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Twenty years of take-home naloxone for the prevention of overdose deaths from heroin and other opioids – Conception and maturation

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Highlights

- Deaths from opioid overdose can be prevented by prompt administration of naloxone
- It has been 20 years since take-home naloxone provision was first proposed
- Take-home naloxone programs have recently overcome legal barriers in many countries
- Take-home naloxone provision remains low compared to evident growing clinical need
- The ‘opt-out’ model of required pre-provision may achieve wider naloxone coverage

Abstract

Background: Opioid overdose is a major cause of mortality, but injury and fatal outcomes can be prevented by timely administration of the opioid antagonist naloxone. Pre-provision of naloxone to opioid users and family members (take-home naloxone, THN) was first proposed in 1996, and WHO Guidelines were issued in 2014. While widespread in some countries, THN is minimally available or absent elsewhere. This review traces the development of THN over twenty years, from speculative harm reduction proposal to public health strategy.

Method: Medline and PsycINFO were searched for peer-reviewed literature (1990-2016) using Boolean queries: 1) “naloxone OR Narcan”; 2) “(opioid OR opiate) AND overdose AND prevention”. Grey literature and specialist websites were also searched. Data were extracted and synthesized as narrative review, with key events presented as chronological timeline.

Results: Results are presented in 5-year intervals, starting with the original proposal and THN pilots from 1996-2001. Lack of familiarity with THN challenged early distribution schemes (2001-2006), leading to further testing, evaluation, and assessment of challenges and perceived medicolegal barriers. From 2006-2011, response to social and legal concerns led to

the expansion of THN programs; followed by high-impact research and efforts to widen THN availability from 2011-2016.

Conclusions: Framed as a public health tool for harm reduction, THN has overcome social, clinical, and legal barriers in many jurisdictions. Nonetheless, the rising death toll of opioid overdose illustrates that current THN coverage is insufficient, and greater public investment in overdose prevention will be required if THN is to achieve its full potential impact.

Keywords: opiate, naloxone, overdose, prevention, drug-related deaths, harm reduction

1. Introduction

Over the past two decades, take-home naloxone (THN) has moved from its initial conceptualization as harm reduction measure for preventing opioid overdose deaths to becoming an evidence-based public health strategy with organized implementation (UNODC/WHO, 2013). Strong advocacy by local early adopters has enabled emergence of THN initiatives around the world. In Italy, a harm reduction service on the outskirts of Turin reportedly provided naloxone access to clients as early as 1991 (ForumDroghe, 2016). Today, formal THN programs exist in Australia, Canada, at least nine European countries (EMCDDA, 2016), and the US; as well as pilots in low- and middle-income countries, including Afghanistan, China, India, Kazakhstan, Kyrgyzstan, Russia, Tajikistan, Thailand, Ukraine, and Vietnam (UNODC/WHO, 2013). The World Health Organization issued new guidelines for community-based overdose management, suggesting that “[p]eople likely to witness an opioid overdose should have access to naloxone and be instructed in its administration” (WHO, 2014).

Despite these recent advances, dissemination of THN remains remarkably slow. THN was first proposed in 1996, and it was not until the late 2000s that serious consideration of THN implementation at state or national level began.

Opioid overdose continues to account for approximately 68,000-104,000 annual deaths worldwide (UNODC, 2016b), with sharp increases reported for the UK (ISD, 2016; ONS, 2016) and US (CDC, 2016). Many of these deaths could be prevented if THN was available: A recent analysis of the time course of opiate metabolites post-mortem found that survival times post-injecting exceeded 20-30 minutes in the majority of heroin overdose deaths (Darke and Duflou, 2016), suggesting that there is indeed sufficient time to intervene (Darke and Duflou, 2016; Tas and McDonald, 2016). However, adequate intervention is only possible where witnesses recognize the opioid overdose. In addition to naloxone supply, it is thus essential for THN programs to teach awareness of overdose risk factors (e.g., using alone, street injection), crisis detection (e.g., snoring following opioid use may signal overdose), interim emergency care aid, and need for continued care (McAuley et al., 2010; Seal et al., 2005; Strang et al., 2008a).

This brief history chronicles major milestones and events in the emergence and evolution of THN.

2. Method

2.1. Literature search

The first author (RM) searched Medline and PsycINFO for THN-related peer-reviewed literature published between January 1990 and December 2016 using the Boolean queries: 1) “naloxone OR Narcan”; 2) “(opioid OR opiate) AND overdose AND prevention”. Specialist websites and databases of Public Health England, the European Monitoring Centre for Drugs and Drug Addiction, US National Institute on Drug Abuse, and United Nations

agencies were also searched for THN-related entries. Additional materials from the non-peer-reviewed literature were consulted to reconstruct the historical timeline.

2.2. Data extraction and evidence synthesis

THN-related evidence was extracted and synthesized as narrative review by all three authors (RM, NC, JS). Relevant events were considered according to occurrence in one of four developmental phases of constructed quinquennia (with some overlap naturally occurring), which cover the 20-year period from 1996 to 2016.

3. Results

We present results in four sections which discuss the following themes. Firstly, we examine formal articulation of the need for THN, along with preliminary testing and implementation (1996-2001; section 3.1.). We then document early THN schemes and challenges (2001-06; section 3.2.). We then explore new national or state-level naloxone programs made possible through the identification and response to legal concerns (2006-11; section 3.3.). Finally, we review the emergence of research studies meeting higher evidentiary standards and examine efforts to widen THN availability (2011-16; section 3.4.). Key events are also summarized as a chronological timeline (see Table 1).

3.1. 1996-2001 circa: Conception, testing the notion, and early implementation

3.1.1. Original articulation

Naloxone was first synthesized and patented in the early 1960s (Blumberg et al., 1961; Lewenstein and Fishman, 1966) and FDA-approved in 1971 for intravenous, intramuscular, and subcutaneous administration for partial or complete reversal of opioid overdose (Garfield, 1983) (see Table 1). Although not the first opiate antagonist, naloxone was the first largely free of agonist effects. Naloxone became standard rescue medication in emergency management of heroin overdose in hospital and ambulance settings and has been included in the WHO List of Essential Medicines since 1983 (WHO, 2011, 2014).

The idea to enable opioid users and/or family and friends to take naloxone home did not arise until more than two decades after initial FDA-approval. It was first mooted at the 3rd International Harm Reduction Conference in March 1992 (Strang, 1992, 1993; Strang and Farrell, 1992) as a mere throwaway example of harm reduction alternatives that were being overlooked. However, the first serious consideration of THN was in the 1996 BMJ editorial (Strang et al., 1996) which identified key elements of the intervention, including provision to: (1) individuals at high risk of overdose, e.g., those leaving emergency care following overdose and those who lost tolerance due to detoxification, incarceration, or abstinence-based treatment; (2) patients enrolled in treatment programs (despite treatments' protective benefits, they remain at risk); and (3) active users.

The editorial also described the poor suitability of existing naloxone products (ampoules, vials) compared to pre-filled syringes and identified medico-legal challenges raised by the prospect of third parties, such as family members, requesting or administering naloxone. Finally, the editorial urged reconsideration of naloxone's prescription-only medication status. These central points of the editorial shaped implementation and research in the subsequent years.

3.1.2. Early implementation

The introduction of THN was made possible through user advocates working with physicians willing to prescribe naloxone despite medicolegal barriers. First THN provision occurred in the late 1990s, in the United States (Chicago, San Francisco), Germany (Berlin), the UK (Jersey), and Italy (Turin, Bologna, Padua).

3.1.2.1 United States

The Chicago Recovery Alliance (CRA) began obtaining and distributing naloxone in 1996. Due to high user demand during a fourfold increase in drug-related deaths from 1996 to

2000, distribution by mobile van was introduced in 1998 and converted into a formal training curriculum in 2001 (Bigg, 2002).

During the late 1990s, CRA began discussions with harm reduction advocates in other places around starting THN-programs and served as central clearinghouse for THN across the US.

San Francisco Needle Exchange introduced a small-scale THN pilot for youth in the Haight-Ashbury district in 1999 (Bigg, 2000; Giuliano, 2000; Seal et al., 2001). The pilot was later scaled up in conjunction with the DOPE (Drug Overdose Prevention and Education) project (Giuliano, 2000; Seal et al., 2001) and moved to the San Francisco Public Health Department in 2003.

In 2000, the Drug Policy Alliance (formerly Lindesmith Center) partnered with the University of Washington Alcohol and Drug Abuse Institute to explore pragmatic approaches to “Preventing Heroin Overdose,” which included sessions on naloxone distribution.

3.1.2.2 Continental Europe

Multiple sources point to largely undocumented early community-based naloxone availability in parts of Italy, notably Turin (1991) and the Emilia Romagna region (incl. Bologna, 1998) (ForumDroghe, 2016; Simini, 1998).

There were reports of THN distribution in Padua in 1996, where a methadone clinic distributed 150 naloxone vials within 18 months. While overdose deaths decreased citywide, there was no formal evaluation of THN usage (Schifano, 2001).

Two pilot schemes in Berlin and the British island of Jersey (Dettmer et al., 2001) constitute the first published outcomes report on THN provision. Between 1998 and 2000, 101 clients of a community-based drug clinic in Jersey were trained in overdose management and received THN kits, with five reported overdose reversals (Dettmer et al., 2001). In Berlin, THN was introduced at a mobile needle and syringe exchange scheme (“Fixpunkt”) in

1999. Within 16 months, 124 THN kits had been issued; 22 users reported administering naloxone for a total of 29 overdose reversals (Dettmer et al., 2001). The article attracted support but also sharp criticism (Ashworth, 2001; Blackwood, 2001; Mountain, 2001), noting low response rate and the lack of systematic follow-up, objective mortality data, and risk assessment – concerns echoed in the THN debate throughout the 2000s. The Berlin pilot was discontinued after 2002 due to lack of funding (AIDS-Hilfe, 2013; Dettmer, 2014).

3.1.3. Testing the notion: is the intervention necessary?

Several studies in the late 1990s and early 2000s identified situations in which naloxone should be made available:

3.1.3.1 Injecting use

In a London-based community sample of heroin users, the vast majority of reported overdoses occurred among injection users (Gossop et al., 1996). Injecting bears a much higher risk of fatal overdose than ‘chasing the dragon’ (i.e., inhalation following sublimation with heat) (Strang et al., 1997), snorting or oral use. (It was later estimated that one in four injecting drug users would experience an overdose each year (Darke et al., 2003)).

3.1.3.2 Return into the community

An influential early study by Seaman et al. (1998) identified the period following release from prison as the most striking high-risk situation, with within two weeks of release (Bird and Hutchinson, 2003). (The finding of increased risk up to four weeks post prison release was subsequently quantified as 1 in 200 prisoners with history of heroin use dying from opioid overdose in the first two weeks post-release and was replicated internationally (Merrall et al., 2010). Similar but less intense concentrations of overdose deaths were subsequently also observed among patients completing in-patient detoxification (Strang et al., 2003), residential rehabilitation (Davoli et al., 2007), and hospital/residential treatment (Merrall et al., 2013; Ravndal and Amundsen, 2010)).

3.1.3.3 Opioid agonist treatment

The first weeks on oral methadone treatment were found to be associated with a transient increase in risk of overdose death (Caplehorn, 1998; Caplehorn and Drummer, 1999).

3.1.4. Testing the notion: is the intervention acceptable for those involved?

Parallel to early THN implementation, research assessed the feasibility and acceptability among users, carers and providers.

3.1.4.1 Opioid users

The 1996 BMJ editorial identified opiate users as the primary target group for THN because they are at risk of future overdose themselves and highly likely to witness and intervene in someone else's overdose. Users have expressed strong support of THN. A London-based survey of injecting drug users (Strang et al., 1999) estimated that two-thirds of witnessed overdose deaths could have been avoided with THN. Most respondents had already witnessed at least one overdose; 89% expressed willingness to administer naloxone in the event of an overdose; 70% agreed with the proposal that naloxone should be provided; and nearly 90% of those who had witnessed an overdose stated that they would have used the medication had it been available. Subsequent interview studies identified opioid users' willingness to be trained in overdose management and naloxone administration (Bennett and Higgins, 1999; Strang et al., 2000).

3.1.4.2 Carers

Most opiate overdoses occur at private homes and/or in presence of peers, family members, and partners (Best et al., 2002; McGregor et al., 1998). Constituting a potential intervention resource, close contacts of users are thus the second target group for THN and training.

3.1.4.3 Health care providers

An early US legal analysis (Burris et al., 2001) found that providers' risk of malpractice liability associated with prescribing THN was no greater than for general health care provision. Prescribing THN to an at-risk patient for administration by a trained partner/family member is analogous to the pre-provision of anti-epileptic medication or injectable adrenaline/epinephrine (EpiPen). However, in situations where naloxone is being prescribed without specific knowledge of who will administer or be administered naloxone, the legal situation becomes murky.

US providers voiced strong concerns over uncertain medico-legal status and potential liability issues and expressed anxieties about patients' 'deputation' as health care providers when injecting naloxone (Burris et al., 2001). Around the same time, Australian providers and service users alike raised concerns about civil or criminal liability (Lenton and Hargreaves, 2000).

3.1.5. Thinking at the national level

In 2000, THN provision received an early public endorsement by the UK Advisory Council on the Misuse of Drugs (ACMD, 2000) who stated: "Our view is that, as a matter of principle, naloxone should be made more widely available (that is beyond hospital, paramedic and ambulance settings) [...]". The statutory advisory body gave clear direction on the need for: (1) enhanced attention to effective overdose management by emergency medical services, including authorization of lower grades of ambulance staff to administer naloxone; (2) uniform agreement that an overdose is primarily a medical emergency (which ordinarily should not involve police attendance); (3) treatment agencies to be teaching overdose management, (4) naloxone to be widely given to friends and partners of drug users, (5) naloxone provision to be extended to prisons and police stations for use by trained staff.

The vision articulated in the ACMD report would shape the naloxone policy debate up to the present (see Table 2).

3.2. 2001-2006 circa: Modest progress amidst concerns over the safety and legality of the intervention

Following the pioneering CRA program, early adopters in the United States included New Mexico, which began THN distribution in early 2001 (Baca and Grant, 2005).

In 2004, the Baltimore Staying Alive Drug Overdose Prevention Program was launched, sponsored by the Baltimore City Health Department and Open Society Institute, and the Lower East Side Harm Reduction Coalition in New York conducted a pilot, which was expanded to all city-funded Syringe Exchange Programs in 2005 (Heller and Stanciliff, 2007).

In Europe, there were reports of THN distribution in Barcelona as early as 2001 (Trujols, 2001). In mainland UK, THN was first introduced in South London in mid-2001 (Strang, 2001).

3.2.1 Training opioid users and their family members

In the first published evaluation of THN training, Seal and colleagues (2005) assessed knowledge of overdose management by asking participants to name risk factors, signs of overdose, and overdose prevention and management strategies. A significant increase in knowledge was maintained at 6-month follow-up (Seal et al., 2005). Despite willingness to participate in THN training, opioid users also expressed concerns about THN, such as fear of experiencing withdrawal symptoms, enabling further drug use, risk of blood-borne virus infection, and potentially having to manage agitation and hostility in those revived (Kerr et al., 2008; Seal et al., 2003; Worthington et al., 2006). Service users also expressed concerns about the risk of confiscation of the antidote and its potential role in escalating already delicate relationships with law enforcement (Seal et al., 2003; Worthington et al., 2006).

In an England-based postal survey (Strang et al., 2008b), the majority of family members expressed strong interest in THN training.

3.2.2 Providers' concerns

Support was weak in the drug treatment field, where the debate was dominated by legal and safety concerns. Providers questioned users' competency in naloxone administration and pointed to the risk of unsafe needle disposal (Ashworth, 2006; Byrne, 2006; Tobin et al., 2005). Even though an early survey of drug users had found that THN was unlikely to lead to increased heroin consumption (Strang, 1999), a common concern among providers was potential promotion of drug use (Ashworth, 2006; Tobin et al., 2005). Negative attitudes were revealed in surveys of Baltimore-based emergency service providers (Tobin et al., 2005) and physicians throughout the US who were likely involved in treatment of opioid users (Beletsky et al., 2007): most believed THN would not reduce drug-related deaths and reported they would never consider prescribing naloxone. A notable exception was a postal survey of New York-based clinicians of whom over a third were willing to prescribe naloxone (Coffin et al., 2003).

3.3. 2006-2011 circa: Identification of legal pathways for take-home naloxone and first national and state-wide programs

3.3.1. Responses to legal barriers

Because THN has come about so recently, most medico-legal barriers to it were unintended consequences of prior legislation passed for other purposes (NPHL, 2016). About ten years after the original THN proposal, some jurisdictions began to pass laws to facilitate THN implementation. Policies are typically of two kinds: those that enable naloxone access via broad standing orders, or those that amend Good Samaritan legislation to extend immunity beyond physicians to first responders, bystanders, or witnesses who extend care in emergency situations.

3.3.1.1 United Kingdom

In 2005, naloxone was incorporated into the Schedule 7 of the UK Medicines Act which allows any member of the general public to administer naloxone with the aim of saving a life, thereby placing naloxone alongside glucagon, adrenaline and snake antivenin (Strang et al., 2006). Naloxone could then lawfully be given by a witness to an overdose victim to whom it was not prescribed, opening doors to naloxone administration by layperson first-responders. At least 16 sites then implemented THN pilots in England (NTA, 2011). However, naloxone remained a prescription-only medication. Hence the UK Department of Health 'Orange Guidelines' (DOH, 2007) stated: *“naloxone [...] must be prescribed to named patients or supplied to an individual by means of a patient group direction [PGD].”*

3.3.1.2 United States

Naloxone is a prescription-only-medication at the federal level, although there is considerable variation due to state-level legislation and lower-court rulings. New Mexico became the first state to remove legal barriers to THN prescribing and distribution in 2001 (Alcorn, 2014) and to grant legal immunity to bystanders via a “Good Samaritan” law in 2007. New York and Connecticut followed with laws that granted immunity from civil liability to healthcare providers with prescribing authority (Sporer and Kral, 2007).

Established in 2006, the Massachusetts THN pilot program used a standing order to enable public health care workers to provide THN without a prescription (Doe-Simkins et al., 2009). The standing order model allows a lead physician within a given jurisdiction to issue a written order that naloxone can be distributed by designated pharmacists or other qualified professionals (OSF, 2013).

At the end of the 2000s, there were fewer than three dozen THN programs in the US, but the standing order model would lead to a dramatic increase in the following years (OSF, 2013).

3.3.2. First national and state-wide programs

In the late 2000s, first THN programs expanded coverage from a local to a state-wide or national level.

3.3.2.1 Catalonia

Following earlier underground distribution of naloxone, the public health agencies of Barcelona and the autonomous region of Catalonia formally launched a THN program in 2008 which allowed staff and clients of participating sites to receive training (EMCDDA, 2016).

3.3.2.2 Scotland

Three local pilots were launched in Glasgow, Lanark and Inverness during or after 2007 using the authority of PGDs for nurses and paramedical staff to issue THN (McAuley et al., 2012). In 2011, the Scottish Procurator Fiscal issued a “Letter of Comfort”, granting immunity to pharmacists who supplied naloxone without prescription to staff working at services with a high rate of overdoses (e.g., hostels) (Angiolini, 2011). These so-called ‘Lord Advocate’s guidelines’ thus permitted naloxone storage in non-medical facilities for emergency use (ACMD, 2012).

The Scottish National Programme was launched in November 2010 (McAuley et al., 2012) and involves THN distribution in the community and to prisoners on release. Services can issue THN to staff, persons at risk of overdose, family members, and peers (with documented consent of the person at risk). The Scottish government funded the program centrally up until 2016. Over the years, the Scottish National Programme would distribute over 20,000 THN kits (McAuley et al., 2017) – approximately 90% in the community and 10% to prisoners on release (ISD, 2016).

3.3.2.3 Wales

Following the 2007 introduction of a THN pilot (Bennett and Holloway, 2011, 2012), Wales launched a national naloxone program in 2011. Between mid-2009 and early 2014,

4,579 THN kits were issued and reportedly used in 375 overdose events (McDonald et al., 2016).

3.3.2.4 Massachusetts

The Massachusetts Department of Public Health has conducted the most comprehensive US program evaluation to date. Boston-based harm reduction activists began THN distribution in the early 2000s without formal approvals and documented the number of naloxone vials distributed and overdose events reversed in a 2005 letter to the mayor of Boston who facilitated a joint meeting between the activists and the Department of Public Health. As a result, Boston Public Health Commission authorized development of a THN program via its mobile needle-exchange scheme in 2006. The Massachusetts THN program was the first to involve distribution of intranasal naloxone and to allow non-medical public health workers to issue naloxone. By 2009, the Massachusetts Department of Public Health had expanded the program to seven more communities, operating out of needle-exchange sites, methadone clinics, homeless shelters, inpatient detoxification programs, community meetings, outpatient and residential addiction-treatment programs, and emergency departments. By 2014, the Massachusetts THN program had trained 4,926 drug users, of whom 373 reported administering naloxone (Doe-Simkins et al., 2014).

3.4. 2011-2016 circa: Emergence of stronger data, alternative implementation models, and recent efforts to widen naloxone access

By the 2010s intervention studies typically reported the number of overdoses reversed with naloxone as a central outcome; high naloxone usage rates confirmed the ‘trainability’ of heroin users to adequately respond to overdose (Green et al., 2008; Lopez-Gaston et al., 2009; Markham-Piper et al., 2008; McAuley et al., 2010; Strang et al., 2008a; Tobin et al., 2009; Wagner et al., 2010). A systematic review of naloxone usage rates found that, for every 100 opioid users trained and supplied with THN, 9% of THN kits are likely used for overdose

reversal within the first three months post-training (McAuley et al., 2015). However, methodological limitations such as small sample sizes, uncontrolled designs, lack of randomization and systematic follow-up made it difficult to quantify the impact of THN provision on overdose mortality.

3.4.1. A growing evidence base

In 2012, the United Nations Commission on Narcotic Drugs passed Resolution 55/7 (UNODC, 2012), which identified need for more effective prevention of drug overdose, and “[e]ncourage[d] all Member States to include effective elements for the prevention and treatment of drug overdose, in particular opioid overdose, in national drug policies, [...], including the use of opioid receptor antagonists such as naloxone.” The same year, the first large-scale randomized trial of THN (N-ALIVE) started recruitment (see section 3.4.3.) (Strang et al., 2013).

In 2013, two cost-effectiveness analyses presented modelling data from the United States and Russia, concluding that THN was cost-effective even when the cost of naloxone increased and the rate of observed overdoses decreased (Coffin and Sullivan, 2013a; Coffin and Sullivan, 2013b). Another 2013 study addressed the impact of THN provision on local overdose rates using an interrupted-time series analysis, finding that Massachusetts-based communities with THN provision had significantly lower overdose mortality rates than communities without (Walley et al., 2013).

Regarding the safety of THN, common concerns were whether THN availability would promote drug use and whether the short half-life of naloxone would result in rebound overdose after the initial dose wore off. A large US retrospective cohort study (n=4,926) concluded that THN provision did not lead to increased heroin use (Doe-Simkins et al., 2014). Previously, a Danish study had found that death from (presumed) ‘rebound’ overdose

toxicity occurred only in 3 out of 3,245 cases of naloxone administration (Rudolph et al., 2011).

A waiting-list randomized trial (Williams et al., 2014) of THN training demonstrated good improvements in the knowledge and competence of carers in overdose management, which were maintained at 3-month follow-up – thus confirming the trainability of potential overdose witnesses in the community.

These results were among the key evidence included in a WHO review of community-based naloxone, which led to the November 2014 launch of the WHO Guidelines on the Community Management of Opioid Overdose (WHO, 2014).

The key recommendation was that “[p]eople likely to witness an opioid overdose should have access to naloxone and be instructed in its administration” (WHO, 2014). Subsequently, a BMJ editorial argued that there is “[n]ow enough experience to justify [THN implementation]” (Strang et al., 2014).

Following release of the WHO Guidelines, three systematic reviews (Clark et al., 2014; EMCDDA, 2015; McDonald and Strang, 2016) reached similar conclusions. The EMCDDA (2015) concluded: ‘there is evidence that educational and training interventions with provision of take-home naloxone decrease overdose-related mortality’ (p. 11). Likewise, Clark et al. (2014) found that participation in THN programs led to improved overdose-related knowledge and appropriate use and administration of naloxone. However, the authors (Clark et al., 2014) also reported that the rate of ambulance calls during overdose events was below 50% in 6 out of 9 studies, which appeared to substantiate the concern that THN might discourage users from calling an ambulance. (This concern was later refuted by McAuley and colleagues (2017) whose interrupted time-series analysis of data from the Scottish National Naloxone Programme found no association between the supply of take-home naloxone kits and the number of ambulance call-outs). The most recent systematic review (McDonald and

Strang, 2016) assessed the safety of THN programs as well as their impact on opioid overdose-related mortality. Evidence from 22 observational studies was evaluated using the nine Bradford Hill criteria (Hill, 1965), devised to assess a potential causal relationship between public health interventions and clinical outcomes when only observational data are available. The analysis confirmed that THN programs met all nine Bradford Hill criteria, reduced overdose mortality among program participants and in the community, and had a low rate of adverse events (McDonald and Strang, 2016).

Finally, in April 2016, the United Nations General Assembly Special Session on Drugs (UNGASS 2016) included “naloxone distribution to prevent overdose deaths associated with opioid use” as example of evidence-based strategies in its scientific summary (UNODC, 2016a).

3.4.2. Dissemination and expansion

3.4.2.1 Australia

Despite immediate endorsement of the original THN proposal by Australian researchers (Darke and Hall, 1997; Fry et al., 2000; Lenton and Hargreaves, 2000), funding for an early naloxone trial in Victoria was affected by the 2000 Australian heroin drought (Dietze, 2016). Intranasal naloxone was explored in ambulance-based trials (Kelly et al., 2005; Kerr et al., 2009), but THN was halted by medico-legal concerns.

Following the emergence of findings from THN schemes overseas, Australian researchers reiterated the case for THN (Dietze and Lenton, 2010; Lenton et al., 2009), which ultimately led to the launch of I-ENNAACT, the first Australian THN program in Canberra, in late 2011.

A preliminary evaluation in late 2014 showed that over 200 injecting drug users had been trained in overdose prevention (including 18 inmates) and reported 57 successful overdose reversals (Dietze, 2016). Naloxone access in Australia was facilitated by the 2012

addition of the antidote to the government Pharmaceutical Benefit Scheme which subsidizes prescription drugs. Australian residents can now obtain naloxone at a concession rate of AUD 5.90, rather than the previous AUD 60 (Fowlie, 2013). The Australian Medical Association endorsed THN in 2013 (Anex, 2013). THN scale-up in New South Wales is currently underway (Dietze, 2016).

3.4.2.2 Continental Europe

In the early 2010s, several northern European countries launched THN projects: Denmark and Estonia in 2013, with Norway following in 2014 and Ireland in 2015 (EMCDDA, 2016).

3.4.2.3 United Kingdom

In 2012, ACMD urged the Department of Health to review naloxone's prescription-only status (ACMD, 2012). Triggered by this request, the Medicines and Healthcare Products Regulatory Agency (MHRA) released a consultation in 2013, asking for feedback on a proposal to increase community-based naloxone access (MHRA, 2013). Thus, new UK legislation was passed in late 2015 which explicitly enabled wider availability to drug users, family members, other carers, and staff working in relevant treatment and social care agencies. New Public Health England (PHE) guidelines exempted naloxone from the usual prescription requirement when it is supplied by a drug service commissioned by a local authority or NHS (PHE, 2015).

3.4.2.4 United States

Amid growing public support, organizations including the US Conference of Mayors, the American Medical Association, the American Public Health Association, and the National Association of Boards of Pharmacy urged states to remove legal barriers to THN (Alcorn, 2014; NPHL, 2016). As of June 2016, forty-eight states had amended laws to relieve provider liability when prescribing or dispensing naloxone, and thirty-seven states had passed

Good Samaritan laws (Burris et al., 2001; DOJ, 2014; NPHL, 2014, 2016). Sustainability has been achieved in several states (CDC, 2012).

As of mid-2014, 136 THN programs were providing naloxone kits to laypersons at 644 sites across the country (CDC, 2015), with programs operated by community-based organizations, public health departments, and Veterans Health Administration facilities (Humphreys, 2015). Between 1996 and mid-2014, naloxone kits had been supplied to a total of 152,283 clients who reported 26,463 overdose reversals (CDC, 2015). Among these cases, CRA alone reported training and providing naloxone kits to a total of 36,708 individuals, with 5,767 peer overdose reversals (CRA, 2014).

3.4.3. Exploration of new settings and workforces

Community-based harm reduction teams have been the ‘default’ resource for THN provision, with users and their primary carers the main target populations. The CDC survey (2015) of current THN programs in the US reported that most program participants are people who use drugs (82%), with friends and family members being the second most common group (12%). Over the past five years, researchers have sought to study whether expansion of the THN intervention to new settings and workforces could enhance its impact.

3.4.3.1 Police and firefighters

In the US, several jurisdictions have passed legal provisions to authorize nonmedical first responders to administer naloxone (Banta-Green et al., 2013). In 2010, Massachusetts was the first state to pioneer equipping firefighters and police with naloxone (Davis et al., 2014), and the Obama administration’s National Drug Control Strategy (ONDCP, 2010) urged training of law enforcement professionals and firefighters “in how to recognize an overdose and [in] how to administer [...] naloxone.”

Law enforcement officers can be successfully trained to respond to overdose (Saucier et al., 2016; Wagner et al., 2016).

Over 220 law enforcement agencies across 24 U.S. states carry naloxone (Davis et al., 2015). Equipping Ohio police with naloxone nasal spray was associated with a decline in opioid overdose deaths (Rando et al., 2015). A New York-based program reported over 100 overdose rescues within a year (NYAG, 2015).

Law enforcement officers generally expressed willingness to receive training in overdose management and naloxone administration (Banta-Green et al., 2013; Ray et al., 2015; Wagner et al., 2016). However, a Seattle-based study found law enforcement officers' knowledge of a Good Samaritan law to be low (Banta-Green et al., 2013). Furthermore, training did not impact law enforcement officers' mixed attitudes toward opioid users (Banta-Green et al., 2013; Wagner et al., 2016). Geographical disparities have also been revealed, with naloxone equipment of emergency responders being more common in urban than rural settings (Rando et al., 2015).

3.4.3.2 Primary care

Despite extensive contact with opioid users and favorable attitudes towards wider naloxone availability, many providers have remained wary of providing THN (Barry et al., 2017; NPHL, 2014). US primary care providers described insufficient time during patient appointments and inability to follow up with patients as main organizational barriers to THN (Binswanger et al., 2015). Canadian primary care providers considered existing naloxone guidelines inadequate and identified the lack of user-friendly naloxone devices, sufficient funding and training as central barriers to THN provision (Leece et al., 2015). Scottish primary care providers reported low awareness of the national THN program, pointing to their need for training (Matheson et al., 2014).

However, a San Francisco-based project of naloxone co-prescribing for primary care patients receiving long-term opioid pain therapy established that the intervention was

feasible, acceptable to patients (Behar et al., 2016) and associated with significantly reduced opioid-related emergency department (ED) visits at 1-year follow-up (Coffin et al., 2016).

3.4.3.3 Emergency care

The Massachusetts THN program provides THN at EDs, and feasibility has recently also been explored elsewhere. A British Columbia survey of ED patients at risk of opioid overdose (Kestler et al., 2017) found that two-thirds accepted THN kits when offered to them at the ED, highlighting the potential of this setting for overdose prevention.

3.4.3.4 Pharmacy-based provision

In pharmacy-based THN provision, pharmacists take on a dual role: a) monitoring patients' opioid prescriptions and assessing their risk of opioid use disorder as well as b) expansion of naloxone access (Green et al., 2015b; Penm et al., 2017). Since October 2015, UK pharmacies providing supervised opioid substitution treatment can supply THN without prescription to individuals likely to witness an opioid overdose provided "the [naloxone] supply is suitably recorded" (PHE, 2015). As of August 2016, US pharmacists can prescribe naloxone in 5 states and dispense naloxone via standing orders in forty-two states (Davis and Carr, 2017). Pharmacy-based provision has been piloted as a strategy to promote naloxone access in rural areas (Green et al., 2015b) and increased dramatically in the US since 2013 (Jones et al., 2016). However, pharmacists' willingness to dispense THN varies (Freeman et al., 2017) and patients and carers report stigma of THN receipt (Green et al., 2017).

3.4.3.5 Peer-led provision

Peer-led naloxone supply is becoming more common. In the UK, (former) service users can be employed or engaged in drug treatment services and supply naloxone to potential overdose witnesses as of October 2015 (PHE, 2015). A Canadian interview study with peer-trainers identified the wish to help others as key motivation and found

psychological benefits associated with the peer-trainer role, including a sense of recovery and empowerment (Marshall et al., 2017).

3.4.3.6 Prison release

THN provision on prison release was the focus of the N-ALIVE randomized trial in England and Wales, which assessed its impact on overdose mortality in the month post-release (Bird and Hutchinson, 2003; Farrell and Marsden, 2008; Strang et al., 2013). N-ALIVE pilot with its target recruitment of 2,800 subjects yielded a marked decrease in opioid-related deaths, a subsequent large-scale trial involving 28,000 prisoners on release was scheduled. However, the pilot was ended prematurely in December 2014 (total enrolment: 1,685 subjects) (Parmar et al., 2017) after the SNNP showed a significant reduction in the proportion of opioid-related deaths in the month following prison release. Among Scottish prisoners supplied with THN, mortality decreased to 4.7% by 2013, compared with the pooled 2006–10 baseline of 9.8% (ISD, 2014). Since program start in 2011, heroin-related deaths within 4 weeks of prison release gradually decreased every year, coinciding with a steady increase in the volume of THN kits (Bird et al., 2016; Bird et al., 2015). Prison-based THN has also been introduced and studied in New York City, California, and Rhode Island (Green et al., 2015a; Jordan, 2015; Rosner, 2015).

3.4.4. Efforts to widen availability of naloxone

Since 2015, significant developments have widened naloxone access through a variety of mechanisms, including reformulation of the product.

3.4.4.1 Non-injectable naloxone

Naloxone's exclusive availability as formulated for injection is one of the main barriers to wider use, as certain jurisdictions restrict the administration of injections to medical professionals (EMCDDA, 2016). Injectable naloxone is not ideal for layperson use and can present a twofold barrier to THN implementation: on a clinical level, carriage rates

for injectable naloxone have been found to be below 20% (McAuley et al., 2016). Laypersons who witness overdose events may be less likely to intervene and administer an injection for lack of familiarity with needle-and-syringe assembly or for fear of needle-stick injury and potential risk of contracting blood-borne diseases (e.g., hepatitis C, HIV) (Wermeling, 2013).

Improvised nasal naloxone kits consisting of a 2 mg/ 2 ml pre-filled syringe with a nasal mucosal atomizer device were first provided in the Massachusetts THN program in 2005 (Doe-Simkins et al., 2009). Since the prefilled naloxone syringe is approved only for injectable use, the improvised nasal kits represent off-label or off-license use (Strang et al., 2016b). The improvised nasal kits were later introduced elsewhere in the United States, Denmark, Norway, and Scotland's Highland region.

The Norwegian THN program distributed 2,056 nasal kits between program start in mid-2014 and late 2015, with 277 overdose reversals reported (Madah-Amiri et al., 2017). The Danish THN kits are unique in that they contain both the mucosal atomizer device for nasal administration and a needle for intramuscular injection in case of non-response to the nasal spray (EMCDDA, 2016).

According to a survey of 136 US-based THN programs, 51% provided only injectable naloxone, 37% provided only improvised nasal kits, and 12% provided both (CDC, 2015).

In 2012, a step-change occurred in the U.S. with the joint initiative of the Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), and National Institute on Drug Abuse (NIDA) to encourage new non-injectable naloxone formulations, alongside FDA clarification of the regulatory benchmark: one or multiple doses of any new non-injectable formulation would need result in similar or greater naloxone exposure than the reference product of intramuscular naloxone 0.4mg (Hertz, 2012). A systematic review identified nasal, buccal and sublingual naloxone delivery as the three

viable routes for naloxone administration in an overdose emergency, of which study of the nasal route was most advanced (Strang et al., 2016a).

Prior to the 2012 FDA initiative, only one patent application (WO/2012/156317) for non-injectable naloxone containing human in-vivo data had been filed, highlighting very limited investment from pharmaceutical industry. With injectable naloxone-hydrochloride solution available as generic and off-patent medication, naloxone was of limited commercial value. Moreover, as an antidote, naloxone is only prescribed for emergency use (unlike e.g., medications for opioid substitution therapy), and its per-patient sales volume limited accordingly.

When NIDA announced that it would fund development of “user-friendly” naloxone delivery systems (Volkow et al., 2014), industry interest finally appeared. Two companies filed separate New Drug Applications for nasal naloxone in 2015, of which only one product was FDA-approved later that year. This concentrated nasal spray product (4mg/0.1ml) has a promising pharmacokinetic profile with good bioavailability (Krieter et al., 2016). Whether it can improve community-based naloxone availability remains to be seen.

3.4.4.2 *Over-the-counter naloxone*

Until recently, Italy was the only country where naloxone was available without a prescription. In 1996, the Italian Ministry of Health classified naloxone as an over-the-counter medication, allowing pharmacists to issue naloxone without a prescription (*Senza Obbligo di Prescrizione*) (ForumDroghe, 2016, 2017; Lenton and Hargreaves, 2000; WHO, 2014). However, naloxone cannot be publicly displayed on shelves to which customers have direct access. Customers must request naloxone directly from the pharmacist. While no causal conclusions may be drawn, the 1996 introduction of over-the-counter status was succeeded by a gradual decline in opioid overdose mortality rates in Italy, with 470 deaths in

1999, 280 in 2005, and 101 in 2015 (ForumDroghe, 2016, 2017). As of 2016, 57 Italian harm reduction services distribute THN, but there are stark regional disparities, with services predominantly clustered in the major metropolitan areas (i.e., Rome, Milan, Bologna, Turin, Naples). Some regions are without THN coverage, which has been linked to the lack of a national harm reduction policy and insufficient investment (ForumDroghe, 2016).

Although THN was only introduced in Australia in 2011, Australia became the second country to have naloxone formally available over-the-counter, following the decision of the Therapeutic Goods Administration to place “naloxone when used for the treatment of opioid overdose” on Schedule 3, thereby approving over-the-counter (OTC) status (Lenton et al., 2016). Since early 2016, Australian community pharmacists have been able to supply naloxone without a prescription.

In Canada, THN programs exist in seven of the 13 provinces and territories, with large programs in British Columbia (120 sites, 6,389 kits distributed) and Ontario (22 sites, 2,734 kits distributed) (CCSA, 2016). In 2016, Health Canada approved the previously FDA-licensed nasal naloxone product and issued an interim order to make the spray available without a prescription (CBCnews, 2016).

Select U.S. pharmacies in at least 15 states have special practice agreements allowing pharmacists to sell naloxone (incl. the FDA-approved nasal spray) without a prescription (EMCDDA, 2016). However, it is unclear if or how soon formal re-classification of naloxone from prescription-only medicine to over-the-counter status may occur. An earlier legal analysis suggested this regulatory process might be lengthy and cost-intensive (Burris et al., 2001), as FDA would require additional data demonstrating the ability of laypersons without medical training to correctly diagnose an overdose and administer the formulation (Compton et al., 2013; FDA, 2012).

In the UK, the 2015 PHE guidelines allow people engaged or employed in NHS drug treatment services to make THN available to opioid users, family members, and hostel staff without prescription, provided the naloxone supply is documented accurately (PHE, 2016). Even though naloxone technically remains a prescription-only medication, the guidelines reduce the staffing burden for THN as staff without prescribing authority can issue THN for emergency use.

3.4.4.3 Calls for universal THN provision

Beyond lack of funding or political support, low prescriber awareness and commitment persist as central barriers to wider THN access. Despite evidence of effectiveness and endorsements from professional organizations (ACMD, 2000, 2012, 2016; AMA, 2012), many providers fail to integrate THN into standard care for at-risk patients. Dissemination was found to be difficult even among addiction treatment staff (Mayet et al., 2011) with the anticipated cascade of the ‘train-the-trainer-model’ occurring at the disappointing pace of one drug user trained per clinician trainee in on average 11 months.

Providers struggle with competing clinical demands, making opt-in medical services low priority. A more proactive approach whereby THN was routinely prescribed to all at-risk patients unless patients declined (‘opt-out’ system) would likely increase coverage.

An international treatment target similar to the UNAIDS (Joint United Nations Program on HIV/AIDS) 90-90-90 ‘test and treat’ strategy (introduced to help end the AIDS epidemic) (UNAIDS, 2014) could potentially improve naloxone access in countries affected by opioid-related mortality. Researchers estimate that target naloxone distribution should exceed 100 kits per 100,000 population (Walley et al., 2013) or at least nine times as many naloxone kits as there are annual opioid-related deaths to impact opioid mortality (Bird et al., 2015; Madah-Amiri et al., 2017).

4. Discussion

4.1. Strengths and limitations

This narrative review represents the first peer-reviewed attempt to reconstruct the development of THN from its conception to present.

To allow for the wide scope of this review, a broad search strategy was applied. While the search strategy was not limited to English-language entries, we cannot rule out that relevant international sources (published in other languages) may have been overlooked. Similarly, it is possible that the chronological timeline (see also Table 2) may include inaccuracies.

We present these data as our best estimates that are based on careful extraction from the referenced source documents. We hope to stimulate discussion and invite feedback from take-home naloxone users, advocates, prescribers and researchers around the world.

4.2. Questions for future research

Many questions are still unanswered about THN, including about routes of administration and optimal dose range (especially for overdose from synthetic opioids) (FDA, 2016), and questions on core elements of overdose trainings and their potential impact on behavior. Finally, the question of co-prescription of naloxone for chronic pain patients being treated with opioids is just now being raised (Coffin et al., 2016) as THN research has been largely confined to heroin users.

THN implementation studies have mostly recruited heroin users via urban harm reduction infrastructures, including needle exchange schemes. Implementation studies are needed for emerging target groups such as rural user populations and prescription opioid users (including chronic pain patients) whose overdose risk awareness may be low (Albert et al., 2011; Coffin et al., 2016; Compton and Volkow, 2006; Paulozzi and Ryan, 2006). The US opioid epidemic has led to a demographic shift in heroin users, from urban minority populations to predominantly white suburban and rural men and women (Cicero et al., 2014).

Overdose mortality rates (any substance) have increased among men and women of non-Hispanic white and black ethnicity (CDC, 2016). It will be important to examine the demographics of prescription opioid users (including chronic pain patients) in greater detail (Coffin et al., 2016; Ling, 2017; Volkow and McLellan, 2016), particularly considering that the prevalence trends of overdoses from prescription opioids and heroin are likely intertwined and indicative of switching from prescription opioid to heroin use (Unick et al., 2013).

4.2.1 Models for implementation

Implementation research will be necessary as THN programs move into new settings. One such feasibility study is currently being undertaken in correctional and reentry settings in California, where stakeholder interviews and focus groups are being conducted to address THN implementation barriers (NIH project number: 5R34DA039101-02).

Research is also needed to systematically compare different settings and distribution models for THN to identify those with biggest reach among target populations. The issue of THN cost also needs to be considered. For instance, it is unknown how likely potential overdose witnesses are to access and obtain naloxone via THN programs at no cost versus as over-the-counter medication for sale. Availability of naloxone solely over-the-counter, i.e., without additional free distribution, may only yield limited community-based coverage. Such is the case in Italy, where naloxone was reclassified to over-the-counter medication in 1996, but some regions remain without community-based naloxone coverage, presumably because of insufficient public investment (ForumDroghe, 2016).

By analogy, in the prevention of sexually transmitted infections (STIs), a systematic review identified cost as barrier to condom use (Ubrihien et al., 2016). Consequently, recent NICE guidelines recommend free-of-charge condom distribution schemes to target populations at highest risk of STIs (Iacobucci, 2017; NICE, 2017).

4.2.2 Naloxone coverage

Future studies will need to look at the extent to which widespread THN provision, as perhaps achieved in Scotland (Bird et al., 2017; McAuley et al., 2017), Norway (Madah-Amiri et al., 2017) and several states in the US (Walley et al., 2013), results in reduction in opioid overdose mortality at state or national level, and what naloxone coverage rates are required to achieve this effect.

4.2.3 Opioid user engagement

Despite increasing THN provision among (recent) injecting drug users from 8% (2006-10 baseline) to 51% (2014-2015) (Bird et al., 2017), the Scottish National Naloxone Programme reported naloxone carriage rates of only 5-16% (McAuley et al., 2016), highlighting the need to improve user engagement in take-home programs.

Qualitative research may help shed light onto barriers to THN intervention uptake. While opioid users in Baltimore and Chicago reported predominantly positive interactions with police and paramedics (Sherman et al., 2008) and expressed interest in THN provision as well as willingness to share information on overdose emergency management with peers and family members (Sherman et al., 2009), naloxone experiences likely differ. Qualitative interviews conducted in Scottish cities in 1997-99 (Neale and Strang, 2015) revealed opiate users' negative views of naloxone and accounts of harm caused by its administration (e.g., acute withdrawal, aggression, self-discharge and further drug-seeking), even though this was not apparent in observational data.

Similarly, opioid users in New York and Los Angeles reported fear of withdrawal and police involvement as key concerns associated with THN distribution (Lankenau et al., 2013; Worthington et al., 2006), and continued use of folk remedies posed a barrier to THN use (Lankenau et al., 2013).

Systematic study of lived naloxone experiences is needed to identify strategies for increasing user engagement in THN programs.

5. Conclusion

Twenty years ago, the very idea of THN was a radical speculative proposal to extend harm reduction beyond needle and syringe exchange. Today THN is increasingly accepted as an effective public health strategy to reduce overdose fatalities and is increasingly being considered as part of routine care and possibly a required standard of care. Nonetheless, THN lags behind its full potential, with only modest distribution of THN relative to the evident (and growing) clinical need. To date, THN distribution has mostly been made possible by community-based harm reduction organizations with limited central funding. To tackle the rising numbers of opioid-related deaths, governments will need to provide political leadership and perhaps specific financial support to improve the necessary extent of coverage of this potentially life-saving intervention.

AUTHOR DISCLOSURES

Contributors:

JS, NC and RM drafted the manuscript. RM conducted the literature search. All authors approved of the final draft of the manuscript.

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No specific funding was sought or secured for the review reported in this paper.

Conflict of Interest:

JS declares that he is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. JS is an NIHR Senior Investigator and is

also supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. He has also worked with a range of governmental and non-governmental organizations, and with pharmaceutical companies to seek to identify new or improved treatments (including naloxone products) from whom he and his employer (King's College London) have received honoraria, travel costs and/or consultancy payments. This includes work with, during past 3 years, Martindale, Indivior, Mundipharma, Braeburn and trial medication supply from iGen and Braeburn. JS has been named as an inventor in a patent application for concentrated naloxone nasal spray. For fuller account, see www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx.

