yes	OODs avoided
13. Details of the subject from whom valuations were obtained are given	Yes	"North Carolina counties with at least five opioid overdose deaths each year in the period immediately preceding implementation."
14. Productivity changes (if included) are reported separately	Not Appropriate	
15. The relevance of productivity changes to the study question is discussed	Not Appropriate	
16. Quantities of resources are reported separately from their unit costs	Yes	In Table 1.
17. Methods for the estimation of quantities and unit costs are described	Yes	"We summed the average per unit price of a naloxone kit and the estimated cost of kit distribution. We used data available on naloxone kits purchased by the NCHRC between 2015 and 2016 to estimate the per unit cost of a naloxone kit. Based on the number of kits distributed between 2015 and 2016, the average per unit price of a naloxone kit was approximately $2/kit. Based on previous research, we estimated the cost associated with kit distribution as $10 per kit."
18. Currency and price data are recorded	Yes	USD currency. $12 per naloxone kit.
19. Details of currency of price adjustments for inflation or currency conversion are given	No	
20. Details of any model used are given	Yes	"Models included an offset term for the log of total population in a county per year and a first order autoregressive working correlation matrix. All models

		included cubic trend terms to account for potential bias due to secular trend."
21. The choice of model used and the key parameters on which it is based are justified	No	
Analysis and interpretation of results		
22. Time horizon of costs and benefits is stated	No	
23. The discount rate(s) is stated	No	
24. The choice of rate(s) is justified	Not Appropriate	
25. An explanation is given if costs or benefits are not discounted	No	
26. Details of statistical tests and confidence intervals are given for stochastic data	Yes	"We calculated descriptive statistics of naloxone kits distributed and opioid overdose deaths by year across counties. We used Poisson regression with generalized estimating equations to estimate measures of association between cumulative rates of naloxone kits distributed per county-year and opioid overdose death rates per county-year. We developed a conceptual figure based on the extant literature and expert understanding of factors affecting naloxone distribution and OOD rates. Based on this figure, we examined the impact of potential confounders, including county age, sex, race, and poverty distributions, as well as county urbanicity, on measures of association."
27. The approach to sensitivity analysis is given	No	
28. The choice of variables for sensitivity analysis is justified	Yes	"Used alternate cut points for distribution rates and an alternative naloxone price estimate"
29. The ranges over which the variables are varied is stated	Yes	0, 1-75, and >75; 1, 1-125, and >125 cumulative naloxone kits distributed per 100,000 population. Used the estimate of $40 per kit
30. Relevant alternatives are compared	Yes	As reported in previous research
31. Incremental analysis is reported	Yes	Cost-benefit ratio: "for every dollar invested in naloxone distribution, $2,742 was saved through the monetary value of death avoidance." Cost-effectiveness measure: "$1605 cost per death avoided."
32. Major outcomes are presented in a disaggregated as well as aggregated form	Yes	Aggregated: "Using model-based estimates of the impact of naloxone kit distribution on OOD rates between August 2013 and December 2016 by kit distribution category, as well as county-year population data, we estimated approximately 352 deaths were avoided during this time." Disaggregated: For 2015 and 2016, the years for which we had NCHRC naloxone cost data, the approximate number of deaths avoided in this specific two-year period was 255; applying a conservative VSL, an estimated $1.122 billion resulted from avoiding the 255 deaths in those two years."

33. The answer to the study question is given	Yes	“Consistent with previous findings, our estimates suggest that community-based naloxone distribution may have a protective effect on annual county OOD rates.”
34. Conclusions follow from the data reported	Yes	“Our estimates suggest that community-based naloxone distribution is associated with lower OOD rates. The program generated substantial societal benefits due to averted OODs. States and communities should continue to support efforts to increase naloxone access, which may include reducing legal, financial, and normative barriers.”
35. Conclusions are accompanied by the appropriate caveats	Yes	“Death certificate data provide information on decedents' county of residence; however, we do not have county of death information. The extent to which the data includes the majority of naloxone available in communities during the time period is unknown. The analysis is ecological in nature and could include cross-level bias. In the analysis, we use benefits and costs in their current year dollars, and we assume reversals have saved new lives. Benefits of naloxone provision could include avoided medical costs, productivity losses, and quality of life losses. Many rural counties were not included in this analysis.”

Appendix C: List of all articles that passed title and abstract review

Included in systematic review following full-text review

1. Bird SM, McAuley A, Perry S, Hunter C. Effectiveness of Scotland's National Naloxone Programme for reducing opioid-related deaths: a before (2006-10) versus after (2011-13) comparison. *Addiction*. 2016;111(5):883-891. doi:10.1111/add.13265

2. Cipriano LE, Zaric GS. Cost-effectiveness of naloxone kits in secondary schools. *Drug Alcohol Depend*. 2018;192:352-361.

