GUIDELINE ON POPULATION SIZE ESTIMATES OF PEOPLE WHO INJECT DRUGS AND HARM REDUCTION COVERAGE

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HA·REACT
JOINT ACTION ON HIV AND CO INFECTION
PREVENTION AND HARM REDUCTION

HA REACT Technical Report:

Guideline on population size estimates of people who inject drugs and Harm Reduction coverage

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HA·REACT
JOINT ACTION ON HIV AND CO INFECTION PREVENTION AND HARM REDUCTION

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CONTENTS

ABOUT THIS GUIDELINE

The Joint Action on HIV and Co-Infection Prevention and Harm Reduction (HA-REACT) is addressing the gaps that exist in the prevention of HIV and other co-infections, especially tuberculosis (TB) and viral hepatitis, among people who inject drugs (PWID), with a time frame of between 2015 and 2019 and with core funding from the European Union (EU).

Among the work packages (WP) of this Action, WP5 was focused on scaling up harm reduction, and one of its activities was an assessment of people who inject drugs (PWID), including epidemiology and HR interventions in selected focus countries.

This guideline has been drafted within the context of those activities and with the objective of serving as a first point of contact with PWID calculation methodologies and the subsequent measurement of that population's Harm Reduction Coverage.

The guideline compiles various sources of information, which are cited in the text. However, it must be mentioned that these sources are generally aligned with the recommendations of the EMCDDA and the WHO and their guidelines on estimating the prevalence of problem drug use in Europe and with the WHO, UNODC, UNAIDS technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users.

The sole objective of this guideline is to summarize and educate about highly useful concepts for scaling up harm reduction in any country.

PART I ESTIMATING THE POPULATION SIZE OF PEOPLE WHO INJECT DRUGS

INTRODUCTION

Estimates of the prevalence of drug use and its consequences have a major influence on many public policies. Estimating prevalence is especially important for forecasting the health needs and costs of the drug user group and for evaluating the coverage and effectiveness of treatment and of harm reduction measures.

This group is defined by three characteristics: first of all, **its members are difficult to identify** due to the fact that they share idiosyncrasies that are difficult to reveal. Second, **these populations lack a sample framework**: we know neither the size nor the distribution. Third, **it is a group whose defining characteristics are stigmatized**, socially penalized and frequently illegal (similar to other groups such as people who engage in prostitution or those who suffer from sexually transmitted diseases) (1, 2). Moreover, people in this group are commonly vulnerable from a social and health perspective, they are frequently left out of health policies, and we could even say that they are left out of society. **It is therefore very important to learn the magnitude and distribution of this group.** This is the necessary preliminary step for determining and being able to take care of the group's needs.

However, precisely because of the aforementioned characteristics, it is rarely possible to accurately determine the number of affected persons. **Conventional methods**, which are called **direct methods** and directly use original information from available sources, such as population surveys, **are not effective at determining the size of these populations**. On the one hand, the reason is because it is less likely that the group's members will be chosen by the usual sampling methods (telephone, fixed residence, health card, etc.). On the other hand, their defining characteristics are aspects of life that are not easy to reveal in a survey (3), meaning that we face a considerable information bias (Table 1).

Therefore, other available methods for estimating the size of these "hidden populations" must be used. Such methods, by making use of other data sources and making certain calculations, are capable of providing an approximate number of the individuals comprised in those populations. These methods are so-called **indirect methods.**

However, as a starting point when calculating prevalence in such hidden populations, often the only thing we know about them comes from incomplete data sources. This is why **we must resort to indirect methods**, which are based on the premise that the available data sources are not complete. These methods therefore use various calculations to estimate the actual prevalence (4).

Table 1: Main methods of direct estimation and limitations in drug users

METHOD	DESCRIPTION	LIMITATIONS
POPULATION SURVEYS	Direct questions asked of the population. The simplest method for finding information.	Difficult to find representative samples: these populations tend to have a lower probability of being chosen by the usual recruiting methods of surveys (by phone, passers-by, etc.).
POPULATION RECORDS	Information about these populations is obtained through records (normally national records): register of addicts undergoing treatment; police records of drug-related crimes; admissions at emergency medical services due to drug-related pathologies, etc.	These records are only useful for the purpose for which they were created and not for others, and therefore part of the information is lost. If we used a certain record (i.e. users receiving treatment), we cannot generalize the information from that record to all our population as a whole.
CASE SEARCH	The systematic, simultaneous use of various databases based on an appropriate case definition, therefore conducting an adequate assessment of available data sources and validating the quality of the data obtained.	The main bias is double counting of the same person due to appearing in several databases, which must be kept in mind to avoid the consequent over-estimation. Despite being the best-assessed direct method, it is not usually used directly to estimate prevalence, rather it is generally used as a preliminary phase of other methods.