RM has undertaken an unpaid student industry placement with Mundipharma Research Ltd., with focus on the analysis of naloxone nasal spray formulations.

King's College London (employer for both JS and RM) has separately applied to register intellectual property on a novel buccal naloxone formulation with which JS and RM are involved.

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Table 1 | Key events in the emergence and evolution of take-home naloxone

Year	Month	Country	Event
1961	March	USA	Drs. Jack Fishman and Mozes J. Lewenstein apply for first US patent for synthesis of naloxone (issued in May 1966)
		USA	Dr. Harold Blumberg and colleagues publish abstract in <i>Federation Proceedings</i> in which he introduces naloxone as “potent, rapid-acting, and relatively pure narcotic antagonist.”
1962	March	UK	Sankyo applies for British patent for naloxone (issued in October 1963)
		Japan	Minakami et al. of Sankyo Company Ltd. Publish first full-length journal article on naloxone in <i>Life Sciences</i>
1971		USA	FDA licenses naloxone as prescription-only medication; naloxone enters clinical practice in Europe in subsequent years
1983		Int'l	Naloxone is included in the 1983 WHO List of Essential Medicines (and subsequent editions)
1991		Italy	Report of community-based naloxone access in Turin suburb
1992	March	Australia	Notion of THN provision to at-risk populations is mooted at 3 rd International Harm Reduction Conference in Melbourne
1996	June	UK	<i>BMJ</i> editorial by Strang et al. states ‘home-based supplies of naloxone would save lives’
	ca. June	USA	Chicago Recovery Alliance (CRA) distributes first THN kits
		Italy	Ministry of Health classifies naloxone as over-the-counter medication
		Italy	Reports of THN distribution in Padua
1998	September	Italy	Simini announces plans to distribute THN in Bologna and surrounding Emilia Romagna region in <i>The Lancet</i>
	October	UK	Island of Jersey starts THN distribution
1999	January	Germany	Fixpunkt Berlin starts THN distribution
	March	USA	San Francisco Needle Exchange starts THN distribution
2001	April	Germany/ UK	First published report of THN distribution by Dettmer et al. in <i>BMJ</i>
		Spain	Reports of underground THN distribution in Barcelona
		USA	New Mexico launches THN program
		UK	Introduction of first mainland THN scheme (south London)
2002	March	USA	Dan Bigg of CRA reports first lives saved using THN in <i>BMJ</i>
2003		USA	San Francisco Public Health Dept. starts THN program
2004	June	USA	Lower East Side Harm Reduction Coalition in New York starts THN distribution
		USA	Baltimore launches Staying Alive Drug Overdose Prevention Program
2005	November	UK	Legal status of naloxone changed to permit emergency administration of naloxone by any member of the general public (Schedule 7 of the Medicines Act)

Year	Month	Country	Event
2006	August	USA	Boston Public Health Commission authorizes start of THN program, including provision of intranasal naloxone kits
2006		UK	National Treatment Agency for Substance Misuse (NTA) funds THN training pilot in 16 sites in England
2007		UK	Scotland and Wales establish THN pilots
2008		UK	Medical Research Council funds N-ALIVE trial
		Spain	Formal THN program launched in Barcelona
2010		USA	ONDCP National Drug Control Strategy endorses community use of naloxone
	November	UK	Scotland launches national THN program
2011		UK	Scottish Lord Advocate issues new guidelines
		UK	Wales launches national THN program
		Australia	First Australian THN program starts in Canberra
2012	March	Int'l	UNODC Resolution 55/7 states 'opioid overdose treatment, including the provision of opioid receptor antagonists such as naloxone, is part of a comprehensive approach to services for drug users'
	April	USA	FDA, CDC, NIDA, and HHS convene naloxone meeting
	May	UK	Advisory Council on the Misuse of Drugs urges Department of Health to review naloxone prescription-only status
	December	Australia	Naloxone is added to the Pharmaceutical Benefit Scheme
2013	March	Denmark	THN program starts (dual kits: intranasal and injectable)
		Estonia	Harju and East-Viru counties start THN distribution
2014	July	Norway	THN program starts (intranasal)
	November	Int'l	WHO releases guidelines on the community management of opioid overdose
2015	May	Ireland	Health Services Executive approves THN by prescription, THN project starts
	October	UK	Public Health England release guidelines allowing drug services to issue THN without prescription
	November	USA	FDA approves a first naloxone nasal spray product
2016	February	Australia	Injectable naloxone becomes available over-the-counter
	April	Int'l	UNGASS 2016 includes naloxone in its scientific summary
	October	Canada	Health Canada approves naloxone nasal spray product without prescription requirement
	October	USA	FDA convenes meeting to discuss naloxone dosing standards

Table 2 | Key statements from the 2000 UK ACMD report, as they relate to target audiences involved in the prevention of opioid overdose deaths

Target audience	Statement
Opioid users and peers	<p>"We believe that heroin and other opioid users, who are most likely to be witnesses to their friends' overdoses, should be given guidance on what to do in those circumstances." (p. 80)</p> <p>"[N]aloxone should be made more generally available, for example, to those who are likely to witness opioid overdoses. This would involve a supply of the drug being kept at home, and advice being given to friends and partners of the drug users on its emergency use." (p. 80)</p> <p>"If it was accepted that this wider availability of naloxone was desirable there would be a need to ensure, through training, that the drug was administered correctly and in the right circumstances; that it was seen only as part of a larger resuscitative response; that fresh supplies were regularly introduced; and that proper arrangements were in place for its prescription, including to whom it might be administered." (p. 81)</p>
Primary care	"Specific interventions available to primary care include [...] response to overdoses" (p. 78)
Emergency Departments	<p>"[H]ospitals should satisfy themselves that the arrangements [for staff training or treatment protocols] [for treating opioid overdoses] [in A & E departments] are satisfactory." (p. 79)</p> <p>"[T]he fact that [A&E departments] see overdosers who have not died and who are subsequently discharged, is an opportunity which we think must be exploited more vigorously. Many such attenders are repeat attenders." (p. 78)</p>
Ambulance / Police	<p>"Our view is that a call to a person who has overdosed should be regarded by the ambulance and police services as a <i>medical emergency</i> in the first instance, rather than as a call to the scene of a crime. It follows that we do not believe that ambulance services should, as a matter of course, inform the police when they are called to a drug overdose." (p. 79)</p> <p>"We think it is probably unrealistic to expect police forces to give a blanket guarantee that witnesses to an overdose will not be prosecuted if officers attend. On the other hand, we think that should be the general presumption." (p. 79)</p>
Police / Prisons	"[N]aloxone might also be made available to prison healthcare staff. And it should be kept at police stations which have custody suites for emergency use by medical staff and other trained personnel." (p. 80)