3. Townsend T, Blostein F, Doan T, Madson-Olson S, Galecki P, Hutton DW. Cost-effectiveness analysis of alternative naloxone distribution strategies: First responder and lay distribution in the United States. *Int J Drug Policy*. 2020;75:102536. doi:10.1016/j.drugpo.2019.07.031

4. Uyei J, Fiellin DA, Buchelli M, Rodriguez-Santana R, Braithwaite RS. Effects of naloxone distribution alone or in combination with addiction treatment with or without pre-exposure prophylaxis for HIV prevention in people who inject drugs: a cost-effectiveness modelling study. *Lancet Public Health.* 2017;2(3):e133-e140. doi:10.1016/S2468-2667(17)30006-3

5. Naumann RB, Durrance CP, Ranapurwala SI, et al. Impact of a community-based naloxone distribution program on opioid overdose death rates. *Drug Alcohol Depend*. 2019;204:107536. doi:10.1016/j.drugalcdep.2019.06.038

6. Langham S, Wright A, Kenworthy J, Grieve R, Dunlop WCN. Cost-Effectiveness of Take-Home Naloxone for the Prevention of Overdose Fatalities among Heroin Users in the United Kingdom. *Value Health*. 2018;21(4):407-415. doi:10.1016/j.jval.2017.07.014

7. Coffin PO, Sullivan SD. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. *Ann Intern Med*. 2013;158(1):1-9. doi:10.7326/0003-4819-158-1-201301010-00003

8. Coffin PO, Sullivan SD. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal in Russian cities. *J Med Econ*. 2013;16(8):1051-1060. doi:10.3111/13696998.2013.811080

9. Acharya M, Chopra D, Hayes CJ, Teeter B, Martin BC. Cost-Effectiveness of Intranasal Naloxone Distribution to High-Risk Prescription Opioid Users. *Value Health*. 2020;23(4):451-460. doi:https://dx.doi.org/10.1016/j.jval.2019.12.002

Excluded from systematic review following full-text review

1. Administration of Naloxone in a Home or Community Setting: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines. Ottawa (ON), Canada: Canadian Agency for Drugs and Technologies in Health; 2014.
    - Excluded because it is a review; references assessed to identify any other studies that should be included

2. Chao Y-S, Loshak H. Administration of Naloxone in a Home or Community Setting: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines. Ottawa (ON), Canada: Canadian Agency for Drugs and Technologies in Health; 2019.
    - Excluded because it is a review; references assessed to identify any other studies that should be included

3. Mueller SR, Walley AY, Calcaterra SL, Glanz JM, Binswanger IA. A Review of Opioid Overdose Prevention and Naloxone Prescribing: Implications for Translating Community Programming Into Clinical Practice. *Subst Abus*. 2015;36(2):240-253. doi:10.1080/08897077.2015.1010032
    - Excluded because it is a review; references assessed to identify any other studies that should be included

4. Holdford DA. Cost effectiveness of prescribing evzio for lay heroin overdose reversal. *Value Heal*. 2015;18(3):A46. doi: 10.1016/j.javl.2015.03.273
    - Excluded because only an abstract is available; contact with author was attempted to determine study details

5. Coffin PO, Sullivan SD. Correction: Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. *Ann Intern Med*. 2017;166(9):687. doi:10.7326/M17-0652
    - Excluded because it is only a correction to an article that is included; was considered at the same time as analysis on the originaly article

6. Barbosa C, Dowd WN, Zarkin G. Economic evaluation of interventions to address opioid misuse: A systematic review of methods used in simulation modeling studies. *Value Heal*. 2020; 23(8): P1096-P1108. doi:10.1016/j.jval.2020.03.015
    - Excluded because it is both a systematic review and because it focused on the methods of studies, rather than the outcomes; references were assessed to identify any other studies that should be included

7. Barra M, Direnzo GFM, Patruno FV, Patti M, Rodoquino G, Rossi E, Santoro R, Badiani A. The cost-effectiveness of naloxone programmes for the treatment of heroin overdoses “on the street”: A 2-year data collection by the street unit of the villa maraini foundation. *Heroin Addict Relat Clin Probl*. 2018;20(4):37-43.
    - Excluded because the study was a comparative analysis of costs, not an economic evaluation

8. Murphy SM, Polsky D. Economic evaluations of opioid use disorder interventions. *Pharmacoeconomics*. 2016;34(9):863-887. doi:10.1007/s40273-016-0400-5
    - Excluded because it is a review and because it focuses on interventions other than community distribution of naloxone

9. Peprah K, Severn M. Intranasal and intramuscular naloxone for opioid overdose in the pre-hospital setting: A review of comparative clinical and cost-effectiveness, and guidelines. Ottawa (ON), Canada: Canadian Agency for Drugs and Technologies in Health; 2019.
    - Excluded because it is a review and because it focuses on comparing the formulations of naloxone rather than distribution strategy; references assessed to identify any other studies that should be included

Appendix D: AMSTAR 2 tool for systematic reviews

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	N/A
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A
13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the	N/A

results of the review?	
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes