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The prevalence of non-fatal overdose among people who inject drugs: a multi-stage systematic review and meta-analysis

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Background: People who inject drugs (PWID) are at an elevated risk of fatal overdose in the first year after experiencing a non-fatal event. Such non-fatal events may also result in overdose-related sequelae, ranging from physical injury to paralysis. Given variation in drug markets and treatment availability across countries and regions, we may see similar variations in non-fatal overdose prevalence. Monitoring non-fatal overdose prevalence among PWID is essential for informing treatment intervention efforts, and thus our review aims to estimate the global, regional, and national prevalence of non-fatal overdose, and determine characteristics associated with experiencing such an event.

Methods: We conducted a systematic review and meta-analyses to estimate country, regional, and global estimates of recent and lifetime non-fatal overdose prevalence among PWID. Using meta-regression analyses we also determined associations between sample characteristics and non-fatal overdose prevalence.

Results: An estimated 3.2 (1.8-5.2) million PWID have experienced at least one overdose in the previous year. Among PWID, 20.5% (15.0-26.1%) and 41.5% (34.6-48.4%) had experienced a non-fatal event in the previous 12 months and lifetime respectively. Frequent injecting was strongly associated with PWID reporting recent and lifetime non-fatal overdose. Estimates of recent non-fatal overdose were particularly high in Asia and North America.

Conclusion: Around one in five PWID are at an elevated risk of fatally overdosing every year, however there is substantial geographical variation. In countries with higher rates of non-fatal overdose there is need to introduce or mainstream overdose prevention strategies such as opioid agonist treatment and naloxone administration training programs.

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Keywords: non-fatal overdose, people who inject drugs, opioid overdose, population size, injecting behavior, drug-related mortality.

Introduction

People who inject drugs (PWID) are vulnerable to experiencing a wide range of harms that can cause extensive morbidity and mortality. It is estimated that there are between 10 and 24 million PWID globally (Degenhardt et al., 2017), and the leading cause of death among this population is drug overdose (Mathers et al., 2013). Due to the rapid onset of intoxication, PWID are more vulnerable to overdose than people who use drugs through other routes of administration (Degenhardt et al., 2011; Hickman et al., 2003; Kaye & Darke, 2004). Thus, monitoring the prevalence of non-fatal overdose among PWID should be key in informing the introduction and appropriate scale-up of interventions that aim to reduce mortality and morbidity (Britton, Wines, & Conner, 2010; Caudarella et al., 2016; Evans et al., 2012; Martins, Sampson, Cerda, & Galea, 2015).

Cocaine, opioids and non-opioid analgesics are most commonly associated with overdose, compared to other substances (Martins et al., 2015). Opioid overdose is characterized by depressed respiration, loss of consciousness and cyanosis (White & Irvine, 1999). Stimulant toxicity, however, may result in arrhythmias, severe tachycardia, increased body temperature, tremors, severe anxiety, agitation, or panic, chest pain, nausea, vomiting, palpitations, seizure or stroke (Karch, 1996; Kaye & Darke, 2003; Vasica & Tennant, 2002). Due to the relatively short half-life of cocaine and other stimulants, the effects of a stimulant overdose are often brief and may not be interpreted as such. Further, polydrug use is typical among PWID and toxicity from a number of drugs is common in overdose presentations (Di Rico, Nambiar, Stoove, & Dietze, 2018). Mortality due to overdose, or poisonings, is often captured in routinely collected data in most developed countries. We therefore have a broad and accurate understanding of the rates of overdose fatality in the general population, but limited understanding of non-fatal events.

Non-fatal overdose is a major risk factor for both subsequent fatal overdose and morbidity (Boyes, 1994). Opioid overdose is associated with sequelae such as physical injury, peripheral neuropathy, paralysis, vomiting and chest infections (Warner-Smith, Darke, & Day, 2002; Warner-Smith, Darke, Lynskey, & Hall, 2001). A sizable proportion of PWID (up to 80%) who overdose on opioids are impacted by one or more of these sequelae (Warner-Smith et al., 2002). It is difficult to assess whether cocaine overdose results in morbidity distinguishable from chronic cocaine use (Kaye & Darke, 2003, 2004; Kontos, Jesse, Tatum, & Ornato, 2003; Vasica & Tennant, 2002),

however both are associated with cardiovascular complications, hyperthermia, and vasospasms (Connors & Hoffman, 2013; Lange & Hillis, 2001).

Ambulance data are often used to understand rates of overdose, but we know that a significant number of those who experience a non-fatal event do not receive medical help (D. Kerr, Dietze, Kelly, & Jolley, 2009). This is where self-report data from PWID are critical in terms of understanding experience of overdose, both personal and witnessed events. A recent systematic review has attempted to synthesize the literature on this topic, however was limited to data from peer-reviewed studies with PWID sampled in Western countries between 1993 and 2006 (Martins et al., 2015).

It is also important to understand the proportion of PWID who are witnessing others' overdoses and have the opportunity to intervene (e.g. through the administration of naloxone). There is good evidence that supports naloxone administration training programs and take-home kits for peers as effective overdose prevention strategies (Barocas, Baker, Hull, Stokes, & Westergaard, 2015; Chronister et al., 2018).

There is capacity for further understanding the prevalence of, and characteristics associated with, personal and witnessed overdose among PWID in countries reported on in the peer-reviewed and grey literature. Contextualizing overdose events from a nuanced geographical perspective is critical for understanding availability and coverage of interventions, such as opioid agonist treatment (OAT), naloxone administration training programs, and supervised injection facilities, to reduce overdose risk.

Thus, the specific objectives of the current review were to:

1. Estimate the prevalence of recent and lifetime non-fatal overdose among PWID by country,
2. Estimate the regional and global prevalence of non-fatal overdose among PWID,
3. Estimate the association between study level factors and non-fatal overdose prevalence,
4. Explore the relationship between non-fatal overdose among PWID and fatal overdose among all people who use drugs, and
5. Estimate the proportion of PWID who reported witnessing an overdose.

Methods

Data source

Data were drawn from our global systematic review on prevalence of injecting drug use (IDU) and sociodemographic and risk profiles of people who recently injected drugs (i.e. those who had injected within the previous year; see Degenhardt et al. (2017) for full details of methods). The protocols for the previous review were registered on PROSPERO (record numbers CRD42016052858 and CRD42016052853), and the methods were in accordance with PRISMA guidelines (Appendix 1). Briefly, we systematically searched peer-reviewed databases (Medline, Embase, and PsycINFO), internet, and grey literature, and disseminated data requests to international experts and agencies for data made available from January 2008. The peer-review literature search was updated twice, first in June of 2017 and then July 2018. We searched for data on IDU prevalence and characteristics of PWID including gender, age, blood borne viruses and sociodemographic risk characteristics, self-reported experience of overdose, self-reported witness of overdose and definitions of overdose. We did not limit our search by drug type (e.g. opioid overdose only) with the intention of looking at all definitions and comparing them. Search terms included keywords with explosions for IDU and epidemiology (Appendix 2 and 3).

For the broader review, studies were included if they presented data on any target characteristics among PWID and were not limited by language. Studies with fewer than 40 participants or samples which represented a subpopulation (e.g. HIV-positive samples or prison populations) were excluded. References were screened by three researchers; full text review was conducted by two researchers, and data from eligible studies were extracted into a database and then double checked. In this review, studies were included if data were presented on the prevalence of self-reported non-fatal overdose among PWID (further details in Appendix 4). Studies were graded by literature type and methodological quality which is outlined in Appendix 5.

Recent non-fatal overdose prevalence was the primary outcome variable and was defined as experiencing an overdose within the previous year (i.e. past 6 or 12 months). Lifetime non-fatal overdose was the secondary outcome variable. There were 11 continuous study-level variables recorded: year of data collection (only baseline data were extracted from longitudinal studies), proportion of female participants, proportion of young participants (24 years or younger), average age, duration of injecting (median and mean years of injecting were extracted as reported in the study; in the event that neither were reported we calculated the duration of injecting using age and onset of injecting

data if available), proportion of engagement in risky injecting behavior (i.e. past month receptive needle or syringe sharing), proportion injecting frequently (i.e. injecting drugs daily or more), proportion recently incarcerated (within the previous 12 months), proportion recently (within the last 12 months) or currently homeless or with unstable housing, proportion engaging in risky sexual behavior (i.e. engaged in sex without a condom within the previous year), and proportion of the sample who are currently engaged in OAT. Global region was the only country-level variable recorded.

To explore the relationship between non-fatal overdose prevalence among PWID and fatal overdose prevalence, we extracted data from the Global Burden of Disease (GBD) study that estimates the rate of deaths per 100,000 people that are due to drug use disorders (Global Burden of Disease Collaborative Network, 2018). The estimates represent fatal overdose rates among all ages in 2017.

Population size estimates of PWID who have experienced non-fatal overdose

Our data analysis approach to create country-, region-, and global-level estimates was informed by methods used in earlier reviews (Degenhardt et al., 2017). Eligible data on the prevalence of non-fatal overdose were selected and, where multiple estimates were available, pooled for each country. Data was pooled separately by timeframe: recent and lifetime. We made initial calculations of country-level pooled proportions in accordance with agreed decision rules around the selection of estimates, approaches to pooling estimates within-country, and determination of uncertainty intervals (UIs) around estimates. Prevalence estimates of non-fatal overdose were pooled via random-effects models. To estimate the number of PWID who had recently or ever experienced non-fatal overdose in each country we used previously reported country-level IDU prevalence estimates (Degenhardt et al., 2017). We multiplied the country-level IDU prevalence by the proportion of recent and lifetime non-fatal overdose (separately) among PWID and then multiplying by the country's adult (aged 15-64 years) population size. The 95% UIs were simulated using the Monte Carlo method taking 100,000 draws and, because we were estimating using proportions, we used the binomial distribution. We derived sample size estimates based on the 95% CIs and standard errors (SE) of the proportion estimates in each country. Further details are presented in Appendix 6.

Regional groupings were based on those used by the United Nations Programme on HIV/AIDS (UNAIDS), World Health Organization (WHO), and United Nations Office on Drug and Crime (UNODC). We calculated region-specific, PWID population-weighted prevalence estimates of non-fatal overdose using all the observed estimates and

95% CIs for each country within the regions. Where non-fatal overdose estimates were unavailable for more than one country in a region, we imputed the global (compared to regional) non-fatal overdose estimate for countries with evidence of IDU to generate that region's estimate. The exception was when a region had only two countries (i.e. Australasia and North America) and a non-fatal overdose estimate was available for the country that had more than 50% of the PWID population for that region. This approach was developed and used in previous global reviews (Degenhardt et al., 2017; Mathers et al., 2008). We then derived a weighted estimate and CIs, considering country population size. We used UN Population Division estimates of country population size in 2015 (age 15-64 years). We then used regional estimates to estimate the global prevalence.

Ecological analysis of variables associated with non-fatal overdose prevalence in PWID

To explore the associations between variations in the prevalence of recent and lifetime non-fatal overdose by study-level characteristics of the PWID samples, we used meta-regression analyses in STATA 15. The random effects meta-regression analyses were conducted with recent non-fatal overdose prevalence as the outcome variable, considering the within-study standard errors. We did not build models for variables that were available for 25% or fewer studies with non-fatal overdose prevalence estimates in the database, therefore current engagement in OAT was excluded as a predictor variable (n=17).

Results

The search resulted in a total of 55,692 studies, from which 75 unique studies had data on non-fatal overdose among PWID and were included in this paper. This included 40 studies with recent non-fatal overdose data, and 46 studies with lifetime non-fatal overdose data (Table 1). Appendix 7 presents the inclusion flowchart. The median years of data collection were 2013 and 2011 for recent and lifetime non-fatal overdose data, respectively. Only 10% of the estimates were nationally-representative, and only 15% had A-grade methodological quality (Appendix 8).

< Table 1 here >

Of the 75 studies included in the dataset, only 16 (21.3%) provided a definition of non-fatal overdose in the text, of which 13 (17.3%) characterized heroin or opioid overdose (e.g. loss of consciousness, turning blue, collapsing etc.). The other three (4.0%) studies that provided definitions included drug non-specific characteristics such as "heart stopping" and "thought of yourself as at risk of injury". Among the 59 (78.7%) studies that did not provide definitions of overdose, seven (9.3%) asked about heroin or opioid overdose specifically, seven (9.3%) asked

samples who use heroin or opioids, and 45 (60.0%) gave no indication of the type of drug overdose the study might be referencing. There were no studies that asked about stimulant, or other non-opioid drug class, overdose.

Out of 179 countries with evidence of IDU, data on prevalence of recent and lifetime non-fatal overdose among PWID were available for 26 and 29 countries, respectively (Table 2). Globally, we estimated that 20.5% (95% CI: 15.0-26.1%) of PWID had experienced a recent non-fatal overdose, equating to an estimated 3.2 (95% UI: 1.8-5.2) million people. It was also estimated that 41.5% (95% CI: 34.6-48.4%) of PWID have experienced a non-fatal overdose in their lifetime, equating to 6.4 (95% UI: 3.6-9.9) million people (see Table 2).

< Table 2 here >

Studies suggested that PWID in Australasia (11.9% [95% CI: 7.9-16.2%]) and Western Europe (15.6% [95% CI: 14.1-17.2%]) experienced the lowest rates of recent non-fatal overdose. Estimates were highest in Central Asia (25.4% [95% CI: 21.6-29.5%], and East and Southeast Asia (23.5% [95% CI: 19.5-27.9%]). East and Southeast Asia, North America, and Eastern Europe made up nearly two thirds of the estimated number of PWID who had recently overdosed (0.9 [95% UI: 0.7-1.2], 0.5 [95% UI: 0.2-0.9], and 0.5 [95% UI: 0.2-1.0] million people respectively). We found that the lowest point estimates for recent non-fatal overdose were Thailand (2.9% [95% CI: 1.3-5.7%]) and Moldova (4.8% [95% CI: 3.5-6.1%]) (see Appendix 9 for national estimates). The Central Asian countries all had estimates above the global estimate (Kyrgyzstan, 23.7% [95% CI: 20.1-27.6%]; Kazakhstan, 24.1% [95% CI: 20.4-28.0%]; Tajikistan, 34.1% [95% CI: 29.6-38.8%]), and Viet Nam had the highest estimate for recent non-fatal overdose among PWID (36.1%, 95% CI: 30.7-41.9%).

< Figure 1 here >

< Figure 2 here >

Lifetime experience of non-fatal overdose was lowest in East and Southeast Asia (34.4% [95% CI: 29.6-39.4%]) and Western Europe (40.7% [95% CI: 33.3-48.4]). Estimates were highest in Australasia (Australia; 51.4% [95% CI: 40.1-62.7%]), Central Asia (50.3% [95% CI: 46.4-54.2%]) and Sub-Saharan Africa (49.8% [95% CI: 42.6-57.0%]). Again, East and Southeast Asia, Eastern Europe and North America accounted for the largest number of recent PWID who have ever experienced a non-fatal overdose (1.4 [95% UI: 1.0-1.8], 1.3 [95% UI: 0.6-2.1], and 1.1 [95% UI: 0.4-1.9] million people respectively).

The results of the meta-regressions on recent non-fatal overdose are presented in Table 3, and study-level data characteristics and definitions of overdose are presented in Appendix 8. We found that studies with higher percentages of PWID with frequent injecting (meta-regression coefficient = 0.18, 95% CI: 0.09-0.26, $p<0.001$), homeless/unstable housing ($\beta = 0.30$, 95%CI: 0.14-0.46, $p=0.001$), and younger ($\beta = 0.18$, 95%CI: 0.01-0.36, $p=0.04$) samples were positively associated with the prevalence of non-fatal overdose. Duration of injecting ($\beta = -0.01$, 95%CI: -0.01-0.00, $p=0.039$) and year of data collection ($\beta = -0.01$, 95%CI: -0.02-0.00, $p=0.010$) were associated with lower prevalence of recent non-fatal overdose. Compared to Eastern Europe, Asian ($\beta = 0.14$, 95%CI: 0.05-0.22 $p<0.002$) and North American ($\beta = 0.11$, 95%CI: 0.05-0.17, $p=0.001$) studies had higher prevalence estimates of recent non-fatal overdose. Age, gender, injecting and sexual risk behaviours, and recent incarceration of the sample were not associated with recent non-fatal overdose. Prevalence of lifetime non-fatal overdose was associated with frequent injecting ($\beta = 0.19$, 95%CI: 0.05-0.33 $p=0.010$); samples with higher prevalence of frequent injecting had a higher prevalence of PWID reporting lifetime non-fatal overdose (Appendix 10). All other variables were not significantly associated with lifetime non-fatal overdose prevalence.

< Table 3 >

To illustrate the relationship between non-fatal overdose and fatal overdose, we plotted our available country-level prevalence estimates against drug use disorder death rate (per 100,000 people) data sourced from the GBD study (Figures 3 and 4). The graphs suggest a weak, but positive relationship between non-fatal overdose and drug use disorder deaths.

< Figure 3 here >

< Figure 4 here >

There were 11 studies that asked PWID whether they had witnessed an overdose. Results were varied: the proportion of PWID who reported witnessing an overdose in their lifetime (five estimates, from Spain, Viet Nam and the USA) ranged from 45.0% to 76.3%. The proportion of PWID who had recently (previous six or 12 months) witnessed an overdose ranged from 22.1% to 84.0%, however, outside of Australia all estimates were above 45% (Appendix 11). Due to a small number of estimates for each time frame we did not pool the available estimates of the proportion of PWID who had witnessed an overdose.

Discussion

This review builds on a body of work investigating the epidemiology of IDU and is the first quantification of non-fatal overdose prevalence among PWID. Using studies from 41 countries we estimated that around one in five PWID, or 3.2 million people, have experienced an overdose in the previous year, and that one in three PWID have ever experienced an overdose. There is large variation in non-fatal overdose rates between and within major global regions. Notably, studies from North American and Asian countries recorded higher rates of non-fatal overdose compared to other regions. Higher levels of recent non-fatal overdose were associated with younger participants, higher levels of daily or more injecting, and higher levels of homelessness among samples. We undertook some exploratory analyses to see whether the published non-fatal overdose estimates were associated with the modelled drug-related fatalities reported in the GBD study and found that the trend of the former mapped onto the latter.

The prevalence estimates presented are consistent with findings from a previous systematic review investigating fatal and non-fatal overdose among people who use drugs (Martins et al., 2015). They found that among samples of PWID, recent non-fatal overdose ranged from 6.7% to 32.7% (compared to 20.5%, 95%CI 15.0-26.1%) and lifetime non-fatal overdose ranged from 29.0% to 59.0% (compared to 41.5%, 95%CI: 34.6-48.4%). Unlike the present review, they only included studies from the UK, the USA, Russia and Canada and most of the included data were collected before 2005.

Our findings also highlight that overdose is associated with elevated exposure to other risks and harms (Fairbairn et al., 2008; T. Kerr et al., 2007). Interestingly, younger and more inexperienced samples of PWID had higher prevalence of non-fatal overdose, however there is evidence to suggest that older PWID with longer injecting careers are at a higher risk of fatally overdosing (Brady, Giglio, Keyes, DiMaggio, & Li, 2017; Darke, Ross, Zador, & Sunjic, 2000; Darke & Zador, 1996).

Our findings may be used to investigate the extent to which PWID are at risk of morbidity and mortality associated with non-fatal overdose. An Australian study found that more than 80% of PWID who had overdosed on heroin had experienced at least one sequelae, a large proportion of those due to physical injuries sustained when falling while comatose (Warner-Smith et al., 2002). With respect to mortality, the ratio of non-fatal to fatal heroin overdose has been measured at 31.3:1 (Darke, Mattick, & Degenhardt, 2003). If we consider these results in conjunction with findings from this study, it may be that over 2.5 million PWID are living with overdose-related morbidity and

100,000 are dying from overdose each year. Although coarse, we can compare this to the Global Burden of Disease study that estimated over 160,000 people died from overdose and other drug-related deaths in 2017 (Gakidou et al., 2017). Thus, PWID may be making up a sizable proportion of people who die from overdose every year.

The financial burden of overdose on the community is significant. For example, studies analysing emergency department data consistently show that presentations of opioid overdose are increasing in the USA (Calcaterra, Glanz, & Binswanger, 2013; Hasegawa, Espinola, Brown, & Camargo, 2014; Jones & McAninch, 2015; Martins et al., 2015). These presentations equate to nearly $100 million USD for heroin overdose, and over $600 million USD for opioid overdose every year (Hsu, McCarthy, Stevens, & Mukamal, 2017). In Australia, it was estimated that annual ambulance call outs for overdose cost around $1 million AUD in 1997-98 (Dietze, Cvetkovski, Rumbold, & Miller, 2000).

Intervention efforts have been implemented to reduce the financial burden of overdose. Studies from Europe, the USA and Russia have conducted cost-benefit analysis on naloxone training distribution to increase treatment of overdose and prevent fatalities (Coffin & Sullivan, 2013a, 2013b; Langham, Wright, Kenworthy, Grieve, & Dunlop, 2018). It was repeatedly found that distributing naloxone to adults at risk of witnessing an overdose (i.e. PWID or friends and family of PWID) with training was highly cost effective across settings (Coffin & Sullivan, 2013a, 2013b; Langham et al., 2018). We found that around half, and up to 84%, of PWID reported recently witnessing an overdose. These data reflect participants who have witnessed at least one overdose and likely underestimates the capacity there is to prevent fatalities by training and equipping PWID with overdose prevention strategies. Naloxone administration training programs are also considered useful and effective by PWID, one study found that there was a 43% increase in PWID self-perceived ability to inject naloxone into someone who was overdosing (Chronister et al., 2018).

Other intervention efforts that reduce the risk of overdose and the morbidity associated with non-fatal overdose include OAT programs, and supervised injection facilities. OAT is a necessary intervention to reduce the risk of overdose (Davoli et al., 2007; Schwartz et al., 2013; Sordo et al., 2017); however, many countries are yet to introduce OAT or have only very low levels of coverage (Larney et al., 2017). There was not enough statistical power to investigate the relationship between study-level OAT engagement and non-fatal overdose, however future research is encouraged to see if OAT also reduces the risk of non-fatal events. Supervised injection facilities have

been implemented in 10 countries, including Australia, Canada and in Europe (International Network of Drug Consumption Rooms, 2015). These facilities aim to assist in reversing overdose events in real time (Wood, Kerr, Montaner, et al., 2004). They have also been successful in acting as low-threshold targets for drug treatment services (Kimber et al., 2008), and decreasing public injecting, public overdosing, and ambulance callouts for overdose (T. Kerr, Tyndall, Li, Montaner, & Wood, 2005; Madah-Amiri et al., 2018; Salmon, Van Beek, Amin, Kaldor, & Maher, 2010; Wood, Kerr, Small, et al., 2004).

Finally, stimulant overdose is relatively unexplored compared to opioids. Most studies (60%) did not include definitions of "overdose", and we found that 36% of studies either defined heroin or opioid-specific overdose characteristics, asked about heroin- or opioid-overdose, or asked samples specifically using heroin or opioids. It is likely, however, that many PWID have either experienced or witnessed a stimulant overdose. Unfortunately, there were no included data sources that specified overdose due to non-opioid drug types, therefore we could not compare the difference in prevalence across overdose types. Future research investigating overdose by different drug classes as well as drug combinations remains important for informing harm reduction, medical and emergency services. Knowledge about the characteristics of a stimulant overdose need to be communicated to this community, as has been done with recognising an opioid overdose, so that interventions may be developed and implemented as we progress to reduce overdose fatalities.

Our review was subject to several limitations. Firstly, non-fatal overdose is biologically complex and there is no clear universal definition that encompasses all drug classes. We found that most studies implicitly refer to opioid overdose when surveying PWID, however, we know that stimulant injecting makes up a substantial proportion of IDU in many countries including Czechia, Denmark, Serbia, Slovenia, Thailand, Puerto Rico, and Nigeria (Degenhardt et al., 2017). Knowledge of opioid overdose symptoms is generally good among people who use drugs (Chronister et al., 2016; Mcgregor, Darke, Ali, & Christie, 1998; Nielsen et al., 2018), however, it remains unclear whether they can equally identify the characteristics of a stimulant overdose. Further, a clear definition is necessary for investigators so as not to underestimate the prevalence of stimulant or polydrug overdose. Future studies are needed to provide universal definitions for non-fatal overdose for different and combined drug classes, and when studies employ definitions of non-fatal overdose it is important that they report them in their publications.

Secondly, the estimates were limited by the data available. Some countries had robust, recent estimates from multiple studies with substantial geographical variation, such as those in Australasia, North America and Europe. Other regions lacked data and were driven by one or two countries with less sub-national geographical variation, such as Latin America, East and Southeast Asia and Central Asia. Countries in Sub-Saharan Africa, the Middle East and North Africa, the Caribbean, and the Pacific Islands had very little or no data at all. These regions include countries with the highest population size estimates of non-fatal overdose. These high rates may be driven by the riskier nature of IDU in that country (or by the sub-region within a country), in so much that injecting is more prevalent in that country and therefore has been targeted for this type of research. Therefore, we may have overestimated the pooled regional prevalence of non-fatal overdose if studies were only conducted in a small number of high-risk locations within the region. It may also be likely, however, that neighbouring countries are experiencing similar rates of overdose but there are few resources to investigate the prevalence of this issue. For example, in South Asia, Iran has the highest prevalence rate of recent non-fatal overdose and is the only country in that region with an estimate. In other countries within South Asia where we know the size of the PWID population, but do not know the prevalence rate of recent non-fatal overdose, the prevalence rates were imputed based on the global prevalence rate for the purpose of deriving the pooled regional estimate. However, if the other countries in south Asia are experiencing non-fatal overdose in similar proportions to Iran, then we have grossly underestimated the regional prevalence.

Our review was limited to looking at country-level data, when we know that there can be substantial variation within a country. For example, in the USA, there were eligible studies with estimates of recent non-fatal overdose ranging from 9% in San Francisco to over 50% in Boston (Leon, Cardoso, Mackin, Bock, & Gaeta, 2018; Robinson et al., 2017). Similarly, pooling studies in Viet Nam reporting on lifetime non-fatal overdose resulted in a lower estimate than recent non-fatal overdose in our results. This is an artefact of using different studies to generate estimates for these two different outcomes that are temporally nested. Also, to have as complete data as possible we included all studies that were published since 2008, which included data that were collected from 2002 onward. The risk of non-fatal overdose varies over time according to many factors, including drug market characteristics and the introduction of harm reduction interventions (such as naloxone administration training and prescriptions), which was not captured in this review. The recent overdose epidemic has been well documented in the United States and Canada, for example (British Columbia Coroner's Service, 2018; Centers for Disease Control and Prevention (CDC), 2015;

United Nations Office on Drugs and Crime (UNODC), 2018). It may be likely, therefore, that our results are not representative of the current climate and are in fact an underestimate due to the rises in overdose that have occurred more recently.

The meta-regression analyses resulted in several inconsistencies with what we know about overdose. For example, recent incarceration was not associated with non-fatal overdose prevalence, but younger age and shorter injecting careers were associated with overdose. This is surprising given that older age, longer injecting careers and recent prison release are frequently reported as risk factors for fatally overdosing (Binswanger et al., 2007; Brady et al., 2017). One explanation might be that our findings represent a survival bias; in so much that survivors of overdose events are more likely to enter into and be captured in a study. This complicates identifying those individuals at elevated risk and in need of targeted harm reduction through this methodology.

Finally, our results may be an under-estimate due to our exclusive inclusion of self-report data. Ambulance or hospital presentation data may assist with making our estimates more reliable. However, due to the illicit nature of IDU, many PWID are concerned about calling emergency services when they are with someone who has overdosed (Chronister et al., 2016) which may mean that a limited number of non-fatal overdose presentations get recorded through these systems. If we are to rely on self-report data to inform intervention practice, it is necessary to construct and use an appropriate definition for non-fatal overdose. Employing a global definition will aid epidemiology research that aims to compare different countries and regions, and in doing so advise intervention policies accordingly.

