Opioid overdoses and overdose prevention:

The establishment of take-home naloxone in Norway

Desiree Madah-Amiri

Norwegian Centre for Addiction Research (SERAF)

Institute of Clinical Medicine

Faculty of Medicine

University of Oslo

Oslo, Norway

2017

UiO : University of Oslo

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

ISBN 978-82-8377-110-7

Cover: Hanne Baadsgaard Utigard.
Print production: Reprosentralen, University of Oslo.

Acknowledgements

There are so many people I would like to thank who have helped me during this PhD process. Without all of the encouragement and support this would have been a much less enjoyable experience.

First, I would like to express my deepest gratitude to all of the staff and participants that took part in these studies. This literally could not have existed without you. The time you spent filling out the forms-- disclosing personal and often difficult information does not go unnoticed, and for this I truly am grateful.

I would also like to thank the amazing project coordinators: Åse Merete Solheim, Øystein Bruun Ericson, and Henriette Sørum. Each one of you has been crucial to the project and a pleasure to work with. Your creativity, flexibility, and organization has made the project is what it is today.

Next, the administrative staff at SERAF have been nothing short of incredible. Bente Vasbotten, Pål Lillevold, Julie Nybakk Kvaal, and Pernille Karlsen, I am so thankful for you. Pål, you have always been so kind and approachable with all of my questions, even though I'm sure it got pretty annoying sometimes. Bente, where to even begin: you have been not only helpful in countless ways for the project, but you have become a dear friend to me as well. To all of my colleagues at SERAF, thank you for the supportive and fun environment. Some of the friendships I have formed here are among my most cherished in Norway.

Thank you to Natanya Robinowitz, my harm reduction sister and one of my best friends. Our journey into harm reduction together has been transformative for me, and I can't thank you enough for how much you have pushed and inspired me. Thank you to everyone from the Baltimore Student Harm Reduction Coalition and the staff from the Baltimore needle exchange van. Without you and everything you taught me I would not be in this position today. Thank you to all of the naloxone programs who have generously shared their insights, and made their training resources and curriculum available online. Thank you to the activists who have been working to improve naloxone access for decades now.

I am forever grateful for my supervisors, Dr. Philipp Lobmaier and Professor Thomas Clausen. Working with both of you has been a period of such growth and learning for me. Throughout this time, I have felt encouraged and supported. You have helped to inspire me as a researcher and I have grown so much under your supervision. You have both given me

space to be creative and tackle obstacles with the project, while still being available for critical feedback. Thank you for being so flexible with the news of me moving to Kosovo, and allowing me to work remotely for a period of this. As I begin my research career, I credit you both so much for my development, for which I am grateful.

To my family, my ‘svigerfamilie’, and friends, thank you for all of your kindness and support. Last, it is likely that words do not exist to convey my gratitude for my husband, Stein-Ivar. Thank you for giving me so much love and encouragement. Our discussions about the project have been so valuable, and I trust and respect your advice more than you know. You have always seemed genuinely enthusiastic to talk about the same topic with me for three years now! Without a doubt, I couldn’t have done this without you. Thank you for everything, I love you.

Desiree

Summary

Background

Opioid overdoses are a major cause of preventable deaths. Naloxone, the antidote to an opioid overdose, has long been used by health personnel to reverse the respiratory depression caused by an opioid overdose. In the 1990s, take-home naloxone programs emerged, equipping non-medical bystanders to intervene with naloxone in the event of an opioid overdose. Many of the programs that exist worldwide are run on a pilot basis, and few have government support to be large-scale. Investigating and evaluating the implementation of a large-scale naloxone program is important in understanding how to best scale-up such initiatives.

Study aims

The overall aims of this thesis were to describe characteristics of opioid overdoses occurring in Bergen, Norway, and to evaluate the introduction and implementation of a widespread take-home naloxone program in Norway. The specific aims were a) to investigate epidemiological patterns of non-fatal overdoses attended by ambulance services, b) to evaluate the impact of a staff training course towards distributing naloxone, c) to describe the characteristics of participants trained to use naloxone, including an investigation into overdose risk factors, d) to monitor naloxone distribution coverage, following a broad public health approach and distribution scheme, and e) interpret findings in relation to defined implementation outcomes.

Materials and methods

This thesis included three different samples. The ambulance cohort included non-fatal opioid overdoses attended by Bergen emergency medical services from 2012-2013 (n=463). The staff trainer course included staff who completed a pre-test post-test analysis following a naloxone trainer course during a two-month period (n=54). Participants who attended a naloxone training from one of the 20 distribution sites from June 2014-December 2015, and consented to fill out the questionnaire survey were included in this study (n=433 for initial training, n=401 for refill). Naloxone coverage rates were based on naloxone distribution numbers reported from the participating facilities. An implementation evaluation framework was used to assess whether various outcome goals were met.

Results

The temporal patterns of opioid overdoses indicated mostly non-recreational use, with overdoses following sleep-wake patterns with no significant weekend increase. Ambulance response time varied (median 6.8 minutes), but was significantly longer to private homes (RR=1.66, 95% CI, 1.05-2.60). Those that were picked up from private homes were more likely to not be transported for further care following ambulance treatment (RR=1.47, 95% CI, 1.10-1.96).

Staff that participated in the training survey were assessed on four areas of knowledge (risks for overdosing, signs of an overdose, actions to take for an overdose, and how to use naloxone) prior to and directly following the trainer course. Scores in all areas improved significantly ($p<0.001$), and total scores improved from 78.4% correct to 91.1%. Self-reported attitude scores increased following the training from 3.17 (SD=0.95) to 4.3 (SD=0.45) on a Likert Scale of 1 to 5.

Most of the participants during the initial naloxone training were either current or previous opioid users (n=369, 85%). Of these, nearly all (n=338, 92%) had reported at least one known risk factor for overdosing. Ninety-one percent (n=394) had witnessed an overdose and 79% (n=305) had experienced an overdose during their lifetime. Of the 401 that completed the refill questionnaire, 70% (n=277) reported to have used their original naloxone spray on an overdose. The victim survived in 96% of the cases (n=265), with the remaining outcomes being unknown (n=3, 1%) or missing (n=9, 3%).

There were 2,056 naloxone sprays distributed in total from the 20 participating facilities from June 2014-December 2015. The distribution rate was 144 per 100,000 for both of the cities, meeting the distribution goals.

Using the implementation evaluation framework, most of the outcomes had areas that were both met and unmet from the intervention. Recurrent themes and issues that came up post-training were related to staff buy-in, and found the staff to be generally positive towards the intervention; however there were also reports of concern and skepticism.

Discussion and conclusion

The findings from the ambulance study can be helpful to guide and monitor local overdose prevention efforts. The longer arrival time to private homes, and the increased likelihood of not being transported illustrate a risk factor for those overdosing at home. The use of a train-the-trainer model appeared to be effective in preparing staff involved with the intervention; however long-term adherence and fidelity monitoring should be done to determine to what degree the staff training was utilized. Participants who attended a naloxone training were primarily from at-risk groups, exhibiting known risk factors for overdosing. Naloxone distribution goals were met within the first year, demonstrating that the use of multiple existing facilities achieved rapid, high volume distribution of naloxone. Evaluation of the implementation of the intervention revealed that many of the outcome domains were both met and unmet, shedding light on facilitators and barriers to successful implementation of a widespread naloxone distribution program. While overall staff were positive towards the intervention, increased attention to promoting staff and leadership buy-in may have improved the project adoption. The government support for the intervention provided funding and the ability to distribute naloxone at no cost and without an individual prescription, likely avoiding potential barriers.

Norwegian summary

Bakgrunn

Overdoser er blant de hyppigste dødsårsakene for opiatbrukere. Nalokson, en motgift som virker mot opiatoverdoser, har lenge vært brukt av medisinsk personell for å reversere pustevanskene forårsaket av en opiatoverdose. På 1990-tallet så man en fremvekst av «take-home» naloksonprosjekter, hvor ikke-medisinsk personell ble utstyrt med motgiften, for å kunne håndtere situasjoner hvor de ble vitne til en opiatoverdose. Mange av disse prosjektene, som finnes i flere land, er drevet som mindre, lokale tiltak, og kun et fåtall har støtte fra relevante myndigheter. Å undersøke og evaluere implementeringen av et storskala naloksonprogram er viktig for å forstå hvordan man best kan oppskalere slike initiativer.

Studiens formål

De overordnede målene med denne studien var å beskrive hovedtrekkene ved opiatoverdoser i Bergen,samt å evaluere innføringen og implementeringen av et storskala «take-home» naloksonprogram i Norge. De konkrete målene var a) å gjøre en epidemiologisk undersøkelseav ikke-dødelige overdoser hvor ambulanse blir tilkalt, b) å evaluere effekten av et opplæringskurs foransatte som skal distribuere nalokson, c) å beskrive deltakerne som ble opplært i bruk av nalokson, inkludert en nærmere undersøkelse knyttet til kjente risikofaktorer for overdoser, d) å undersøke naloksondistribusjonsprogrammets dekning, basert på en folkehelsetilnærming, og e) tolke funnene i lys av forhåndsdefinerte implementeringsutfall.

Material og metode

Denne studien inkluderte tre ulike datasett. Ambulansestudien inkluderte ikke-dødelige opiatoverdoser i Bergen hvor ambulanse ble tilkalt fra 2012-2013 (n=463). Av deltakerne som fulgte kurset for instruktører som skal distribuere nalokson, deltok et utvalg (n=54) i en pre-test post-test analyse i løpet av en to-måneders periode. Deltakere som deltok på opplæringen i bruk av nalokson ved en av de 20 distribusjonsstedene mellom juni 2014 og desember 2015, og som samtykket i å fylle ut spørreskjemaet, er inkludert i denne studien. (n=433 for første opplæring, n=401 for påfyll). Dekningsraten for nalokson ble regnet ut på bakgrunn av de rapporterte distribusjonstallene fra de deltakende distribusjonsstedene. Et rammeverk for å evaluere implementeringen ble brukt for å vurdere hvorvidt ulike målsetninger ble nådd.

Resultater

Opiatoverdosenes tidsmessige fordelingindikerte hovedsakelig ikke-rekreasjonell bruk, og overdosene fulgte normal døgnrytme uten signifikant økning i helgene. Ambulansens responstid varierte (mediantid 6.8 minutter), og var betydelig lengre i tilfeller hvor overdosen fant sted i et privat hjem. (RR=1.66, 95% CI, 1.05-2.60). De som ble plukket opp i private hjem hadde større sannsynlighet for å ikke bli transportert videre til medisinsk oppfølging etter å ha mottatt assistanse fra ambulansepersonell (RR=1.47%, 95%, CI, 1.10-1.96)

Ansatte som deltok i spørreundersøkelsen tilknyttet kurset for instruktører ble vurdert på fire kunnskapsområder (kjente risikofaktorer for overdose, tegn på en overdose, tiltak for å respondere på en overdose, og hvordan man bruker nalokson) før og umiddelbart etter gjennomføringen av kurset. Innen alle fire områder økte kunnskapen signifikant ($p<0.001$), og prosentvis riktige besvarelserøkte fra 78.4% til 91.1%. Selvrapportert holdning til nalokson økte etter gjennomføring av kursetfra 3.17 (SD=0.95) til 4.3 (SD=0.45) på en Likertskala fra 1 til 5.

De fleste deltakerne på førstegangsopplæring i bruk av nalokson var enten nåværende eller tidligere brukere av opiater (n=369, 85%). Av disse rapporterte nesten alle (n=338, 92%) minst en kjent risikofaktor for overdose. 91% (n=394) hadde vært vitne til en overdose og 79% (n=305) hadde selv opplevd en overdose i løpet av livet. Av de 401 som gjennomførte spørreskjemaet for påfyll, rapporterte 70% (n=277) å ha brukt den første naloksonsprayen de mottok på en overdose. Overdoseofferet overlevde i 96% av tilfellene (n=265), mens utfallet i de resterende tilfellene var ukjent (n=3, 1%) eller ikke oppgitt (n=9, 3%).

Totalt ble 2056 naloksonsprayer distribuert fra de 20 deltakende distribusjonsstedene fra juni 2014 til desember 2015. Distribusjonsraten var 144 pr 100,000 for begge byene, hvilket var tilstrekkelig for å møte det forhåndsdefinerte måltallet for dekningsgrad.

Rammeverket for å evaluere implementeringen av prosjektet viser at de fleste av indikatorene hadde både oppfylte og ikke-oppfylte mål. Utfordringer som gikk igjen var knyttet til eierskap blant ansatte ved distribusjonsstedene. Ansatte var hovedsakelig positive til prosjektet, men det ble også rapportert om bekymring og skepsis.

Diskusjon og konklusjon

Funnene fra ambulansestudien kan være til hjelp for å tilrettelegge og vurdere lokale tiltak for å redusere omfanget av overdoser. Både det at tok lengre tid for ambulansen å komme til private hjem, og den økte sannsynligheten for ikke å bli transportert videre til medisinsk oppfølging, illustrerer risikofaktorer for personer som opplever overdoser i private hjem- Bruken av en «train-the-trainers»-modell viste seg å være effektiv i opplæringen av ansatte ved distribusjonsstedene. Samtidig bør man på sikt evaluere i hvilken grad opplæringen ble anvendt. Personer som deltok på opplæring i bruk av nalokson var hovedsakelig fra risikogrupper som hadde en eller flere kjente trekk som medfører økt risiko for å oppleve en overdose. Distribusjonsmålene for nalokson ble oppnådd i løpet av det første året, hvilket illustrerer at bruk av flere eksisterende fasiliteter førte til rask og utbredt distribusjon av nalokson. Evalueringen av forhåndsdefinerte implementeringsutfall indikerte både oppfylte og ikke-oppfylte mål, hvilket peker i retning av forhold som enten fasiliterer ellerforhindrer vellykket implementering av et storskala naloksondistribusjonsprogram. Mens ansatte i hovedsak var positive til prosjektet, kunne økt oppmerksomhet rundt eierskap ført til større aksept for og bedre gjennomføring av prosjektet. Myndighetenes støtte til prosjektet sikret finansiering, samt mulighet for å distribuere nalokson kostnadsfritt og uten krav om individuell resept.

List of Papers

I. Madah-Amiri D, Clausen T, Myrmel L, Brattebø G, Lobmaier P. Circumstances surrounding nonfatal opioid overdoses attended by ambulance services. *Drug and Alcohol Review*. 2016;36(3):288-294.

II. Madah-Amiri D, Clausen T, Lobmaier P. Utilizing a train-the-trainer model for multi-site naloxone distribution programs. *Drug and Alcohol Dependence*. 2016;163.153-156.

III. Madah-Amiri D, Clausen T, Lobmaier P. *Rapid widespread distribution of intranasal naloxone*. Drug and Alcohol Dependence. 2017;173:17-23.

Abbreviations

Analysis of variance (ANOVA)

Cardio-pulmonary resuscitation (CPR)

Confidence Interval (CI)

Emergency medical services (EMS)

Foreningen for human narkotikapolitikk (FHN): Norwegian association for humane drug policies

γ-Hydroxybutyric acid (GHB)

Odds ratio (OR)

Opioid maintenance treatment (OMT)

Opioid overdose knowledge scale (OOKS)

People who inject drugs (PWID)

Relative Risk (RR)

Standard deviation (SD)

Take-home naloxone (THN)

Definitions

Drug-induced deaths: deaths that occur shortly after the consumption of drugs and are directly caused from the consumption of drugs.

Drug-related deaths: all deaths to which drugs can be attributed. This includes overdoses, as well as medical conditions resulting from chronic drug use, and including accidents attributable to drug intoxication.

High-risk opioid user: injecting opioid use or long duration or regular use of opioids.

White paper: official communication to the Storting (Parliament) by the Government on various matters that the Government wishes the Storting to consider.

Preface

My motivation for working in the field of overdose prevention started while in graduate school in Baltimore, Maryland where I volunteered with the city's mobile health clinic. Our patients were primarily sex workers and people who use drugs, who, for the most part lacked access to health care other than what was provided in the van. The mobile clinic offered clean needles, overdose prevention trainings, and some basic primary and reproductive health care. The clients that came to the clinic were victims to the societal injustices and pitfalls of the American healthcare system. I found their situation extremely difficult: on the one hand struggling with addiction and on the other hand lacking access to the services and housing needed in order for their situation to improve. Without access to housing, many of the women resorted to sex work, and without clean needles, people would share and reuse them. It was here that I was introduced to harm reduction, and what I viewed as its compassionate, pragmatic, non-judgmental messages.

Along with a friend, we started the Baltimore Student Harm Reduction Coalition, an interest and advocacy group for students from the medical, nursing, and public health schools at Johns Hopkins University. By inviting a range of clinicians and researchers who were applying harm reduction into their work, we learned ways that we could aim to incorporate it into our future clinical practices.

After meeting my (future) husband and moving to Norway, I was interested in finding a way to continue working within the field. I reached out to several facilities and organizations hoping that my experience could be useful. The Norwegian Directorate of Health declared a National Overdose Prevention Strategy in 2014 that was to include a pilot project with the distribution of naloxone. The Norwegian Centre for Addiction Research was tasked with developing and implementing the intervention. The primary mandate was to implement the intervention, allowing for people to be trained to use naloxone regardless of their participation in a research study. It was a transformative moment for me to receive the PhD position and be able to participate in the first take-home naloxone program in Norway.

During the PhD period I was involved with various aspects of the project. I designed curriculum and conducted the trainer courses, developed the questionnaires used for the study, and collected and analyzed data from the questionnaires. I assisted the coordinators with monthly monitoring of distribution rates and maintained contact with participating facilities. This allowed for very hands on participation in the implementation of the project.

1.0 Introduction

This thesis covers the development and implementation of a take-home naloxone program in Norway. The studies examined various aspects of this process, and included 1) an epidemiological investigation of non-fatal overdoses through the use of ambulance data, 2) an assessment of a training program for the staff implementing the project, and 3) an evaluation of the implementation of the intervention, applying descriptive data from those receiving naloxone rescue kits.

Background

Opioid overdoses are a significant concern globally, with devastating and deadly outcomes. In Europe, Scandinavia is particularly affected, experiencing some of the highest overdose rates. In response to this problem, the Norwegian Directorate of Health launched a National Overdose Prevention Strategy in 2014 in attempts to reduce overdoses (1). Take-home naloxone was a key component of this multifaceted strategy, and aimed to equip bystanders with the antidote needed to reverse opioid overdoses. Government-supported, large-scale naloxone distribution initiatives are relatively new, with the majority of programs in the world operating as single-site operations. This thesis covers the establishment of a multi-site intervention, including an evaluation of the implementation and an epidemiological analysis of overdoses in an area where the intervention was implemented as part of a large-scale public health intervention.

1.1 Opioid overdoses

1.1.1 Epidemiology and risk factors

Opioids were responsible for many of the over 200,000 drug-related deaths reported worldwide in 2014 (2). Overdoses accounted for up to half of these deaths (2), with approximately half of these occurring in the United States (3). There are an estimated 1.3 million high-risk opioid users in Europe, with heroin being the most widely used opioid (4). Opioids are the most commonly injected drug, and injecting drug users experience the highest rates of health problems associated with their drug use (4). Overdoses are the most serious health concern, and are a leading cause of death for young people in Europe and Norway.

People who inject drugs (PWID) have an estimated 10 to 17 times increased mortality risk when compared to the general population (5, 6). In addition to the increased mortality risk,

approximately 17-68% of PWID experience at least one non-fatal overdose during their lifetime (7). Non-fatal overdoses have been identified as a predictor for both future non-fatal (8) and fatal overdoses (9, 10), as well as a significant contributor to morbidity (11).

Several factors have been identified that increase the risk of both fatal and non-fatal overdoses. These include: loss of tolerance after a period of abstinence (e.g. recent release from prison (12) or inpatient treatment (13)), frequent injecting (5), and poly-drug use (14). The location where overdoses occur may have important health implications (15), with 'shooting gallery' (illicit injection room) attendance having been found to be associated with an increased risk of being HIV positive (16). Those who use opioids while alone risk not receiving the help they need in the event that they overdose. Further, factors such as homelessness (17) and physical health (18, 19) also play a role in the increased risk of overdosing. As PWID age, their risk of overdose increases, due to physiological changes and poorer physical health (20). In the Nordic countries, the high number of deaths is attributed to poly-drug use, indicating that multiple issues or risks are present at the time of an overdose (21). The more recent use of potent opioids, such as fentanyl, is also a risk factor for overdosing (22, 23). Overall, overdoses are commonly a multifactorial event, and victims typically have multiple risk factors (24, 25). Interventions aimed towards preventing this complex phenomenon must be multifaceted. Many of these risk factors can be modified, and demonstrate the important interplay between epidemiological investigations and strategies to prevent overdoses.

1.1.2 Mechanisms of an opioid overdose

Opioids act on the same receptors in the brain that are responsible for controlling the signal to breathe. When opioids bind to these receptors, the person experiences a diminished signal to breathe, and thus the slowing of their breathing. If the person does not breathe enough, oxygen decreases in the body and carbon dioxide increases. Because the respiratory center is affected by the opioids, the body is unable to mount its normal response to this change in blood gases. The result of this hypoxia is acidosis, respiratory depression, and possible or eventual death (26). To survive the overdose, the victim needs pulmonary ventilation support and/or the antidote to an opioid overdose, naloxone.

1.1.3. Naloxone

Naloxone can be administered intramuscularly, intravenously, subcutaneously, or intranasally. It is most commonly used in the injection form of 0.4mg/mL or 1mg/mL solution, and is available in single dose or multi-dose vials and prefilled syringes. In April 2014, the Food and Drug Administration in the United States approved an auto-injectable device for intramuscular and subcutaneous use, which was followed by a single-dose intranasal device in November 2015 (27).

Prior to these recent developments, which are limited to the United States, off-label intranasal naloxone 'kits' have been created by attaching a nasal atomizer device to a syringe. In 2013, nearly 40% of naloxone distribution programs in the United States exclusively used off-label intranasal solutions (28). Given the risk for transmission of blood-borne infections, such as hepatitis C (29) with injectable solutions, intranasal options have also been found to be a suitable alternative for ambulance staff (30, 31).

Despite the benefits of off-label intranasal use, concern over unlicensed formulations that lack pharmacokinetic and bioavailability studies (32) and issues with the use of a complicated device (33) have been raised. Without such studies, critics argue that too much is unknown in terms of the onset of action, dose-equivalence, and the non-response rate (32). Additionally, it has been argued that the continued use of an off-label device does not necessarily make it acceptable (34). Notably, Strang and McDonald have argued that new naloxone products aimed towards PWID should be subject the same level of testing as new medications for other populations (32).

On the other hand, several studies have demonstrated similar effectiveness for both intranasal and injectable naloxone (31, 35, 36). Additionally, several have argued that waiting for more optimal solutions and devices could be deadly, and that clinicians and outreach workers need to respond to the overdose epidemic with what is available to broaden access to naloxone (37, 38). The use of an intranasal device allows for broader dissemination, which is crucial in potentially reducing overdose mortality (38). Importantly, Winstanley has pointed out that with the significant regulatory barriers that take-home naloxone (THN) programs have experienced, we must use the data on intranasal naloxone that is available and work to translate it into the real-world (39). Critics may view the off-label spray as a second-best option; however no fatalities directly related to intranasal use have been reported. While this debate remains unsettled, a single-dose spray is now available in the US, and development is

underway in Norway of a high-concentration/low-volume nasal spray that has the necessary pharmacokinetic studies (40).

Although the use of an off-label spray has been viewed as problematic (34), its use continues. When a THN program was included as part of the National Overdose Prevention Strategy in Norway, the use of a needleless device was decided. Therefore, instead of waiting for the approval of a licensed nasal spray, an interim spray was approved by the Norwegian Medicines Agency for the duration of the project. This deviation from procedure meant that the project was able to roll-out with a nasal device years before an approved spray was on the market in Norway.

1.2 Monitoring overdoses through the use of ambulance data

Addressing the opioid overdose epidemic requires the utilization of public health measures, including the use of local data to target interventions (41). Monitoring of opioid overdoses traditionally relies on mortality registries. While valuable, this method only captures rare, fatal events, with relevant information released often months after the event has occurred. Further, they do not provide information on non-fatal overdoses, which are more frequent than fatal overdoses (7). Nonfatal overdoses can be studied through indirect sources, such as ambulance data. Ambulances are often the first responders for overdose calls and in addition to providing life-saving treatment, epidemiologic data about the circumstances surrounding the events is gathered. Depending on the ambulance service capacity and documenting routines, ambulance data may provide real-time surveillance of overdose patterns (42). This may be especially relevant for monitoring and response to new psychoactive substances and changing patterns or characteristics of drug use.

Information from ambulance records has been used to understand patterns associated with various drug-related emergencies, such as γ-Hydroxybutyric acid (GHB) overdoses (43, 44), pharmaceutical drug misuse (45-47), cannabis (48), and volatile substance use (49). Studies from Australia (50, 51), the United States (42, 52, 53), and Europe (54-56) have used ambulance data to examine opioid overdoses locally. These studies have demonstrated how ambulance information can be useful to guide and evaluate prevention services on a local level.

1.3 Approaches to opioid addiction

Evidence-based treatment for opioid addiction includes both pharmacological and behavioral treatment. Abstinence-based approaches require the complete cessation of substance use, and

have largely been replaced by pharmacological interventions as the recommended treatment. Pharmacological interventions such as opioid maintenance therapy (OMT) with methadone or buprenorphine, full and partial opioid agonists respectively, are the mainstays of opioid addiction treatment (57). Naltrexone, an opioid antagonist is an option for those that have withdrawn from opioids and are interested in abstinence to prevent relapse (58). These treatments have been shown to be most effective when combined with psychosocial assistance (57).

As an adjunct to traditional treatment modalities, harm reduction is also a useful addition to standard practices. When used in combination with other interventions (such as OMT), the impact of these services is potentiated (59). Epidemiological studies have shown decreases in HIV and hepatitis C transmission with combined harm reduction and OMT practices (60).

Harm reduction refers to a variety of policies and practices that aim to minimize unnecessary harms associated with illicit drug use (61). The aim is to reduce the burden to the individual, to community, and society, with an emphasis on reducing the health-related harms associated with drug use. At its core, harm reduction is a social justice movement that respects the rights for people who use drugs. Harm reduction supports the role that people who use drugs have in being agents of change, and seeks to empower them to engage in ways to reduce harm. Ultimately, harm reduction accepts that illicit drug use exists, and attempts to improve conditions rather than condemn or ignore it (62). Harm reduction services often reach people outside of formal treatment, and can also be used as an entry point into formal treatment at a later stage (63). Some examples of harm reduction include: syringe distribution, education on safe injection techniques, drug consumption rooms, and overdose prevention programs that include the distribution of naloxone.

1.3.1 Take-home naloxone

Take-home naloxone programs were first described in the 1990s as a method to potentially prevent overdose fatalities (64, 65). These programs train bystanders to respond to an overdose with naloxone, an opioid antagonist. The trainings provided are often brief, and typically cover how to prevent an overdose, how to recognize the signs of an overdose, how to effectively intervene in the event of an overdose (including giving cardio-pulmonary resuscitation (CPR) and naloxone), and how to monitor the victim afterwards (66).

Over the past 20 years, over 200 programs have been implemented worldwide (67-71), with over 26,000 reported overdose reversals in the United States alone (28). Some programs in the United States (5, 72, 73) and Scotland (74) have experienced decreases in overdose mortality with the implementation of large-scale naloxone programs. Take-home naloxone programs have been found to be effective in reducing overdose mortality with relatively low rates of adverse events (75), and have demonstrated that in order to have a substantial impact on overdose mortality, widespread and often population-based interventions are necessary (73, 76).

Throughout the countries where THN programs are located, there is variability among the types of programs and their funding sources. In 2012, there was no federally secured funding for THN programs in the United States (66). Public health departments in some US states have sought funding by integrating THN into existing programs; however this does not provide any additional support staff or infrastructure (66). Programs in the US have also sought funding from grants or private donations. A survey from the US showed that the majority of the THN programs are community based (n=86), followed by healthcare facilities (n=28), public health departments (n=18), and pharmacies (n=6) (28). The fragmented organization results in the majority of sites being single-site, without coordination among different facilities offering services for PWID.

In Europe there is also variability among the countries that have THN programs. Programs range from a pilot project in Ireland (77), to nationwide programs in Scotland (78) and Wales (79). In 2015 there were programs in Norway, Germany, Estonia, Italy, Spain, Denmark, and the United Kingdom (UK) (26), all with varying degrees of size, distribution rates, and funding. Programs also exist in Canada (69), Australia (80), and as pilot projects in Afghanistan, China, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, India, Thailand, Vietnam, and the Ukraine (26). Together these programs demonstrate that while there is interest, support and actual implementation of these programs vary.

Despite the merits of large-scale THN programs, multi-site programs remain relatively rare. Although naloxone was first patented in the early 1960s, THN programs did not emerge until decades later (65). The first government-supported initiative started in 2011 in Scotland (78). By 2014 when this project in Norway began, it was still one of only a handful of multi-site programs with direct governmental support, be it from state, federal, or municipal funding. In general, public health interventions that are coordinated across several settings are more

successful (81). Although strategic multi-level involvement and collaboration can be challenging, it is critical for best improving public health outcomes (81).

Barriers to increased naloxone access have been identified, and resemble what is described in section 1.4.2 as barriers for scaling-up public health interventions (specifically financing and political will). Financial restraints may severely limit the scope in which THN programs can distribute. Without federally secured funding, many programs in the US rely on grants or donations to purchase naloxone and a dedicated clinician available to prescribe (76, 82-85). Recently, pricing of naloxone has seen a dramatic increase in the United States, with a price increase between 95%-500% since 2012 depending on the different formulations (86). Also, in the United States legal concerns for prescribers and responders exist in some states. However, by September 2014, 43 states have passed laws that increase access to naloxone (87). Naloxone remains a prescription drug throughout most of the world, yet some states in the US are pushing towards enhanced naloxone access by making the drug available over-the-counter. In some states, responders risk liability when intervening in a medical emergency, and the possibility of arrest at the scene. However, in recent years improvements in prescribing, standing orders, and Good Samaritan laws (legal protection for those who assist a person in danger) have increased access to naloxone in many US states (87). Many of these barriers are also described for the scaling-up of THN in Australia, particularly in regards to cost and prescribing (70).

Before October 2015, naloxone was only available by physician prescription in the UK (26). New legislation afterwards expanded the law to allow for naloxone to be distributed without a prescription by drug treatment services throughout all of the UK (88). Drug treatment services include: specialist drug treatment services, primary care services, needle exchange programs, and pharmacies that provide opioid substitution medicines (89). The law allows for parenteral naloxone only, and require that suitable training accompanies (89). Naloxone remains a prescription medication, but is exempt from prescription requirements when being supplied by a drug treatment service (89). Despite these legislative advancements allowing for increased access, there remains to be wide variability in actual naloxone distribution in the different countries in the UK.

Establishing a THN program requires several steps for developing, implementing, and monitoring a program. Funding, purchasing of naloxone, establishing the role of the medical provider, documentation and data collection, trainings, and outreach strategies are all part of

establishing a THN program (66). In addition to these aspects, consideration should be given as to how to effectively implement and scale-up public health initiatives (90, 91).

1.4 Implementation research

Implementation research aims to improve the effectiveness of public health programs (92). It is the scientific study of the process of implementing interventions and the contextual factors that influence it (93). Implementation research explores issues regarding what is working or not working with health interventions (93). A feature of implementation research is its ability to be applied to real-life circumstances. This includes a recognition of the complex interplay of social, cultural, and political influences, beliefs of stakeholders, the health structures and systems, and epidemiological conditions (92). Implementation research aims to uncover contextual factors that impact the implementation of a program, ultimately aiming to improve its real-life application (93).

Implementation research was not envisioned as part of this study at the outset, but as the project evolved it became evident that insights from implementation research could help categorize the findings, and serve as a basis for evaluation of the implementation of the intervention. Implementation research acknowledges the importance of understanding the process, and not just the impact of a study. Therefore, this thesis uses an implementation evaluation framework developed by Proctor et al. to describe factors believed to affect implementation outcomes (94). The aim of this was to use this framework post-hoc to explore to what extent these implementation outcomes were met or unmet, allowing for an assessment on what worked or did not work during the set-up of the study.

1.4.1 Implementation outcomes and strategies

As the field of implementation research develops, issues with a common terminology are evident. Inconsistent language and inadequate definitions lead to confusion and lack of clarity when describing implementation interventions (95). Terms such as ‘diffusion’, ‘dissemination’, and ‘knowledge transfer’ display an example of the inconsistent language used to describe concepts in the field (96). As a result, efforts have been made to clarify terminology. One of the most notable developments is an implementation evaluation framework developed by Proctor et al. which defines eight distinct factors for evaluating implementation outcomes (Table 1) (94).

The taxonomy of these outcomes gave a framework for conceptualizing successful implementation (94). Specifically, these include: acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, coverage, and sustainability (94) (Table 1). By articulating these implementation specific outcomes, they can be used for comparative effectiveness studies on different implementation strategies, as well as a guide for monitoring current interventions (93, 94). Throughout different stages of the intervention different implementation outcome variables may be more relevant (94). For example, existing interventions may focus more on fidelity, costs, and coverage, whereas new interventions may focus on acceptability, adoption, and appropriateness (93).

Table 1: Eight implementation outcomes defined

Implementation outcome	**Definition and terms**
Acceptability	Satisfaction of the intervention; belief among stakeholders that the intervention is legitimate
Adoption	The uptake and initial utilization of the intervention
Appropriateness	The perceived fit or relevance of the intervention
Feasibility	The practicality, fit, or utility of the intervention
Fidelity	How closely the intervention resembles what is intended
Implementation cost	Includes the marginal costs, cost-effectiveness, and cost-benefit of the intervention
Coverage	The degree to which the relevant population actually received the intervention
Sustainability	The ability for the intervention to be maintained, integrated, or incorporated into routines

Adapted from Proctor et al., 2011 (94) and Implementation Research in Health: A Practical Guide (93).

Acceptability and adoption can relate to staff or stakeholder buy-in. Buy-in refers to the "shared vision" from staff that is crucial in implementing change (97). While it is understood that agreement is necessary for successful change, information on how to promote buy-in is more scarce (97). In regards to THN programs, Drainoni et al. found that implementation is challenging, and that staff buy-in and uptake of a new naloxone intervention relied on more than just a shared vision or acceptance (98). The feasibility and fidelity of an intervention

explore to what extent an intervention can be carried out, and how closely the intervention follows the intended plan. Coverage refers to how much of the population receives the intervention, and is an important aspect of THN programs, given the benefits (reduction in overdose mortality) with widespread coverage (73). The extent into which an intervention can successfully implement the aforementioned elements will likely contribute to the sustainability of an intervention.

Implementation strategies refer to what is needed to help deliver an intervention (93). Strategies are often aimed towards multiple actors, and underline the importance of multi-level engagement. Powell et al. created a compilation of various implementation strategies and found six distinct processes: planning, educating, financing, restructuring, managing quality, and attending to the policy context (99) (Table 2). Elements of planning strategies relate to implementation outcomes (Table 1). For example, information gathering ("appropriateness"), building buy-in ("acceptability") and developing relationships ("acceptability" and "sustainability") can all relate to the outcomes from the implementation evaluation framework. By identifying and defining strategies, they can be used across a variety of settings by diverse groups of stakeholders (99).

Table 2: Implementation strategies and their components

Implementation strategy	**Components**
Plan	Gather data, select strategies, build buy-in, initiate leadership, develop necessary relationships
Educate	Inform a range of stakeholders about the innovation/ implementation effort
Finance	Incentivize the use of clinical innovations and provide resources for training and support
Restructure	Alter staffing, professional roles, physical structures, equipment, and data systems
Quality management	Put data systems and support networks into place to continually evaluate and enhance quality of care, and ensure that clinical innovations are delivered with fidelity
Attend to policy context	Encourage the promotion of clinical innovations through accrediting bodies, licensing boards, and legal systems

Adapted from Powell et al., 2013 (99).

Similar to issues with poorly defined terms for implementation outcomes, implementation strategies are often inconsistently labelled or inadequately described (100). Therefore, it has been suggested that implementation strategies be reported with enough precision to allow for measurement and reproducibility (95). In this project, which involved multiple intervention locations, two municipalities, and hundreds of staff members, successful implementation may have depended on distinct and local interplay of implementation strategies and processes. However, specific strategies were not explicitly defined prior to the implementation of the project, but will be discussed in light of the evaluation of the implementation.

1.4.2 Scaling-up public health interventions

One aim of implementation research is how to best scale-up public health interventions. Success factors and barriers have been identified for interventions in a variety of settings (91). Some success factors include: 1) infrastructure that supports the implementation (such as training), 2) active engagement of the implementers and the target community, 3) tailoring needs to the local context, 4) use of evidence-based practices, 5) establishing monitoring systems, 6) political will, 7) clarity of the implementer's role, 8) financing, and 9) integration into existing resources (91). Scaling-up also requires an identification of barriers that may impact an intervention's ability to be successful. Common barriers that have been identified include: not adapting to the local context, budget constraints, lack of staff, resistance to new practices (capacity limitations), lack of political will, leadership changes, poor engagement with stakeholders, and poor role delineation (91).

To address the factor of infrastructure support, training of the staff who implement the intervention is necessary. Active engagement of the implementers has been identified as a success factor for scaling-up and can be achieved through staff trainings. One method that has been effective in disseminating public health interventions is the train-the-trainer model (101). This involves a central trainer, who trains others, who can then train others in a target population. This method has been effective in various fields, including HIV education (102) and mental health services (103). A benefit to this method is its ability to train a high volume of trainers in a relatively short amount of time. The participants are often already working directly with the target group, and are in a prime position to carry out the intervention once trained. The use of existing facility infrastructure has been identified as a success factor, and this method focuses on the local use of staff and their participation in implementation.

However, integrating an intervention into existing structures is also a complex process which requires alignment of attitudes, budgets, regulations, and policies (93).

1.5 Nordic context

1.5.1 Norwegian Government

Norway is a democratic constitutional monarchy, wherein power is shared between three branches: the executive (Government), legislative/ house of Parliament (Storting), and judicial (courts). The government is formed by the party, or parties, that have a majority in the Storting. In other words, the Government is only indirectly chosen by the electorate. The last general elections took place in September 2013 and resulted in a change of government from a center-left majority coalition (Arbeiderpartiet, Sosialistisk venstreparti and Senterpartiet) to a right-wing minority coalition (Høyre and Fremskrittspartiet), with parliamentary support from two centrist parties (Kristelig Folkeparti and Venstre). This change took place during the progression of the project, and is a significant contextual factor, since that political support was sustained through this change of government (Table 3). The democratic changes did not affect the progress of the project, likely as a result of a somewhat homogenous political climate in Norway towards drug policies and treatment.

1.5.2 Norwegian health services

The Norwegian national insurance scheme (Folketrygden) is based on automatic and universal enrollment and provides access to health care for all residents in Norway. This single-payer social welfare system guarantees a primary care provider, as well as subsidized costs for long-term medications and visits. Each municipality is responsible for providing health services to its residents. For people who use drugs, an extensive network of services are available, including mental health services, primary care, street outreach, low-threshold facilities, and treatment. Treatment units provide detoxification, outpatient treatment, and long and short inpatient treatment (104). Opioid maintenance treatment is offered from the national system, and although applicants in the past were often wait-listed prior to being accepted into the program (105), today in Norway there is next-day start up as well as drop-in centers that do not require a referral.

Low-threshold facilities exist in many of the Norwegian municipalities. Many of these services are available through partnership with volunteer organizations, or integrated into existing health services. Whether private or public, these are publically funded facilities that

offer a variety of health and social services for PWID at no cost to the client. Some of these include drop-in day centers, overnight housing, needle exchange, street outreach, and a drug consumption room.

1.5.3 Take-home naloxone in Scandinavia

Variability exists within Scandinavia in regards to harm reduction and THN. Prior to the start of this project in 2014 there were no THN programs in Norway. In Denmark in 2013, a take-home naloxone program was introduced by the Danish Ministry of Health (26). The project initially began in the four Danish municipalities known to have an open drug scene, with plans for future expansion. Within the first year and a half, 100 people were trained to distribute naloxone, resulting in 121 drug users trained. Each naloxone distributed in Denmark requires a personal prescription (26).

To date, neither Sweden nor Finland have THN programs in place. There has been interest in Sweden to start a THN program; however political obstacles appear to make it difficult to begin. Sweden has a goal for a drug-free society as part of its National Action Plan on Drugs. While an abstinence-based policy inherently provides insufficient harm reduction services, the United Nations Office on Drugs and Crime praises Sweden's restrictive policies for lowering prevalence and incidence rates of drug abuse in comparison with other European countries (106). Among substitution treatment programs in Scandinavia, Denmark, Norway, and Finland explicitly list 'harm reduction' as a goal of treatment, whereas Sweden focuses on the cessation of drug use (107). This ideological difference likely has implications for the development of harm reduction interventions, such as THN within the Nordic context.

1.6 Objectives this thesis

The overall objectives of this thesis were to 1) describe characteristics of opioid overdoses occurring in Bergen, Norway, and 2) evaluate the introduction and implementation of a widespread take-home naloxone program in Norway.

The specific aims were to:

I) Investigate demographic, geographic, and temporal patterns of nonfatal opioid overdoses attended by ambulance services (paper I)
II) Evaluate the impact of a staff training course on knowledge and attitudes towards distributing naloxone (paper II)
III) Describe the characteristics of participants trained to use naloxone, including an investigation into overdose risk factors (paper III)
IV) Monitor naloxone coverage (paper III)
V) Interpret findings in relation to implementation outcomes

2.0 Material and Methods

2.1 Design

This thesis included three different samples. To address aim I, cohort ambulance data from Bergen emergency medical services (EMS) included opioid overdose patients from January 1, 2012 to December 31, 2013 (paper I). Paper II was a quasi-experimental study that utilized a pretest-posttest study design during staff training sessions to address aim II. Paper III was part of a longitudinal survey study to establish a cohort, with a convenience sample of those that were trained and came back for a refill of naloxone (aims III and IV). Paper III monitored the distribution of naloxone and the characteristics of participants trained in Oslo and Bergen from June 2014 to December 2015 (aims III and IV).

To address aim V, a post-hoc evaluation of the implementation of the project was done using findings from the above mentioned studies, communication with the project coordinators and staff, and from recurrent feedback and themes that revealed themselves as the project progressed.

2.2 Setting and study populations

2.2.1 Setting

Overdose mortality rates in Norway are among the highest in Europe (108). Oslo and Bergen are the two largest cities in Norway and experience the highest overdose rates in the country (109). Oslo has a population of approximately 650,000 and Bergen has 275,000 (110). There are estimated to be between 7,000-10,000 PWID in Norway, with heroin being the most commonly injected drug (111). From 2009-2013 there was an average of 250 drug-induced deaths each year, with one third of these occurring in Oslo and Bergen (109).

Opioid maintenance treatment in Norway began in 1998, and buprenorphine became available in 2001. By 2013 a little over half of patients in OMT in Norway were receiving buprenorphine/naloxone treatment (104). Unlike some other OMT programs in Europe, in Norway it started out as high threshold and restrictive (112). The program was borne out of a societal framework of restrictive drug policies and resistance from professionals and the public (112). Gradually the program has expanded and become more accepted and liberal, with approximately 50-60% coverage for opioid users today (113). This has come alongside a more general shift in Norway, adopting harm reduction practices as an integrated part of

health services (such as the establishment of a drug consumption room in Oslo in 2005 and ongoing discussions on allowing heroin-assisted treatment).

Although Norway ranks among the highest in Europe for overdose mortality, cross-national comparisons may be problematic (114). Countries that have high rates of AIDS or hepatitis C-related deaths could see lower rates of deaths due to overdoses due to competing risks (114). Additionally, the methods that different countries use to detect and code overdose deaths will impact the reporting (114). However, within the Norwegian setting, people who use drugs exhibit many known risk factors for overdosing. A high proportion of heroin users in Norway inject, along with significant poly-drug use (115). In total, most of the overdose deaths today in Norway are complex and multifactorial: the older and aging user population may face co-morbidities associated with their drug using past, but may also indicate longer survival within a cohort of PWID who initiated use several decades ago (116). Further, the restrictive treatment policies of the past may have implications for the health of people who use drugs today in Norway, as they experienced prolonged periods of illicit drug use outside of treatment.

2.2.2 Process of establishing take-home naloxone in Norway

The project has evolved since its conception in 2009 (Table 3). It began as a pilot in 2014 in Oslo and Bergen. In 2016, the project began expanding to additional municipalities. By May 2017, the majority of the municipalities who experienced the highest numbers of overdoses were included in the project, as a result of the stepwise introduction of the intervention. As shown in Table 4, this PhD project is part of a growing program with plans for continued expansion.

Table 3: Process of establishing THN in Norway prior to PhD period from 2009-2014

Date	Event
Late 2009	Conception of THN by a user advocacy group[1] who voiced concerns and requested immediate action for access to THN
November 2009	Members of parliament, Jon Jæger Gåsvatn, Kari Kjønaas Kjos, and Per Arne Olsen propose to Parliament that the Government should conduct an assessment regarding a pilot with intranasal naloxone (117)
December 2009	The Minister of Health, Anne-Grethe Strøm-Erichsen, communicates in a letter to Parliament that she will instruct the Directorate of Health to evaluate the proposal to conduct a pilot project with naloxone to prevent overdose deaths (118)
March 2010	A negative evaluation, due to lack of evidence, is issued by the Directorate of Health in response to the request from the Minister of Health
2010	The Norwegian Cochrane branch (Kunnskapssenteret) approaches Philipp Lobmaier at SERAF with a request to publish readily available data on THN
2011	A review paper is published and recommends a trial with naloxone (preferably intranasal) in Norway (119)
2012	American researcher Alex Kral on sabbatical in Sweden strongly advocates for THN in Sweden and Norway backed by his experiences from San Francisco. State Secretary Kjell Erik Øie visited Alex Kral in San Francisco and returned to Norway positive towards beginning a naloxone program
2012-2013	Epidemiological analysis time period (paper I)
June 2012	In White Paper 30 (2011-2012) presented to Parliament in June 2012, the Government announces plans to develop a National Overdose Prevention Strategy (120)
March 2013	White Paper 30 is adopted by Parliament, endorsing the proposal on a National Overdose Prevention Strategy (121)
June 2013	SERAF is assigned to develop, implement, and evaluate a THN project. The Directorate of Health hosts and facilitates SERAF meetings with the Norwegian Medicines Agency to discuss intranasal options
October 2013	The Solberg Government replaces the Stoltenberg III Government
January 2014	National Overdose Prevention Strategy introduced
January 2014	PhD project period begins

THN: Take-home naloxone, SERAF: Norwegian Centre for Addiction Research, [1] FHN: Norwegian association for humane drug policies

Table 4: Evolution of take-home naloxone in Norway during PhD period from 2014-2017

2014			
Winter	**Spring**	**Summer**	**Fall**
January: PhD period begins Development of overdose prevention training, staff training course, and data collection forms	April: Trip to the United States to visit existing naloxone programs and meet experts in the field to discuss implementation May: Staff trained from distribution sites (Paper I) (ongoing)	June: Take-home naloxone begins in Oslo and Bergen Data collection begins (Paper III)	Ongoing data collection, staff training, and project expansion
2015			
Winter	**Spring**	**Summer**	**Fall**
Ongoing data collection, staff training, and project expansion	Ongoing data collection, staff training, and project expansion	Ongoing data collection, staff training, and project expansion	Ongoing data collection, staff training, and project expansion
2016			
Winter	**Spring**	**Summer**	**Fall**
December (2015): Data collection period ends (Paper III)	Expansion of project to additional municipalities[1]	Ongoing data collection, staff training, and project expansion	Ongoing data collection, staff training, and project expansion
2017			
Winter	**Spring**	**Summer**	**Fall**
January: Implementation evaluation framework identified	May: PhD period ends Naloxone program continues to expand	Naloxone program continues to expand	Naloxone program continues to expand

Seasons as defined by the Nordic climate- Winter: December, January, February; Spring: March, April, May; Summer: June, July, August; Fall: September, October, November

[1] Tønsberg, Fredrikstad, Porsgrunn, Tromsø, Arendal, and Skien

2.2.3 Study populations

Each study investigated different populations. The study population in paper I (n=463) included those treated for an opioid overdose by Bergen ambulance services during the study period. A positive response to naloxone (increased respiration or consciousness) was the

inclusion criteria, and exclusion criteria included patients that did not respond to naloxone, indicating some other life-threatening event, such as a GHB overdose or myocardial infarction, or if they were deceased.

Paper II included staff who attended a naloxone trainer course during the two-month study period (n=54). The trainer course was available to all staff at the participating facilities, and answering the questionnaire survey was voluntary. The questionnaire was given immediately before and after the trainer course. Scores were tallied only for those who answered both the pre-training test and post-test completely.

Paper III included participants who attended a naloxone training from one of the several participating low-threshold facilities from June 2014 – December 2015. Initial training facilities involved were those that provide services for active injection drug users. Sites included drop-in day centers, overnight housing shelters, medical facilities, a prison, and a safe injection facility. Training sessions were available to anyone interested in being trained who were at risk of either experiencing or witnessing an overdose. Participation in the questionnaire study was voluntary. Data was analysed from those who consented to participate in the study.

2.3 Study Instruments and naloxone training

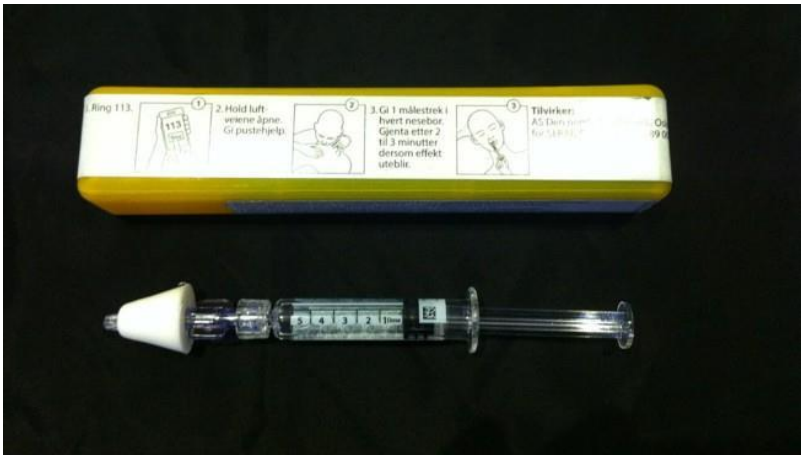
2.3.1 Opioid overdose prevention training with naloxone

The curriculum for the staff training was created using elements from existing resources (66), and utilized feedback from a pilot reference group with PWID and staff members from one facility. Adaptations were made from the US-based training curriculum to incorporate the comments from the group. The major themes covered in the training included 1) background for THN programs, 2) mechanisms of an opioid overdose, 3) effects of naloxone, 4) signs of an overdose, 5) response to an overdose, 6) project record-keeping documentation, 7) assembly and administration of intranasal naloxone, and 8) possibilities for implementation within each site. The course also introduced the potential new role that the trainers would have when discussing past overdoses with their clients, and the possible need for debriefing services. The didactic course used a PowerPoint presentation and took approximately two hours to complete. No online or automated trainer programs were used. There was no follow-up with the staff in terms of fidelity or retained knowledge.

The staff that were trained to be trainers (paper II) conducted overdose prevention trainings, including instructions on the use of naloxone for interested participants (paper III). The client trainings were brief and flexible, lasting between 5-10 minutes. Trainings could be done individually or in a group format. The staff reviewed with participants common risk factors for overdosing, how to identify the signs of an overdose, and what actions to take if witnessing an overdose. Trainings were taught to be performed in a dialogue format, engaging the participant by asking questions, rather than in a lecture format. This was a direct result from the experiences learned during our visit to existing THN programs in the US.

Staff demonstrated how to assemble and administer naloxone, and participants were encouraged to practice assembling the device (Figure 1). The 2.0 mL prefilled syringe consisted of five- 0.4 mL doses with a concentration of 1mg/1mL. Participants were taught to titrate the dose, giving one dose in each nostril and then observing for the return of breathing. If no effect, they could repeat while awaiting ambulance. There was also a video with instructions for assembly available on the project website (www.stoppoverdose.no). The importance of calling the ambulance and follow-up monitoring was emphasized. Participants received one nasal spray, a breathing mask, a training confirmation card, and instructions for use and follow-up if/when they used the naloxone.

Figure 1: Naloxone nasal spray used for the project



The Norwegian Medicines agency approved the assembly of the novel device by a local drug manufacturing company (Den Norske Eterfabrikken). The approval allowed for the project to proceed with an interim spray while awaiting a licensed intranasal product in Norway. The device was chosen due to its relatively simple assembly and the option to titrate the doses.

Upon returns for refills, the staff trainers inquired about the previous use of the spray and the outcome. Participants were offered an opportunity to debrief and discuss the overdose with the possibility for follow-up from the staff.

2.3.2 The Opioid Overdose Knowledge Scale and Trainer Attitudes

The opioid overdose knowledge scale (OOKS) is a questionnaire that assesses knowledge about risk factors for overdosing, the signs of an overdose, response to an overdose, and the use of naloxone. The scale was developed by Williams et al. to evaluate take-home naloxone programs (122). The self-administered multiple-choice questionnaire has proven to be internally reliable, and to have a high level of test-retest reliability after a mean time of 14 days (122). The questionnaire takes approximately 10 minutes to complete, and consists of 4 multiple choice questions, 4 forced choice questions, and 6 true-false statements (122). Each correct response receives a point out of a total 45 points. There were two questions that were removed from the original questionnaire as they related to injectable naloxone, and this project used intranasal (appendices I and II).

Additional questions were added to assess the trainer's attitudes towards naloxone. A 5-point Likert scale was used (1=low, 5=high) to assess the participant's perception of their understanding and comfort teaching others about naloxone, overdose prevention techniques, risk factors for overdosing, and responding to an overdose. They were also asked about their perceived preparedness to train others, the usefulness of the course, and their intention to train others afterwards. A sum score was calculated for each area by dividing the number of completed items with the total score.

2.3.3 Naloxone enrollment questionnaire

A questionnaire was developed for staff to administer to participants in the naloxone study and was used to describe participant characteristics for paper III. The questionnaire was made with the intention of identifying specific overdose risk factors with the participant, so that the trainer could aim to discuss overdose prevention messages that were individually tailored. The questionnaire was first piloted among a small group of staff from one of the low-threshold facilities that participated in the project. Following their suggestions to shorten the questionnaire, a 10-item 1-page form was finalized (appendix III). The first version was used for 2-months before additional feedback from staff using the forms was received. A second version of the questionnaire included their suggestions to 1) increase the number options for

how many times an overdose had been witnessed and experienced from 1-5, 6-10, and more than 10 to 1-10, 11-20, and more than 20, 2) add in "not applicable" options to each question, and 3) add in 'CPR' as an option for what the respondent does when witnessing an overdose.

The enrollment questionnaire included: 1) location of the training, 2) training date, 3) participant's date of birth and gender, 4) frequency of opioid use, 5) recent detoxification or imprisonment, 6) use of methadone, 7) use of opioids while alone, 8) use of opioids together with other substances, 9) mode of administration, 10) how many times they have witnessed and experienced an overdose, and 11) what actions they took when they witnessed an overdose. National identity numbers were also requested.

2.3.4 Naloxone refill questionnaire

A separate questionnaire for refills was developed for staff to administer to participants when they returned for naloxone replenishment (appendix IV). Similar to the enrollment questionnaire, it was first piloted among a small group of staff. After eight months with the original form, the questionnaire was altered to include an inquiry into if the victim experienced any withdrawal symptoms following the administration of naloxone.

The refill questionnaire included questions about the 1) the rescuer's relationship with the victim, 2) which drugs the victim used, 3) where the overdose happened, and 4) what actions they took (calling the ambulance, stimulation, recovery position, CPR, injecting with salt, water, or other drugs). Participants were asked if the ambulance came, and about the outcome for the victim. National identity numbers were requested, which provided information on age and gender.

2.4 Study factors and outcome variables

2.4.1 Bergen ambulance study (paper I)

In this study, demographic information included age and gender. Outcome measures included the overdose location (public or private), time from dispatch until ambulance arrival (less than or more than ten minutes), and the disposition for the victim following ambulance care (transported further or left at the scene). Overdose frequencies for the different times of the day, days of the week, and months of the year were analyzed.

2.4.2 Train the trainer study (paper II)

This study measured the effectiveness of a staff training course on their knowledge and attitudes towards distributing naloxone. Demographic information included gender, profession, the type of facility they worked at, and their number of years of experience working with people who use drugs. The outcome variables included pre- and post- testing of their knowledge on risk factors for overdosing, signs of an overdose, actions to take when witnessing an overdose, and how to use naloxone. Staff attitudes were measured using a five-point Likert scale.

2.4.3 Description of the characteristics of participants trained (paper III)

This study described the characteristics of participants who attended a naloxone training. For the initial training, gender, age, and risk factors for overdosing (frequency of opioid use, recent periods of non-use, mixing opioids with other drugs, most common mode of administration, and past witnessed and experienced overdoses) were measured. Upon return for a refill, variables included the participant's relationship to the victim, location of the overdose, actions taken during the overdose, reported symptoms after giving naloxone, the dose of naloxone used, and the outcome for the victim. Factors associated with having 10 or more self-reported overdoses (indicating a high burden/severe substance use disorder) in the participant's lifetime were explored.

2.4.4 Monitoring naloxone distribution (paper III)

In attempts to adequately reach the target population, estimations for distribution goals must be made. One method of calculating necessary naloxone coverage is based on suggested naloxone distributed per population. Walley et al. found the greatest reduction in overdose mortality when naloxone saturation was greater than 100 per 100,000 population (73). An alternative method is based on an assumption from a study in Scotland that trainees encounter a 6% fatality rate (based on synthesis evidence from the US and UK), therefore needing 9-20 times the amount of naloxone for observed overdose fatalities in a location to assure adequate coverage (78). This is based on the average of three witnesses being present at an overdose, the chances of them having been trained to use naloxone, and the likelihood that they would be carrying their naloxone (78). Based on these two methods, estimated annual distribution goals were between 923-2194 sprays for the two cities combined, using population statistics (123)and average annual fatality numbers from 2009-2013 (109).

2.5 Data analysis

Analyses were performed using SPSS version 22.0.

Different analyses were performed for papers I-III (Table 5). Descriptive statistics and frequency measures were used to describe each study sample. A p-value of <0.05 was considered statistically significant.

In paper I, independent–samples t-tests were used to compare if the mean of the continuous variable (age) was different among genders. Chi square tests were used to analyze if the frequencies for various categorical variables (weekday, month) differed from each other, and to explore the relationship between ambulance arrival time (more than 10 minutes/less than 10 minutes) for drug related and non-drug related calls. Analysis of variance (ANOVA) was used to compare the continuous variable (age) during the various months. To explore factors predicting the likelihood of overdosing in a public location, Cox regression analysis was used with the covariates of age, gender, and month. The interpretation of odds ratio as a surrogate for relative risk with logistic regression can be problematic for common events (>10%) as it overestimates the risk (124). In this case, an estimation of relative risk can be done using Cox regression. Since the outcome variable (overdosing in a public location) was a common event in this study, Cox regression was used to allow for an interpretation of relative risk.

In paper II, the Wilcoxon Signed Rank Test was used to measure the repeated knowledge scores for the staff participants. Effect scores were interpreted using the Cohen criteria where 0.10-0.29=small effect, 0.30-0.49=medium effect, and greater than 0.50=large effect. Means from the 5-point Likert Scale investigating changes in attitude were calculated and compared pre-training and post-training. The non-parametric Wilcoxon Signed Rank Test was chosen due to the non-normally distributed data (125). The histograms of the data displayed non-normal distribution. Both the Kolmogorov-Smirnov and Shapiro-Wilk numerical tests for normality showed values less than 0.5, indicating non-normal distribution.

Binary logistic regression was used in paper III to explore predictors for having a high rate of past overdoses. On the original the survey, the question asked if the participant had experienced 1-10 overdoses, more than 10 overdoses, or never had an overdose. Although this was later changed to include an option for responding ‘more than 20 overdoses,’ the dichotomous variable of ‘more than 10/less than 10 overdoses’ for current opioid users was used for the analysis. Univariate analyses were first performed on a variables thought to be relevant, and significant associations of p<0.1 were included in the multifactorial model. The

distribution rate per 100,000 population was calculated using population estimates as of January 1, 2015 (110) and the reported naloxone distributed from the participating sites.

Table 5: Statistical analyses for papers I-III

Statistical analysis	Paper I	Paper II	Paper III
Descriptive statistics	X	X	X
Chi-square test	X		
Independent samples t-test	X		
ANOVA	X		
Cox regression analysis	X		
Wilcoxon paired signed rank test		X	
Binary logistic regression			X

2.6 Ethics

Participation in the studies was always voluntary, and participants signed consent forms allowing for the use their data. Studies were conducted in accordance with the Declaration of Helsinki (126). Participants were also able to withdraw from the study at any time without explanation, where their data would then be removed from the files. Receiving a naloxone training was independent of filling out the forms or participating in the research study, and approximately 40% were trained without filling out forms. Paper I was approved by the Norwegian Data Protection Official for Research and the Regional Ethics Committee (Reference number: 2014/1742). Paper III was issued an exemption from the Regional Ethics Committee (Reference number: 2014/850) and issued a waiver from the Norwegian Data Protection Authority (Reference number: 14/01008-2/RCA). The analyses of ambulance data did not require any changes to routine overdose treatment, as data was extracted from existing sources (paper I). Paper II collected data anonymously among staff. Analyses were only conducted on those that provided consent for paper III.

3.0 Results

3.1 Aim I: Non-fatal overdose patterns

A total of 463 patients were treated by Bergen ambulance services during the 2-year study period. The majority of the patients were male (n=313, 67.6%), and ranged from 17-63 years old (mean=32.8, SD=9.42). The temporal overdose patterns followed sleep-wake cycles, with the majority occurring in the late-afternoon and evening hours. There was no significant difference in overdose call-outs for the different days of the week (p=0.08), however Fridays and Sundays had the fewest call-outs (n=59, 12.7% and n=48, 10.4% respectively).

Monthly variation showed significant differences ($p<0.001$) and August had the most overdoses during the study period (n=71, 15.3%). The peak in August was particularly pronounced for overdoses in public locations, with a nearly doubled risk for overdosing in a public location during August (RR= 1.92, 95% CI, 1.02-3.62).

The ambulance response times ranged from 1.7 to 51 minutes (median 6.8 minutes). For 18.4% of the cases (n=85), the ambulance arrival time was greater than 10 minutes. The strongest predictor for arrival times greater than 10 minutes was dispatch to a private home (RR= 1.66, 95% CI, 1.05-2.60). There was no difference in ambulance response time for drug-related and nondrug-related calls (p=0.69).

Patient disposition following ambulance care was split between being transferred for further follow-up (n=237, 51.2%) and not transferred (n=226, 48.8%). Those that were picked up from a private location were more likely to be left at the scene following ambulance treatment (RR=1.47, 95% CI, 1.10-1.96).

3.2 Aim II: The impact of a staff training course

From 2014 to 2015, 511 staff were trained to be trainers during 41 trainer sessions. During the 2-month study period, a convenience sample of 54 staff were asked to participate in the survey. The majority were female (n=40, 74%) and nurses and social workers made up the majority of the group (n=37, 68.5%). Nearly half of the participants had over five years' experience working with people who use drugs (n=23, 42.6%).

In all four areas of knowledge assessed (risks for overdosing, signs of an overdose, actions to take, and the use of naloxone) scores improved significantly ($p<0.001$). The total average score increased from 78.4% correct to 91.1% correct on the post-test.

Self-reported attitude mean scores were based on a Likert Scale of 1 to 5. The staffs' self-reported understanding on overdose risk factors, prevention techniques, and recognition and response to an overdose significantly increased from 3.17 (SD=0.95) to 4.3 (SD=0.45) following the training. In addition, their attitude towards the role of naloxone in prevention work improved after the training ($p<0.001$). The largest post-training change was seen in the staffs' reported preparedness to train others and to respond to an overdose if they themselves encounter one (2.22, SD=0.97 to 4.22, SD=0.55).

Most staff felt that the two-hour training course was an adequate amount of time (n=49, 90.7%) and that a PowerPoint presentation was an appropriate delivery method (n=37, 68.5%). On the scale of 1(least useful) to 5 (most useful), the staff rate the course a mean score of 4.68 (SD=0.7).

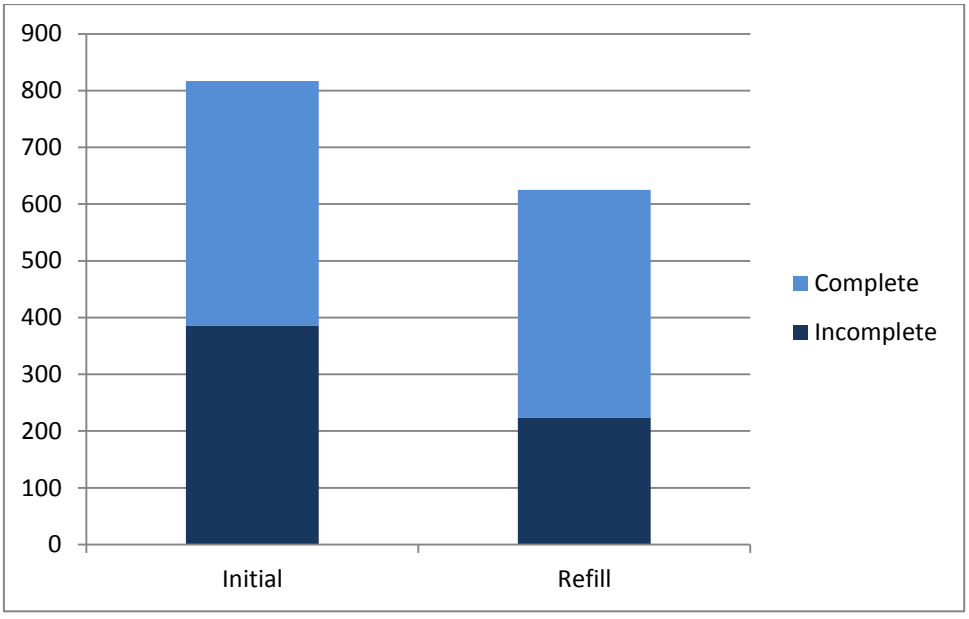
There was no follow-up with the staff in terms of fidelity or retained knowledge. While knowledge and attitude scores were assessed pre- and post- training, there was no observance of actual trainings and adherence to the training protocol in real life clinical practice.

3.3 Aim III: Characteristics of participants trained to use naloxone

The questionnaire response rate from the total number of sprays distributed was 32.8% (n=433) for the initial training and 54.6% (n=401) for refill visits. There were 389 initial training forms and 224 refill forms that were submitted but lacked the signed consent form and therefore were not included in the analysis (Figure 2). Due to the use of multiple facilities and paper forms; it was not possible to link data from the participants for their initial and refill visits.

For the initial training, ages of respondents ranged from 19 to 65 (median age 36.8) and the majority were male (n=289, 67%). Most of the participants were either current or previous opioid users (n=369, 85%). Of these current and previous users, nearly all (n=338, 92%) had reported at least one risk factor for overdosing (recent periods of non-use, using drugs while alone, mixing opioids with benzodiazepines, or injecting).

Figure 2: Complete and incomplete questionnaires from June 2014- December 2015 in Oslo and Bergen



Complete forms included those that had filled out both the questionnaire and signed the consent form. Incomplete forms were those that filled out the questionnaire, but lacked the signed consent form.

Almost all of the participants in the initial training had either witnessed (n=394, 91%) or experienced (n=305, 79%) an overdose in their life. For those that had experienced an overdose, 23% (n=86) had reported having 10 or more overdoses in their lifetime. Logistic

regression analysis was used to identify factors associated with having had the highest rates of previous reported overdoses (more than 10). In an adjusted model, injecting (OR=2.4, 95% CI=1.14, 5.00) and concomitant benzodiazepine use (OR=2.6, 95% CI= 1.31, 5.23) were significant predictors for having more than 10 overdoses.

For those that returned for a refill, ages of respondents ranged from 22 to 61 (median age 36.7). Males made up 54.6% (n=223) of the group. The recipient of the naloxone was most often the rescuer's friend (n=78, 30%) or acquaintance (n=75, 29%). When asked about the use of the original naloxone spray, 70% (n=277) reported to have used it on an overdose. The victim survived in 96% (n=265), with the remaining outcomes being unknown (n=3, 1%) or missing (n=9, 3%).

3.4 Aim IV: Naloxone coverage

For the study period of June 2014-December 2015, 2,056 naloxone nasal sprays were distributed in total from the 20 participating facilities. Based on the methods for estimating goals for naloxone coverage (section 2.4.4), this study met its distribution goals of distributing over 100 per 100,000 population. A distribution rate of 144 per 100,000 population was achieved in total for both of the cities, as well as 12 times the cities mean annual overdose deaths in 2015. Oslo and Bergen had similar distribution numbers in 2015, however, when population size is taken into account; Bergen more than doubled their distribution goal. Oslo distributed 100 per 100,000 and Bergen distributed 249 per 100,000 in 2015. Unpublished distribution numbers from June 2014 until December 2016 (Figure 3) show an increasing amount of naloxone distributed as the project progressed.

Figure 3: Initial and refill naloxone distribution from June 2014 to December 2016 for all distribution sites

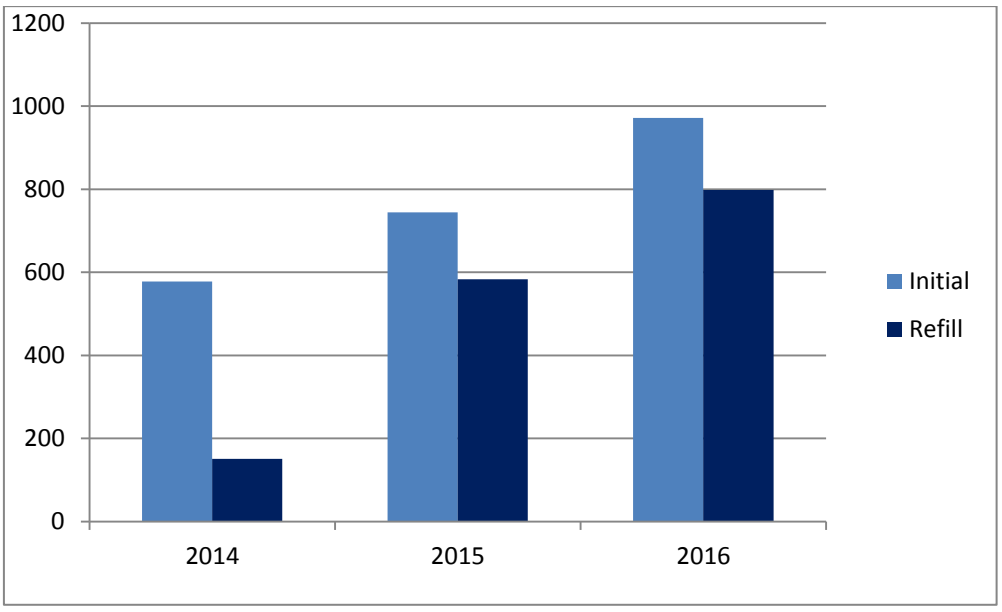
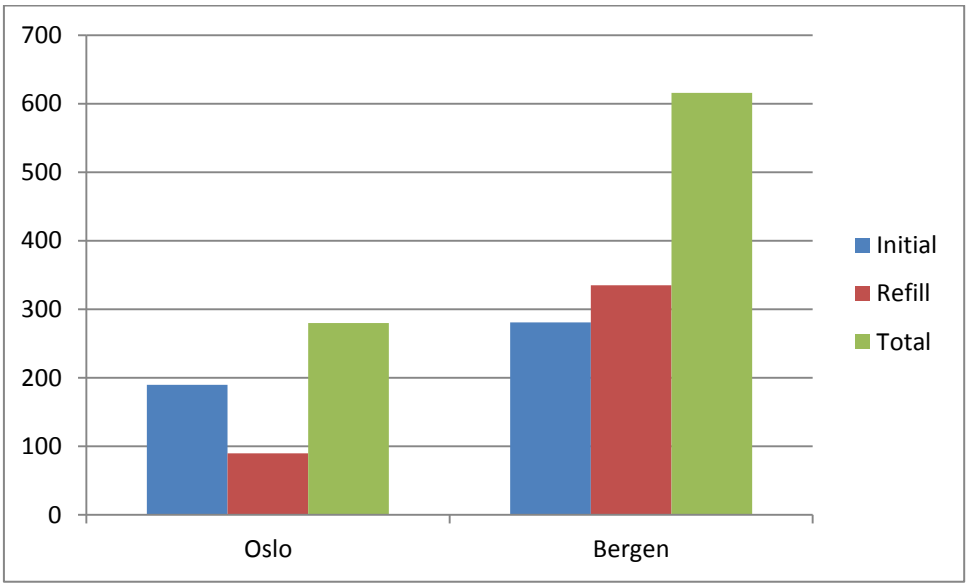


Figure 4 shows the accumulated distribution rates for the cities when adjusted for population size (unpublished). The number of refills has surpassed the number of initial sprays that were distributed in Bergen, indicating a saturation of the target group.

Figure 4: Accumulative naloxone distribution rates for Oslo and Bergen from June 2014 to December 2016 adjusted per 100,000 population



3.5 Aim V: Evaluation of implementation

3.5.1 Implementation outcomes and strategies

The implementation outcome variables described in section 1.4.1 provide a framework for evaluating the implementation of the project, as well as future monitoring. Each of the outcomes in the table is evaluated to what degree it was met with examples from published papers, discussions with the two project coordinators, and recurrent themes and feedback. In most of the outcome domains there were areas that were both met and unmet by the project (Table 6).

Various strategies were used when developing the intervention; however they were not explicitly defined prior to the project. In relation to the strategies defined in Table 2, the main implementation strategy relied on the trainer course ("plan" and "educate") which covered what was needed for a new site to participate in the intervention ("restructure"). The course focused primarily on the overdose prevention curriculum, and did not provide time for "quality management," including in-depth discussions into how the new site would accommodate the new trainer role, how the leaders would help to establish this change, and what specific actionable steps were needed to implement the intervention (i.e. practical issues such as where to store the naloxone and who was responsible for reporting back the distribution numbers). To help promote buy in ("plan"), "naloxone ninjas" (enthusiastic contact persons from within various sites) were invited to meetings and social events to create a forum for feedback, as well as a chance for the project staff to convey appreciation for their efforts.

Table 6: Evaluation of implementation of take-home naloxone in Norway

Implementation outcomes	Findings
Acceptability	
User perception that the intervention is agreeable	**Met:** User feedback included numerous cases of satisfaction with the intervention (section 3.5.4). A popular user advocacy group (FHN) participated in distributing naloxone as peer trainers.
Staff perception that the intervention is agreeable	**Met:** Staff trainer course resulted in improved attitude scores towards the intervention (section 3.2) and staff reported interest in the intervention (section 3.5.4). **Unmet:** Anecdotal feedback from some staff reported concerns over if the intervention "enabled riskier drug use," concerns over its ability to be effective for buprenorphine overdoses, increases in workload, and the possibility to lose people to follow-up if not met in the usual channels (i.e. people not calling the ambulance) (section 3.5.4).
Government perception that the intervention is agreeable	**Met:** Funding and permission were granted to carry out intervention in additional municipalities from the government (section 2.2.2). Meetings with the Norwegian Medicines Agency resulted in the ability for the project to use the unlicensed nasal spray in the interim while awaiting a licensed product.
Adoption	
Staff uptake of the intervention	**Met and unmet:** Varied responses from staff and facilities in participating in the project once trained. Not all staff trained continued as trainers (section 3.5.4). Some resistance over filling out data collection forms as they added to existing workloads. There was no follow-up with the staff who had attended a training to assess to what degree they engaged in the project (section 3.2).
User uptake of the intervention	**Met**: High volumes of naloxone were distributed to the target at-risk group (section 3.4).
Appropriateness	
The relevance or perceived fit of the intervention	**Met:** Nonfatal overdoses were a concern in Bergen (see section 3.1). High rate of previous overdoses witnessed and experienced in the group trained (section 3.3). **Unmet:** Project was unable to establish in prisons to provide trainings upon release, a well-known at-risk group (section 3.5.3).
Feasibility	
Ability for the intervention to be carried out	**Met and unmet:** Certain facilities were more able to carry-out the intervention than others. Feedback included time constraints from the staff (section 3.5.4). Staff reported user interest to be higher in facilities where they were "coming for services" than shelters which operated as their home (section 3.5.4).
Fidelity	
Intervention similar to original plan	**Unknown:** Hundreds of staff were trained to be trainers. No follow-up analysis of the fidelity was conducted to test how accurate the staff trainings were over time (section 3.2).
Coverage	
How much of the relevant population received the intervention	**Met:** Naloxone coverage met the suggested distribution levels for an at-risk group (section 3.4). **Unmet:** Unable to establish in high-risk prison release setting (section 3.5.3).
Sustainability	
Degree in which the intervention can be maintained	**Met:** From the start of the project until present, the program has grown in terms of participating facilities and naloxone distribution numbers (section 3.4). **Unknown:** The project is expanding (section 2.2.2) and it is yet to be seen how long and to what degree the project can be maintained.

3.5.2 Barriers to implementation

Common barriers to scaling-up public health interventions were described in section 1.4.2, and included: not adapting to the local context, budget constraints, lack of staff, resistance to new practices (capacity limitations), lack of political will, leadership changes, poor engagement with stakeholders, and poor role delineation (91). Each of these barriers is explored with an explanation of its presence in the project (Table 7).

Table 7: Presence of barriers to the implementation of take-home naloxone in Norway

Barrier	Yes	No	
Not adapting to local context	X		Towards the beginning of the project, THN trainings were very similar to those done in the United States. Following feedback, changes were made to better suit the Norwegian user context (primary mode of use is injecting, relatively lower use of pharmaceutical opioids, and different user relationship with EMS and law enforcement). Also, Norwegian society has a relatively flat decision making process, where mass participation in the decision making process is encouraged (127). This cultural context was overlooked while implementing the project, with occasional staff resistance to this "top down" approach to implementing.
Budget constraints		X	Funding was secured for the duration of the project.
Lack of staff		X	Existing staff from participating facilities were eligible and accessible as trainers.
Resistance to new practices	X		As presented in section 3.5.4, although the majority of staff were positive and engaged, some were resistant to new practices. This was due to a variety of reasons, whether ideologically opposed to this approach, time constraints, or concerns over user behavior ("enabling riskier drug use").
Lack of political will		X	By being part of the National Overdose Prevention Strategy, there was political support (Table 3). The political support withstood a change of political power during the duration of the project (see section 1.5.1). The Minister of Health, Bent Høie, was present at the launch of the project in June 2014.
Leadership changes	X		Both leadership and staff turnover resulted in the project being vulnerable to these changes.
Poor engagement with stakeholders		X	By utilizing existing low-threshold facilities, many of the relevant stakeholders were involved in the project.
Poor role delineation	X		Staff were trained on their role as trainers during the trainer course, however some staff were hesitant to adopt the role (see section 3.5.4)

THN: take-home naloxone, EMS: emergency medical services

3.5.3 Project management

Project management is an essential part of implementation, and is included in the evaluation of the implementation of the project. First, a significant amount of time was used to monitor distribution numbers and collect surveys from the multiple facilities. Given that we were only a team of three researchers (responsible for the implementation, research, and formal issues, such as medication waivers) and two municipality coordinators (responsible for trainer trainings, facility follow-up, and distribution monitoring), this proved to be quite time and labor intensive. It was not uncommon during the start of the project for the sites to voice confusion over how to document and report their distribution numbers. Attempts were made to answer questions as they arose, however the project did not provide sites with a policy and procedure manual or a questionnaire guide. Further, the use of paper questionnaires allowed for incomplete or imprecise data collecting and time consuming data entry.

Second, although we did include a reference group which met regularly to discuss the project, we did not include a strong naloxone reference group of staff to meet regularly to allow for consistent and continual adaption to the local context. Contact with leaders from the facility was varied, and largely depended on initiation from the leader. There were no regular or recurring leader meetings.

Despite repeated attempts, we were unable to establish the project within the prison setting. Multiple staff trainings were held, and there was interest, however they were unable to uptake the intervention. During a training session of diverse prison staff, two guards stated that they didn't feel it was their job, and that the nurses should do it. One nurse reported that although she was in the position to train people (and interested), she did not have access into seeing the inmate's release date. Therefore it was difficult to reconcile doing a naloxone training close to the release date. These practical barriers appeared to limit the capacity in which the prisons could participate.

3.5.4. Staff feedback and buy-in

A finding from this study that is not captured in the papers is the reported feeling of empowerment from this intervention. Feedback from both the staff implementing the intervention and people who received the naloxone training echoed the empowerment they felt by participating. Several of the staff trainers expressed a sentiment of the value in giving their clients something "practical" and "tangible." Numerous staff trainers also reported

rescuing someone with naloxone themselves, and were convinced that the victim would not have survived had they not had naloxone. Many clients also felt empowered by the intervention and became "unofficial naloxone ambassadors" in their community, promoting that others get trained. Our collective impression of this intervention has been a positive response from both staff and PWID who welcomed an intervention that showcased their potential to help save lives.

Another unpublished finding from this study involved staff buy-in. From the numerous participating facilities, there were differences observed in the staffs' adoption of the intervention, seen by the naloxone distribution numbers. Staff from different facilities had different opinions and engagement in the project. Anecdotal feedback from hesitant staff reported concerns if the intervention "enabled riskier drug use," concerns over its ability to be effective for buprenorphine overdoses, and the possibility to lose people to follow-up if not met in the usual channels (i.e. people not calling the ambulance). This issue was also brought forward to the media with concerns over if the project would "cause more overdoses" by an interest group for family members of people who use drugs (128). Some disliked the data collection forms, as they added additional work. Certain staff reported that if they didn't feel completely confident in holding a training, they would forego doing it, as to avoid doing something wrong. This was especially true for nonmedical staff (social workers, outreach workers) who did not feel as comfortable discussing a medication as many of the nurses and doctors. There appeared to be a trend in sites where PWID would come regularly for services (example: the safe injection facility, a nursing outreach van, or drop-in day shelter) had a more natural rapport in discussing and delivering naloxone than sites where PWID lived (overnight housing shelters). Lastly, as a result of a "top down" approach, some staff reacted to being "told what to do" from an external source without being involved in the process from earlier on.

One facility was responsible for distributing nearly half of the total naloxone for the study period, whereas other facilities may have only distributed a handful. Ongoing feedback and dialogue revealed that staff buy-in alone was not enough. Leadership buy-in was also critical in promoting the project, as well as continuous coordinator follow-up. The facilities that had the highest distribution and refill numbers were those in which clients, staff, and leadership were interested. Leadership interest allowed for the time and space to conduct the trainings, which proved to be crucial for the staff to adopt the intervention, as seen from the highest distributing site.

3.6 Brief summary of findings

The temporal patterns of overdoses in Bergen suggest that opioid overdoses occur primarily during non-recreational time periods. Longer ambulance arrival times to private addresses provide potential for peer-rescue interventions and the temporal patterns may be useful in guiding local overdose prevention services (i.e. during the summer time).

The train-the-trainer model appeared to be effective in preparing staff involved with the intervention. Following the naloxone trainer course, their scores improved in both knowledge and their intention to distribute naloxone, however long-term fidelity, uptake, or adherence was not assessed.

The use of multiple existing facilities achieved rapid, high volume naloxone distribution for an at-risk group. Distribution goals were met within the first year, and were done so to a group that exhibited known risk factors for overdosing.

Using an implementation evaluation framework, different outcome domains were both met and unmet by the project. Many staff and clients reported feelings of empowerment from participating in the intervention. Stakeholder buy-in from both staff and leadership appeared to influence naloxone distribution rates. Staff had varying interest and engagement in the project from the different facilities, with a spectrum from enthusiasm to skepticism towards the intervention. The site that had the highest rates of naloxone distribution and refills was the facility with the most engaged leaders and a project coordinator on-site.

4.0 Methodological considerations

All studies are subject to sources of error. Methodological issues related to selection bias, information bias, and confounding can all present problems in a study (129). Systematic errors arise from issues related to the study's design and would be expected to occur repeatedly in similar studies. Random errors are due to chance, and would not be expected to occur repeatedly in similar studies (129). Typically random errors would not skew the data in a certain direction. In this section, each of these issues are explored for the various studies, and are discussed to what extent they may have impacted the results and generalizability.

4.1 Selection bias

Selection bias is a type of systematic error that arises from the selection of participants in a study, specifically when the participants are not chosen randomly. The process in which participants are selected, or the characteristics of those that participate, may impact the findings of a study (130). Random allocation to treatment is usually used to reduce the risk of selection bias, typically in experimental designs. For the studies in this thesis, testing between two groups was not a research priority, and randomization to receiving the intervention was not done. Therefore, the studies represent a more naturalistic/observational design.

The selection of non-fatal opioid overdoses was central for paper I, and the selection criteria from EMS services is outlined in the methods section 2.2.3. The ability for our study to correctly identify these cases relies completely on the ability of the EMS services to appropriately recognize an opioid overdose, and to document the cases in which victims responded to receiving naloxone. The lack of a central digital registration of these cases relies on the individual identification of each case in order for it to have been included in the dataset. It is therefore possible that cases that should have been included in the study were not. This selection bias would likely result in an underreporting and an underestimation of overdose cases in the study, and would likely be random, and not likely to introduce systematic bias to the study.

This underreporting may be due to the lack of the EMS services classifying a case as overdose, but it may also represent an underreporting of the total overdoses in the city due to the EMS not being called. It is documented that the ambulance is not always called in the event of an overdose (131), so therefore the patients in this study only include those in which the ambulance was called, and represent a minimum number and a conservative estimate of prevalence.

For the missed cases, it is most likely that the cases were missed at random. It is unlikely that the EMS would document or report on overdoses differently (i.e. more severe or less severe circumstances). If paramedics were systematically not documenting on cases when the patient refused transport, for example, then there would be a concerning bias. However, there is no reason to believe that they have deviated from protocol, which includes documenting on all patients that they encounter. By selecting only cases of non-fatal overdoses, it is possible that if fatal overdoses had been included, differences in overdose characteristics could have been observed, specifically in regards to overdoses from private locations (132). For the results presented in paper I, although potentially an underestimation of the occurrence of non-fatal overdoses overall in Bergen, the selection of cases does not appear to be threatened by any systematic selection bias.

In paper II, the recruitment of participants relied on the staff that attended the naloxone trainer trainings. The decision for a facility to become a distribution site was made prior to the participation in the questionnaire study. Different types of facilities were involved, and the questionnaire was given at all trainings during the two-month study period. The decision for a facility to participate may reflect staff and leader attitudes that at baseline were already relatively positive towards the intervention. This may have resulted in a selection bias for sites that agreed to be part in the project having higher attitude scores at baseline, than other sites which did not participate. Nevertheless, changes in attitude scores were measured and these results are not as likely to be affected by the potential selection bias mentioned.

Also in paper II, there was not a record of all of the types of facilities and staff demographics for the entire group trained. While it cannot be said with absolute certainty how representative the characteristics of this sample of trainers are of the entire group, all interested facilities within the two cities were eligible to participate, and there was no selection of specific sites during the study period. A general assumption is that the 54 participants share many characteristics with all those trained and importantly that the learning outcomes from these sessions were similar to the trainings performed during all sessions.

In paper III, a self-selected/presented sample was used to gather information about those that returned for a refill of naloxone. Convenience sampling has advantages, such as ease, and that it is less expensive and time consuming than other methods, yet it may have resulted in an increased risk of selection bias (133). It is possible to assume that people would be more likely to come back for a refill for instances when naloxone was successfully used, than for

naloxone that was lost, or was unsuccessful in reversing an overdose. This would skew the data towards an over-reporting of successful reversals. However, because the project was available to participants in their existing facilities, it is also likely that if naloxone was not successful, it would have been reported to the staff trainers, along with complaints of the spray/program. Further, there was no tracked follow-up of participants due to available resources, so a portion of this potential over-reporting may be negated by the fact that cases when naloxone was used, but the rescuer did not return, was not reflected in the results. However there are no reports to distribution sites about naloxone sprays that failed, that we are aware of in the project group. It is considered that the characteristics of the users of naloxone sprays as displayed via refill requests are representative of the target population primarily outside of formal treatment as recruited through low-threshold sites in the participating communities.

Overall prevalence estimates may have been influenced by some underreporting (i.e. paper I) and recruitment methods may potentially have led to a more positive self-selected sample in paper III. Nevertheless the observed associations presented are considered robust findings as these measures were not directly related to the prevalence estimates or the potential positive attitudes to the respondents in their outcome measures.

4.2 Information bias

Information bias is a type of systematic error that occurs when the information collected about the participant is incorrect or misclassified (130).

Recall bias is a type of information bias, and occurs when questions are answered incorrectly based on memory. The use of ambulance patient records in paper I eliminates recall bias, as paramedics document their actions while they are attending the patient. It is however possible that errors in paramedic documentation led to the misclassification of participants or their characteristics in the study. The data in this study is limited to the thoroughness and accuracy of paramedic documentation. Errors in documentation are more likely than recall bias, and would likely be random, as paramedics should have relatively standard precision when documenting on patients, including if the medication (naloxone) that was used. These random errors would be unlikely to create bias. Random errors in a dataset would tend to weaken associations; therefore observed associations are considered robust findings.

In paper II the OOKS questionnaire was used in its original English language, and was not translated or validated in Norwegian. Participants may have answered the questionnaire

differently had it been in Norwegian. For example, any confusion with the terminology may have caused them to not pick a response on the pre-test, but then when the terminology was used during the training course, they became more comfortable with it and answered it differently on the post-test. Therefore, the measured increase in knowledge may not have to do directly with learning about the topic, but learning the vocabulary. This could potentially result in inflated knowledge improvement scores, but only if the staff misunderstood the same words, and in the same direction. Nevertheless, the Norwegians that attended were highly proficient in English, and it is unlikely that language was an issue in a systematic direction. The staff participants were able to ask questions (in Norwegian) to clarify any language questions.

In paper III, questionnaires were administered by any of the hundreds of staff trainers. Although all of the trainers attended a trainer session that reviewed how to administer the questionnaire, it is possible that there were errors in the collection of information from the participants. Each trainer may have had a different interpretation of some of the questions, leading to differences in answers reported. This issue became evident in the initial questionnaire (see appendix III). Certain responses were problematic (example: for those that had answered that they have never seen and overdose on question number 9, but then reported calling the ambulance when they see an overdose in number 10) display an inherent issue in the questionnaire and how it was administered. After discussing with staff, some reported that they interpreted that question to mean what *would* you do, instead of what *did* you do. This question about actions taken for an overdose was therefore not used in the analysis given the uncovered issues.

Recall bias may have been an issue for the refill questionnaires in paper III. There was no inquiry into the amount of time between the use of naloxone and returning to fill out the questionnaire. The question most likely to present an issue of potential recall bias is the one about the dosage of naloxone used. This detail may have been easily forgotten in the time period between use and reporting. However, there was the option to answer "don't know" which could have easily been selected if the participant couldn't remember. There is not a reason to anticipate that people would systematically under-report or over-report on the dosage used, and that people who would forget the dosage would do so in any direction. Therefore, the responses of the doses used likely represent the rescuer's best estimate of how much naloxone was used during the overdose. When witnessing the stressful experience, such as an overdose, the accuracy of the rescuer's memory may be enhanced or reduced depending

on the individual's stress response (134). However, even with potential memory impairment, when compared to remembering everyday occurrences, less detailed questions, such as their relationship to the victim, and if the victim survived would likely not easily be forgotten, and therefore not subject to recall bias.

Also in paper III, it is possible that social desirability bias influenced the participant's answers. They may have reported to the staff member answers that they believe to be the most acceptable answer (135). While on the one hand having a trusting relationship with the staff member may facilitate returning to discuss negative experiences, it may also mean that the participant would not disclose details about the situation that they perceive the staff member would disapprove of (thus an under-reporting of risky behavior). This is unlikely, given that 85% of our participants reported current or previous opioid use, indicating a relative comfort in discussing their illicit drug use. It may also mean an over-reporting of responding with the "correct" answer of what to do to respond to an overdose. As mentioned previously, this question from the initial questionnaire was problematic and not included in the analysis. Further, given the design of the study, it was not possible to cross validate their responses with corroborated stories from those also at the scene of the overdose.

The questionnaires were piloted, and adjustments were made in an attempt to avoid issues with the design of the questions and the questionnaire, as well as how the questionnaire was administered (136). But even with the best intentions, it is possible that the reliability of the questionnaire is threatened, given the hundreds of interpretations from the various trainers. Ideally more time would have been spent developing and validating the questionnaires, allowing for them to be more consistently administered from the different staff trainers. An interview guide could have also been useful. Online questionnaires could have been designed to reject nonsensical answers (i.e. what actions they have taken when witnessing an overdose only if they report to have witnessed an overdose). However, online forms may not have been tenable in all of the facilities and it was not feasible to develop them during the start of the project.

4.3 Confounding

Confounding refers to a type of bias where the association between the exposure and the outcome is distorted from another (typically unobserved) variable (130). The questionnaires used in paper III were intentionally kept brief to allow for rapid completion; however this

also left the study vulnerable to unmeasured confounding variables, which are discussed below.

In paper I, when exploring predictors for longer ambulance arrival time, a potential confounder could have been season or weather. In the often extreme Nordic winter climate, it is possible that winter conditions would increase the likelihood of using drugs at home (not outside in a public place), and it could also affect the road conditions (i.e. ambulance arrival time). However, there were no significant associations when adjusting for month and the temporal patterns we observed showed relatively similar use in public and private locations during from December to February.

In paper III, predictors for having a high number of previous overdoses were investigated. Significant predictors were found to be those who primarily inject, and those who mix opioids with benzodiazepines. The questionnaires did not include potential confounding factors such as the frequency of injecting, number of years of drug use, social status, and the general health status of the participants, all of which could also have contributed to high rates of previous overdoses. Specifically, an exploration into how the number of years of drug use may have contributed to the frequency of previous overdoses could have been done. Darke et al. found that for each year of heroin use, there was an increased likelihood of daily injecting, poly-drug use, and having previously overdosed (20). Although this question was not specifically asked in our study, age was included in the regression model and was not a statistically significant predictor. While age and years of drug use are not the same, they are related, and therefore give an indication that this variable may have not impacted the findings in major directions.

Selection bias, information bias and confounding as discussed above all would influence a study's internal validity if they influenced the results. Although such mechanisms cannot be ruled out, the studies are considered fairly well designed and the research designs applied have aimed at reducing bias and their influence, for example by conducting multivariate analyses adjusting for potential confounding factors. It is considered that the studies are not severely affected by biases and therefore have an acceptable internal validity.

4.4 External validity

External validity refers to if the study results are able to be generalizable to other settings or populations (137). Internal validity refers to a study's ability to minimize systematic error. In

order to have external validity a study needs to have good internal validity which is considered the case for these studies, as presented above.

Both the quasi-experimental design from paper II and the descriptive study from paper III are subject to threats to internal validity due to confounders (Harris et al., 2004). However, for paper II the duration between the pre-test and the post-test was two hours, leaving very little opportunity for something other than the trainer course to influence the post-test. Additionally, while confounders for paper III were discussed previously, it is unlikely that it would have impacted the findings in major ways.

The surveys from paper III do not capture the entirety of people who were trained to use naloxone. The study design did not include mandatory reporting or tracked follow-up, and therefore represent only a self-selected portion of the participating population. While there remains a risk of selection bias in this sample, and thus a threat to generalizability (133), the studies appear to be ecologically valid, meaning that they resemble real-world conditions and characteristics from the participants in general. A key aim of this project was to make naloxone widely available, and as a result questionnaires were kept brief, participation in the study questionnaires was completely voluntary, and participants could remain anonymous. While in some ways this impacted the research designs and results (i.e. the number of signed consent forms), it also represents the real-life preferences and characteristics of the target group. The wide inclusion criteria, (with virtually no exclusion criteria other than the facility being outside of the two pilot cities), allowed for access to a heterogeneous sample of PWID in Norway, primarily outside of formal treatment, with findings that can likely be generalizable to other similar settings and populations.

The ability for this project to operate as it did relied heavily on coordinated framework of existing health structures and services. Papers II and III illustrate some of the benefits of these organized efforts, but also some of the research limitations of widespread implementation-focused initiatives, rather than primarily and ideally designed research designs. The findings from the studies and the overall project, that rapid widespread distribution of take-home naloxone is feasible, emphasize the need for coordinated efforts among existing resources, and communities. Those communities that do not have similar existing networks may face challenges with similar training programs.

Overall the results from paper I, particularly associations presented, are considered to be applicable to populations at risk for non-fatal overdoses in urban centers in Norway and

similar settings internationally. The results from paper II are likely to represent the staff that were trained for the project and staff working in low-threshold facilities in Norway, but may also be generalizable to staff working with PWID in other locations with similar attitudes and approaches to working with PWID. It is possible that settings with different views on harm reduction (i.e. Sweden, see section 1.5.3) would not experience the same changes in attitudes following a two-hour trainer session. The results from paper III likely represent the characteristics of people who were trained to use naloxone in Norway. Many of the demographic and risk factor findings were similar to that of other studies internationally, and suggest that the findings from this study can be generalizable to similar settings.

4.5 Strengths

The three studies included had several strengths. Together these studies provide an investigation into Norway's first naloxone distribution program.

The use of ambulance data in paper I gave a proxy indication of nonfatal overdoses occurring in the city, prior to the intervention. This method allowed for monitoring of more common nonfatal overdoses which are not captured by analyses of mortality data or emergency departments. This data also allowed for an epidemiological investigation which can lend insight into local preventative services.

Paper III was a multi-site study in two cities that allowed for the inclusion of several different facilities. This approach provided a heterogeneous network for reaching at-risk groups. The reports of naloxone being used on an overdose supported the appropriateness of the study's intervention sites and the participants involved. The ability to reach the target distribution coverage was due to the strong network of distribution sites and their participation in the project.

Overall the presented results in this thesis are considered to be generally robust, and no major selection bias, information bias, or confounding factors are believed to have severely influenced the results. Together the studies in this thesis demonstrate the strength in coordinated public health efforts for increased access to naloxone, and the realities of researching this setting while implementing a new, widespread intervention.

5.0 Discussion of results

5.1 Non-fatal overdose patterns

The findings from this study were similar to demographic (50, 51, 55, 138) and temporal (51, 52) trends from previous opioid overdose ambulance studies. The non-fatal opioid overdose temporal patterns did not follow late-night party patterns seen with GHB (43) or ecstasy overdoses (139), suggesting that opioid overdoses were from regular and primarily non-recreational users.

The peak in overdoses in August was similar to a seasonal peak found by others (42). This summer phenomenon may be due to the influx of PWID that migrate from other areas of Norway to the bigger cities during the summer. A previous Norwegian study found that nearly 30% of fatal overdoses that occur in the city were non-residents, supporting this migration hypothesis (140).

Fewer of our patients were found in private homes compared to other studies (51, 52). This may be due to the fact that at the time an illegal open drug scene was located in the city center, and accounted for a significant proportion of overdoses that occurred in public locations. Location also appeared to play a role in the disposition of the patient, with those picked up in private homes not being transported as often for further treatment. Those who overdosed in private homes likely had someone else present (the caller) who could monitor the victim if the ambulance did not transport them further. This is contrary to those who were picked up in public locations, who may not have had someone with them to help with monitoring after ambulance treatment.

Others have found that the location of an overdose influences the likelihood of calling the ambulance. Ambrose et al. found that the odds of calling an ambulance were 10 times higher when the overdose occurred in a public location compared to in a private home (141). This was similar to Tracy et al. who found that victims from public locations were more likely to be treated by the ambulance than those from private homes (142). The resistance to calling the ambulance for overdoses from private homes may be influenced by the possible exposure (i.e. neighbors seeing the ambulance come) (142), the inability to flee the scene if necessary (143), and the possibility for repercussions if illicit drugs are found at the house (143). This illustrates one of the dangers of overdosing in a private home, and the potential for peer-administered naloxone if the ambulance is less likely to be called. However, THN does not negate the need for calling the ambulance, and naloxone trainings should continue to educate

on the need to call for help. This is especially true in light of reports that fentanyl overdoses may need for larger and repeated naloxone doses [134, 135].

Together, the epidemiological findings shed light on circumstances surrounding non-fatal overdoses. With non-fatal overdoses being a predictor for future fatal overdoses (10), these patterns can be incorporated into monitoring and evaluating local overdose prevention efforts.

5.2 Impact of a staff training course

Although naloxone distribution programs have existed since the 1990s, the existence of large-scale programs is more recent. In order to support large-scale naloxone programs, adequate numbers of dedicated and trained staff is necessary. Scaling-up of public health interventions requires the infrastructure that supports the implementation, and active engagement of the implementers (91). Scaling-up also requires avoiding potential barriers such as lack of staff and staff resistance to new practices (91). By utilizing the train-the-trainer model, this study was able to train over 500 staff that were already positioned within the existing infrastructure to carry out the intervention within the first year and a half. Further, the use of a central trainer likely supported the fidelity of the program, possibly avoiding the pitfalls of a cascade training method, in which fidelity is loosened with each new trainer (144). With the train-the-trainer model, those that were trained were not able to train others to become trainers. Mayet et al. found that the cascade training, wherein trainers can train others to become trainers was only modestly successful in training clinicians to distribute naloxone (144). From their study, the most cited barriers included clinician time and resources, client willingness, clinician confidence, and issues with the naloxone formulation (144).

Consistent with others (77, 144-146), we found a significant improvement in knowledge scores after attending a naloxone training. While these previous studies focused primarily on the transfer of knowledge directly to the rescuer, our study trained the trainer. These trainers became the intervention implementers, and were central to making the intervention widely available. Additionally, as a strategy for helping to deliver an intervention (93), the training of existing staff helps to improve an organization.

The staffs' attitude scores improved following the training, both in their reported understanding of the different areas assessed, but also in their attitude towards the role of naloxone in overdose prevention work. This staff buy-in is critical for the acceptance and adoption of the intervention (147). The reported feelings of empowerment from training their clients, illustrates the ability of such interventions to promote staff buy-in. While a shared

vision is essential among the staff and those initiating change (148), this shared vision and communication must also include leadership (97). The findings from our study supported this, with the sites that had stakeholder buy-in from both the staff and the leadership having the highest naloxone distribution rates.

However, the findings from the questionnaire survey present only the immediate impact of the naloxone training course. This is similar to what others have found with naloxone trainings directly to clients, in that knowledge was only assessed immediately following the training (145, 149, 150). An important follow-up to this would be to assess the trainer's adherence to the protocol, the feasibility of implementing the trainings into their workplace, and factors that predict the likelihood of performing a training after attending a session. Not all people trained continued as trainers, and it would be interesting to investigate what influences the adoption or rejection of the new role. It would also be interesting to see if incentives or certificates ("official naloxone trainer") would promote staff embracing the new trainer role.

The training delivery method was a mostly didactic lecture course, which is a result of the resources available. Large-scale training initiatives require resources, and research on such large-scale training initiatives is often scarce (151). To effectively promote behavioral change in practice, Beidas et al. suggest that rehearsal training can serve as a marker of fidelity (152). The active learning model of a simulated behavioral rehearsal between trainees may provide not only an effective training strategy, but also allow for measurement of fidelity (152). While this may have been a more ideal teaching method, time constraints, from both the staff and the central trainer, make this more difficult to actually carry-out.

An alternative consideration could have been to explore technology and online options to aid in the training sessions, both for the training of trainers and the training of clients. Clark et al. developed an iBook for overdose prevention training after uncovering that the trainings were fragmented and needed to be manualized (153). The iBook is an interactive device with video, quizzes, and animations. The authors found that the tool allowed for a standardized approach to training with the ability to modify to the needs of the client. The use of an innovative tool such as this could have been useful in the implementation of this project to provide support for insecure staff, to provide consistency in the trainings, as well as a simplified resource with all of the key points. Online overdose prevention trainings have been found by others to be an acceptable and feasible option for training people professionally or personally interested in

overdose prevention (154, 155). Because this project was implemented in a variety of settings, how new technology is embraced will likely result in different uptake from different settings (i.e. street outreach trainings vs. inpatient trainings). Several staff reported that the trainings allowed for a dialogue that they otherwise would not have had with the clients about overdose. Would a scripted or automated training take away from that organic conversation? Regardless, online trainings, monitoring, and data collection should be incorporated in varying degrees as part of the project's continued expansion and monitoring.

Although more optimal training modalities could have been further explored (i.e. behavioral rehearsal, online options), continued support should have been explicitly planned during the implementation (156, 157). Research on implementation evaluation feedback from the trainers would give insight into the feasibility, acceptability, and sustainability of the intervention in the real-world (157). Continued evaluation and feedback from the implementers can provide insight into what extent they are able to actually utilize the intervention. While we continually received anecdotal feedback from the staff, a more standardized, explicit approach to measure this feedback should have been included. As Beidas et al. suggest, the continued use of the "one-way broadcast from expert to trainer" provides only minimal feedback (151). The feedback loop between the central trainer and the trainers could have provided valuable feedback in this study both in regards to how the trainers were preforming the sessions, but also in how the procedures functioned in the real-world.

5.3 Characteristics of the participants trained to use naloxone

Through the use of existing low-threshold facilities, over 2,000 naloxone sprays were distributed for bystander administration to a group at risk of overdosing within the first year and a half. Nearly all of the participants reported at least one known risk factor for overdosing. Frequent injectors are known to be at risk (25), and over half of our participants reported injecting. A history of previous overdoses is a risk for future overdoses (8, 10), and participants in this study reported high rates of past overdoses.

In addition to the reported risk factors, this study also used the reported saves as an indicator of reaching the target group. With 277 rescues reported in the first year and a half, this study had relatively similar rescue rates when compared to others (72, 158, 159), however these rates are for different settings and various time periods. In Chicago from 2001 to 2006, over 3,500 naloxone vials were distributed with 319 reported reversals (9% of total) (72). A THN

program in Boston distributed 385 intranasal naloxone sprays with 74 successful reversals in 15 months (19% of total) (159). From 2003 to 2009 a THN program in San Francisco distributed nearly 2000 naloxone vials (158). They had 1020 returns for refills, of which 40% (n=399) were reported to have been used on an overdose.

In our study, the reports of refills and the completed questionnaires present different response rates. Nearly 70% of the refills from the completed questionnaires had been used on an overdose. Looking at the total number reported as distributed from the facilities (including complete, incomplete, and not filled out forms), 38% had been used on an overdose. Regardless of the rate, the reported rescues in this study indicate that the naloxone training reached relevant groups in situations where it was needed. The findings also demonstrate the importance of obtaining completed questionnaires to help present more robust findings. The difference in the reported refills versus the consented questionnaire reports indicate that for participants who had successfully used naloxone, they may have been more inclined to participate in the study, thus giving an overestimate of its use. Efforts towards improving completed questionnaires would have improved the data available in this study.

The design of this study did not allow for an investigation into knowledge gained for participants who attended a naloxone training. Others have found that brief trainings are sufficient in transferring knowledge (149, 160), however the extent into which this articulated knowledge results in risk reducing behavioral change is more nuanced (161). Dietze et al. uncovered a paradoxical effect where in some cases, knowledge of overdose risk behaviors actually was associated with an increase in that risk behavior (161). This underlines the complexity of overdoses, and the importance of messages towards promoting external responses, such as calling the ambulance (161) and using naloxone.

5.4 Naloxone coverage

Naloxone distribution goals were met within the first year and a half of the project. Based on estimates for projects aiming to have a population-level impact (73, 78), this project was able to achieve its target. The findings from our study are consistent with others who suggest that high volume naloxone distribution is possible when positioned as a public health intervention (73, 78, 158, 162). Coverage is an important marker of successful implementation, and refers to how much of the target intervention received it (94). Walley et al. found that the areas with the highest rates of naloxone distribution experienced a greater reduction in overdose fatalities (73). Bird et al. recommend distributing 9-20 times the number of overdose fatalities,

and found a 20-30% reduction in overdose deaths in the 4 week period post-prison release (78). Based on the naloxone coverage goals presented by Walley et al. using population estimates (73), and by Bird et al. using overdose fatality reports (78) this project had adequate coverage for a widespread program.

The ability to achieve this coverage is likely due to the coordinated use of existing low-threshold facilities with staff that were already positioned to reach the target group. It is also likely due to the ease in which facilities could receive naloxone. The ability for naloxone to be distributed without an individual prescription, and at no cost to the facility or client is most likely a major contributor in the ability to distribute large volumes of naloxone, meeting the distribution goals. It may also be that the approval of an off-label device was influenced by the fact that this was a government-initiated and supported project. It is possible that lives have been saved during the years since 2014, as a result of the availability of the device. In addition, the project team was small, and was able to be flexible and responsive to the needs of the participating facilities. For example, after reports that the multiple questionnaire forms were confusing, the forms were stapled and reorganized in a better system according to the staff. This change was able to be implemented very quickly and resulted in improved survey responses.

Monitoring overdose fatalities is a natural marker of the project's impact on overdose prevention, and will be continued in the evaluation of the project post this PhD period. The most recent available numbers of overdose deaths in Norway are from 2015, which show a slight increase in overdose deaths from 266 in 2014 to 289 in 2015 (163). While the country as a whole experienced an increase, Bergen experienced a decrease from 31 deaths in 2014 to 17 in 2015. One possible explanation for Bergen's decrease in deaths may be attributed to their significantly higher distribution rates per population when compared to Oslo. However, at the time, multiple overdose prevention initiatives were simultaneously put into place in Bergen, such as the closing of an open drug scene park and changes in ambulance protocol. The change in protocol involved giving suspected opioid overdose patients ventilation support while transporting them to the acute drug center (emergency department specifically for drug overdoses) where they would receive a 'gradual' awakening with titrated naloxone. Further investigation will be needed to determine to what extent naloxone distribution may have impacted overdose fatalities after the implementation of this widespread program.

5.5 Evaluation of implementation

The use of an evaluation framework that identifies distinct implementation outcomes was useful in articulating specific elements of the project that were working or not working. Nearly all of the outcomes had some form of an unmet or unknown domain. This finding is somewhat unsurprising, given that the framework was not identified until after the implementation of the project. Had we familiarized ourselves better with commonly reported issues and barriers, some of them may have been avoided throughout the process. However, the issue of bridging the gap between research and practice is not new.

Acceptability (staff buy-in) is an outcome that is crucial for the success of a THN program (164). While overall there was acceptability from staff, PWID, and the government for the project, there were also concerns similar to those reported by Wilder et al. in a treatment center in the United States (164). This included lack of time for new duties, discomfort from nonmedical staff to teach something perceived to be from the medical domain, and a feeling that the program had been imposed on them without their input (164). By uncovering these staff issues, the implementers were able to address these concerns in attempts to make it more tenable to their workplace (164). In order to further improve the staff acceptability for this project, ongoing feedback and addressing of concerns may help to promote buy-in. Identifying one crucial staff member, who is particularly motivated or engaged in the THN program can also help to promote buy-in from the "inside" (164). This staff member may help to navigate strategies to optimize implementation internally, by working with the leaders and refining practical issues. As this project expands, continual feedback, reflection of staff acceptance, and the building up of "naloxone ninjas" (enthusiastic staff from the different facilities) will be necessary for the feasibility and sustainability of the project.

The adoption of an intervention requires more than acceptance (98). The various distribution sites had wide variability in the adoption of the project. While one site distributed half of the entire naloxone sprays for the project, others distributed none, or very few. An investigation into why some sites quickly and enthusiastically adopted the intervention, while others rejected it can be useful in a) addressing staff concerns, and b) tailoring future expansion to the needs and preferences for successful adoption. The site that distributed the most naloxone had markedly the most engagement from the leaders and a project coordinator on site. Their interest provided staff with the space to do the naloxone trainings, as well as a clear prioritization of this intervention. Additionally, prior to this project, this site was already talking about overdoses and prevention with their clients. On an ideological level the THN

program was aligned with their existing approach, and the site appreciated the very tangible addition to their existing CPR and overdose prevention discussions. Other sites, such as treatment facilities, may face issues in regards to the messaging of a THN program (164). While it may be difficult for recovery services to incorporate the message of overdose prevention into their practices (i.e. giving the client a message that they are expected to 'fail') the importance of using language that can empower the client to possibly save someone, and not that they will 'fail' should be considered an important component of recovery services (164).

In regards to the remaining implementation outcomes: rapid, widespread coverage of naloxone to the target group indicated that the intervention met outcomes related to appropriateness (defined as the perceived fit/relevance) and feasibility (staff able to carry out the intervention). This was also likely aided by the fact that all implementation costs were covered by the project. As described in section 5.4, the coordinated use of existing low-threshold facilities provided the necessary venue for broad dissemination. Similar to Walley et al., the use of a variety of training sites resulted in 'high level' distribution (73). As mentioned previously, fidelity was not assessed (section 5.2), and future sustainability studies should be completed to evaluate the project over time. Such studies can give insight into the long-term effects of the intervention's design.

Step-wise implementing the project in multiple facilities was an opportunity for continual improvement in project management. Our team of five included diverse backgrounds which were helpful to the project, however none of us had specific experience in implementing a public health intervention. As mentioned in section 3.3, the response rate for the questionnaires with the signed consent form was between 33%-55%. Data collection was an issue for some staff, similar to what Horyniak et al. found when evaluating their overdose prevention campaign (165). In 2016, the questionnaires were stapled to the consent form (as opposed to being two separate documents). This simple change appeared to improve the number of signed consent forms we received. Additionally, concerns about how the data was going to be used was discussed with the staff so they could better explain to clients after reported client skepticism. The data collection forms were both reported to have been barriers to doing a training ("confusing" and additional work), but also seen a tool to guide them through the training and uncover specific overdose risk factors. The use of the paper questionnaires was the only feasible option at the start of the project, however online data collection and monitoring will be a necessary part of sustainably monitoring the program as it

expands. This project could have included a policy and procedure manual, as outlined by the Harm Reduction Coalition (66). The manual could have assisted in clarifying routines and rationale for the project, as well explicit roles, logistics, educational materials, and an interview guide (66).

Some recurring reasons for poor implementation have been identified as: issues related to costs, limited human resources, inefficient distribution channels, and issues with patient access [56]. While different communities will inevitably face different challenges, an awareness of these issues may help in potentially avoiding them. The decision for the use of a nasal spray could have presented a significant project barrier, given that at the time no licensed intranasal options were available in Norway. The concerning number of overdose deaths in Norway warranted a novel action, and the ability to use an interim off-label device for the project was crucial for the rapid roll-out of the intervention. The top-down support of the intervention likely influenced the ability to use the interim spray, despite the critics of the use of an unlicensed nasal spray (32, 34).

It is estimated that it takes an average of 17 years for research evidence to arrive at clinical practice (166). One explanation as to why this may be, suggests that while the production of research is centralized in institutions, the application of public health is decentralized (167). This then results in a chasm between research, policies, and adoption of interventions. Although it is known that THN programs are effective, especially when implemented on a large-scale (73), widespread THN programs remain relatively rare. As THN programs continue to expand, attention towards this dissemination issue, as well as the alignment of local stakeholders, governments, clinicians, and researchers will be needed in order to optimize efforts and assure the adoption and sustainability of the intervention. Further, the evaluation of large-scale programs should not only aim to assess the impact of an intervention, but also how and why an intervention functions.

5.6 Concluding remarks and lessons learned

The main finding from this thesis is that widespread distribution of naloxone is possible through the use of coordinated community efforts. Distribution goals were met within the first year and a half of the study, and participants in the study were mostly people who exhibited known risk factors for overdosing. The utilization of a train-the-trainer course effectively trained a high volume of existing staff, and the staff reported improvements in attitudes towards distributing naloxone.

The alignment of political, research, and community goals helped to support this intervention. Evaluation frameworks and strategies can be useful for scaling-up public health interventions. In particular, the taxonomy that the framework provides identifies key concepts that may impact the successful implementation of an intervention. The findings from this multi-site THN program in Norway may help others implementing a widespread program, but may also help in the scaling-up of this project. Despite inherent differences and challenges that various communities will face, the following lessons learned may be applicable to other programs:

a. Widespread distribution of naloxone was made possible through the use of multiple existing distribution sites and staff trainers. This design was critical for the ability to meet distribution goals and reach the target at-risk group.
b. Sites had varying degrees of adoption of the intervention, which likely relied on a combination of staff and leadership buy-in, facility ideology, and clients.
c. The train-the-trainer model was able to reach a large volume of staff, while the use of a central trainer helped to maintain oversight and stable quality of trainings. However, it is unknown what facilitated the acceptance of the new trainer role, and to what extent trainers adhered to the training protocol. Online trainings, certificates, incentives, and follow-up to determine adoption and fidelity to the training protocol should be considered in the development of widespread staff trainings.
d. The government support for the project likely facilitated the approval of an off-label intranasal device. The funding that allowed for naloxone to be distributed at no cost to the client, and the ability to distribute without a prescription likely removed significant potential barriers
e. The use of an evaluation framework was helpful in articulating what was working and not working for the implementation of the project. Ideally these would have been useful during the development of the intervention.
f. Specific implementation goals, strategies, and plans for feedback should be incorporated during the development of an intervention to allow for the intentional and evidence-based use of implementation research.

6.0 Implications

This study has several clinical and public health implications. The number of ambulance-attended nonfatal overdoses that occurred in Bergen is alarming. With each of these overdoses having potential for future fatal overdoses, as well as significant morbidity, prevention efforts are critical. The high rate of overdoses was also seen in the questionnaire survey, with a vast majority of participants either witnessing or experiencing an overdose in their lifetime. This was particularly worrisome for the number that had reported multiple previous overdoses. The harms associated with overdosing are severe, and potentially fatal. As the findings indicate, there is a local need for the enhancement of overdose prevention services in order to respond to the high rates of overdoses.

The monitoring of opioid overdoses is important in evaluating and guiding preventative services. Relying solely on the use of mortality registries provides information only for fatal overdoses, often several months following the event. The use of ambulance data as a proxy source for non-fatal overdoses can be a timely and useful resource. Our investigation into local epidemiological trends gives a current description of overdose patterns, and provides the baseline for future evaluations of prevention efforts.

While take-home naloxone programs have existed for decades, and have been shown to be effective in reducing mortality (73, 74), barriers still prevent their adoption as mainstream public health interventions. Widespread programs remain relatively rare, and it is evident that a disconnect between evidence and practice exists. Continued efforts should be targeted towards promoting large-scale programs, as these have been shown to have the greatest impact on reducing overdose mortality. Improved access to naloxone, including optimal intranasal devices may be influenced by government pressures on drug development within the pharmaceutical industry. Improving the standards of care for PWID could include shifting from an opt-in model, where people interested in getting trained seek it out, to an opt-out option, where everyone who is prescribed opioids either for pain management or as maintenance treatment is offered the training. Efforts should also be made in applying implementation research, along with evaluation frameworks when implementing new widespread programs. The findings from this study support the feasibility of government-supported naloxone programs, and ideally can provide insight for others implementing a large-scale program.

7.0 Future research

This thesis covered the implementation of a widespread take-home naloxone program. The participating distribution sites were largely low-threshold facilities that provide services to at-risk groups. However, this project did not focus on one group that is known to be at risk: people upon release from prison. Their risk of overdosing in the days following release is well documented, and future research should cover the establishment and implementation of widespread naloxone distribution to prisoners in Norway.

The development of a licensed intranasal naloxone device is underway, but consideration should be given when changing the device in the community. Future studies should examine the perceptions and reactions from clients after using a 'new' spray to uncover if there is, as John Strang has called, a "reputational toxicity" from using devices with different concentrations from before.

A key next step for future research would be to evaluate the impact of this intervention on overdose mortality. An investigation into fatal overdoses, through the use of registry data and a stepped-wedge design (random and sequential roll-out of an intervention over multiple time periods (168)) should be considered to compare the impact of the intervention among sites that received the same intervention at different points in time. An investigation into non-fatal overdoses attended by ambulance services following the start of the intervention can also provide additional crucial evidence on the impact of this large-scale program.

References

1. Norwegian Directorate of Health. National Overdose Strategy 2014-2017, 2014.

2. UNODC. World Drug Report 2016. United Nations Office on Drugs and Crime, 2016.

3. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in Drug and Opioid Overdose Deaths--United States, 2000-2014. MMWR Morbidity and Mortality Weekly Report. 2016;64(50-51):1378-82.

4. EMCDDA. European Drug Report: Trends and developments. European Monitoring Centre for Drugs and Drug Addiction, 2014.

5. Evans JL, Tsui JI, Hahn JA, Davidson PJ, Lum PJ, Page K. Mortality among young injection drug users in San Francisco: a 10-year follow-up of the UFO study. American Journal of Epidemiology. 2012;175(4):302-8.

6. Hickman M, Carnwath Z, Madden P, Farrell M, Rooney C, Ashcroft R, et al. Drug-related mortality and fatal overdose risk: pilot cohort study of heroin users recruited from specialist drug treatment sites in London. Journal of Urban Health : bulletin of the New York Academy of Medicine. 2003;80(2):274-87.

7. Martins SS, Sampson L, Cerda M, Galea S. Worldwide Prevalence and Trends in Unintentional Drug Overdose: A Systematic Review of the Literature. American Journal of Public Health. 2015;105(11):e29-49.

8. Coffin PO, Tracy M, Bucciarelli A, Ompad D, Vlahov D, Galea S. Identifying Injection Drug Users at Risk of Nonfatal Overdose. Academic Emergency Medicine. 2007;14(7):616-23.

9. Caudarella A, Dong H, Milloy MJ, Kerr T, Wood E, Hayashi K. Non-fatal overdose as a risk factor for subsequent fatal overdose among people who inject drugs. Drug and Alcohol Dependence. 2016;162:51-5.

10. Stoove MA, Dietze PM, Jolley D. Overdose deaths following previous non-fatal heroin overdose: record linkage of ambulance attendance and death registry data. Drug and Alcohol Review. 2009;28(4):347-52.

11. Warner-Smith M, Darke S, Day C. Morbidity associated with non-fatal heroin overdose. Addiction. 2002;97(8):963-7.

12. Merrall EL, Kariminia A, Binswanger IA, Hobbs MS, Farrell M, Marsden J, et al. Meta-analysis of drug-related deaths soon after release from prison. Addiction. 2010;105(9):1545-54.

13. Ravndal E, Amundsen EJ. Mortality among drug users after discharge from inpatient treatment: an 8-year prospective study. Drug and Alcohol Dependence. 2010;108(1-2):65-9.

14. Riley ED, Evans JL, Hahn JA, Briceno A, Davidson PJ, Lum PJ, et al. A Longitudinal Study of Multiple Drug Use and Overdose Among Young People Who Inject Drugs. American Journal of Public Health. 2016;106(5):915-7.

15. Easterling KW, Mack KA, Jones CM. Location of fatal prescription opioid-related deaths in 12 states, 2008-2010: Implications for prevention programs. Journal of Safety Research. 2016;58:105-9.

16. Fuller CM, Vlahov D, Latkin CA, Ompad DC, Celentano DD, Strathdee SA. Social circumstances of initiation of injection drug use and early shooting gallery attendance: implications for HIV intervention among adolescent and young adult injection drug users. Journal of Acquired Immune Deficiency Syndromes. 2003;32(1):86-93.

17. Baggett TP, Hwang SW, O'Connell JJ, Porneala BC, Stringfellow EJ, Orav EJ, et al. Mortality among homeless adults in Boston: shifts in causes of death over a 15-year period. JAMA Internal Medicine. 2013;173(3):189-95.

18. Warner-Smith M, Darke S, Lynskey M, Hall W. Heroin overdose: causes and consequences. Addiction. 2001;96(8):1113-25.

19. Darke S, Kaye S, Duflou J. Systemic disease among cases of fatal opioid toxicity. Addiction. 2006;101(9):1299-305.

20. Darke S, Mills KL, Ross J, Williamson A, Havard A, Teesson M. The ageing heroin user: career length, clinical profile and outcomes across 36 months. Drug and Alcohol Review. 2009;28(3):243-9.

21. Simonsen KW, Edvardsen HM, Thelander G, Ojanpera I, Thordardottir S, Andersen LV, et al. Fatal poisoning in drug addicts in the Nordic countries in 2012. Forensic Science International. 2015;248:172-80.

22. Tomassoni AJ, Hawk KF, Jubanyik K, Nogee DP, Durant T, Lynch KL, et al. Multiple Fentanyl Overdoses - New Haven, Connecticut, June 23, 2016. MMWR Morbidity and Mortality Weekly Report. 2017;66(4):107-11.

23. Sutter ME, Gerona RR, Davis MT, Roche BM, Colby DK, Chenoweth JA, et al. Fatal Fentanyl: One Pill Can Kill. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2016.

24. Rowe C, Santos GM, Behar E, Coffin PO. Correlates of overdose risk perception among illicit opioid users. Drug and Alcohol Dependence. 2016;159:234-9.

25. Kinner SA, Milloy MJ, Wood E, Qi J, Zhang R, Kerr T. Incidence and risk factors for non-fatal overdose among a cohort of recently incarcerated illicit drug users. Addictive Behaviors. 2012;37(6):691-6.

26. Strang J, McDonald R. Preventing opioid overdose deaths with take-home naloxone. Luxembourg: European Monitoring Centre for Drugs and Drug Addiction, 2016.

27. Elzey MJ, Fudin J, Edwards ES. Take-home naloxone treatment for opioid emergencies: a comparison of routes of administration and associated delivery systems. Expert Opinion on Drug Delivery. 2016:1-14.

28. Wheeler E, Jones TS, Gilbert MK, Davidson PJ. Opioid Overdose Prevention Programs Providing Naloxone to Laypersons - United States, 2014. MMWR Morbidity and Mortality Weekly Report. 2015;64(23):631-5.

29. Yazdanpanah Y, De Carli G, Migueres B, Lot F, Campins M, Colombo C, et al. Risk factors for hepatitis C virus transmission to health care workers after occupational exposure: a European case-control study. Clinical Infectious Diseases : an official publication of the Infectious Diseases Society of America. 2005;41(10):1423-30.

30. Robertson TM, Hendey GW, Stroh G, Shalit M. Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. Prehospital Emergency Care. 2009;13(4):512-5.

31. Kerr D, Kelly AM, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction. 2009;104(12):2067-74.

32. Strang J, McDonald R, Tas B, Day E. Clinical provision of improvised nasal naloxone without experimental testing and without regulatory approval: imaginative shortcut or dangerous bypass of essential safety procedures? Addiction. 2016;111(4):574-82.

33. Edwards ET, Edwards ES, Davis E, Mulcare M, Wiklund M, Kelley G. Comparative Usability Study of a Novel Auto-Injector and an Intranasal System for Naloxone Delivery. Pain and Therapy. 2015;4(1):89-105.

34. Dale O. Ethical issues and stakeholders matter. Addiction. 2016;111(4):587-9.

35. Barton ED, Ramos J, Colwell C, Benson J, Baily J, Dunn W. Intranasal administration of naloxone by paramedics. Prehospital Emergency Care. 2002;6(1):54-8.

36. Barton ED, Colwell CB, Wolfe T, Fosnocht D, Gravitz C, Bryan T, et al. Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. Journal of Emergency Medicine. 2005;29(3):265-71.

37. Coffin P, Rich J, Dailey M, Stancliff S, Beletsky L. While we dither, people continue to die from overdose: Comments on 'Clinical provision of improvised nasal naloxone without experimental testing and without regulatory approval: imaginative shortcut or dangerous bypass of essential safety procedures?'. Addiction. 2016;111(10):1880-1.

38. Lobmaier PP, Clausen T. Radical red tape reduction by government supported nasal naloxone: the Norwegian pilot project is innovative, safe and an important contribution to further development and dissemination of take-home naloxone. Addiction. 2016;111(4):586-7.

39. Winstanley EL. Tangled-up and blue: releasing the regulatory chokehold on take-home naloxone. Addiction. 2016;111(4):583-4.

40. Tylleskar I, Skulberg AK, Nilsen T, Skarra S, Jansook P, Dale O. Pharmacokinetics of a new, nasal formulation of naloxone. European Journal of Clinical Pharmacology. 2017;73(5):555-62.

41. Davis CS, Green TC, Zaller ND. Addressing the overdose epidemic requires timely access to data to guide interventions. Drug and Alcohol Review. 2015.

42. Knowlton A, Weir BW, Hazzard F, Olsen Y, McWilliams J, Fields J, et al. EMS runs for suspected opioid overdose: implications for surveillance and prevention. Prehospital Emergency Care. 2013;17(3):317-29.

43. Boyd JJ, Kuisma MJ, Randell TT. Temporal differences in gamma-hydroxybutyrate overdoses involving injecting drug users versus recreational drug users in Helsinki: a retrospective study. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 2012;20:7.

44. Dietze PM, Cvetkovski S, Barratt MJ, Clemens S. Patterns and incidence of gamma-hydroxybutyrate (GHB)-related ambulance attendances in Melbourne, Victoria. The Medical Journal of Australia. 2008;188(12):709-11.

45. Lloyd BK, McElwee PR. Trends over time in characteristics of pharmaceutical drug-related ambulance attendances in Melbourne. Drug and Alcohol Review. 2011;30(3):271-80.

46. Hutton J, Dent A, Buykx P, Burgess S, Flander L, Dietze P. The characteristics of acute non-fatal medication-related events attended by ambulance services in the Melbourne Metropolitan Area 1998-2002. Drug and Alcohol Review. 2010;29(1):53-8.

47. Heilbronn C, Lloyd B, McElwee P, Eade A, Lubman DI. Trends in quetiapine use and non-fatal quetiapine-related ambulance attendances. Drug and Alcohol Review. 2013;32(4):405-11.

48. Kaar SJ, Gao CX, Lloyd B, Smith K, Lubman DI. Trends in cannabis-related ambulance presentations from 2000 to 2013 in Melbourne, Australia. Drug and Alcohol Dependence. 2015;155:24-30.

49. Cvetkovski S, Dietze P. The incidence and characteristics of volatile substance use related ambulance attendances in metropolitan Melbourne, Australia. Social Science & Medicine (1982). 2008;66(3):776-83.

50. Dietze P, Jolley D, Cvetkovski S. Patterns and characteristics of ambulance attendance at heroin overdose at a local-area level in Melbourne, Australia: implications for service provision. Journal of Urban Health : bulletin of the New York Academy of Medicine. 2003;80(2):248-60.

51. Clark MJ, Bates AC. Nonfatal heroin overdoses in Queensland, Australia: an analysis of ambulance data. Journal of Urban Health : bulletin of the New York Academy of Medicine. 2003;80(2):238-47.

52. Merchant RC, Schwartzapfel BL, Wolf FA, Li W, Carlson L, Rich JD. Demographic, geographic, and temporal patterns of ambulance runs for suspected opiate overdose in Rhode Island, 1997-20021. Substance Use and Misuse. 2006;41(9):1209-26.

53. Alexander JL, Burton JH, Bradshaw JR, Colin F. Suspected opioid-related emergency medical services encounters in a rural state, 1997-2002. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors. 2004;8(4):427-30.

54. Degenhardt L, Hall W, Adelstein BA. Ambulance calls to suspected overdoses: New South Wales patterns July 1997 to June 1999. Australian and New Zealand Journal of Public Health. 2001;25(5):447-50.

55. Seidler D, Schmeiser-Rieder A, Schlarp O, Laggner AN. Heroin and opiate emergencies in Vienna: analysis at the municipal ambulance service. Journal of Clinical Epidemiology. 2000;53(7):734-41.

56. Klimas J, O'Reilly M, Egan M, Tobin H, Bury G. Urban overdose hotspots: a 12-month prospective study in Dublin ambulance services. The American Journal of Emergency Medicine. 2014;32(10):1168-73.

57. WHO. Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence. Geneva: World Health Organization, 2009.

58. Lobmaier PP, Kunoe N, Gossop M, Waal H. Naltrexone depot formulations for opioid and alcohol dependence: a systematic review. CNS Neuroscience & Therapeutics. 2011;17(6):629-36.

59. Rhodes T, Hedrich D. Harm reduction: evidence, impacts and challenges. Spain: Publiations Office of the Europen Union; 2010.

60. Van Den Berg C, Smit C, Van Brussel G, Coutinho R, Prins M. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. Addiction. 2007;102(9):1454-62.

61. International Harm Reduction. What is harm reduction? (Cited January 2017). [Available from: https://www.hri.global/what-is-harm-reduction.

62. Stancliff S, Phillips BW, Maghsoudi N, Joseph H. Harm Reduction: Front Line Public Health. Journal of Addictive Diseases. 2015;34(2-3):206-19.

63. Van den Brink W, Haasen C. Evidenced-based treatment of opioid-dependent patients. Canadian Journal of Psychiatry. 2006;51(10):635-46.

64. Darke S, Hall W. The distribution of naloxone to heroin users. Addiction. 1997;92(9):1195-9.

65. Strang J, Darke S, Hall W, Farrell M, Ali R. Heroin overdose: the case for take-home naloxone. BMJ. 1996;312(7044):1435-6.

66. Wheeler E, Burk K, McQuie H, Stancliff S. Guide to developing and managing overdose prevention and take-home naloxone projects, 2012.

67. Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. Journal of Addiction Medicine. 2014;8(3):153-63.

68. Dettmer K, Saunders B, Strang J. Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes. BMJ. 2001;322(7291):895-6.

69. Leece PN, Hopkins S, Marshall C, Orkin A, Gassanov MA, Shahin RM. Development and implementation of an opioid overdose prevention and response program in Toronto, Ontario. Canadian Journal of Public Health. 2013;104(3):e200-4.

70. Lenton S, Dietze P, Olsen A, Wiggins N, McDonald D, Fowlie C. Working together: Expanding the availability of naloxone for peer administration to prevent opioid overdose deaths in the Australian Capital Territory and beyond. Drug and Alcohol Review. 2014.

71. Kan M, Gall JA, Latypov A, Gray R, Bakpayev M, Alisheva D, et al. Effective use of naloxone among people who inject drugs in Kyrgyzstan and Tajikistan using pharmacy- and community-based distribution approaches. The International Journal on Drug Policy. 2014;25(6):1221-6.

72. Maxwell S, Bigg D, Stanczykiewicz K, Carlberg-Racich S. Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths. Journal of Addictive Diseases. 2006;25(3):89-96.

73. Walley AY, Xuan Z, Hackman HH, Quinn E, Doe-Simkins M, Sorensen-Alawad A, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ. 2013;346:f174.

74. 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. 2015.

75. McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. Addiction. 2016.

76. Heller DI, Stancliff S. Providing naloxone to substance users for secondary administration to reduce overdose mortality in New York City. Public Health Reports. 2007;122(3):393-7.

77. Klimas J, Egan M, Tobin H, Coleman N, Bury G. Development and process evaluation of an educational intervention for overdose prevention and naloxone distribution by general practice trainees. BMC Medical Education. 2015;15(1):206.

78. Bird SM, Parmar MKB, Strang J. Take-home naloxone to prevent fatalities from opiate-overdose: Protocol for Scotland's public health policy evaluation, and a new measure to assess impact. Drugs: Education, Prevention, and Policy. 2015;22(1):66-76.

79. Morgan G, Smith J. Harm Reduction Database Wales: Take Home Naloxone 2014-2015. Cardiff: Public Health Wales, 2015.

80. Lancaster K, Ritter A. Making change happen: a case study of the successful establishment of a peer-administered naloxone program in one Australian jurisdiction. The International Journal on Drug Policy. 2014;25(5):985-91.

81. Smedley BD, Syme SL. Promoting health: intervention strategies from social and behavioral research. American Journal of Health Promotion. 2001;15(3):149-66.

82. Bennett AS, Bell A, Tomedi L, Hulsey EG, Kral AH. Characteristics of an overdose prevention, response, and naloxone distribution program in Pittsburgh and Allegheny County, Pennsylvania. Journal of Urban Health. 2011;88(6):1020-30.

83. Wagner KD, Valente TW, Casanova M, Partovi SM, Mendenhall BM, Hundley JH, et al. Evaluation of an overdose prevention and response training programme for injection drug users in the Skid Row area of Los Angeles, CA. International Journal of Drug Policy. 2010;21(3):186-93.

84. Tobin KE, Sherman SG, Beilenson P, Welsh C, Latkin CA. Evaluation of the Staying Alive programme: training injection drug users to properly administer naloxone and save lives. International Journal of Drug Policy. 2009;20(2):131-6.

85. Winstanley EL, Clark A, Feinberg J, Wilder CM. Barriers to Implementation of Opioid Overdose Prevention Programs in Ohio. Substance Abuse. 2015:0.

86. Gupta R, Shah ND, Ross JS. The Rising Price of Naloxone — Risks to Efforts to Stem Overdose Deaths. New England Journal of Medicine. 2016;375(23):2213-5.

87. Davis CS, Carr D. Legal changes to increase access to naloxone for opioid overdose reversal in the United States. Drug and Alcohol Dependence. 2015;157:112-20.

88. The Human Medicines (Amendment) (No. 3), (2015). (Cited May 2017). [Available from: http://www.legislation.gov.uk/uksi/2015/1503/made.

89. Widening the availability of naloxone, 2016 (Cited May 2017). [Available from: https://www.gov.uk/government/publications/widening-the-availability-of-naloxone/widening-the-availability-of-naloxone.

90. Norton WE, Mittman BS. Scaling-up Health Promotion/Disease Prevention. Patrick and Catherine Weldon Donaghue Medical Research Foundation, 2010.

91. Milat AJ, Newson R, King L, Rissel C, Wolfenden L, Bauman A, et al. A guide to scaling up population health interventions. Public Health Research & Practice. 2016;26(1):e2611604.

92. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Implementation research: what it is and how to do it. BMJ. 2013;347:f6753.

93. Peters DH, Tran N, Adam T. Implementation research in health: a practical guide. Alliance for Health Policy and Systems Research, World Health Organization, 2013.

94. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Administration and Policy in Mental Health. 2011;38(2):65-76.

95. Proctor EK, Powell BJ, McMillen JC. Implementation strategies: recommendations for specifying and reporting. Implementation Science : IS. 2013;8:139.

96. Proctor EK, Landsverk J, Aarons G, Chambers D, Glisson C, Mittman B. Implementation research in mental health services: an emerging science with conceptual, methodological, and training challenges. Administration and Policy in Mental Health. 2009;36(1):24-34.

97. Applequist J, Miller-Day M, Cronholm PF, Gabbay RA, Bowen DS. "In Principle We Have Agreement, But in Practice It Is a Bit More Difficult": Obtaining Organizational Buy-In to Patient-Centered Medical Home Transformation. Qualitative Health Research. 2016.

98. Drainoni ML, Koppelman EA, Feldman JA, Walley AY, Mitchell PM, Ellison J, et al. Why is it so hard to implement change? A qualitative examination of barriers and facilitators to distribution of naloxone for overdose prevention in a safety net environment. BMC Research Notes. 2016;9(1):465.

99. Powell BJ, McMillen JC, Proctor EK, Carpenter CR, Griffey RT, Bunger AC, et al. A compilation of strategies for implementing clinical innovations in health and mental health. Medical Care Research and Review. 2012;69(2):123-57.

100. Michie S, Fixsen D, Grimshaw JM, Eccles MP. Specifying and reporting complex behaviour change interventions: the need for a scientific method. Implementation Science. 2009;4:40.

101. Yarber L, Brownson CA, Jacob RR, Baker EA, Jones E, Baumann C, et al. Evaluating a train-the-trainer approach for improving capacity for evidence-based decision making in public health. BMC Health Services Research. 2015;15(1):547.

102. Williams AB, Le ST, Colby D, Thu Le TT, Pollack T, Cosimi L. Effectiveness of train-the-trainer HIV education: a model from Vietnam. Journal of the Association of Nurses in AIDS Care. 2014;25(4):341-50.

103. Limm H, Heinmuller M, Gundel H, Liel K, Seeger K, Salman R, et al. Effects of a Health Promotion Program Based on a Train-the-Trainer Approach on Quality of Life and Mental Health of Long-Term Unemployed Persons. BioMed Research International. 2015;2015:719327.

104. EMCDDA. Norway country overview. European Monitoring Centre for Drugs and Drug Addiction, 2016 (Cited May 2017). [Available from: http://www.emcdda.europa.eu/countries/norway#harmReductionResponses.

105. Clausen T, Anchersen K, Waal H. Mortality prior to, during and after opioid maintenance treatment (OMT): a national prospective cross-registry study. Drug and Alcohol Dependence. 2008;94(1-3):151-7.

106. UNODC. Sweden's successful drug policy: a review of the evidence. United Nations Office on Drugs and Crime, 2007. (Cited May 2017). [Available from: https://www.unodc.org/pdf/research/Swedish_drug_control.pdf.

107. Selin J, Perälä R, Stenius K, Partanen A, Rosenqvist P, Alho H. Opioid substitution treatment in Finland and other Nordic countries: Established treatment, varying practices. Nordic Studies on Alcohol and Drugs. 2015;32(3):311-324.

108. EMCDDA. European Drug Report. Lisbon: European Monitoring Centre for Drugs and Drug Addiction, 2015.

109. Amundsen EJ. Narkotikautløste dødsfall. Statens institutt for rusmiddelforskning, 2015.

110. Estimated population growth and population Statistics Norway, 2015. (Cited February 2017). [Available from: https://www.ssb.no/en/befolkning/statistikker/folkemengde/aar-berekna/2015-12-17.

111. The Drug Situation in Norway 2014. Annual Report to the European Monitoring Centre for Drugs and Drug Addiction. SIRUS, 2015.

112. Waal H. Merits and problems in high-threshold methadone maintenance treatment. Evaluation of medication-assisted rehabilitation in Norway 1998-2004. European Addiction Research. 2007;13(2):66-73.

113. Clausen T. The Norwegian OMT program: benefits and challenges. The Norwegian Journal of Pharmacy. 2014(10):39-42.

114. Waal H, Gossop M. Making sense of differing overdose mortality: contributions to improved understanding of European patterns. European Addiction Research. 2014;20(1):8-15.

115. Amundsen EJ, Bretteville-Jensen AL. Hard drug use in Norway. Nordisk Alkohol- & Narkotikatidskrift. 2010;27.

116. Pirona A, Guarita B, Montanari L, Noor A. Ageing and addiction: challenges for treatment systems, 2015. (Cited June 2017). [Available from: http://www.emcdda.europa.eu/publications/posters/2016/ageing-and-addiction-challenges-treatment-systems.

117. Representantforslag 17 S. Norwegian Storting. 2009;8(17). (Cited May 2017). [Available from: https://www.stortinget.no/globalassets/pdf/representantforslag/2009-2010/dok8-200910-017.pdf.

118. Strøm-Erichsen A. Representantforslag 17 S (2009-2010) om en utredning knyttet til prøveprosjekt med Naloxon nesespray til bekjempelse av overdosedødsfall. Helse og omsorgsdepartementet, 2009.

119. Lobmaier P, Dalsbø T, Clasen T. Nalokson nesespray kan redusere risikoen for dødelige heroinoverdoser. Norwegian Journal of Epidemiology. 2011;21(1).

120. Se meg! En helhetlig rusmiddelpolitikk. Helse- og omsorgsdepartement, 2012. p. 113.

121. Vedtak 405. Norwegian Storting.2012. (Cited May 2017). [Available from: https://www.stortinget.no/no/Saker-og-publikasjoner/Vedtak/Vedtak/Sak/?p=54206.

122. Williams AV, Strang J, Marsden J. Development of Opioid Overdose Knowledge (OOKS) and Attitudes (OOAS) Scales for take-home naloxone training evaluation. Drug and Alcohol Dependence. 2013;132(1-2):383-6.

123. Population and land area in urban settlements, 1 January 2016. (Cited June 2017). [Available from: https://www.ssb.no/en/beftett/.

124. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA. 1998;280(19):1690-1.

125. Kuhnast C, Neuhauser M. A note on the use of the non-parametric Wilcoxon-Mann-Whitney test in the analysis of medical studies. German Medical Science. 2008;6:Doc02.

126. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4.

127. Jobert B, Kohler-Koch B. Changing Images of Civil Society: From protest to governance. New York, NY: Routledge; 2008. p.236.

128. Nicholaisen C, Jansen K. Frykter motgift kan gi flere nesten-overdoser. Bergens Tidende. October 20, 2013.

129. Sessler DI, Imrey PB. Clinical Research Methodology 1: Study Designs and Methodologic Sources of Error. Anesthesia and Analgesia. 2015;121(4):1034-42.

130. Rothman K. Epidemiology: An Introduction. Second ed. New York, New York: Oxford University Press; 2012.

131. Tobin KE, Davey MA, Latkin CA. Calling emergency medical services during drug overdose: an examination of individual, social and setting correlates. Addiction. 2005;100(3):397-404.

132. Siegler A, Tuazon E, Bradley O'Brien D, Paone D. Unintentional opioid overdose deaths in New York City, 2005-2010: a place-based approach to reduce risk. The International Journal on Drug Policy. 2014;25(3):569-74.

133. Bornstein MH, Jager J, Putnick DL. Sampling in Developmental Science: Situations, Shortcomings, Solutions, and Standards. Developmental Review. 2013;33(4):357-70.

134. Lacy JW, Stark CE. The neuroscience of memory: implications for the courtroom. Nature Reviews Neuroscience. 2013;14(9):649-58.

135. Althubaiti A. Information bias in health research: definition, pitfalls, and adjustment methods. Journal of Multidisciplinary Healthcare. 2016;9:211-7.

136. Choi BC, Pak AW. A catalog of biases in questionnaires. Preventing Chronic Disease. 2005;2(1):A13.

137. Veierød M, Lydersen S, Petter L. Medical Statistics. Oslo: Gyldendal; 2012.

138. Buajordet I, Naess AC, Jacobsen D, Brors O. Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. European Journal of Emergency Medicine. 2004;11(1):19-23.

139. Horyniak D, Degenhardt L, Smit de V, Munir V, Johnston J, Fry C, et al. Pattern and characteristics of ecstasy and related drug (ERD) presentations at two hospital emergency

departments, Melbourne, Australia, 2008-2010. Emergency Medicine Journal. 2014;31(4):317-22.

140. Gjersing L, Jonassen KV, Biong S, Ravndal E, Waal H, Bramness JG, et al. Diversity in causes and characteristics of drug-induced deaths in an urban setting. Scandinavian Journal of Public Health. 2013;41(2):119-25.

141. Ambrose G, Amlani A, Buxton JA. Predictors of seeking emergency medical help during overdose events in a provincial naloxone distribution programme: a retrospective analysis. BMJ Open. 2016;6(6):e011224.

142. Tracy M, Piper TM, Ompad D, Bucciarelli A, Coffin PO, Vlahov D, et al. Circumstances of witnessed drug overdose in New York City: implications for intervention. Drug and Alcohol Dependence. 2005;79(2):181-90.

143. Lankenau SE, Wagner KD, Silva K, Kecojevic A, Iverson E, McNeely M, et al. Injection drug users trained by overdose prevention programs: responses to witnessed overdoses. Journal of Community Health. 2013;38(1):133-41.

144. Mayet S, Manning V, Williams A, Loaring J, Strang J. Impact of training for healthcare professionals on how to manage an opioid overdose with naloxone: effective, but dissemination is challenging. International Journal of Drug Policy. 2011;22(1):9-15.

145. Behar E, Santos GM, Wheeler E, Rowe C, Coffin PO. Brief overdose education is sufficient for naloxone distribution to opioid users. Drug and Alcohol Dependence. 2015;148:209-12.

146. Williams AV, Marsden J, Strang J. Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes. Addiction. 2014;109(2):250-9.

147. Nutting PA, Crabtree BF, Miller WL, Stewart EE, Stange KC, Jaen CR. Journey to the patient-centered medical home: a qualitative analysis of the experiences of practices in the National Demonstration Project. Annals of Family Medicine. 2010;8 Suppl 1:S45-56; s92.

148. Gesme D, Wiseman M. How to implement change in practice. Journal of Oncology Practice. 2010;6(5):257-9.

149. Jones JD, Roux P, Stancliff S, Matthews W, Comer SD. Brief overdose education can significantly increase accurate recognition of opioid overdose among heroin users. The International Journal on Drug Policy. 2014;25(1):166-70.

150. Ashrafioun L, Gamble S, Herrmann M, Baciewicz G. Evaluation of knowledge and confidence following opioid overdose prevention training: A comparison of types of training participants and naloxone administration methods. Substance Abuse. 2016;37(1):76-81.

151. Beidas RS, Koerner K, Weingardt KR, Kendall PC. Training research: practical recommendations for maximum impact. Administration and Policy in Mental Health. 2011;38(4):223-37.

152. Beidas RS, Cross W, Dorsey S. Show Me, Don't Tell Me: Behavioral Rehearsal as a Training and Analogue Fidelity Tool. Cognitive and Behavioral Practice. 2014;21(1):1-11.

153. Clark A, Winstanley EL, Martsolf DS, Rosen M. Implementation of an inpatient opioid overdose prevention program. Addictive Behaviors. 2016;53:141-5.

154. Roe SS, Banta-Green CJ. An Initial Evaluation of Web-Based Opioid Overdose Education. Substance Use and Misuse. 2016;51(2):268-75.

155. Simmons J, Rajan S, Goldsamt L, Elliott L. Implementation of online opioid overdose prevention, recognition and response trainings for professional first responders: Year 1 survey results. Drug and Alcohol Dependence. 2016;169:1-4.

156. Edmunds JM, Beidas RS, Kendall PC. Dissemination and Implementation of Evidence-Based Practices: Training and Consultation as Implementation Strategies. Clinical Psychology : a publication of the Division of Clinical Psychology of the American Psychological Association. 2013;20(2):152-65.

157. Proctor EK, Rosen A. From Knowledge Production to Implementation: Research Challenges and Imperatives. Research on Social Work Practice. 2008;18(4):285-91.

158. Enteen L, Bauer J, McLean R, Wheeler E, Huriaux E, Kral AH, et al. Overdose prevention and naloxone prescription for opioid users in San Francisco. Journal of Urban Health. 2010;87(6):931-41.

159. Doe-Simkins M, Walley AY, Epstein A, Moyer P. Saved by the nose: bystander-administered intranasal naloxone hydrochloride for opioid overdose. American Journal of Public Health. 2009;99(5):788-91.

160. Green TC, Heimer R, Grau LE. Distinguishing signs of opioid overdose and indication for naloxone: an evaluation of six overdose training and naloxone distribution programs in the United States. Addiction. 2008;103(6):979-89.

161. Dietze P, Jolley D, Fry CL, Bammer G, Moore D. When is a little knowledge dangerous? Circumstances of recent heroin overdose and links to knowledge of overdose risk factors. Drug and Alcohol Dependence. 2006;84(3):223-30.

162. Piper TM, Stancliff S, Rudenstine S, Sherman S, Nandi V, Clear A, et al. Evaluation of a naloxone distribution and administration program in New York City. Substance Use and Misuse. 2008;43(7):858-70.

163. Amundsen EJ. Narkotikautløste dødsfall i Norge i 2015, 2016. (Cited June 2017). [Available from: https://www.fhi.no/hn/statistikk/statistikk2/narkotikautloste-dodsfall-i-norge-i-2015/.

164. Wilder CM, Brason FW, 2nd, Clark AK, Galanter M, Walley AY, Winstanley EL. Development and implementation of an opioid overdose prevention program within a preexisting substance use disorders treatment center. Journal of Addiction Medicine. 2014;8(3):164-9.

165. Horyniak D, Higgs P, Lewis J, Winter R, Dietze P, Aitken C. An evaluation of a heroin overdose prevention and education campaign. Drug and Alcohol Review. 2010;29(1):5-11.

166. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. Journal of the Royal Society of Medicine. 2011;104(12):510-20.

167. Green LW, Ottoson JM, Garcia C, Hiatt RA. Diffusion theory and knowledge dissemination, utilization, and integration in public health. Annual Review of Public Health. 2009;30:151-74.

168. Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ : British Medical Journal. 2015;350.

Appendix I. Opioid overdose training pre-test

Opioid Overdose Training Pre-Test:

Type of facility:					
□ Medical	□ Outreach	□ Housing	□ Prison	□ Other	
Profession/Title:					
□ Nurse	□ Social worker	□ Outreach worker	□ Physician	□ Leader	□ Other
Gender:					
□ Male		□ Female			
Years of experience working with drug users:					
□ <1	□ >1	□ 2-5	□ >5		

Please answer the following questions about heroin overdose (or an overdose from other opioids such as: methadone, morphine, oxycodone, tramadol, fentanyl or codeine):

1. **Which of the following factors increase the risk of a heroin (opioid) overdose? (tick all that apply)**
   - □ Taking larger than usual doses of heroin
   - □ Switching from smoking to injecting heroin
   - □ Using heroin with other substances, such as alcohol or sleeping pills
   - □ Increase in heroin purity
   - □ Using heroin again after not having used for a while
   - □ Using heroin when no one else is present around
   - □ A long history of heroin use
   - □ Using heroin again soon after release from prison
   - □ Using heroin again after a detox treatment

2. **Which of the following are indicators of an opioid overdose? (tick all that apply)**
   - □ Having blood-shot eyes
   - □ Slow/shallow breathing
   - □ Lips, hands or feet turning blue
   - □ Loss of consciousness
   - □ Unresponsive
   - □ Fitting
   - □ Deep snoring
   - □ Very small pupils
   - □ Agitated behavior
   - □ Rapid heartbeat

3. **Which of the following should be done when managing an opioid overdose? (tick all that apply)**
   - □ Call an ambulance
   - □ Stay with the person until an ambulance arrives
   - □ Inject the person with salt solution or milk
   - □ Mouth to mouth resuscitation
   - □ Give stimulants (e.g. cocaine or black coffee)
   - □ Place the person in the recovery position (on their side with mouth clear)
   - □ Give Naloxone (opioid antidote)
   - □ Put the person in a bath of cold water
   - □ Check for breathing
   - □ Check for blocked airways (nose and mouth)
   - □ Put the person in bed to sleep it off

4. What is naloxone used for?

- ☐ To reverse the effects of an opioid overdose (e.g. heroin, methadone)
- ☐ To reverse the effects of an amphetamine overdose
- ☐ To reverse the effects of a cocaine overdose
- ☐ To reverse the effects of any overdose
- ☐ Don't know

5. How long does naloxone takes to start having effect?

- ☐ 2-5 minutes
- ☐ 5-10 minutes
- ☐ 10-20 minutes
- ☐ 20-40 minutes
- ☐ Don't know

6. How long do the effects of naloxone last for?

- ☐ Less than 20 minutes
- ☐ About one hour
- ☐ 1 to 6 hours
- ☐ 6 to12 hours
- ☐ Don't know

Please mark "true", "false" or "don't know"	**True**	**False**	**Don't know**
7. If the first dose of naloxone has no effect a second dose can be given	☐	☐	☐
8. There is no need to call for an ambulance if I know how to manage an overdose	☐	☐	☐
9. Someone can overdose again even after having received naloxone	☐	☐	☐
10. The effect of naloxone is shorter than the effect of heroin and methadone	☐	☐	☐
11. After recovering from an opioid overdose, the person must not take any heroin, but it is ok for them to drink alcohol or take sleeping tablets	☐	☐	☐
12. Naloxone can provoke withdrawal symptoms	☐	☐	☐

Please rate from 1-5 (Circle response)					
13. I would rate my understanding about:					**(1= Low 3= Medium 5= High)**
Opioid overdose risk factors	**1**	**2**	**3**	**4**	**5**
Opioid overdose prevention techniques	**1**	**2**	**3**	**4**	**5**
How to recognize the signs of an opioid overdose	**1**	**2**	**3**	**4**	**5**
How to respond to an opioid overdose	**1**	**2**	**3**	**4**	**5**
14. I would rate my comfort teaching others about:					**(1= Low 3= Medium 5= High)**
Opioid overdose risk factors	**1**	**2**	**3**	**4**	**5**
Opioid overdose prevention techniques	**1**	**2**	**3**	**4**	**5**
How to recognize the signs of an opioid overdose	**1**	**2**	**3**	**4**	**5**
How to respond to an opioid overdose	**1**	**2**	**3**	**4**	**5**
15. I feel prepared to:					**(1= Low 3= Medium 5= High)**
Train others on overdose prevention and the use of naloxone	**1**	**2**	**3**	**4**	**5**
Respond to an overdose if I encounter one	**1**	**2**	**3**	**4**	**5**
					(1= strongly disagree, 3= neutral, 5= strongly agree)
16. I believe that people who use drugs should be trained to use naloxone	**1**	**2**	**3**	**4**	**5**
					(1=not important at all, 3= somewhat important, 5= very important)
17. What role do you think naloxone has in overall overdose prevention work?	**1**	**2**	**3**	**4**	**5**

This scale has been developed and validated by Anna Williams, John Strang and John Marsden from the Addictions Department, Institute of Psychiatry and Psychology and Neuroscience, King's College London. Williams AV, Strang J & Marsden J (2013). Development of Opioid Overdose Knowledge (OOKS) and Attitudes (OOAS) Scales for take-home naloxone training evaluation. Drug Alcohol Dependence.132(1-2):383-6.

Appendix II. Opioid overdose training post-test

Opioid Overdose Training Post-Test:

Type of facility:
□ Medical □ Outreach □ Housing □ Prison □ Other
Profession/Title:
□ Nurse □ Social worker □ Outreach worker □ Physician □ Leader □ Other
Gender:
□ Male □ Female
Years of experience working with drug users:
□ <1 □ >1 □ 2-5 □ >5

Please answer the following questions about heroin overdose (or an overdose from other opioids such as: methadone, morphine, oxycodone, tramadol, fentanyl or codeine):

1. **Which of the following factors increase the risk of a heroin (opioid) overdose? (tick all that apply)**
   - □ Taking larger than usual doses of heroin
   - □ Switching from smoking to injecting heroin
   - □ Using heroin with other substances, such as alcohol or sleeping pills
   - □ Increase in heroin purity
   - □ Using heroin again after not having used for a while
   - □ Using heroin when no one else is present around
   - □ A long history of heroin use
   - □ Using heroin again soon after release from prison
   - □ Using heroin again after a detox treatment
2. **Which of the following are indicators of an opioid overdose? (tick all that apply)**
   - □ Having blood-shot eyes
   - □ Slow/shallow breathing
   - □ Lips, hands or feet turning blue
   - □ Loss of consciousness
   - □ Unresponsive
   - □ Fitting
   - □ Deep snoring
   - □ Very small pupils
   - □ Agitated behavior
   - □ Rapid heartbeat
3. **Which of the following should be done when managing an opioid overdose? (tick all that apply)**
   - □ Call an ambulance
   - □ Stay with the person until an ambulance arrives
   - □ Inject the person with salt solution or milk
   - □ Mouth to mouth resuscitation
   - □ Give stimulants (e.g. cocaine or black coffee)
   - □ Place the person in the recovery position (on their side with mouth clear)
   - □ Give Naloxone (opioid antidote)
   - □ Put the person in a bath of cold water
   - □ Check for breathing
   - □ Check for blocked airways (nose and mouth)
   - □ Put the person in bed to sleep it off
4. **What is naloxone used for**?
   - □ To reverse the effects of an opioid overdose (e.g. heroin, methadone)
   - □ To reverse the effects of an amphetamine overdose
   - □ To reverse the effects of a cocaine overdose
   - □ To reverse the effects of any overdose
   - □ Don't know

5. **How long does naloxone takes to start having effect?**
   - ☐ 2-5 minutes
   - ☐ 5-10 minutes
   - ☐ 10-20 minutes
   - ☐ 20-40 minutes
   - ☐ Don't know
6. **How long do the effects of naloxone last for?**
   - ☐ Less than 20 minutes
   - ☐ About one hour
   - ☐ 1 to 6 hours
   - ☐ 6 to12 hours
   - ☐ Don't know
7. **The amount of time used for this training was:**
   - ☐ Adequate
   - ☐ Too much
   - ☐ Too little
8. **The use of a PowerPoint was an appropriate delivery method:**
   - ☐ Yes
   - ☐ No
9. **I would have preferred: (choose one)**
   - ☐ Online learning module
   - ☐ A video
   - ☐ PowerPoint course was ok
   - ☐ Instruction from a colleague

Please mark "true", "false" or "don't know"	**True**	**False**	**Don't know**
10. If the first dose of naloxone has no effect a second dose can be given	☐	☐	☐
11. There is no need to call for an ambulance if I know how to manage an overdose	☐	☐	☐
12. Someone can overdose again even after having received naloxone	☐	☐	☐
13. The effect of naloxone is shorter than the effect of heroin and methadone	☐	☐	☐
14. After recovering from an opioid overdose, the person must not take any heroin, but it is ok for them to drink alcohol or take sleeping tablets	☐	☐	☐
15. Naloxone can provoke withdrawal symptoms	☐	☐	☐

Please rate from 1-5 (Circle response) (1= Low 3= Medium 5= High)					
16. My understanding about:					
Opioid overdose risk factors	**1**	**2**	**3**	**4**	**5**
Opioid overdose prevention techniques	**1**	**2**	**3**	**4**	**5**
How to recognize the signs of an opioid overdose	**1**	**2**	**3**	**4**	**5**
How to respond to an opioid overdose	**1**	**2**	**3**	**4**	**5**
17. My comfort teaching others about:					
Opioid overdose risk factors	**1**	**2**	**3**	**4**	**5**
Opioid overdose prevention techniques	**1**	**2**	**3**	**4**	**5**
How to recognize the signs of an opioid overdose	**1**	**2**	**3**	**4**	**5**
How to respond to an opioid overdose	**1**	**2**	**3**	**4**	**5**
18. I feel prepared to:					
Train others on overdose prevention and the use of naloxone	**1**	**2**	**3**	**4**	**5**
Respond to an overdose if I encounter one	**1**	**2**	**3**	**4**	**5**
19. I believe that people who use drugs should be trained to use and carry naloxone (1= strongly disagree 3= neutral 5= strongly agree)	**1**	**2**	**3**	**4**	**5**
20. What role do you think naloxone has in overall overdose prevention work? (1=not important at all, 3= somewhat important, 5= very important)	**1**	**2**	**3**	**4**	**5**
21. I am in a position to distribute naloxone (1=not at all, 3= somewhat, 5= very)	**1**	**2**	**3**	**4**	**5**
22. The information provided in this course was useful to me	**1**	**2**	**3**	**4**	**5**
23. I intend to distribute naloxone to the patients/clients that I meet	**1**	**2**	**3**	**4**	**5**
24. After this training, I feel confident to train others in the use of naloxone	**1**	**2**	**3**	**4**	**5**

This scale has been developed and validated by Anna Williams, John Strang and John Marsden from the Addictions Department, Institute of Psychiatry and Psychology and Neuroscience, King's College London. Williams AV, Strang J & Marsden J (2013). Development of Opioid Overdose Knowledge (OOKS) and Attitudes (OOAS) Scales for take-home naloxone training evaluation. Drug Alcohol Dependence.132(1-2):383-6.

Appendix III. Initial naloxone questionnaire

(Originally administered in Norwegian. Translated to English for thesis)

Initial Training

ID # Location: _____Date:_____

Birthdate: ____/____/____
Gender: Male Female
Have you had a naloxone training before? Yes: (→ refill form)

1. Opioid use:
   - ☐ Opioid use- daily/almost daily
   - ☐ Opioid use- not daily/sporadic
   - ☐ Never used opioids
   - ☐ Previous opioid use
     - ☐ Less than one month ago
     - ☐ 1-3 months ago
     - ☐ More than 3 months ago

2. Admitted to detoxification in the past 30 days (cross only one)
   - ☐ No
   - ☐ Yes
   - ☐ No applicable

3. Have you been in prison in the past 30 days? (cross only one)
   - ☐ No
   - ☐ Yes
   - ☐ Not applicable

4. Do you use methadone?
   - ☐ No
   - ☐ Yes, from OMT
   - ☐ Yes, from the street
   - ☐ Not applicable

5. Do you use drugs/opioids while alone (cross only one)
   - ☐ Never
   - ☐ Seldom
   - ☐ Often
   - ☐ Most of the time
   - ☐ Always
   - ☐ Not applicable

6. Do you mix opioids together with: (multiple responses permitted)
   - ☐ Alcohol
   - ☐ Benzodiazepines
   - ☐ Cocaine
   - ☐ Meth/amphetamine
   - ☐ GHB/GBL
   - ☐ Other (specify)
   - ☐ Not applicable

7. How do you usually take opiates/opioids (cross only one)
   - ☐ Inject
   - ☐ Smoke
   - ☐ Snort
   - ☐ Swallow
   - ☐ Other (specify):
   - ☐ Don't use opioids
   - ☐ Not applicable

8. How many times in your life have you overdosed? (cross only one)
   - ☐ 1-10 times
   - ☐ 11-20 times
   - ☐ More than 20 times
   - ☐ Never
   - ☐ Not applicable

9. How many times have you witnessed an overdose (cross only one)
   - ☐ 1-10 times
   - ☐ 11-20 times
   - ☐ More than 20 times
   - ☐ Never
   - ☐ Not applicable

10. What did you do when you saw an overdose? (multiple responses permitted)
    - ☐ Called the ambulance
    - ☐ Tried to wake them
    - ☐ CPR
    - ☐ Recovery position
    - ☐ Injected the person with a central stimulating drug (ex. amphetamine)
    - ☐ Nothing
    - ☐ Not applicable

Appendix IV. Refill naloxone questionnaire

(Originally administered in Norwegian. Translated to English for thesis)

REFILL QUESTIONNAIRE

Date:		**Location:**	
Name:		**Identity number:**	
Trainer name:		**ID#** (ex. HAU0602)	

FOR INTERVIEWER: READ EACH QUESTION. PICK WHICH ANSWER FITS BEST.
Information given should be in relation to their most previously witnessed overdose

1. What happened with your last naloxone nasal spray?			
☐	Used on an overdose (→ #2)	☐	Other:
☐	Not used: lost, stolen, broken, etc. (→ #5)	☐	Not applicable
2. If used on an overdose, who needed it?			
☐	Friend	☐	Self
☐	Acquaintance	☐	Child
☐	Boyfriend/girlfriend	☐	Other
☐	Stranger	☐	Not applicable/ declines to answer
☐	Partner/spouse		
3. Do you know which drugs were used when the overdose happened? (multiple responses permitted)			
☐	Heroin:	☐	Alcohol
☐	Buprenorphine (Subutex/Suboxone)	☐	Antidepressants/antipsychotics
☐	Benzodiazepines	☐	GHB/GBL
☐	Cocaine	☐	Don't know
☐	Methadone	☐	Other drugs: (specify)
☐	Meth/amphetamine	☐	Not applicable
4. Where did the overdose happen?			
☐	In own home	☐	Car
☐	In someone else's home	☐	Other: (specify)
☐	On the street/public location	☐	Not applicable

5. The last time you saw an overdose, what did you (or another witness) do?

	Yes	**No**	**Unsure**		**Yes**	**No**	**Unsure**
a. Called the ambulance	☐	☐	☐	d. Tried to wake them	☐	☐	☐
b. Recovery position	☐	☐	☐	e. Injected with a central-stimulating drug, water, or salt	☐	☐	☐
c. CPR	☐	☐	☐	f. Naloxone	☐	☐	☐
Other: (specify)				Not applicable			☐

6. How many doses (0.4mL = 1 dose) of naloxone were given for the overdose? (Multiple responses permitted)					
☐ 0.4 (1 dose)	☐ 0.4 (1 dose)	☐ 0.4 (1 dose)	☐ 0.4 (1 dose)	☐ 0.4 (1 dose)	☐ Don't know ☐ N/A

7. How was naloxone administered?			
☐	In the nose	☐	Other: (specify)
☐	Injected	☐	Don't know/ not applicable

8. Any withdrawal symptoms afterwards? (multiple responses permitted)

Nauseous ☐	Confused ☐	Shock ☐	Tired ☐	Vomited ☐	Angry ☐	Nothing ☐	Other: (specify)

9. If naloxone wasn't given, what was the reason? (multiple responses permitted)			
☐	Did not have naloxone	☐	Did not think to give naloxone
☐	Did not know how to use naloxone	☐	Someone else gave naloxone
☐	Knew how to use naloxone, but didn't give it for some other reason	☐	Person did not want naloxone
Not applicable: ☐			

10. If the ambulance came, was the person transported to the:			
☐	Hospital	☐	Other:_____
☐	Acute center	☐	Person was not transported
☐	Emergency department	☐	Unknown
☐ Not applicable			

11. How confident are you today to use naloxone if you encounter someone that is having an overdose?				
☐ Not really	☐ Somewhat	☐ Unknown	☐ Very	☐ Extremely

12. Did the person survive?			
☐ Yes	☐ No, died	☐ Unknown	☐ Not applicable

13. To witness an overdose can be a traumatic and difficult experience. Would you like the chance to discuss with someone about it?		
☐ Yes	☐ No	☐ Not applicable

Write about the experience here (optional):

Your information is very valuable to us and we are very grateful for your responses.

(Adapted from naloxoneinfo.org)

Papers I-III

I

Drug and Alcohol REVIEW

APSAD

Drug and Alcohol Review (May 2017), 36, 288–294
DOI: 10.1111/dar.12451

Circumstances surrounding non-fatal opioid overdoses attended by ambulance services

DESIREE MADAH-AMIRI[1], THOMAS CLAUSEN[1], LARS MYRMEL[2], GUTTORM BRATTEBØ[2,4] & PHILIPP LOBMAIER[1,3]

[1]*The Norwegian Centre for Addiction Research, The University of Oslo, Oslo, Norway,* [2]*Bergen Emergency Medical Services, Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway,* [3]*Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway, and* [4]*Department of Clinical Medicine, University of Bergen, Bergen, Norway*

Abstract

Introduction and Aims. *Opioid overdose fatalities are a significant concern globally. Non-fatal overdoses have been described as a strong predictor for future overdoses, and are often attended by the ambulance services. This paper explores characteristics associated with non-fatal overdoses and aims to identify possible trends among these events in an urban area in Norway.* ***Design and Methods.*** *This is a retrospective analysis of non-fatal overdoses from Bergen ambulance services from 2012 to 2013. Demographic, temporal and geographic data were explored.* ***Results.*** *During the two years, 463 non-fatal opioid overdoses were attended by ambulance services. Ambulance call-outs occurred primarily during the late afternoon and evening hours of weekdays. Summer months had more overdoses than other seasons, with a peak in August. Overdoses were nearly twice as likely to occur in a public location in August (risk ratio 1.92, P = 0.042). Ambulance response times were more likely to be longer to private locations, and these victims were more likely to be treated and left at the scene. There was no difference in arrival time for drug-related and non-drug related dispatch.* ***Discussion and Conclusions.*** *The temporal patterns suggest that non-fatal overdoses occur during non-recreational time periods. The longer ambulance response time and disposition for private addresses indicate potential opportunities for peer interventions. Our analysis describes circumstances surrounding non-fatal overdoses and can be useful in guiding relevant, targeted prevention interventions.* [Madah-Amiri D, Clausen T, Myrmel L, Brattebø G, Lobmaier P. Circumstances surrounding non-fatal opioid overdoses attended by ambulance services. *Drug Alcohol Rev* 2017;36:288-294]

Key words: non-fatal overdose, EMS, ambulance, opioid, pre-hospital.

Introduction

There are estimated to be over one million problem drug users in Europe, many who face severe burdens associated with their disease [1]. Opioid overdose fatalities are the most serious consequence of drug use, and northern Europe and Scandinavia are particularly affected [1]. Annual fatality rates in Norway are estimated to be around 70 per million, as compared to the European mean estimate of 17 deaths per million [1]. Further, Norway's second largest city, Bergen, experienced an annual drug fatality rate of 119 per million during 2012 and 2013, with 80–90% being opioid related [2,3]. Given that these alarming fatality rates are the highest in the country, monitoring and prevention efforts in the region are needed.

Of all opioid overdoses, approximately 5% are fatal [4,5]. Non-fatal opioid overdoses make up a majority of overdoses experienced, and have severe implications for people who inject drugs (PWID) [6]. Between 17 and 68% of PWID experience and 50 and 96% witness an overdose in their lifetime [6]. Non-fatal opioid overdose victims face high rates of morbidity following an overdose, including broken bones, head injuries, neuropathy and paralysis [7]. Furthermore, non-fatal overdoses have been described as a predictor for future fatal opioid overdoses [8–10].

Fatal opioid overdoses are primarily reported through direct measures, such as police reports and mortality registries. This method results in a significant time lag before reports are made public. The Norwegian annual cause-of-death reports present data on incidents that occurred from one to two years after the actual event. Hence, this information may not necessarily represent the current trends surrounding drug use and overdose patterns. Additionally, this information only describes fatalities deemed as a result of illicit drug use. Whether

Desiree Madah-Amiri FNP, Doctoral student, Thomas Clausen MD, PhD, Professor, Lars Myrmel RN, Guttorm Brattebø MD, FERC, Medical Director, Professor II, Philipp Lobmaier MD, PhD, Researcher. Correspondence to Miss Desiree Madah-Amiri, Norwegian Centre for Addiction Research, Institute of Clinical Medicine, The University of Oslo, P.O. Box 1039 Blindern, 0315 Oslo, Norway. Tel.: +47 23 36 89; E-mail: desireem@medisin.uio.no

Received 22 January 2016; accepted for publication 31 May 2016.

from underreporting, surveys subject to bias or a lack of a systematic reporting database, adequate information on non-fatal opioid overdoses in Norway is lacking.

Addressing the opioid overdose epidemic requires the utilisation of public health measures, including the use of local data to target interventions [11]. Information from ambulance records has been used to understand patterns associated with various drug related emergencies, such as γ-hydroxybutyric acid (GHB) overdoses, pharmaceutical drug misuse, cannabis and volatile substance use. As demonstrated in these studies, ambulance information can be useful to guide and evaluate prevention services on a local level. Studies from Australia [12,13], the United States [14–16] and Europe [17–19] have used ambulance data to examine opioid overdoses locally, and have also contributed globally to developing an evidence base to better understand the global diversity in practices and outcomes.

Drug use patterns and treatment responses vary across the world, and it is therefore necessary to have estimates from a variety of settings to better understand mechanisms of actions that can be targeted with prevention measures. In Dublin, opioid overdose hotspots determined from ambulance calls identified areas of increased incidence, giving guidance for prevention programs in the most affected areas [19]. Australia has extensive data collection and monitoring of drug related ambulance attendances, which have relevance for influencing public health programs and health policy [20]. These epidemiological studies have provided the necessary data to guide and eventually evaluate the effect of prevention efforts. Although Bergen, Norway experiences some of the highest rates of fatal drug overdoses per population globally, prior local ambulance monitoring studies have not been conducted.

This study examined characteristics of non-fatal overdoses attended by emergency medical services (EMS) in Bergen, Norway from 2012 to 2013 by retrospectively reviewing ambulance records. The aim of this study was to: (i) describe the demographic, temporal and geographic conditions surrounding non-fatal opioid overdoses; and (ii) investigate possible trends among these cases.

Methods

Setting

There are estimated to be between 7000 and 10 000 PWID in Norway [21]. There were more than 7400 clients enrolled in opioid maintenance treatment in 2014, yet large numbers are still outside of formal treatment [22]. Heroin is the most commonly reported injected drug [21], and for heroin users, injection is the preferred route of administration [23]. Despite access to treatment in the target population, overdose fatalities remain high in the society and are highest among those outside of formal treatment.

Bergen is the second largest city in Norway, with a population of approximately 270 000 [3]. Although smaller in size than the capital city of Oslo, in recent years Bergen has experienced more drug-induced deaths per population [2].

Study design

The study was a retrospective analysis of non-fatal opioid overdoses attended by Bergen EMS from 1 January 2012 to 31 December 2013.

Bergen Emergency Medical Services

The Bergen EMS attend to approximately 31 000 emergency calls annually and use standardised paper records for documentation on all patients. Documentation in these forms includes patient demographics, clinical and treatment information, and details of disposition after treatment.

Every ambulance call is dispatched by the Bergen emergency medical dispatch centre, which collects information on the caller, location, various time variables, the patient's response to treatment and where the patient is admitted in an electronic database.

The ambulance crews are equipped with naloxone, an opioid antagonist that reverses the effects of an opioid overdose. Treatment protocols include the use of this drug for a suspected opioid overdose. Indication for treatment includes reduced consciousness, respiratory depression and decreased pupil size.

Case selection

Opioid overdose victims typically present with decreased respiratory rate and loss of consciousness [24]. A positive response following naloxone administration has been used by others as an indication of an opioid overdose [25], and was used for case selection in this study. Cases were included if a positive response (increased respiratory rate) followed naloxone administration by the ambulance staff. Cases were excluded if the patient did not respond to naloxone, or if the patient did not survive.

Possible opioid overdoses were identified through the emergency medical dispatch centre electronic data base based on caller information and ambulance feedback. In addition, all ambulance records coded as an 'acute response' were screened for possible opioid overdoses. The data from the records on suspected opioid overdoses were reviewed manually. Each entry represents an independent opioid overdose event; hence, the number of overdosing individuals was not analysed.

Exposure measures

When not treated as outcome measures, several key variables were considered exposure measures. These included: demographic, temporal and location measures; time from call until arrival; caller-reported symptoms and disposition after treatment.

Outcome measures

These measures included the overdose location (public or private), time from dispatch until ambulance arrival (less than or more than 10 min) and the disposition for the victim (being transported for further treatment or left at the scene).

Data analysis

Statistical analyses were conducted using SPSS Version 22.0. Age differences among genders were tested using the independent samples *t*-test. χ^2 tests were used to analyse differences between days of the week, months of the year, and to explore the relationship between ambulance arrival times and the symptoms reported (drug related and non-drug related). Analysis of variance was used to compare the age of the victim during the various months. Cox regression was used to analyse categorical outcomes [26].

Ethics

This study was approved by the Norwegian Data Protection Official for Research and the Regional Ethics Committee.

Results

Demographic data

During the 2 year period the Bergen EMS successfully treated 463 patients with suspected opioid overdoses with naloxone. The yearly incidence of non-fatal opioid overdoses was estimated to be approximately 84 per 100 000 population. Table 1 shows the main characteristics of the victims. There were significantly more males ($n = 313$, 67.6%) than females ($n = 105$, 22.7%). Ages ranged from 17 to 63 years (M = 32.8, SD = 9.42), and was not statistically different between men (M = 33, SD = 9.42) and women (M = 32.4, SD = 9.52; $P = 0.632$).

Temporal data

Time of day, week day and month of year were analysed. Non-fatal opioid overdoses were categorised by day of the week and hour of the day (Figure 1). The patterns generally followed normal sleep–wake cycles, with the fewest occurring from 4:00 until 9:00 in the morning. The majority occurred during late afternoon and evening hours, with the highest occurrences between the hours of 16:00 and 17:00 ($n = 36$, 7.8%) and 20:00 and 21:00 ($n = 34$, 7.3%). There was no significant difference for calls among the different days of the week ($P = 0.08$). The majority occurred on weekdays, with the fewest occurring on Fridays ($n = 59$, 12.7%) and Sundays ($n = 48$, 10.4%) (Table 1).

There was a statistically significant difference for non-fatal opioid overdoses among the various months ($P < 0.001$). August had the most overdoses during the two years ($n = 71$, 15.3%) with the lowest rates in April ($n = 16$, 3.5%) (Table 1). The monthly average the 2 year period was 19.3, totally approximately 232 non-fatal

Table 1. *Characteristics of overdose dispatch to Bergen ambulance services from January 2012–December 2013 for public and private locations*

	Public space *n* (%)	Private residence *n* (%)	Total *n* (%)
Non-fatal overdoses	261 (56.4)	202 (43.6)	463 (100)
Mean age	33	32.7	
Median age	31	31	
Gender			
Male	172 (76.1)	141 (73.4)	313 (67.6)
Female	54 (23.9)	51 (26.6)	105 (22.7)
Missing			45 (9.7)
Weekday			
Monday	34 (13)	30 (14.9)	64 (13.8)
Tuesday	42 (16.1)	27 (13.4)	69 (14.9)
Wednesday	38 (14.6)	29 (14.4)	67 (14.5)
Thursday	53 (20.3)	31 (15.3)	84 (18.1)
Friday	36 (13.8)	23 (11.4)	59 (12.7)
Saturday	37 (14.2)	35 (17.3)	72 (15.6)
Sunday	21 (8)	27 (13.4)	48 (10.4)
Month			
January	13 (5)	17 (8.4)	30 (6.5)
February	18 (6.9)	20 (9.9)	38 (8.2)
March	14 (5.4)	14 (6.9)	28 (6.0)
April	10 (3.8)	6 (3)	16 (3.5)
May	21 (8)	10 (5)	31 (6.7)
June	23 (8.8)	29 (14.4)	52 (11.2)
July	26 (10)	17 (8.4)	43 (9.3)
August	49 (18.8)	22 (10.9)	71 (15.3)
September	22 (8.4)	17 (8.4)	39 (8.4)
October	18 (6.8)	8 (4)	26 (5.6)
November	23 (8.8)	18 (8.9)	41 (8.9)
December	24 (9.2)	24 (11.9)	48 (10.4)
Total	261(56.4)	202 (43.6)	463 (100)
Ambulance response times			
0–4 min	74 (28.4)	34 (16.8)	108 (23.3)
5–10 min	108 (41.4)	96 (47.5)	204 (44.1)
More than 10 min	36 (13.8)	49 (24.3)	85 (18.4)
Missing	43 (16.5)	23 (11.4)	66 (14.3)
Total	261 (56.4)	202 (43.6)	463 (100)

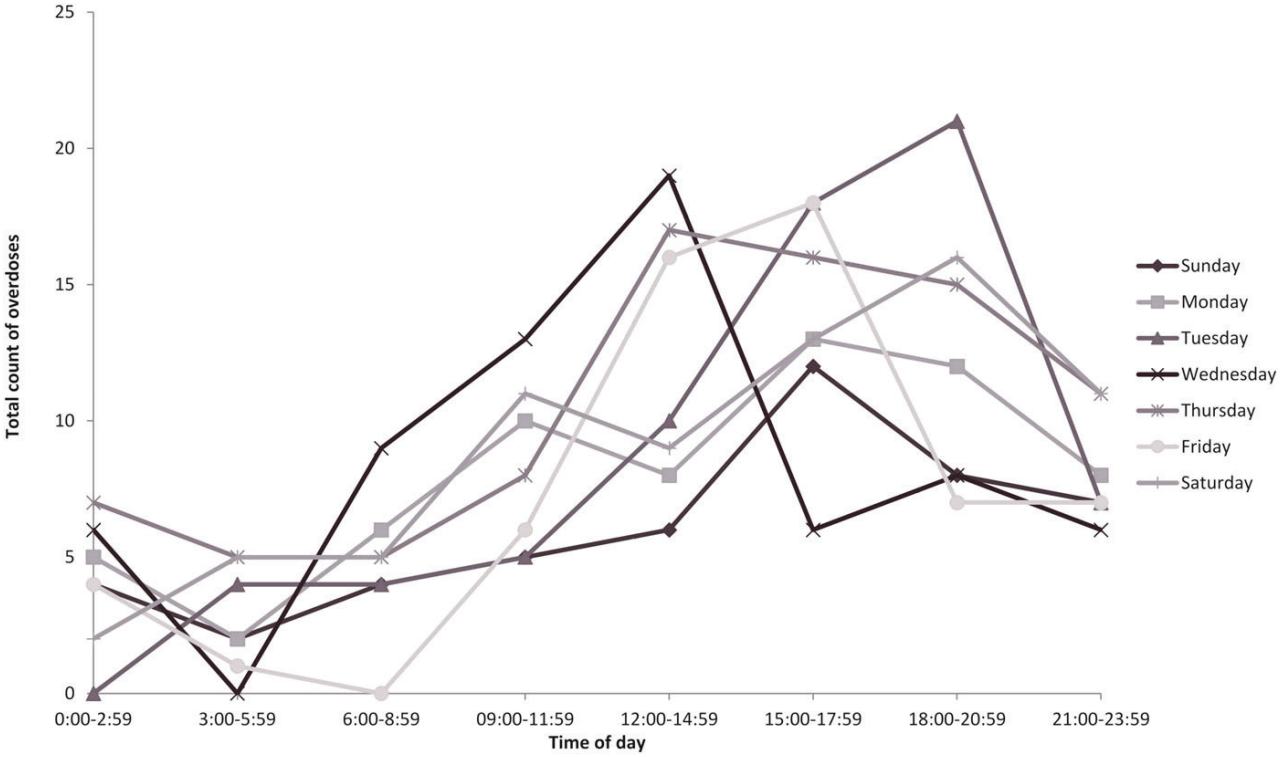


Figure 1. *Ambulance call-out frequency for overdoses according to the day of the week and time of day in Bergen, Norway 2012–2013. [Colour figure can be viewed at wileyonlinelibrary.com]*

opioid overdoses a year (Table 1). The age of the victim was not significantly different for the various months ($P = 0.137$).

Geographical location

Ambulance pick-up locations were categorised into either being public or private. Public pick-up locations included: indoor and outdoor public spaces ($n = 223$, 48.2%), a popular low-threshold facility ($n = 25$, 5.4%), medical facilities ($n = 10$, 2.2%) and other locations ($n = 3$, 0.6%). Private locations included private homes ($n = 176$, 38%) and overnight housing facilities ($n = 26$, 5.6%) (Table 1).

Non-fatal opioid overdoses in public locations peaked in August (Figure 2). These represented nearly 20% of the total non-fatal opioid overdoses in public places for the period. In multivariable model (adjusting for age, gender and month), assessing factors associated with overdosing in a public location, overdosing in August was the only significant finding in the model (risk ratio 1.92, $P = 0.042$, 95% confidence interval 1.024, 3.618) (Table 2).

Ambulance response time

The ambulance response time ranged from 1.7 to 51 min, with median response time of 6.9 min. The response

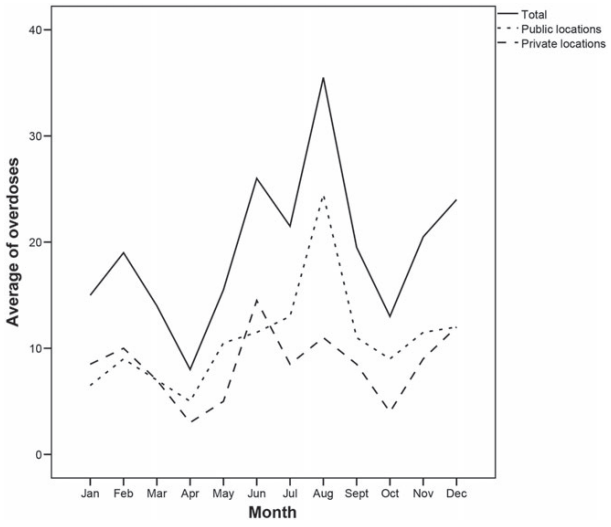


Figure 2. *Average numbers of monthly nonfatal overdoses attended by Bergen Emergency Medical Services for public and private locations during January 2012– December 2013.*

times were split into three groups (less than 5 min, 5–10 min more than 10 min), and nearly half ($n = 204$, 44.1%) arrived within 5–10 min (Table 1). In 23.3% ($n = 108$) of the cases the ambulance arrived in less than 5 min, and took more than 10 min for 18.4% ($n = 85$) of the cases. Information was missing for the remaining ($n = 66$, 14.3%).

Table 2. *Factors predicting the likelihood of overdosing and being picked up by the Bergen ambulance services in a public location*

Covariate	RR	95% CI	*P* value
Gender	1.03	0.73, 1.45	0.857
Age	1.00	0.99, 1.02	0.949
Month			
January	1.12	0.49, 2.56	0.784
February	1.25	0.59, 2.65	0.553
March	1.46	0.67, 3.16	0.337
April	1.95	0.80, 4.72	0.140
May	1.69	0.77, 3.72	0.189
June	1.12	0.55, 2.31	0.749
July	1.26	0.60, 2.65	0.540
August	1.92	1.02, 3.62	0.042*
September	1.39	0.67, 2.88	0.383
October	1.55	0.69, 3.48	0.292
November	1.43	0.70, 2.91	0.330
December	Ref		

Cox regression, adjusted for the following variables: age, gender and month.
*$P < 0.05$.
CI, confidence interval; RR, risk ratio.

The strongest predictor of longer response times (more than 10 min) was dispatch to a private home (risk ratio 1.66, $P = 0.03$, 95% confidence interval 1.053, 2.602) in an adjusted model (gender, month and pick-up location). The majority of callers reported that victims were unconscious ($n = 279$, 60.3%) or suffered from reduced consciousness ($n = 79$, 17.1%). Ambulance response time was not significantly different for drug-related ('intoxicated') and nondrug-related ('unconscious, reduced consciousness, respiratory or cardiac problems and other') dispatch ($P = 0.692$).

Overall, disposition after treatment was approximately evenly split between being left at the scene following treatment ($n = 226$, 48.8%) and taken to a medical facility for further follow-up ($n = 237$, 51.2%). Of those that were picked up from a public location, 41.4% ($n = 108$) were left at the scene and 58.6% ($n = 153$) were transported further. The strongest predictor of being left at the scene was having overdosed at a private location (risk ratio 1.47, $P = 0.009$, 95% confidence interval 1.100, 1.956) in a regression model adjusting for age, gender, month and pick-up location.

Discussion

Through analysis of available ambulance records, we have described circumstances surrounding non-fatal opioid overdoses in Bergen, Norway. Non-fatal opioid overdoses occurred most often in the evening, with no increase seen on the weekends. Summer months had higher rates than the other seasons, with an almost doubled risk during August. Ambulance response times differed for public and private locations, yet we found no difference for drug-related and non-drug-related dispatch.

Demographic data

Gender and age distribution was similar to previous studies [12,13,18,27]. This is similar to the gender distribution assumed among people in opioid maintenance treatment [28], demonstrating little risk difference among the genders [1]. Although there is reported to be an ageing population in Norway, our average age was similar to a previous Norwegian study from 1999 [27].

Temporal trends

Our study found that the majority of non-fatal opioid overdoses occurred in the late afternoon and evenings, with consistently high rates during the weekdays. This is similar to other studies [12], demonstrating that non-fatal opioid overdose patterns do not follow a late-night weekend peak seen with volatile substances [29], GHB [30] and ecstasy-related overdoses [31]. This weekday pattern suggests that non-fatal opioid overdoses are non-recreational in origin, and may primarily occur with daily users.

Similar to a seasonal peak described by others [16], this study found the majority of overdoses happened during the summer, peaking in August. In particular, we found a sharp increase in overdoses in public locations in August. In Norway, this corresponds with a 'drug holiday' phenomenon, where residents from more rural areas in the country come to the cities to purchase and ingest drugs during the summer month of August. A previous study has shown that nearly 30% of overdose fatalities that occur in the city are non-residents, supporting this possible migration pattern with a seasonal twist [32]. This means an extra responsibility for cities experiencing such influx to provide PWID with low-threshold interventions and services. Moreover, these findings demonstrate the need for regions experiencing high rates of overdoses to examine their local temporal patterns in order to prepare appropriately.

Location

The location for ambulance dispatch differed when compared to previous studies [13,14]. In Rhode Island, Merchant *et al.* reported 71% to a private residence, where we found only 43.6% were to a private residence. This may be explained by the use of drugs in the 'open drug scene' park instead of in a private residence. Ambulance response times to a private residence were more likely to be longer than to public locations, likely because private address could be suburban, whereas

public locations for drug consumption mainly remained central. In addition, ambulance dispatch to a private home was more likely to treat the victim at the scene, as opposed to transporting for further medical care. This may be because of the likelihood that the victim has someone home with them (the emergency caller), able to continue monitoring after ambulance discharge and following naloxone administration. It also reflects that at the time, the ambulance protocol was to treat the victim and leave them at the scene once stabilised.

Strengths and limitations

Limitations exist for this study. The data was collected exclusively from ambulance records and does not include information about non-fatal opioid overdoses from other non-ambulance sources. Given the demonstrated reluctance to always call the ambulance in the event of an overdose [33], the ambulance may not serve as a complete source. Additionally, the data provided was analysed anonymously, which allowed only for an analysis of independent non-fatal opioid overdose events, not individuals. Ideally, more thorough information about the victims, such as their place of residence, specific substances ingested, injection drug use and their dose and response to naloxone could have been useful for a prehospital analysis. It is likely that the true number of non-fatal opioid overdoses is higher than what is estimated by this study, because some overdoses may not have been reported, such as if the victim was alone. Despite the limitations, this study provides ambulance data on non-fatal opioid overdoses for one of the most affected areas in Europe, and demonstrates the potential utility of ambulance data in the development of prevention work.

Implications

With non-fatal opioid overdoses being associated with subsequent fatal overdoses [9], the need for understanding and responding to the circumstances surrounding non-fatal instances is critical. Hence, our findings may have practical implications for public health interventions aiming to reduce morbidity and mortality associated with opioid overdoses. While we observe that non-fatal opioid overdoses most often occur during late afternoon and evenings and during 'summer holiday months,' the services provided to PWID are not necessarily at peak availability at these times—on the contrary, opening hours are during the daytime and vacation for staff members at service facilities are typical during holiday seasons as well. In order to provide appropriate and 'tuned in' services, better knowledge of the local scene and flexibility to adjust service provision systems according to the periods of highest need is recommended.

Naloxone distribution programs have gained acceptance over the past two decades for their effectiveness in overdose prevention [34], and may be particularly relevant for opioid overdoses experienced in private homes. These events may be potential opportunities for ambulance services to engage in preventative initiatives, such as peer naloxone trainings and distribution of referrals. Implementing tailored prevention programs requires the application of local-level data to the communities in which they intend to serve. Proxy information provided by ambulances can give an indication of specific times, locations and populations most affected by injection drug use. This information can be used to optimise prevention programs, as well as serve as a baseline to evaluate their efforts.

Acknowledgements

The authors would like to thank the Bergen Ambulance services for their recording and entry of data used for this article. Funding was received by the Norwegian Directorate of Health.

Conflict of interests

PL has acted as paid consultant for Indivior, a pharmaceutical company involved in the development and supply of a range of drugs for the addiction field.

References

[1] European Drug Report. Lisbon: European Monitoring Centre for Drugs and Drug Addiction, 2015 (cited 2015 June 5). Available at http://www.emcdda.europa.eu/attachements.cfm/att_239505_EN_TDAT15001ENN.pdf.
[2] Amundsen EJ. Narkotikautløste dødsfall. Statens institutt for rusmiddelforskning: Oslo, 2015.
[3] Statistical yearbook of Norway 2013. Oslo: Statistics Norway, 2013.
[4] Darke S, Mattick RP, Degenhardt L. The ratio of non-fatal to fatal heroin overdose. Addiction 2003;98:1169–71.
[5] Bird SM, Parmar MKB, Strang J. Take-home naloxone to prevent fatalities from opiate-overdose: protocol for Scotland's public health policy evaluation, and a new measure to assess impact. Drugs (Abingdin Engl) 2015;22:66–76.
[6] Martins SS, Sampson L, Cerda M, Galea S. Worldwide prevalence and trends in unintentional drug overdose: a systematic review of the literature. Am J Public Health 2015;105:29–49.
[7] Warner-Smith M, Darke S, Day C. Morbidity associated with non-fatal heroin overdose. Addiction 2002;97:963–7.
[8] Coffin PO, Tracy M, Bucciarelli A, Ompad D, Vlahov D, Galea S. Identifying injection drug users at risk of nonfatal overdose. Acad Emerg Med 2007;14:616–23.
[9] Stoove MA, Dietze PM, Jolley D. Overdose deaths following previous non-fatal heroin overdose: record linkage of ambulance attendance and death registry data. Drug Alcohol Rev 2009;28:347–52.
[10] Gjersing L, Bretteville-Jensen AL. Are overdoses treated by ambulance services an opportunity for additional interventions? A prospective cohort study. Addiction 2015;110:1767–74.
[11] Davis CS, Green TC, Zaller ND. Addressing the overdose epidemic requires timely access to data to guide interventions. Drug Alcohol Rev 2015; doi: 10.1111/dar.12321 [Epub ahead of print].

[12] Dietze P, Jolley D, Cvetkovski S. Patterns and characteristics of ambulance attendance at heroin overdose at a local-area level in Melbourne, Australia: implications for service provision. J Urban Health 2003;80:248–60.
[13] Clark MJ, Bates AC. Nonfatal heroin overdoses in Queensland, Australia: an analysis of ambulance data. J Urban Health 2003;80:238–47.
[14] Merchant RC, Schwartzapfel BL, Wolf FA, Li W, Carlson L, Rich JD. Demographic, geographic, and temporal patterns of ambulance runs for suspected opiate overdose in Rhode Island, 1997–20021. Subst Use Misuse 2006;41:1209–26.
[15] Alexander JL, Burton JH, Bradshaw JR, Colin F. Suspected opioid-related emergency medical services encounters in a rural state, 1997–2002. Prehosp Emerg Care 2004;8:427–30.
[16] Knowlton A, Weir BW, Hazzard F, *et al.* EMS runs for suspected opioid overdose: implications for surveillance and prevention. Prehosp Emerg Care 2013;17:317–29.
[17] Degenhardt L, Hall W, Adelstein BA. Ambulance calls to suspected overdoses: New South Wales patterns July 1997 to June 1999. Aust N Z J Public Health 2001;25:447–50.
[18] Seidler D, Schmeiser-Rieder A, Schlarp O, Laggner AN. Heroin and opiate emergencies in Vienna: analysis at the municipal ambulance service. J Clin Epidemiol 2000;53:734–41.
[19] Klimas J, O'Reilly M, Egan M, Tobin H, Bury G. Urban overdose hotspots: a 12-month prospective study in Dublin ambulance services. Am J Emerg Med 2014;32:1168–73.
[20] Lloyd B, Matthews S, Gao XC. Trends in alcohol and drug related ambulance attendances in Victoria: 2012/13. Fitzroy, Victoria: Turning Poing; 2014 (cited 2016 April). Available at: http://www.turningpoint.org.au/site/DefaultSite/filesystem/documents/TP.ambocallout.fullreport.080514.pdf.
[21] The Drug Situation in Norway 2014. Oslo: SIRUS, 2015 (cited 2015 April). Available at: http://wpstatic.idium.no/www.sirus.no/2015/01/TheDrugSituationInNorway2014.pdf.
[22] Waal H, Bussesund K, Clausen T, Skeie I, Håseth A, Lillevold P. Statusrapport 2014. Norwegian Centre for Addiction Research: Oslo, 2015.
[23] Amundsen EJ, Bretteville-Jensen AL. Hard drug use in Norway. Nord Stud Alcohol Drug 2010;27:87–94.
[24] O'Connor P. Opioids: Merck manual, 2008 [Available at: http://www.merckmanuals.com/professional/special-subjects/drug-use-and-dependence/opioids (accessed 19 May 2015).
[25] Dietze PM, Cvetkovski S, Rumbold G, Miller P. Ambulance attendance at heroin overdose in Melbourne: the establishment of a database of Ambulance Service records. Drug Alcohol Rev 2000;19:27–33.
[26] Nijem K, Kristensen P, Al-Khatib A, Bjertness E. Application of different statistical methods to estimate relative risk for self-reported health complaints among shoe factory workers exposed to organic solvents and plastic compounds. Norsk Epidemiologi 2005;15:111–6.
[27] Buajordet I, Naess AC, Jacobsen D, Brors O. Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. Eur J Emerg Med 2004;11:19–23.
[28] European Drug Report. European Monitoring Centre for drugs and Drug Addiction, 2015. Report No. Available at http://www.emcdda.europa.eu/edr2015 (accessed 4 November 2015).
[29] Cvetkovski S, Dietze P. The incidence and characteristics of volatile substance use related ambulance attendances in metropolitan Melbourne, Australia. Soc Sci Med 2008;66:776–83.
[30] Boyd JJ, Kuisma MJ, Randell TT. Temporal differences in gamma-hydroxybutyrate overdoses involving injecting drug users versus recreational drug users in Helsinki: a retrospective study. Scand J Trauma Resusc Emerg Med 2012;20:7.
[31] Horyniak D, Degenhardt L, Smit de V, *et al.* Pattern and characteristics of ecstasy and related drug (ERD) presentations at two hospital emergency departments, Melbourne, Australia, 2008–2010. Emerg Med J 2014;31:317–22.
[32] Gjersing L, Jonassen KV, Biong S, *et al.* Diversity in causes and characteristics of drug-induced deaths in an urban setting. Scand J Public Health 2013;41:119–25.
[33] Bennett AS, Bell A, Tomedi L, Hulsey EG, Kral AH. Characteristics of an overdose prevention, response, and naloxone distribution program in Pittsburgh and Allegheny County, Pennsylvania. J Urban Health 2011;88:1020–30.
[34] Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. J Addict Med 2014;8:153–63.

II

Drug and Alcohol Dependence 163 (2016) 153–156

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Utilizing a train-the-trainer model for multi-site naloxone distribution programs

Desiree Madah-Amiri[a,*], Thomas Clausen[a], Philipp Lobmaier[a,b]

[a] Norwegian Centre for Addiction Research, Institute of Clinical Medicine, The University of Oslo, P.O. Box 1039 Blindern, 0315 Oslo, Norway
[b] The Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway

ARTICLE INFO

Article history:
Received 29 February 2016
Received in revised form 8 April 2016
Accepted 10 April 2016
Available online 14 April 2016

Keywords:
Multi-site
Naloxone
Opioid
Overdose prevention
Train the trainer
Scaling-up

ABSTRACT

Background: In order to have a substantial impact on overdose prevention, the expansion and scaling-up of overdose prevention with naloxone distribution (OPEND) programs are needed. However, limited literature exists on the best method to train the large number of trainers needed to implement such initiatives.

Methods: As part of a national overdose prevention strategy, widespread OPEND was implemented throughout multiple low-threshold facilities in Norway. Following a two-hour 'train-the trainer course' staff were able to distribute naloxone in their facility. The course was open to all staff, regardless of educational background. To measure the effectiveness of the course, a questionnaire was given to participants immediately before and after the session, assessing knowledge on overdoses and naloxone, as well as attitudes towards the training session and distributing naloxone.

Results: In total, 511 staff were trained during 41 trainer sessions. During a two-month survey period, 54 staff participated in a questionnaire study. Knowledge scores significantly improved in all areas following the training ($p < 0.001$). Attitude scores improved, and the majority of staff found the training useful and intended to distribute naloxone to their clients.

Conclusion: Large-scale naloxone distribution programs are likely to continue growing, and will require competent trainers to carry out training sessions. The train-the-trainer model appears to be effective in efficiently training a high volume of trainers, improving trainers' knowledge and intentions to distribute naloxone. Further research is needed to assess the long term effects of the training session, staffs' subsequent involvement following the trainer session, and knowledge transferred to the clients.

1. Introduction

Overdose prevention education with naloxone distribution (OPEND) programs train bystanders to intervene during an overdose with naloxone, an opioid antagonist. Over the past two decades, hundreds of OPEND programs have been established worldwide, with over 25,000 reported overdose reversals in the United States alone (Wheeler et al., 2015). Collectively, OPEND programs have demonstrated their feasibility and effectiveness (Clark et al., 2014), reporting decreases in overdose mortality following implementation (Evans et al., 2012; Maxwell et al., 2006; Walley et al., 2013).

With this demonstrated impact on overdose fatalities, some have called for the scaling-up of these programs as widespread public health interventions (Coffin et al., 2010; McAuley et al., 2012; Walley et al., 2013). Scaling-up could improve access to naloxone for at-risk individuals. Barriers to scaling-up health programs have been described as (a) maintaining sustained interest and commitment from the staff and leadership at the facilities, (b) lack of resources, and (c) high staff turnover (Norton and Mittman, 2010). Staff members may interpret an externally initiated project as an additional burden of work, without additional compensation. Lack of resources can impact a facility's ability to participate in implementing the program. High staff turnover results in a lack of qualified staff able to carry-out the program, and leadership turnover may result in programs being lost entirely once new leadership is in place

The scaling-up of OPEND programs will need to acknowledge these barriers and attempt to facilitate acceptability within the facilities. Project buy-in, consistent funding, and a high volume of

* Corresponding author.
E-mail addresses: desireem@medisin.uio.no (D. Madah-Amiri), thomas.clausen@medisin.uio.no (T. Clausen), p.p.lobmaier@medisin.uio.no (P. Lobmaier).

http://dx.doi.org/10.1016/j.drugalcdep.2016.04.007

Table 1
Participant characteristics.

	Number (%)
Gender	
Male	13 (24.1)
Female	40 (74.1)
Missing	1 (1.9)
Profession	
Nurse	20 (37.0)
Social worker	17 (31.5)
Leader	1 (1.9)
Outreach worker	1 (1.9)
Other	15 (27.8)
Facility	
Medical	28 (51.9)
Outreach	14 (25.9)
Housing	7 (13.0)
Other	3 (5.6)
Missing	2 (3.7)
Years of experience working with people who use drugs	
1–2 years	16 (29.6)
2–5 years	15 (27.8)
More than 5 years	23 (42.6)

trained staff may help to assure sustained participation, despite high turnover rates. Therefore, one of the key components of expanding OPEND programs will focus on the preparation and involvement of a large trainer workforce.

One method that has been effective in disseminating and scaling-up public health interventions are the train-the-trainer (TT) model (Yarber et al., 2015). This involves a central trainer, who trains others, who can then train others in a target population. This method has been effective in various fields, including HIV education (Williams et al., 2014a) and mental health services (Limm et al., 2015). A benefit to this method is its ability to train a high volume of trainers in a relatively short amount of time. The participants are often already working directly with the target group, and are in a prime position to carry out the intervention once trained. Although studies have evaluated OPEND programs (Clark et al., 2014), few have discussed the experiences of training the trainers necessary for large-scale OPEND operations.

Over the past several years, advocacy organizations, researchers, and politicians have discussed the importance of peer-administered naloxone in Norway. This discussion fostered the launch of a **national** overdose strategy in 2014 by the Department of Health. The strategy included funding for a University initiative to implement and evaluate multi-site OPEND throughout Norway's two largest cities (Norwegian Directorate of Health, 2014). Widespread naloxone distribution was a focus for the project and involved key existing community staff and facilities as distribution sites (Lobmaier and Clausen, 2016). A brief TT course was developed to prepare staff at the targeted facilities to distribute naloxone to their clients. The aims of this study are to (a) describe the development of a TT course for OPEND at multiple facilities, and (b) evaluate the impact of the course on knowledge and attitudes towards being a naloxone trainer for the diverse staff.

2. Methods

2.1. Setting

From June 2014–November 2015, trainer sessions were held at various low-threshold facilities. The decision for a facility to participate was initiated by each site, primarily by the facility leadership. All sites were located within Oslo and Bergen, Norway's two largest cities.

2.2. Participants

The trainer course was available to all staff employed at the facilities, regardless of educational background or position. Attendance at a trainer course was voluntary, yet most sites encouraged all staff to attend. Information on those that did not choose to attend was not collected. During a two-month survey period a questionnaire was issued sequentially during all trainer sessions. All participants who attended training for their first time during this period responded. The questionnaire was given immediately before and after the trainer course to evaluate changes in knowledge and attitudes.

2.3. Intervention

2.3.1. Development of the train-the-trainer course. The curriculum for the naloxone training was adapted from existing resources (Wheeler et al., 2012), and utilized the feedback received from focus and reference groups. The trainer course covered (1) background and rationale for OPEND, (2) mechanisms of an opioid overdose, (3) effects of naloxone, (4) signs of an overdose, (5) response to an overdose, (6) project record-keeping documentation, (7) assembly and administration of intranasal naloxone, and (8) possibilities for implementation within each site.

2.3.2. Sessions. Standard trainer sessions were performed by three central trainers. The sessions lasted approximately two hours and utilized a PowerPoint presentation. Following the presentation, participants practiced assembling the intranasal device and filling out the necessary record-keeping documentation. An upcoming impact study is underway, and trainers were instructed on how to keep track of distribution and refill rates at their sites through the use of questionnaires. Participants left with a one-page curriculum summary of the course.

2.3.3. Access to intranasal naloxone. An agreement with the Norwegian Medicines Agency allowed for the distribution of naloxone to occur without a prescription or physician for the duration of the project. This gave non-healthcare staff the ability to distribute to any client interested and likely to witness or experience an overdose, but required that the necessary training and documentation accompanied. The names and workplace were recorded for all staff that attended the trainer course, and only those attending were allowed to distribute naloxone. Trained staff were not able to subsequently train their colleagues to be trainers.

2.4. Assessment measures

2.4.1. Knowledge scale. The opioid overdose knowledge scale (OOKS; Williams et al., 2013) was modified to anonymously assess pre- and post- knowledge with the trainer course. The OOKS assesses knowledge about risk factors for overdosing, the signs of an overdose, response to an overdose, and the use of naloxone. The self-administered multiple-choice questionnaire has proven to be internally reliable (Williams et al., 2013).

2.4.2. Trainer attitudes. Additional questions were asked about the participants' perception (rated from 1 = low, to 5 = high) of their understanding and comfort teaching others about (a) overdose risk factors, (b) prevention techniques, (c) recognizing risk factors, and (d) response to an overdose, as well as their preparedness to train others. Comparable ratings about their attitudes towards peer-administered naloxone, the format and usefulness of the training, and their intention and confidence in training others were collected.

Table 2
Participant responses to opioid overdose knowledge scale.

Item	Pre-training mean (SD)	Post-training mean (SD)	Wilcoxon Z/P-value
Knowledge total[a]	30.56 (5.05)	35.52 (2.46)	−6.19, P < 0.001
Risks (out of 9)	6.46 (2.03)	7.39 (1.57)	−4.50, P < 0.001
Signs (out of 10)	7.78 (1.57)	8.81 (1.18)	−4.31, P < 0.001
Action (out of 11)	10.11 (1.06)	10.83 (0.42)	−4.46, P < 0.001
Naloxone use (out of 9)	6.32 (1.96)	8.48(0.67)	−5.82, P < 0.001

[a] Two questions were removed from the scale as they applied to injectable naloxone and this project utilizes intranasal naloxone. The modified scale comprised 17 pre- and 24 post-test items. Removing six possible points from the original scale resulted in total scores from 0 to 39.

2.5. Statistical analyses

Descriptive statistics and frequency measures were used to describe the characteristics of the sample. The Wilcoxon Paired Signed Rank test was used. Effect scores were interpreted using Cohen criteria (0.1 = small effect, 0.3 = medium effect, 0.5 = large effect). Only questionnaires that were filled out completely in the pre-test and post-test were used for analysis. A 5-point Likert scale was used to assess various areas of attitudes, and means were calculated from the responses. Data was analyzed using SPSS Version 22.

2.6. Ethical approval

This study was approved by the Norwegian Data Protection Official for Research and the Regional Ethics Committee.

3. Results

3.1. Train the trainer method and staff characteristics

During an 18 month period, 41 trainer sessions were carried out by one of the three lead trainers. This prepared 511 staff to distribute naloxone, which then resulted in nearly 2000 naloxone kits distributed during that time. During a two-month period, staff (n = 54) were asked to participate in the survey study. Females accounted for 74% of the sample, and the majority of staff had over five years of experience working with people who inject drugs (PWID) (n = 23, 42.6%). Thirty-seven percent were nurses (n = 20) from medical facilities (n = 28, 51.9%) (Table 1).

3.2. Knowledge scale

There was a significant ($p < 0.001$) increase in scores for all areas of knowledge assessed (Table 2). The effect size was medium to large in all areas, with the largest in naloxone use ($r = 0.56$) and the total overall score ($r = 0.6$). The total average score increased from 78.4% to 91.1% correct in the post-test.

3.3. Attitudes scale

Prior to the training, staff reported their understanding of risk factors, prevention techniques, recognition and response to an overdose to be on average 3.17 (SD = 0.95). Following the training, self-reported scores significantly increased ($p < 0.001$) to 4.3 (SD = 0.56). In addition, their comfort teaching others in these areas increased ($p < 0.001$) from 2.85 (SD = 0.98) to 4.07 (SD = 0.59).

There was a significant increase in the staffs' attitudes towards naloxone's role in overall prevention work ($p = 0.001$), increasing from a mean score of 4.24 (SD = 0.74) to 4.57 (SD = 0.57). The staffs' reported preparedness to train others and to respond to an overdose if they themselves encounter one significantly increased ($p < 0.001$) from 2.22 (SD = 0.97) to 4.22 (SD = 0.55). Staffs' beliefs that PWID should be trained and equipped with naloxone were comparably high pre-and post-test (4.68 and 4.75 respectively, $p = 0.569$).

3.4. Usefulness and intentions following the course

The majority (n = 49, 90.7%) of the sample rated the 2-h training course an adequate amount of time and most respondents (n = 37, 68.5%), felt that the PowerPoint presentation was an appropriate delivery method. The usefulness of the course had a mean score of 4.68 (SD = 0.7) and their intent to distribute was 4.51 (SD = 0.88). Participants on average responded that their confidence to train others following the course was high, 4.37 (SD = 0.64).

4. Discussion

Overdose prevention programs must find effective and efficient ways to respond to the growing overdose epidemic. Large-scale naloxone distribution programs have been suggested as a means to reach a large number of at-risk individuals, but must strive to avoid potential barriers while scaling-up. The TT method utilized in this study significantly increased knowledge and positive attitudes for the staff participants. The ability for three central trainers to train over 500 staff in 18 months demonstrated the efficiency of the method. The majority of responding staff found the trainer course appropriate in time and delivery method.

Knowledge scores improved in all areas assessed which is consistent with others who have reported increases following naloxone training (Behar et al., 2015; Klimas et al., 2015; Mayet et al., 2011; Williams et al., 2014b). These studies have focused on the transfer of knowledge from the trainer to various recipients, including relatives (Williams et al., 2014b), PWID (Behar et al., 2015), and general practitioners (GPs; Klimas et al., 2015), and concluded that their training sufficiently equipped participants to use naloxone in the event of an overdose. In our study, we found that along with increased knowledge scores, the self-reported rating of their comfort teaching others about overdoses improved. This indicates that the course not only prepared them didactically, but strengthened their self-efficacy in the role as trainer.

The scores for 'actions to take while witnessing an overdose' were generally high among the trainers. This is consistent with Mayet et al. who found that their clinician participants were knowledgeable in actions to take during an overdose (Mayet et al., 2011). For all areas assessed, the greatest improvement was seen in scores on naloxone use. This increase suggests that although staff have existing knowledge on actions to take while witnessing an overdose, and many years of relevant experience, specific training in naloxone can be beneficial before implementing an OPEND program.

4.1. Limitations

Findings from this study should be considered in regards to its limitations. First, this study did not measure retained trainer knowledge, or the propensity to train clients after being trained. Although this data is important, our study primarily focused on the

method used for training trainers. Further studies will be needed to confirm the lasting effectiveness of the method, including trainer acceptability and ownership in an OPEND intervention. Second, the training session and the survey were administered in English, not in the native Norwegian language. Although most Norwegians are fluent in English, it is possible that the testing in a foreign language was more difficult for the participants. This however would likely result in our reported results being a more conservative estimate of change and effect.

4.2. Conclusions

Widespread naloxone distribution initiatives need substantial program support, (Coffin et al., 2010; Heller and Stancliff, 2007) with a large trainer workforce available to perform trainings. A lack of trained colleagues has been described by others as a barrier for scaling-up public health programs (Norton and Mittman, 2010). Having an abundance of trained colleagues would not only provide the trainers necessary in the face of high turnover, but may also improve accessibility. Training this group can be achieved through a centrally organized host, utilizing the TT model allowing for knowledge gains and attitude improvement towards naloxone distribution. Although this appears to be an effective method in training trainers, the subsequent trainer acceptance, dissemination to clients, as well as the clients' correct use of naloxone will serve as a true marker of its effectiveness. Participation and prioritization in an externally initiated OPEND program will not only require attendance to a training session, but will to rely on interests among leadership, staff, and clients aligning in order to accept and adopt the initiative. As naloxone programs continue to scale-up, further research is needed to assess the long term effects of the training, staffs' subsequent involvement following the trainer session, and the knowledge transferred to the clients.

Role of the funding source

Nothing declared.

Contributors

D. Madah-Amiri contributed to the study design, data collection and analysis, and drafted the manuscript. P. Lobmaier and T. Clausen both contributed to the study design, data interpretation, and manuscript revision. All authors approved the final article.

Conflict of interest

P. Lobmaier has acted as paid consultant for Indivior, a pharmaceutical company providing a range of drugs relevant to the addiction medicine field.

Acknowledgements

The authors would like to acknowledge all of the staff and facilities that participated in the study. We would also like to acknowledge the project coordinators and focus group participants who contributed to the development of the training sessions. The Norwegian Ministry of Health and the Norwegian Directorate of Health provide funding for this project, including implementation, medication costs, and evaluation of the intervention for the duration of the project period.

References

Behar, E., Santos, G.M., Wheeler, E., Rowe, C., Coffin, P.O., 2015. Brief overdose education is sufficient for naloxone distribution to opioid users. Drug Alcohol Depend. 148, 209–212.

Clark, A.K., Wilder, C.M., Winstanley, E.L., 2014. A systematic review of community opioid overdose prevention and naloxone distribution programs. J. Addict. Med. 8, 153–163.

Coffin, P.O., Sherman, S., Curtis, M., 2010. Underestimated And Overlooked: A Global Review Of Drug Overdose And Overdose Prevention. Global State Of Harm Reduction 2010: Key Issues For Broadening the Response. International Harm Reduction Association, London, UK, pp. 113–119 (Last accessed 06.01.16) http://www.ihra.net/files/2010/06/29/GlobalState2010_Web.pdf.

Evans, J.L., Tsui, J.I., Hahn, J.A., Davidson, P.J., Lum, P.J., Page, K., 2012. Mortality among young injection drug users in San Francisco: a 10-year follow-up of the UFO study. Am. J. Epidemiol. 175, 302–308.

Heller, D.I., Stancliff, S., 2007. Providing naloxone to substance users for secondary administration to reduce overdose mortality in New York City. Public Health Rep. 122, 393–397.

Klimas, J., Egan, M., Tobin, H., Coleman, N., Bury, G., 2015. Development and process evaluation of an educational intervention for overdose prevention and naloxone distribution by general practice trainees. BMC Med. Educ. 15, 206.

Limm, H., Heinmuller, M., Gundel, H., Liel, K., Seeger, K., Salman, R., Angerer, P., 2015. Effects of a health promotion program based on a train-the-trainer approach on quality of life and mental health of long-term unemployed persons. Biomed. Res. Int. 2015.

Lobmaier, P.P., Clausen, T., 2016. Radical red tape reduction by government supported nasal naloxone: the Norwegian pilot project is innovative, safe and an important contribution to further development and dissemination of take-home naloxone. Addiction 111, 586–587.

Maxwell, S., Bigg, D., Stanczykiewicz, K., Carlberg-Racich, S., 2006. Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths. J. Addict. Dis. 25, 89–96.

Mayet, S., Manning, V., Williams, A., Loaring, J., Strang, J., 2011. Impact of training for healthcare professionals on how to manage an opioid overdose with naloxone: effective, but dissemination is challenging. Int. J. Drug Policy 22, 9–15.

McAuley, A., Best, D., Taylor, A., Hunter, C., Robertson, R., 2012. From evidence to policy: the Scottish national naloxone programme. Drugs Educ. Prev. Policy 19, 309–319.

National Overdose Strategy, 2014–2017. Sure You Can Quit Drugs, But First You Have To Survive (Publication No. IS-0418E). (2014). Norwegian Directorate Of Health, Oslo, Norway.

Norton, W.E., Mittman, B.S., 2010. Scaling-Up Health Promotion/Disease Prevention Programs In Community Settings: Barriers, Facilitators, And Initial Recommendations. Patrick and Catherine Weldon Donaghue Medical Research Foundation. http://donaghue.org/wp-content/uploads/Cover-Final-Study.pdf (accessed January 2016).

Walley, A.Y., Xuan, Z., Hackman, H.H., Quinn, E., Doe-Simkins, M., Sorensen-Alawad, A., Ruiz, S., Ozonoff, A., 2013. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ 346.

Wheeler, E., Burk, K., McQuie, H., Stancliff, S., 2012. Guide To Developing And Managing Overdose Prevention And Take-Home Naloxone Projects. The Harm Reduction Coalition. http://harmreduction.org/wp-content/uploads/2012/11/od-manual-final-links.pdf (accessed January 2016).

Wheeler, E., Jones, T.S., Gilbert, M.K., Davidson, P.J., 2015. Opioid overdose prevention programs providing naloxone to laypersons—United States, 2014. MMWR 64, 631–635.

Williams, A.V., Strang, J., Marsden, J., 2013. Development of opioid overdose knowledge (OOKS) and attitudes (OOAS) scales for take-home naloxone training evaluation. Drug Alcohol Depend. 132, 383–386.

Williams, A.B., Le, S.T., Colby, D., Thu Le, T.T., Pollack, T., Cosimi, L., 2014a. Effectiveness of train-the-trainer HIV education: a model from Vietnam. J. Assoc. Nurses AIDS Care 25, 341–350.

Williams, A.V., Marsden, J., Strang, J., 2014b. Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes. Addiction 109, 250–259.

Yarber, L., Brownson, C.A., Jacob, R.R., Baker, E.A., Jones, E., Baumann, C., Deshpande, A.D., Gillespie, K.N., Scharff, D.P., Brownson, R.C., 2015. Evaluating a train-the-trainer approach for improving capacity for evidence-based decision making in public health. BMC Health Serv. Res. 15, 547.

III

Drug and Alcohol Dependence 173 (2017) 17–23

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Rapid widespread distribution of intranasal naloxone for overdose prevention

Desiree Madah-Amiri[a,*], Thomas Clausen[a], Philipp Lobmaier[a,b]

[a] Norwegian Centre for Addiction Research, Institute of Clinical Medicine, The University of Oslo, P.O. Box 1039 Blindern, 0315 Oslo, Norway
[b] The Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway

ARTICLE INFO

Article history:
Received 13 September 2016
Received in revised form 7 December 2016
Accepted 10 December 2016
Available online 28 January 2017

Keywords:
Opioid
Overdose prevention
Naloxone
Implementation
Public health
Policy

ABSTRACT

Background: Take home naloxone programs have been successful internationally in training bystanders to reverse an opioid overdose with naloxone, an opioid antagonist. A multi-site naloxone distribution program began in Norway in 2014 as part of a national overdose prevention strategy. The aim of this study was to a) describe the program, and b) present findings from the government-supported intervention.
Methods: From July 2014 to December 2015, staff from multiple low-threshold facilities trained clients on how to use intranasal naloxone. Distribution occurred without an individual prescription or physician present. Questionnaires from initial and refill trainings were obtained, and distribution rates were monitored.
Results: There were 2056 naloxone sprays distributed from one of the 20 participating facilities, with 277 reports of successful reversals. Participants exhibited known risks for overdosing, with injecting ($p = 0.02$, OR = 2.4, 95% CI = 1.14, 5.00) and concomitant benzodiazepine use ($p = 0.01$, OR = 2.6, 95% CI = 1.31, 5.23) being significant predictors for having had high rates of previous overdoses. Suggested target coverage for large-scale programs was met, with an annual naloxone distribution rate of 144 per 100,000 population, as well as 12 times the cities mean annual number of opioid-related deaths.
Conclusion: A government-supported multisite naloxone initiative appears to achieve rapid, high volume distribution of naloxone to an at-risk population.

1. Introduction

Take home naloxone (THN) programs were first described in the 1990s as a method to prevent overdose fatalities (Darke and Hall, 1997; Strang et al., 1996). These programs train bystanders to respond to an overdose with naloxone, an opioid antagonist. Over the past 20 years, over 200 programs have been implemented worldwide (Clark et al., 2014; Dettmer et al., 2001; Kan et al., 2014; Leece et al., 2013; Lenton et al., 2014), with over 26,000 reported overdose reversals in the United States alone (Wheeler et al., 2015). The majority of these programs have adopted injectable naloxone developed for use by health care staff, yet interest in a more user-friendly intranasal option has emerged. Some programs in the United States (Evans et al., 2012; Maxwell et al., 2006; Walley et al., 2013) and Scotland (Bird et al., 2015a) have experienced decreases in overdose mortality with the implementation of large-scale naloxone programs. Collectively, THN has been found to be effective (McDonald and Strang, 2016), and has demonstrated that in order to have a substantial impact on overdose mortality, widespread and often population-based interventions are necessary (Heller and Stancliff, 2007; Walley et al., 2013).

In 2011, Scotland became one of the first countries to implement a nationally-supported THN program (McAuley et al., 2012), and in its first two years distributed 7300 naloxone rescue kits, mainly injectable (Bird et al., 2015b). They subsequently found a 36% reduction in the proportion of overdose fatalities following prison release during this period (Bird et al., 2015a). Wales also implemented a national program with over 7300 naloxone kits distributed to nearly 3800 individuals since their pilot in July 2009 (Morgan and Smith, 2015). A study from Massachusetts demonstrated that by partnering public health policy with community organizations, high volume intranasal naloxone distribution was possible (Walley et al., 2013). Furthermore, they found an almost 50% reduction in overdose deaths in areas where distribution rates exceeded 100 per 100,000 population (Walley et al., 2013). Governments in Wales (Bennett and Holloway, 2011), Estonia, Norway (National Overdose Strategy, 2014; Lobmaier and Clausen, 2016), and certain health departments in the United States (Seal et al.,

* Corresponding author.
E-mail address: desireem@medisin.uio.no (D. Madah-Amiri).

http://dx.doi.org/10.1016/j.drugalcdep.2016.12.013

2005; Tobin et al., 2009; Walley et al., 2013; Winstanley et al., 2015) have also adopted policies that support peer-administered naloxone as part of a large-scale, multi-faceted public health intervention.

Despite the merits of large-scale THN programs, barriers to increased naloxone access have been identified, primarily in regards to financial and legal issues (Coffin et al., 2010; Heller and Stancliff, 2007; Piper et al., 2008). First, financial restraints may severely limit the scope in which THN programs can distribute. Many rely on independent funding to purchase naloxone and a dedicated clinician available to prescribe (Bennett et al., 2011; Heller and Stancliff, 2007; Tobin et al., 2009; Wagner et al., 2010; Winstanley et al., 2015). Second, legal concerns for the prescribers and responders exist. Prescribers have had concerns over liability while prescribing a drug not knowing whom the actual recipient of the drug will be. Responders risk liability in intervening in a medical emergency, and the possibility of arrest at the scene. However, in recent years improvements in third party prescribing, standing orders, and Good Samaritan laws have increased access to naloxone in many US states (Davis and Carr, 2015). Additionally, in 2015 legislation in the UK changed to allow naloxone to be distributed without a prescription (The Human Medicines Amendment, 2015). Lastly, issues with needle-based naloxone have been a barrier for central Asia and Sweden. Although, an intranasal preparation may be a relevant option for countries facing this type of barrier, issues with off-label intranasal use (Strang et al., 2016), ideal concentration (Strang et al., 2016), and complicated assembly (Edwards et al., 2015) continue to exist.

Although Norway has a robust social welfare system, including around 60% coverage of opioid maintenance treatment (OMT) and other treatments and services for people who inject drugs (PWID), overdose mortality remains a significant concern. The average overdose mortality rate in Europe is estimated to be 18 per million population, with Scandinavian countries experiencing greater than 40 deaths per million (European Drug Report, 2016). In recent years, advocacy organizations, researchers, and politicians have played an important role in advocating for increased naloxone access for bystanders in Norway. As a response to this persistent public health concern, in 2014 the Norwegian government launched a national overdose strategy, including an intranasal naloxone distribution project (National Overdose Strategy, 2014). Though large-scale naloxone programs have existed in the past, few have done so with the use of intranasal naloxone, and none have previously been implemented in Scandinavia. The aims of this paper are to: 1.) describe characteristics of a multi-site naloxone distribution project in Norway, and 2.) present findings from this government-supported intervention, including: a.) characteristics of the population trained, specifically identifying factors associated with having the highest rates of repeated overdoses, b.) outcomes following the use of naloxone, and c.) distribution rates.

2. Material and methods

2.1. Setting

There are approximately 6200–10,300 high-risk opioid users in Norway, with the majority injecting heroin (The Drug Situation in Norway, 2015). Since 1998, OMT has been available nationwide, and by the end of 2015 nearly 7500 clients were currently enrolled (Waal et al., 2016). The Norwegian health system provides drug treatment, healthcare, shelter, and low-threshold services for PWID at no cost to the client. All costs associated with the project, as well as funding for evaluation, were covered by the Norwegian Directorate of Health.

This project utilized an extensive network of existing facilities as naloxone distribution sites. In the first year of the project, targeted groups were those outside of formal treatment, as they are known to be at highest risk of overdosing (Clausen et al., 2008; Rowe et al., 2015). Therefore sites included: drop-in day centres, medical facilities, overnight shelters, a prison, and a safe injection facility. The majority of the sites are publically funded low-threshold facilities, which require no referral or payment from the clients. All sites were located within Norway's two cities with the highest overdose rates, Oslo and Bergen (Amundsen, 2015).

2.2. Study participants

From June 2014 – December 2015, interested participants from low-threshold facilities volunteered to take part in this study. Naloxone training sessions were available to anyone interested and likely to experience or witness an overdose. Recruitment occurred via posters and brochures, or word-of-mouth by the facility staff. The majority of trainings were targeted towards PWID; however, trainings were also available to those likely to be in contact with someone at risk of overdosing. Therefore, courses for relatives, police, and security staff were also available.

2.3. Opioid overdose prevention training

All trainings were performed by facility employees who had attended the staff trainer course, enabling them to distribute naloxone without the presence of a physician (Madah-Amiri et al., 2016). Sessions were brief, flexible, and offered as individual or group sessions. The curriculum covered in training is comparable to similar THN programs (Clark et al., 2014). Clients were instructed to administer 0.4 mL of naloxone in each nostril (total 0.8 mL) and give rescue breathes while awaiting response. If there was no response after two minutes, the client was instructed to administer another 0.4 mL in each nostril. If still no response and the ambulance had not yet arrived, the client was advised to commence with cardiopulmonary resuscitations. Information on aftercare, side effects, including potential withdrawal symptoms and risk for future overdoses was given. Clients were instructed to practice opening and assembling a sample device and at some locations could practice administering on a doll. Naloxone kits included the prefilled syringe, nasal atomizer, breathing mask, and instructions for use. It was mandatory that clients attend an initial training in order to receive naloxone.

An intranasal device was chosen carefully by the Norwegian Directorate of health, given its demonstrated effectiveness (Barton et al., 2005; Kerr et al., 2009; Lobmaier et al., 2011; Robertson et al., 2009) and user-friendly administration. However, at the time, an ideal pre-assembled registered intranasal preparation was unavailable. The Norwegian Medicines Agency issued a waiver for this project allowing for the assembly and distribution of a novel nasal spray device (Fig. 1). The 2.0 mL pre-filled syringe consisted of five 0.4 mL doses with a concentration of 1 mg/1 mL naloxone (total 2 mg/2 mL). Clients were instructed on how to titrate dosing. A nasal atomizer was added and the needles were removed from the original Prenoxad package. Norwegian instructions and pictorial information was also added to the packaging. The expiration date was written on the outer packaging, with a three-year shelf life.

A key component for accessibility for this project included the approval to distribute intranasal naloxone without need for individual prescription. This was achieved by involvement of a community physician appointed to the project, who could order naloxone in bulk from contracted pharmacies for the facilities involved. This allowed for distribution to occur without a physician present, given that the appropriate rescue training was accompanied.

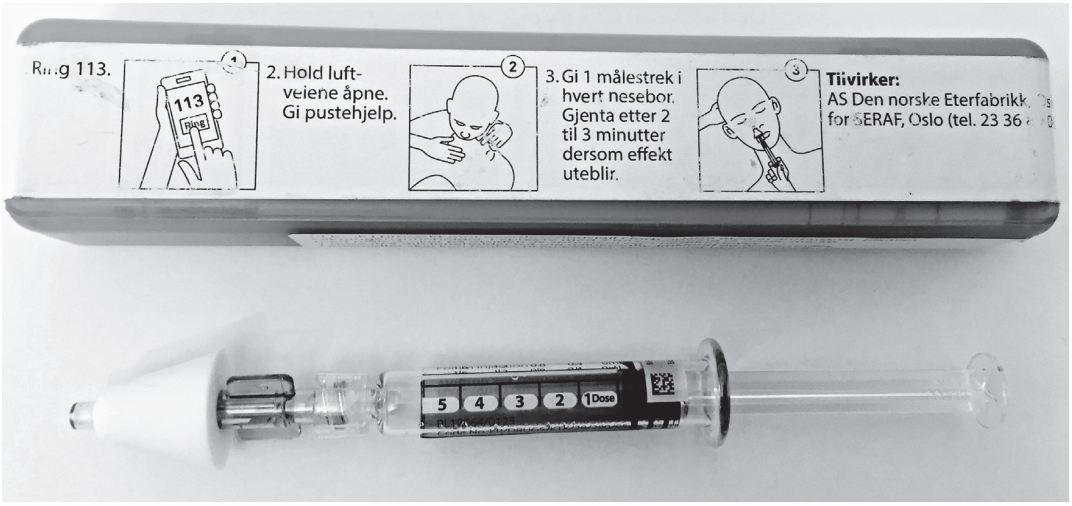


Fig. 1. The Norwegian Medicines agency approved the assembly of the novel device by a local drug manufacturing company (Den Norske Eterfabrikken). The device is distributed by the Norwegian Centre for Addiction Research.

2.4. Documentation for monitoring and evaluation

In order to help evaluate the project, an optional one-page questionnaire was collected for consenting participants upon enrolment and returns for replenishment. Participants were asked for their personal identity number, but could decline and still receive the training. Analysis was done only on those who provided consent. Questionnaires were completed with the help of a staff member. The questionnaires were piloted with a small focus group before being implemented. The enrolment form included questions on: a.) demographics, b.) drug use, c.) overdose risk factors, d.) how many overdoses they had experienced or witnessed in their lifetime (less than 10, more than 10, and never), and e.) what actions they take when they witness an overdose. The definition of "overdose" was according to the participant's interpretation, given that the questionnaires were self-reported and would not be linked with medical data to corroborate.

Upon returning for replenishment, the form included questions about the witnessed overdose and their use and dosage of naloxone. Questions included: a.) their relationship with the victim, b.) drugs used, c.) location, d.) interventions, e.) ambulance involvement, and f.) the outcome for the victim.

2.5. Data analysis

Descriptive statistics were calculated for participants that had attended a training session. Naloxone coverage was calculated using population estimates as of January 1, 2015 and reported naloxone distribution from participating facilities. Binary logistic regression was used to explore predictors for experiencing more than 10 self-reported overdoses during their lifetime for current and previous opioid users. The "more than 10" cut-off was used because of the subgrouping the questionnaires used. First, the univariate relationship of variables (gender, age, primary injection drug use, concomitant opioid and benzodiazepine use, and use of opioids while alone) and high rates of overdoses were examined. Significant associations of $p < 0.1$ were included in a multifactorial model, and values with $p < 0.05$ were considered significant. All analyses were performed using SPSS version 22.

3. Results

From June 2014 until December 2015, 2056 naloxone nasal sprays were distributed from approximately 20 participating facilities. Distribution numbers represent the actual number of sprays given out, not the number of individuals trained. Questionnaire response rates were 32.8% (n = 433) for the initial training and 54.6% (n = 401) during refill visits.

3.1. Characteristics of population trained

3.1.1. Initial opioid overdose prevention training. For the period, 64.3% (n = 1322) of the total number of naloxone kits distributed was for the initial training. Characteristics of those that completed the questionnaire survey are seen in Table 1. Ages ranged from 19 to 65, with a median age of 36.8. Males accounted for 67% (n = 289) of the sample and the majority (n = 369, 85%) reported having used opioids, including both current and previous use (Table 1).

Many of the participants (n = 366, 85%) exhibited risk factors for overdosing, including recent periods of non-use, using drugs while alone, mixing opioids with benzodiazepines, or injecting. For those that had reported using opioids (including current and previous use, n = 369), 92% (n = 338) had at least one risk factor for overdosing, as compared to those who had never used opioids (n = 49), 43% (n = 21). Of those that had reported using opioids, over half reported injecting to be their most common mode of administration (n = 223, 60%). There were seven participants who reported injecting as their primary mode, but were not opioid users.

Almost all of the participants had either witnessed (n = 394, 91%) or experienced (n = 305, 79%) an overdose at some time in their life (Table 1). Of those that had witnessed an overdose, over half had reported to have witnessed more than 10 (n = 241, 61.2%). For those that had experienced an overdose, 23% (n = 86) had reported experiencing 10 or more overdoses themselves. For those that had previously witnessed an overdose (n = 394), most of the participants responded that they would usually take action to intervene. The most common actions included: calling the ambulance (n = 361, 92%) and trying to wake the victim (n = 323, 82%).

Logistic regression analyses were performed to identify factors associated with having had the highest rates of previous self-reported overdoses (more than 10) (Table 2). In a model adjusted for gender, age, injection as primary mode of use, concomitant opioid and benzodiazepine use, and use of opioids while alone; injecting (OR = 2.4, 95% CI = 1.14, 5.00, p = 0.02) and concomitant benzodiazepine use (OR = 2.6, 95% CI = 1.31, 5.23, p = 0.01) were significant predictors for having more than 10 overdoses.

Table 1
Characteristics of project participants presenting for their initial training in Oslo and Bergen, Norway (July 2014-December 2015).

Variable	N	%
Gender (n = 433)		
Male	289	66.7
Female	141	32.5
Missing	3	0.01
Opioid use (n = 433)		
Daily	174	40.2
Sporadic	69	15.9
Previous	126	29.1
Never	49	11.3
Missing	15	0.03
Detoxification in the past 30 days (n = 369)[a]	91	25
Incarcerated in the past 30 days (n = 369)[a]	36	10
Use of opioids while alone (n = 369)[a]		
Never	54	15
Seldom	101	27
Often	104	28
Most of the time	67	18
Always	19	5
Not applicable	18	5
Missing	6	2
Use of opioids together with: (n = 369)[a]		
Alcohol	92	25
Benzodiazepines	217	59
Cocaine	54	15
Methamphetamine	163	44
GHB/GBL	52	14
Other	67	18
Most common mode of use (n = 369)[a]		
Injecting	223	60
Smoking	29	8
Snorting	14	4
Swallowing	22	6
Other/doesn't use	32	9
Missing	49	13
Witnessed an overdose (n = 433)		
1–10 times	153	35
More than 10 times	241	56
Never	28	7
Missing	11	3
Experienced an overdose (n = 369)[a]		
1–10 times	206	56
More than 10 times	86	23
Never	68	18
Missing	9	4

[a] These variables are presented only for those who have reported daily, sporadic, or previous use.

3.2. Outcomes following use of naloxone

3.2.1. Naloxone use and replenishment. From the total sprays distributed during the 18-month period, 35.7% (n = 734) were returns for replenishment. Of these, 54.6% (n = 401) participated in the questionnaire survey. Males accounted for 56% (n = 223) of the sample, and ages ranged from 22 to 61 with a mean age of 36.7. For those that returned for a refill, when asked about the use of their original spray, 70% (n = 277) were reported to have been used on an overdose. The remaining (n = 124, 31%) reported that their original was "not used for an overdose" (n = 79, 64%), lost (n = 11, 9%), stolen (n = 11, 9%), or other (n = 16, 13%), with missing data for n = 7, 6%. In these cases where naloxone was used, the victim survived in 96% (n = 265) of the events, with the remaining outcomes being unknown (1%, n = 3) or missing (3%, n = 9).

For the times naloxone was reported as used (n = 277), participants reported heroin to be involved in 84% (n = 233) of the total cases. Nearly one quarter reported instances where the victim had used heroin along with benzodiazepines (n = 62, 22%). The rescuer's relationship to the victim most commonly included: being a friend (28%, n = 78) or an acquaintance (27%, n = 75). There were 19 cases (7%) where the naloxone had been used on themselves (Table 3).

When reporting on which actions were taken when the rescuer used naloxone, nearly all (n = 260, 94%) reported doing at least one action. There were 66% (n = 183) that reported calling the ambulance and, 78% (n = 217) that tried to wake the victim (Table 3). There were 12 (4.3%) that injected the victim with a central-stimulating substance, water, or salt (Table 3), as opposed to the procedures taught.

3.2.2. Titration and side effects. The naloxone training included instructions for titrating the five doses available in each syringe. Upon return for a refill, participants were asked about the dosage used. Most could report the amount that was used, with approximately one quarter using all of the doses available (24%, n = 67) (Table 3). There was one participant that reported using two full sprays (4.0 mg). In regards to side effects, of the participants that responded, the most common answers reported after giving naloxone were "no adverse effects" (27%, n = 76), followed by "confused" (17%, n = 47) (Table 3).

3.3. Naloxone distribution rate

For 2015, a total distribution rate of 144 per 100,000 population was achieved for both cities, meeting the suggested target coverage

Table 2
Results from logistic regression analysis: factors associated with having had more than 10 self-reported opioid overdoses in their lifetime among participants attending their initial naloxone training in Oslo and Bergen, Norway (July 2014–December 2015).

	Unadjusted				Adjusted		
Characteristic	N	OR	95% CI	p-Value	OR	95%CI	p-Value
Gender[**]							
Male	254	Ref	–	–	–	–	–
Female	113	1.22	0.729, 2.045	0.45	1.01	0.561, 1.823	0.97
Age[**]	369	1.01	0.983, 1.033	0.55	1.01	0.983, 1.044	0.40
Injection as primary mode for use							
No	75	Ref	–	–			
Yes	223	2.62	1.266, 5.409	0.009[*]	2.39	1.139, 5.003	0.02[*]
Concomitant opioid and benzodiazepine use							
No	152	Ref	–				
Yes	217	2.47	1.444, 4.233	0.001[*]	2.61	1.305, 5.234	0.007[*]
Always alone while using opioids							
No	350	Ref	–	–	–	–	–
Yes	19	1.19	0.415, 3.392	0.75			

OR = odds ratio. 95% CI = 95% confidence interval.
[*] $p < 0.05$.
[**] Age and gender were kept in the adjusted model.

Table 3
Characteristics reported upon return for naloxone replenishment (when naloxone was reported to have been used on an overdose) in Oslo and Bergen (July 2014-December 2015).

	N	(%)
Relationship to overdose victim (n = 257)		
Friend	78	30
Acquaintance	75	29
Partner	13	5
Stranger	39	15
Self	19	7
Other	33	13
Missing	20	–
Location of the overdose (n = 255)		
Private residence	133	52
Public location	110	43
Other	12	5
Missing	22	–
Actions taken during the last witnessed overdose[a]		
Called ambulance	183	66
Recovery position	150	54
CPR	130	47
Tried to wake the victim	217	78
Injected with other drugs, water, or salt	12	4
Symptoms reported following naloxone administration[a]		
No adverse symptom reported	76	27
Confused	47	17
Angry	29	11
Other	21	8
Nauseous	18	7
Tired	15	5
Shock	7	3
Vomiting	2	1
Dosage used (n = 251)		
0.4 mg	24	10
0.8 mg	81	32
1.2 mg	30	12
1.6 mg	48	19
2.0 mg	67	27
Other	1	0
Unknown	18	–
Missing	8	–
Transport (n = 123)		
Hospital	76	62
Left at scene	39	32
Other	8	7
Missing	154	–

[a] More than one response was possible to report.

(Table 4). Both cities had similar distribution rates for the year, however, based on population estimates, Bergen more than doubled their target coverage by distributing 684 naloxone sprays during 2015.

4. Discussion

This paper describes the development, implementation, and findings for a multi-site take-home naloxone (THN) program. As part of a government-supported initiative, offering training sessions at existing relevant facilities, naloxone distribution rates reached the amount suggested for projects aiming to have a population-level impact (Bird et al., 2015b; Walley et al., 2013). The use of multiple sites coordinated through a central host streamlined the intervention, along with the ability to distribute intranasal naloxone without an individual prescription. Nearly 70% of the refills were reported to have been used on an overdose, with successful reversals reported for 96% of the events. Most of the rescuers were able to report back the titrated dosage they used, giving an indication of the appropriate use of an intranasal device in a real life crisis situation. The ability to accomplish this high rate of naloxone distribution to an at-risk population within the first year and a half is likely explained by collaboration among political, research, and community interests. Our findings support previous studies suggesting that high volume naloxone distribution is possible with multi-site programs positioned as public health interventions (Bird et al., 2015b; Enteen et al., 2010; Piper et al., 2008; Walley et al., 2013).

We found that participant demographics in this study were comparable to that of those entering into opioid maintenance treatment in Norway, with an approximate 70%-30% male to female distribution, and an average age in the mid-30′s (The Drug Situation in Norway, 2015). Many of our participants reported at least one known risk factor for overdosing, including a history of previous overdoses, injection drug use, and concurrent use with benzodiazepines. Those who inject frequently are at risk (Kinner et al., 2012), and nearly half of our participants were in this group. Further, those that have previously experienced an overdose are likely to experience subsequent overdoses if the high-risk behaviour is continued (Coffin et al., 2007). The majority of participants in our study had reported a previous overdose, with an even more alarming number reporting multiple previous overdoses. These findings support the appropriateness of the facilities involved as naloxone distribution points, targeting those still outside of formal treatment. By being present in appropriate facilities, some of the people at greatest risk were reached with this intervention.

Concerns over unlicensed intranasal naloxone, and the usability of the intranasal device have been described by others (Strang et al., 2016). The use of a complicated multi-part nasal device appears difficult for untrained bystanders (Edwards et al., 2015), yet high rates of correct use are seen with a single-dose nasal spray (Krieter et al., 2016). Although the device used in this project was not

Table 4
Annual suggested and actual naloxone distributed during January 2015 –December 2015 by area (Oslo and Bergen).

	Average annual overdose fatalities[a]	Estimated annual fatalities including non-residents[b]	Suggested distribution based on saturation per population[c]	Suggested distribution based on witnessed overdoses[c]	Actual naloxone distributed
Oslo	53	69	648	621–1380	645
Bergen	31	40	275	360–800	684
Total	84	109	923	981–2180	1327

[a] Average annual fatality numbers from 2009 to 2013 (Amundsen, 2015).

[b] Annual fatalities were estimated to include non-residents. An estimated 30% of overdose deaths that occur within a larger city are among non-residents, yet are not registered within the city's statistics which are based on deaths among city residents (Gjersing et al., 2013). Therefore the number of actual deaths taking place in a city is often higher than reported. This project did not require proof of address or residency to participate, so 30% (representing non-residents) was included in the estimated fatalities and coverage calculation.

[c] In attempts to adequately reach the target population, estimations for distribution goals were made. One method of calculating target naloxone coverage is based on suggested naloxone distributed per population, aiming to reach saturation greater than 100 per 100,000 population. This was determined on the basis that the greatest reduction in overdose mortality was seen with higher rates of naloxone distribution (Walley et al., 2013). An alternative method is based on an assumption from a study in Scotland that trainees encounter a 6% fatality rate, therefore needing 9–20 times the amount of naloxone for observed overdose fatalities in a location to assure adequate coverage (Bird et al., 2015b). Based on these two methods, estimated annual distribution goals were between 923 and 2194 sprays for the two cities combined, using population statistics (Population and population changes, 2014) and average annual fatality numbers from 2009 to 2013 (Amundsen, 2015).

as simple as a single-dose spray, the participants reported their titrated dose, with nearly all cases resulting in successful reversals. Over-antagonism is reported as significant concern for PWID (Neale and Strang, 2015). The ability to titrate may help to prevent over-antagonizing the victim, while still reaching the desired effect of sufficient breathing. This real-life application of the device gives an indication of the effectiveness in the field during a crisis. Many of the participants were able to titrate the dosage, with low reports of side effects or adverse events. The amount of naloxone used varied among respondents, with 42% using 1 or 2 doses and 27% using the entire spray. The variability in their dosing demonstrates the relative feasibility and benefits of titrating doses. However, optimal intranasal concentration continues to be discussed, and our findings support the importance of providing ideal intranasal options.

For national distribution programs, naloxone is recommended to be available at as many witnessed overdoses as possible (Bird et al., 2015b). Estimating the target coverage is therefore a necessary part of program planning and implementation. Based on suggested target naloxone coverage as described by others (Bird et al., 2015b; Walley et al., 2013), our distribution rates achieved sufficient coverage within the first year. Both estimation methods produced relatively similar target ranges in the current setting, and both ranges were met by utilizing a multi-site distribution model in this project.

This project found that utilizing multiple existing sites and staff enhanced accessibility and participation in the program. As seen with the establishment of a THN program in Australia (Lancaster and Ritter, 2014), governmental and nongovernmental stakeholder collaboration is essential. The benefits from this organization offered the program both the appropriate venue for THN, as well as the capacity to train and distribute with hundreds of staff members, without the need to establish new extensive organizational structures. By operating throughout the multiple existing sites, this allowed for the opportunity to collaborate with various stakeholders. Outreach workers, drug-user organizations, clinicians, researchers, and politicians all played a role in the execution of the project. This ensured multi-level engagement throughout the development and implementation process. Furthermore, this model allows for future expansion of the project, with the ability to scale-up to other relevant facilities.

The funding and support provided by the Ministry of Health for the duration of the project has assured resources, continuity, access to naloxone, and the ability to evaluate the impact on a population level locally. Local evaluation will provide policy makers and sponsors the evidence of the effect from their inputs, and the opportunity to further develop the evidence base. Programs in Massachusetts and North Carolina attribute much of their success to the changes in laws and policy which facilitated their programs, yet still claim financial and prescriber barriers exist (Davis et al., 2015). As part of a government-supported initiative, several of these described barriers have been potentially mitigated.

4.1. Limitations

Limitations in the study exist. First, the findings reported account for only the first year and a half of this project and further studies demonstrating the impact of these efforts, long-term feasibility, and trainer and client acceptance are needed. Second, limitations in regards to generalizability exist. The ability to implement this large-scale initiative was facilitated by access to dedicated, widespread, government-sponsored community resources, including funding for naloxone. Communities with more limited resources may face challenges with similar implementation. However, this study demonstrates the benefits of systematic efforts directed towards governmental engagement in order to operate as a widespread public health intervention. Lastly, the questionnaires used for the project were optional, and only completed by those who requested naloxone from a distribution site. With the forms being optional, this also meant that this study was not able to monitor the number of individuals trained. Response rates varied among the different distribution sites, but no selection patterns were identified. In the questionnaire, the question about "number of overdoses ever experienced" during their lifetime presents an age-related cumulative issue, and therefore could have been improved by asking more specific time-related questions. Information about the times when naloxone was used was only available from those that returned for replenishment as no tracked follow-up was carried out. We, therefore, may be lacking information of additional cases for those who used it, but did not return, including for both cases of successful and unsuccessful reversals. The use of a convenience sample from those who came back for replenishment may skew the data towards an over-reporting of successful reversals. Nevertheless, in the current setting the project had a high visibility and it would be likely that if naloxone was unsuccessful, it would have been reported to the staff, media, user organizations or other health workers. No such negative reports have been voiced or documented. Nevertheless, data from alternative sources, such ambulance services and mortality reports is crucial, although not yet available.

5. Conclusion

This project supports the feasibility of adopting take home naloxone programs as a mainstream public health intervention. The results from this study demonstrate that widespread, high-volume distribution of naloxone was facilitated by governmental support and involvement of multiple community sites and staff. The use of existing facilities assured access to the target groups most at risk of overdosing within a relatively short amount of time. The target goal for naloxone distribution was met, and done so for those at greatest risk. The use of the intranasal device resulted in safe and effective use reported back from the participants. Our design and development of a large-scale project may serve as a guide for other settings planning to implement or expand their naloxone distribution programs. Our project adds to the discussion on the need for public health policy to respond to the evidence provided by previous naloxone programs, resulting in funded and supported initiatives. We recommend a coordinated framework, aimed as a public health intervention, is best suited to potentially reduce the complex phenomenon of overdoses.

Conflict of interest

None.

Author disclosures

Nothing declared.

Contributors

D. Madah-Amiri contributed to the study design, data collection and analysis, and drafted the manuscript. P. Lobmaier and T. Clausen both contributed to the study design, data interpretation, and manuscript revision. All authors approved the final article.

Acknowledgements

We would like to thank the facilities, staff, participants, and coordinators who have been involved during this project. All costs associated with the project, as well as funding for evaluation were

covered by the Norwegian Directorate of Health. This study was approved by the Norwegian Data Protection Official for Research.

References

Amundsen, E.J., 2015. Narkotikautløste dødsfall. Statens Institutt For Rusmiddelforskning, Oslo.

Barton, E.D., Colwell, C.B., Wolfe, T., Fosnocht, D., Gravitz, C., Bryan, T., Dunn, W., Benson, J., Bailey, J., 2005. Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. J. Emerg. Med. 29, 265–271.

Bennett, T., Holloway, K., 2011. Evaluation of the Take Home Naloxone Demonstration Project. Department of Strategic Planning, Finance and Performance. Welsh Assembly Government Social Research, Merthyr Tydfil.

Bennett, A.S., Bell, A., Tomedi, L., Hulsey, E.G., Kral, A.H., 2011. Characteristics of an overdose prevention, response, and naloxone distribution program in Pittsburgh and Allegheny County, Pennsylvania. J. Urban Health 88, 1020–1030.

Bird, S.M., McAuley, A., Perry, S., Hunter, C., 2015a. Effectiveness of Scotland's national naloxone programme for reducing opioid-related deaths: a before (2006–10) versus after (2011–13) comparison. Addiction 111, 883–891.

Bird, S.M., Parmar, M.K.B., Strang, J., 2015b. Take-home naloxone to prevent fatalities from opiate-overdose: protocol for Scotland's public health policy evaluation, and a new measure to assess impact. Drugs 22, 66–76.

Clark, A.K., Wilder, C.M., Winstanley, E.L., 2014. A systematic review of community opioid overdose prevention and naloxone distribution programs. J. Addict. Med. 8, 153–163.

Clausen, T., Anchersen, K., Waal, H., 2008. Mortality prior to, during and after opioid maintenance treatment (OMT): A national prospective cross-registry study. Drug Alcohol Depend. 94, 151–157.

Coffin, P.O., Tracy, M., Bucciarelli, A., Ompad, D., Vlahov, D., Galea, S., 2007. Identifying injection drug users at risk of nonfatal overdose. Acad. Emerg. Med. 14, 616–623.

Coffin, P.O., Sherman, S., Curtis, M., 2010. Underestimated and Overlooked: A Global Review of Drug Overdose and Overdose Prevention. Global State of Harm Reduction 2010: Key Issues for Broadening the Response. International Harm Reduction Association, London, UK, pp. 113–119 (last accessed 05.05.2016) http://www.ihra.net/files/2010/06/29/GlobalState2010_Web.pdf.

Darke, S., Hall, W., 1997. The distribution of naloxone to heroin users. Addiction 92, 1195–1199.

Davis, C.S., Carr, D., 2015. Legal changes to increase access to naloxone for opioid overdose reversal in the United States. Drug Alcohol Depend. 157, 112–120.

Davis, C.S., Walley, A.Y., Bridger, C.M., 2015. Lessons learned from the expansion of naloxone access in Massachusetts and North Carolina. J. Law Med. Ethics 43, 19–22.

Dettmer, K., Saunders, B., Strang, J., 2001. Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes. BMJ 322, 895–896.

European Monitoring Center for Drugs and Drug Addiction (EMCDDA), 2016. European Drug Report 2016. Trends and Developments, Luxembourg.

Edwards, E.T., Edwards, E.S., Davis, E., Mulcare, M., Wiklund, M., Kelley, G., 2015. Comparative usability study of a novel auto-injector and an intranasal system for naloxone delivery. Pain Ther. 4, 89–105.

Enteen, L., Bauer, J., McLean, R., Wheeler, E., Huriaux, E., Kral, A.H., Bamberger, J.D., 2010. Overdose prevention and naloxone prescription for opioid users in San Francisco. J. Urban Health 87, 931–941.

Evans, J.L., Tsui, J.I., Hahn, J.A., Davidson, P.J., Lum, P.J., Page, K., 2012. Mortality among young injection drug users in San Francisco: a 10-year follow-up of the UFO study. Am. J. Epidemiol. 175, 302–308.

Gjersing, L., Jonassen, K.V., Biong, S., Ravndal, E., Waal, H., Bramness, J.G., Clausen, T., 2013. Diversity in causes and characteristics of drug-induced deaths in an urban setting. Scand. J. Public Health 41, 119–125.

Heller, D.I., Stancliff, S., 2007. Providing naloxone to substance users for secondary administration to reduce overdose mortality in New York City. Public Health Rep. 122, 393–397.

Kan, M., Gall, J.A., Latypov, A., Gray, R., Bakpayev, M., Alisheva, D., Rakhmatova, K., Sadieva, A.S., 2014. Effective use of naloxone among people who inject drugs in Kyrgyzstan and Tajikistan using pharmacy- and community-based distribution approaches. Int. J. Drug Policy 25, 1221–1226.

Kerr, D., Kelly, A.M., Dietze, P., Jolley, D., Barger, B., 2009. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction 104, 2067–2074.

Kinner, S.A., Milloy, M.J., Wood, E., Qi, J., Zhang, R., Kerr, T., 2012. Incidence and risk factors for non-fatal overdose among a cohort of recently incarcerated illicit drug users. Addict. Behav. 37, 691–696.

Krieter, P., Chiang, N., Gyaw, S., Skolnick, P., Crystal, R., Keegan, F., Aker, J., Beck, M., Harris, J., 2016. Pharmacokinetic properties and human use characteristics of an FDA approved intranasal naloxone product for the treatment of opioid overdose. J. Clin. Pharmacol. 56, 1243–1253.

Lancaster, K., Ritter, A., 2014. Making change happen: a case study of the successful establishment of a peer-administered naloxone program in one Australian jurisdiction. Int. J. Drug Policy 25, 985–991.

Leece, P.N., Hopkins, S., Marshall, C., Orkin, A., Gassanov, M.A., Shahin, R.M., 2013. Development and implementation of an opioid overdose prevention and response program in Toronto, Ontario. Can. J. Public Health 104, e200–e204.

Lenton, S., Dietze, P., Olsen, A., Wiggins, N., McDonald, D., Fowlie, C., 2014. Working together: expanding the availability of naloxone for peer administration to prevent opioid overdose deaths in the Australian Capital Territory and beyond. Drug Alcohol Rev. 34, 404–411.

Lobmaier, P.P., Clausen, T., 2016. Radical red tape reduction by government supported nasal naloxone: the Norwegian pilot project is innovative, safe and an important contribution to further development and dissemination of take-home naloxone. Addiction 111, 586–587.

Lobmaier, P., Dalsbø, T., Clasen, T., 2011. Nalokson nesespray kan redusere risikoen for dødelige heroinoverdoser. Norw. J. Epidemiol. 21, 107–111.

Madah-Amiri, D., Clausen, T., Lobmaier, P., 2016. Utilizing a train-the-trainer model for multi-site naloxone distribution programs. Drug Alcohol Depend. 163, 153–156.

Maxwell, S., Bigg, D., Stanczykiewicz, K., Carlberg-Racich, S., 2006. Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths. J. Addict. Dis. 25, 89–96.

McAuley, A., Best, D., Taylor, A., Hunter, C., Robertson, R., 2012. From evidence to policy: the Scottish national naloxone programme. Drugs 19, 309–319.

McDonald, R., Strang, J., 2016. Are take-home naloxone programmes effective?: Systematic review utilizing application of the Bradford Hill criteria. Addiction 111, 1177–1187.

Morgan, G., Smith, J., 2015. Harm Reduction Database Wales: Take Home Naloxone 2014–2015. Public Health Wales, Cardiff.

Neale, J., Strang, J., 2015. Naloxone–does over-antagonism matter? Evidence of iatrogenic harm after emergency treatment of heroin/opioid overdose. Addiction 110, 1644–1652.

Norwegian Directorate of Health, 2014. National Overdose Strategy 2014–2017. Oslo, Norway.

Piper, T.M., Stancliff, S., Rudenstine, S., Sherman, S., Nandi, V., Clear, A., Galea, S., 2008. Evaluation of a naloxone distribution and administration program in New York City. Subst. Use Misuse 43, 858–870.

Population and population changes, 2014. Statistics Norway (SSB), https://www.ssb.no/en/befolkning/statistikker/folkemengde/aar/2015-02-19?fane=tabell&sort=nummer&tabell=218738 (Accessed 19 April 2015).

Robertson, T.M., Hendey, G.W., Stroh, G., Shalit, M., 2009. Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. Prehosp. Emerg. Care 13, 512–515.

Rowe, C., Santos, G.M., Vittinghoff, E., Wheeler, E., Davidson, P., Coffin, P.O., 2015. Predictors of participant engagement and naloxone utilization in a community-based naloxone distribution program. Addiction 110, 1301–1310.

Seal, K.H., Thawley, R., Gee, L., Bamberger, J., Kral, A.H., Ciccarone, D., Downing, M., Edlin, B.R., 2005. Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: a pilot intervention study. J. Urban Health 82, 303–311.

Strang, J., Darke, S., Hall, W., Farrell, M., Ali, R., 1996. Heroin overdose: the case for take-home naloxone. BMJ 312, 1435–1436.

Strang, J., McDonald, R., Tas, B., Day, E., 2016. Clinical provision of improvised nasal naloxone without experimental testing and without regulatory approval: imaginative shortcut or dangerous bypass of essential safety procedures? Addiction 111, 574–582.

The Drug Situation in Norway in 2014, 2015. Annual report to the European Monitoring Centre for Drugs and Drug Addiction SIRUS, Oslo.

The Human Medicines Amendment (No. 3), 2015. No. 1503. Retrieved from http://www.naloxone.org.uk/index.php/lawpolicy/law/uklaw1 on December 5, 2016.

Tobin, K.E., Sherman, S.G., Beilenson, P., Welsh, C., Latkin, C.A., 2009. Evaluation of the Staying Alive programme: training injection drug users to properly administer naloxone and save lives. Int. J. Drug Policy 20, 131–136.

Waal, H., Bussesund, K., Clausen, T., Skeie, I., Håseth, A., Lillevold, P.H., 2016. Statusrapport 2015: Mot gensene for vekst og nytte? (Report No. 1), Retrieved from The University of Oslo website: https://www.med.uio.no/klinmed/forskning/sentre/seraf/publikasjoner/rapporter/2016/nedlastinger/seraf-rapport-nr-1-2016-statusrapport-2015.pdf on December 5 2016.

Wagner, K.D., Valente, T.W., Casanova, M., Partovi, S.M., Mendenhall, B.M., Hundley, J.H., Gonzalez, M., Unger, J.B., 2010. Evaluation of an overdose prevention and response training programme for injection drug users in the Skid Row area of Los Angeles, CA. Int. J. Drug Policy 21, 186–193.

Walley, A.Y., Xuan, Z., Hackman, H.H., Quinn, E., Doe-Simkins, M., Sorensen-Alawad, A., Ruiz, S., Ozonoff, A., 2013. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. BMJ 346, f174.

Wheeler, E., Jones, T.S., Gilbert, M.K., Davidson, P.J., 2015. Opioid overdose prevention programs providing naloxone to laypersons – United States, 2014. MMWR Morb. Mortal Wkly. Rep. 64, 631–635.

Winstanley, E.L., Clark, A., Feinberg, J., Wilder, C.M., 2015. Barriers to implementation of opioid overdose prevention programs in Ohio. Subst. Abus. 37, 42–46.