This study is the first quantification of the global prevalence of non-fatal overdose among PWID, finding that globally over one in three have suffered a non-fatal overdose, equivalent to approximately 3.2 million people. The results in this study have potential utility for estimating service implementation of programs such as OAT, naloxone administration training, and supervised injection facilities.

Authors' Contribution

LD, SL, MH, AP, JG, PV, ML and JL conceived the conception and design of the scope and methods of the original systematic review. SC, LD, SL and AP conceived and designed the present study. All authors made substantial contributions to the acquisition of data. SC, LD, SL, AP and JG contributed to the study methods and analysis plan. SC conducted the analysis and generated the estimates. SC produced figures. SC, LD, SL and AP contributed to the

interpretation of data for the manuscript. SC drafted the first iteration of the manuscript. All authors contributed to revising the manuscript critically for important intellectual content. All authors approved the final version of the study to be published and are accountable for all aspects of the work.

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Declaration of interests

In the past three years, LD has received investigator-initiated untied educational grants for studies of opioid medications in Australia from Indivior, Mundipharma, and Seqirus. SL has received investigator-initiated untied educational grants from Indivior. AP has received investigator-initiated untied educational grants from Mundipharma and Seqirus. JG is a consultant and adviser for and has received research grants from Abbvie, Cepheid, Gilead Sciences, and Merck/MSD. MH reports personal fees from Gilead, Abbvie, and MSD. JS reports non-financial support from Gilead Sciences. All other authors declare no competing interests.

Figure 1: Prevalence of recent non-fatal overdose among people who inject drugs (color)

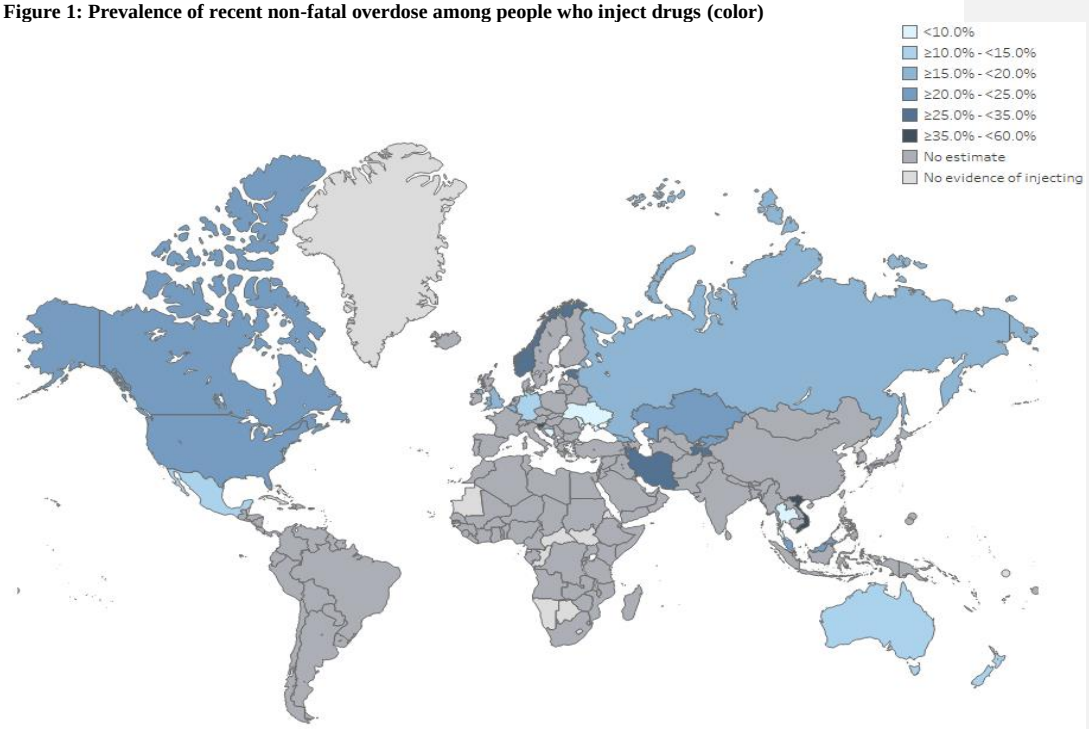

Figure 2: Prevalence of lifetime non-fatal overdose among people who inject drugs (color)

Figure 3: Estimates of recent non-fatal overdose (OD) and drug use disorder death rates reported by the GBD (2017) (color)

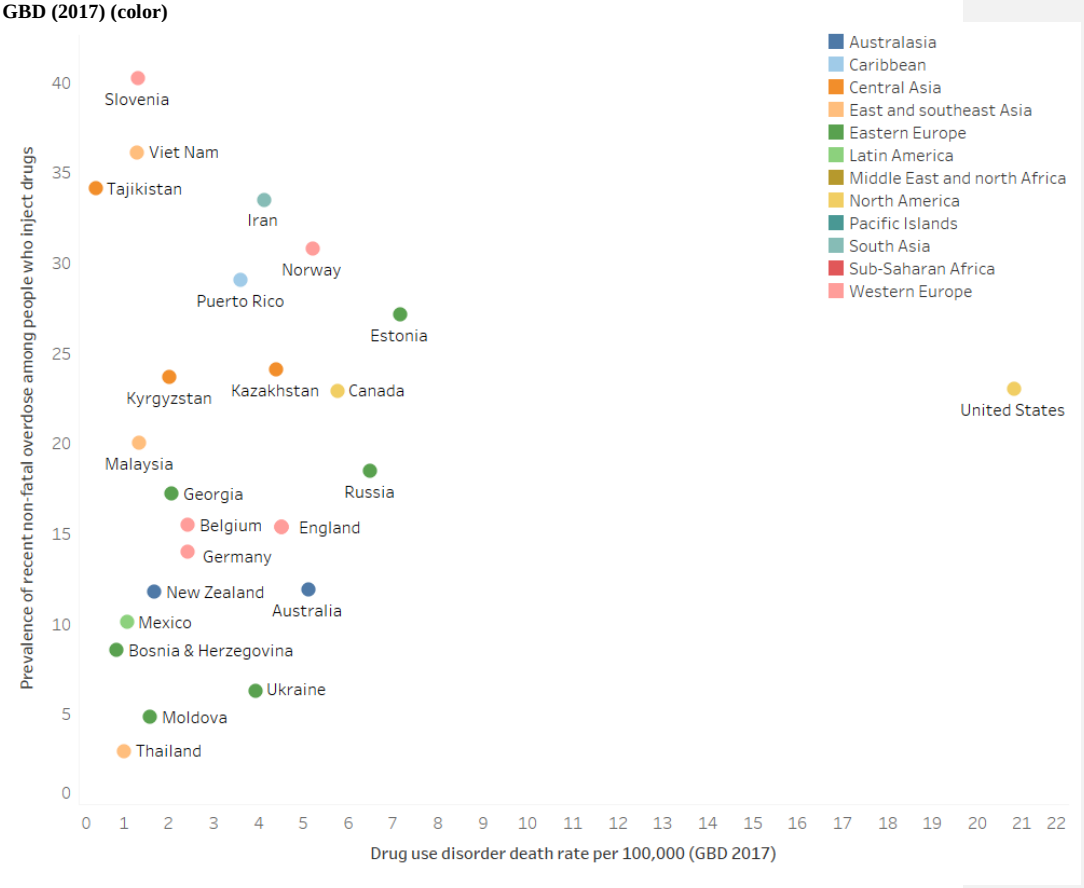

Figure 4: Estimates of lifetime non-fatal overdose (OD) and drug use disorder death rates reported by the GBD (2017) (color)

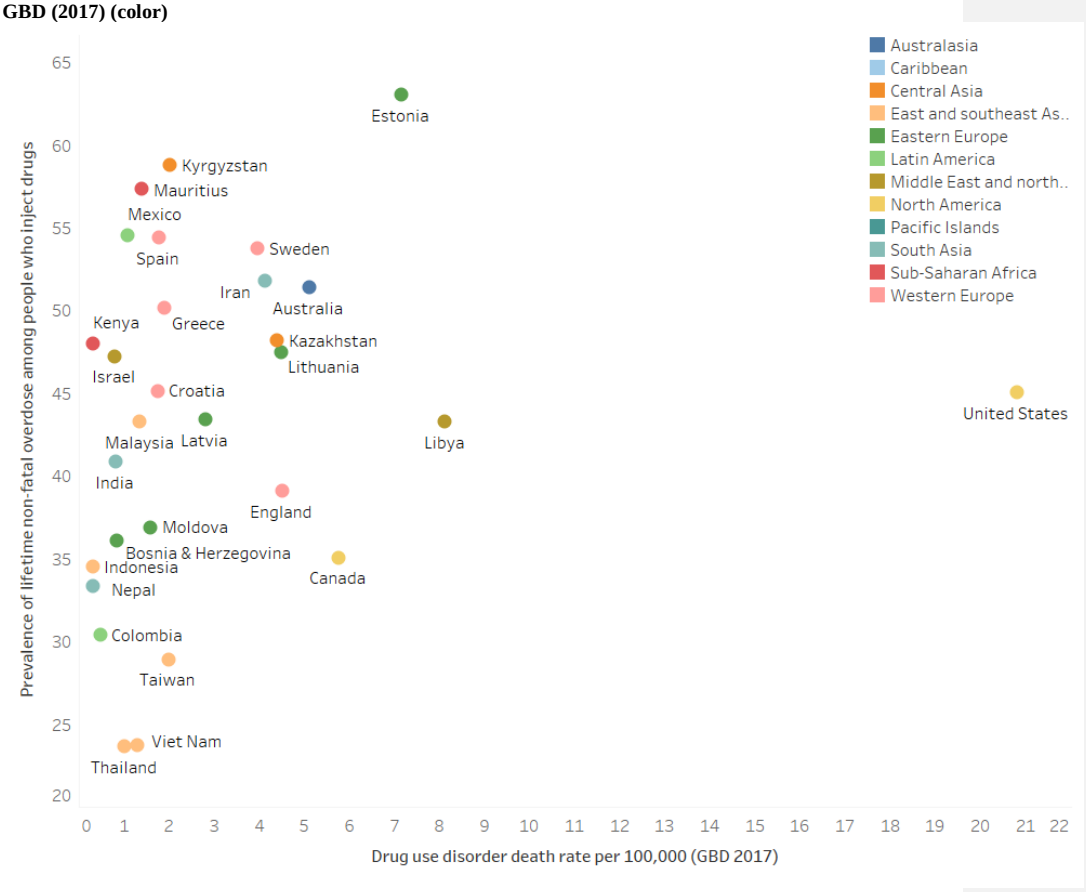

Table 1: Recent and lifetime non-fatal overdose estimates among people who inject drugs

Country	Study year	Estimate timeframe	Sample size	Estimate (%)	Reference
Australia	2002	12 months	3715	11.89	(Kimber et al., 2008; Salmon, Van Beek, Amin, Grulich, & Maher, 2009)
Australia	2006	12 months	246	5.69	(Conroy, Kimber, Dolan, & Day, 2008)
Australia	2014	12 months	99	18.00	(The Kirby Institute, 2015)
Australia	2014	12 months	761	16.00	(The Kirby Institute, 2015)
Australia	2014	12 months	70	3.00	(The Kirby Institute, 2015)
Australia	2014	12 months	490	13.00	(The Kirby Institute, 2015)
Australia	2014	12 months	228	11.00	(The Kirby Institute, 2015)
Australia	2014	12 months	69	6.00	(The Kirby Institute, 2015)
Australia	2014	12 months	436	19.00	(The Kirby Institute, 2015)
Australia	2014	12 months	225	22.00	(The Kirby Institute, 2015)
Australia	2015	12 months	888	8.20	(Stafford & Breen, 2016)
Australia	2007	Lifetime	9778	35.00	(Salmon et al., 2009)
Australia	2002	Lifetime	615	54.31	(Darke, Mills, Ross, & Teesson, 2011)
Australia	2007	Lifetime	99	61.00	(D. Kerr, Dietze, Kelly, & Jolley, 2008)
Australia	2015	Lifetime	888	41.00	(Stafford & Breen, 2016)
Belgium	2009	12 months	219	17.00	(Reitox National Focal Point, Lamkaddem, & Roelands, 2011)
Belgium	2010	12 months	251	15.00	(Reitox National Focal Point et al., 2012)
Belgium	2012	12 months	227	14.50	(Reitox National Focal Point, Plettinckx, Antoine, Blanckaert, & van Bussel, 2014)
Bosnia and Herzegovina	2012	12 months	199	8.54	(Bacak & Dominkovic, 2012)
Bosnia and Herzegovina	2012	12 months	209	11.96	(Bacak & Dominkovic, 2012)
Bosnia and Herzegovina	2012	12 months	200	12.00	(Bacak & Dominkovic, 2012)
Bosnia and Herzegovina	2012	12 months	128	3.13	(Bacak & Dominkovic, 2012)
Bosnia and Herzegovina	2012	12 months	257	8.17	(Bacak & Dominkovic, 2012)
Bosnia and Herzegovina	2012	Lifetime	199	45.73	(Bacak & Dominkovic, 2012)
Bosnia and Herzegovina	2012	Lifetime	209	35.89	(Bacak & Dominkovic, 2012)
Bosnia and Herzegovina	2012	Lifetime	200	27.00	(Bacak & Dominkovic, 2012)
Bosnia and Herzegovina	2012	Lifetime	128	21.88	(Bacak & Dominkovic, 2012)
Bosnia and Herzegovina	2012	Lifetime	257	49.81	(Bacak & Dominkovic, 2012)
Canada	2005	12 months	321	19.00	(Cox et al., 2008)
Canada	2013	12 months	272	29.04	(Shaw et al., 2015)
Canada	2011	Lifetime	115	59.00	(Leclerc, Gutierrez, Morissette, Larouche, & Gagnon, 2012)
Canada	2016	Lifetime	197	24.70	(Mitra et al., 2017)
Colombia	2011	Lifetime	237	38.30	(Berbesi Fernández, Montoya Vélez, Segura Cardona, & Mateu-Gelabert, 2011)
Colombia	2011	Lifetime	297	25.40	(Berbesi Fernández et al., 2011)
Croatia	2015	Lifetime	397	44.10	(Handanagic et al., 2016)
Croatia	2015	Lifetime	255	40.70	(Handanagic et al., 2016)
Croatia	2015	Lifetime	174	33.40	(Handanagic et al., 2016)
Estonia	2013	12 months	328	27.00	(Reitox National Focal Point, 2015)
Estonia	2005	Lifetime	331	65.86	(Talu et al., 2010)
Estonia	2007	Lifetime	350	54.86	(Uuskula et al., 2010)
Estonia	2013	Lifetime	328	68.00	(Reitox National Focal Point, 2015)
Georgia	2009	12 months	307	23.30	(Curatio International Foundation & Public Union Bemoni, 2009)
Georgia	2009	12 months	206	29.50	(Curatio International Foundation & Public Union Bemoni, 2009)
Georgia	2009	12 months	204	16.00	(Curatio International Foundation & Public Union Bemoni, 2009)
Georgia	2009	12 months	205	10.40	(Curatio International Foundation & Public Union Bemoni, 2009)

Country	Study year	Estimate timeframe	Sample size	Estimate (%)	Reference
Georgia	2009	12 months	205	15.30	(Curatio International Foundation & Public Union Bemoni, 2009)
Georgia	2015	12 months	357	6.30	(Curatio International Foundation & Public Union Bemoni, 2015)
Georgia	2015	12 months	290	8.50	(Curatio International Foundation & Public Union Bemoni, 2015)
Georgia	2015	12 months	289	6.60	(Curatio International Foundation & Public Union Bemoni, 2015)
Georgia	2015	12 months	288	9.70	(Curatio International Foundation & Public Union Bemoni, 2015)
Georgia	2015	12 months	277	8.10	(Curatio International Foundation & Public Union Bemoni, 2015)
Georgia	2015	12 months	289	11.80	(Curatio International Foundation & Public Union Bemoni, 2015)
Georgia	2015	12 months	247	5.60	(Curatio International Foundation & Public Union Bemoni, 2015)
Germany	2014	12 months	2077	14.00	(Wenz et al., 2016)
Germany	2014	Lifetime	2077	55.00	(Wenz et al., 2016)
Greece	2008	Lifetime	287	50.17	(Zavitsanou et al., 2010)
India	2013	Lifetime	891	40.85	(Ambekar, Rao, Mishra, & Agrawal, 2015)
Indonesia	2015	Lifetime	171	34.70	(Persaudaraan Korban Napza Indonesia (PKNI), 2014)
Iran	2007	12 months	1416	33.47	(Assari et al., 2014)
Iran	2007	Lifetime	887	44.40	(Amin-Esmaeili, Rahimi-Movaghar, Razaghi, Baghestani, & Jafari, 2012)
Iran	2007	Lifetime	1416	56.41	(Assari et al., 2014)
Israel	2010	Lifetime	199	47.00	(WHO, 2010)
Kazakhstan	2010	12 months	503	24.10	(Population Services International, 2010)
Kazakhstan	2013	Lifetime	600	48.18	(Rosenkranz et al., 2016)
Kenya	2012	Lifetime	150	48.00	(Syvertsen, 2014)
Kyrgyzstan	2010	12 months	520	23.70	(Population Services International, 2010)
Kyrgyzstan	2013	Lifetime	900	58.80	(Rosenkranz et al., 2016)
Latvia	2007	Lifetime	401	44.00	(Expanding Network for Comprehensive and Coordinated Action on HIV/AIDS prevention among IDUs and Bridging Population (ENCAP), 2009)
Libya	2010	Lifetime	328	40.90	(Mirzoyan et al., 2013)
Lithuania	2008	Lifetime	400	48.00	(Expanding Network for Comprehensive and Coordinated Action on HIV/AIDS prevention among IDUs and Bridging Population (ENCAP), 2009)
Malaysia	2010	6 months	460	20.00	(Bazazi et al., 2015)
Malaysia	2010	Lifetime	460	43.30	(Bazazi et al., 2015)
Mauritius	2009	Lifetime	511	25.40	(Johnston, Saumtally, Corceal, Mahadoo, & Oodally, 2011)
Mauritius	2011	Lifetime	499	82.36	(Mauritius: Ministry of Health and Quality of Life, 2011)
Mexico	2012	6 months	735	10.10	(Meacham, 2017)
Mexico	2012	Lifetime	735	54.60	(Meacham, 2017)
Moldova	2013	12 months	365	5.70	(Global Fund, 2013)
Moldova	2013	Lifetime	365	40.50	(Global Fund, 2013)
Moldova	2013	12 months	297	3.60	(Global Fund, 2013)
Moldova	2013	Lifetime	297	34.00	(Global Fund, 2013)

Country	Study year	Estimate timeframe	Sample size	Estimate (%)	Reference
Moldova	2013	12 months	363	5.30	(Global Fund, 2013)
Moldova	2013	Lifetime	363	34.10	(Global Fund, 2013)
Moldova	2013	12 months	115	0.00	(Global Fund, 2013)
Moldova	2013	Lifetime	115	40.50	(Global Fund, 2013)
Nepal	2013	Lifetime	300	33.33	(Ojha, Sigdel, Verthien, & Khadga, 2014)
New Zealand	2014	6 months	102	12.00	(Wilkins, Prasad, Wong, & Rychert, 2015)
Norway	2011	Month	1760	8.13	(Gjersing & Bretteville-Jensen, 2013)
Norway	2013	12 months	1355	30.80	(Bretteville-Jensen, Lillehagen, Gjersing, & Andreas, 2015)
Puerto Rico	2007	12 months	124	29.30	(Zerden, Marilis Lopez, & Lundgren, 2010)
Russian Federation	2010	12 months	285	7.02	(Cepeda, Niccolai, Eritsyan, Heimer, & Levina, 2013)
Russian Federation	2010	12 months	299	32.78	(Cepeda et al., 2013)
Russian Federation	2014	12 months	811	16.28	(Heimer, Lyubimova, Barbour, & Levina, 2016)
Slovenia	2008	12 months	107	40.19	(Reitox National Focal Point, 2010)
Spain	2009	Lifetime	726	54.41	(Sarasa-Renedo et al., 2014)
Sweden	2007	Lifetime	81	58.00	(Hakansson, Isendahl, Wallin, & Berglund, 2011)
Sweden	2009	Lifetime	68	48.53	(Hakansson, Isendahl, Wallin, & Berglund, 2012)
Taiwan	2013	Lifetime	827	28.90	(Yen et al., 2014)
Tajikistan	2010	12 months	431	34.10	(Population Services International, 2010)
Thailand	2009	6 months	273	2.93	(Fairbairn et al., 2012)
Thailand	2008	Lifetime	252	29.76	(T. Kerr et al., 2010)
Thailand	2009	Lifetime	738	24.00	(Prybylski et al., 2015)
Thailand	2009	Lifetime	309	17.50	(Prybylski et al., 2015)
Thailand	2010	Lifetime	202	13.37	(Visavakum et al., 2016)
Thailand	2011	Lifetime	438	27.17	(Fairbairn et al., 2015)
Ukraine	2013	12 months	5304	6.90	(Makarenko et al., 2017)
Ukraine	2015	12 months	9405	6.00	(Barska & Sazonov, 2016)
United Kingdom (exc. Scotland)	2014	12 months	3850	15.35	(O'Halloran et al., 2017)
United Kingdom (England)	2011	Lifetime	156	39.10	(Marufu, Williams, Hill, Tibble, & Verma, 2012)
United States	2006	12 months	348	43.10	(Zerden et al., 2010)
United States	2010	6 months	283	2.80	(Stephens, 2017)
United States	2009	12 months	51	31.37	(Bazazi, Yokell, Fu, Rich, & Zaller, 2011)
United States	2009	12 months	443	16.25	(Jenkins et al., 2011)
United States	2017	12 months	1943	19.40	(Glick et al., 2018)
United States	2012	12 months	512	18.80	(Robinson et al., 2017)
United States	2012	12 months	557	9.30	(Robinson et al., 2017)
United States	2012	12 months	639	15.70	(Robinson et al., 2017)
United States	2014	6 months	576	7.90	(Meacham, 2017)
United States	2015	12 months	486	21.80	(Tsui, Burt, Thiede, & Glick, 2018)
United States	2015	12 months	592	21.79	(Al-Tayyib, Koester, Langegger, & Raville, 2017)
United States	2016	Month	222	52.70	(Leon et al., 2018)
United States	2016	12 months	283	33.00	(Hunter et al., 2018)
United States	2012	Lifetime	462	31.00	(Grau, Zhan, & Heimer, 2016)
United States	2010	Lifetime	283	36.80	(Stephens, 2017)
United States	2010	Lifetime	91	54.95	(Bonar & Rosenberg, 2011)
United States	2012	Lifetime	543	30.57	(Barocas et al., 2015)

Country	Study year	Estimate timeframe	Sample size	Estimate (%)	Reference
United States	2014	Lifetime	576	41.50	(Meacham, 2017)
United States	2016	Lifetime	222	75.68	(Leon et al., 2018)
United States	2008	Lifetime	195	31.28	(Havens et al., 2011)
Viet Nam	2003	12 months	299	36.12	(Bergenstrom et al., 2008)
Viet Nam	2003	Lifetime	299	43.48	(Bergenstrom et al., 2008)
Viet Nam	2014	Lifetime	603	17.90	(Michel et al., 2017)

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Table 2: Prevalence of recent and lifetime experience of non-fatal overdose (OD) among people who inject drugs (PWID) by region and globally

	Recent non-fatal OD			Lifetime non-fatal OD		
	Number of countries with data	**Prevalence among PWID (95% CI)**	**Number of PWID who experienced recent non-fatal OD (95% CI)**	**Number of countries with data**	**Prevalence among PWID (95% CI)**	**Number of PWID who have ever experienced non-fatal OD (95% CI)**
Eastern Europe	6/17	16.6 (7-26.2)	500,500 (161,500-986,500)	5/17	41.5 (33.8-49.1)	1,252,500 (591,000-2,062,000)
Western Europe	7/33	15.6 (14.1-17.2)	157,500 (106,500-219,000)	5/33	40.7 (33.3-48.4)	410,500 (255,500-600,500)
East and southeast Asia	3/17	23.5 (19.5-27.9)	936,500 (678,500-1,234,500)	5/17	34.4 (29.6-39.4)	1,372,000 (1,013,500-1,777,000)
South Asia	1/9	22 (16.6-27.6)	225,500 (180,000-376,000)	3/9	44.6 (41.7-47.6)	456,500 (347,500-575,500)
Central Asia	3/5	25.4 (21.6-29.5)	71,500 (43,000-105,000)	2/5	50.3 (46.4-54.2)	141,500 (86,500-204,000)
Caribbean	1/15	23.2 (16.5-30.2)	18,500 (10,500-29,000)	0/15	*NK*	*NK*
Latin America	1/20	19.1 (13.5-24.9)	349,000 (229,000-518,000)	2/20	42.4 (38.6-46.1)	772,500 (560,000-1,008,000)
North America	2/2	23 (18.7-27.3)	545,000 (232,500-931,000)	2/2	44.5 (31.5-57.6)	1,055,500 (432,000-1,879,500)
Pacific Island states & terr.	0/17	*NK*	*NK*	0/17	*NK*	*NK*
Australasia	2/2	11.9 (7.9-16.2)	13,500 (8,000-20,500)	1/2	51.4 (40.1-62.7)	59,500 (39,500-82,000)
Sub-Saharan Africa	0/47	*NK*	*NK*	2/47	49.8 (42.6-57.0)	685,500 (195,500-1,383,000)
Middle East & North Africa	0/22	*NK*	*NK*	2/22	46.2 (39.6-53.0)	161,500 (85,500-251,500)
Global	**26/206**	**20.5 (15-26.1)**	**3,167,500 (1,765,500-5,161,000)**	**29/206**	**41.5 (34.6-48.4)**	**6,411,000 (3,631,500-9,887,500)**

NK: not known; [a] Among total number of countries in that region, including those without evidence of injecting

Table 3: Correlates of recent non-fatal overdose

Models on recent non-fatal overdose prevalence among people who inject drugs	N	Median value	Unadjusted models				
			β[a]	SE[b]	95% CIs	p[c]	Adjusted R^2
Study-level exposure variables							
Percentage of sample female	66	22.9%	0.01	0.10	(-0.19, 0.22)	0.918	-1.66%
Median/mean age of sample[d]	62	37	0.00	0.00	(-0.01, 0.01)	0.749	-1.61%
Duration of injecting[d]	46	16	-0.01	0.00	(-0.01, -0.00)	0.039	7.97%
Percentage of sample engaging in injecting risk behaviour	33	14.0%	0.07	0.10	(-0.14, 0.28)	0.487	-1.56%
Year of data collection	70	2013	-0.01	0.00	(-0.02, -0.00)	0.010	8.39%
Percentage of sample injecting daily or more	49	43.0%	0.18	0.04	(0.09, 0.26)	<.001	25.95%
Percentage of sample with recent incarceration	20	11.4%	0.12	0.10	(-0.08, 0.32)	0.220	3.86%
Percentage of sample who were recently homeless	23	31.4%	0.30	0.08	(0.14, 0.46)	0.001	40.03%
Percentage of sample who are young	41	11.7%	0.18	0.09	(0.01, 0.36)	0.040	8.11%
Percentage of sample who are engaging in risky sexual behaviour	35	13.8%	0.09	0.07	(-0.05, 0.23)	0.198	1.81%
Region (vs. Eastern Europe)	70						19.84%
Western Europe			0.08	0.04	(0.00, 0.16)	0.054	
North America			0.11	0.03	(0.05, 0.17)	0.001	
Australasia			0.01	0.04	(-0.06, 0.08)	0.796	
Asia (Central Asia, East and South east Asia, South Asia)			0.14	0.04	(0.05, 0.22)	0.002	
South America			0.08	0.07	(-0.07, 0.22)	0.299	

[a] meta-regression co-efficient; [b] standard error; [c] p-value; [d] reported in years

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