Indirect methods can be classified according to various premises. Depending on the origin of the information, we can distinguish between **methods based on social networks** (this term is understood as a set of individuals who have some type of personal relationship or common interest) and **methods based on databases or records** (number of people in treatment due to drug addiction, number of drug-related arrests, number of drug-related deaths, etc.).

Moreover, depending on the type of method used for sampling, we can distinguish between **conventional methods**, in which the design is based only on information known in advance (before the study begins), and **adaptive methods**, in which the selection of persons to be included in a sample is adapted according to observations made during the study. In other words, after an initial random sample, samples of additional respondents are taken according to a respondent's responses to the questionnaire, according to the information provided about their social network or according to the geographic location of their home (Table 2).

Table 2. Classifications of the main indirect methods

According to how information is extracted	According to the type of sampling method
Based on databases • Benchmark-Multiplier method. • Capture-Recapture method. • Multivariate Indicator method. • Truncated Poisson method. • Adaptive sampling designs.	**Conventional methods** 1. Benchmark-Multiplier method. 2. Capture-Recapture method. 3. Truncated Poisson method. 4. Multivariate Indicator method. 5. Network Scale-up method.
Based on social networks • Respondent-Driven Sampling (RDS) method. • Random-Walk method. • Network Scale-up method.	**Adaptive methods** • Respondent-Driven Sampling (RDS) method. • Random-Walk method. • Adaptive sampling designs.

This chapter does not aim to elaborate on new indirect methods or conduct a comprehensive review of such methods. Rather, it endeavours to inform about and introduce methodologies used within the scope of studies on drug use, by following a simple and educational approach. Initially, the methodologies are related to PWIDs, but a few broad examples show how the they can go beyond this population. In this regard, we develop eight different indirect methods for estimating hidden populations.

THESE METHODS ARE THE MOST USEFUL
and are those applied the most in studies published to date.

1. METHODS BASED ON DATA EXTRACTION

1.1 BENCHMARK-MULTIPLIER METHOD

To apply this method, we only need **one absolute figure as the point of reference** (the so-called Benchmark) and **a related incident rate** (the multiplier). Based on these two data, the prevalence is estimated by **multiplying the Benchmark by the inverse of the multiplier.**

Let's imagine that the hidden population we want to estimate is the number of drug users in a certain city and for a certain year. To do the calculation according to this method, we could begin with the number of drug-related deaths (Benchmark) for that year and in that city (accessible and reliable data in death records). We would also need a multiplier, which in this case could be the mortality rate of drug users obtained in cohort studies of these populations. Thus, if we had 405 deaths in one year (the Benchmark) and a death rate of 2.3% (2.3 per 100 people per year), we would obtain an estimated prevalence of 17,609 people using drugs in that city in a year (5) (Figure 1).

However, when applying this method, we must keep a number of requirements in mind, which represent limitations: 1) The reference point or Benchmark must be comprehensive and be completely reliable (3, 4); 2) the sampling used to estimate the multiplier must be representative of the target population and must be obtained independently from the benchmark (3, 4); and 3) the case definition used for the benchmark must match (in time and place) that which is used to obtain the multiplier (3, 4).

When we talk about estimates of parameters, we need to know the level of uncertainty of those estimates, which must be accompanied by their standard error and/or confidence interval. However, when using the Benchmark-Multiplier method, the confidence interval could provide a false sense of security, given that many biases are possible (5).

Consequently, what some authors recommend is to compare the outcomes of this method with those of other Benchmark-multiplier studies or of other methodologies and then assess the level of concordance (5).

Figure 1: Formulation and example of the Benchmark-Multiplier method.
Source: Own preparation.

$$\text{Mortality rate of drug users (known)} = \frac{\text{number of drugs-related deaths (known)}}{\text{drug user population x time (unknown) (N)}}$$

N= number of drugs-related deaths x (1/Drug users mortality rate)

N = 405 . (1/0,023) = 405 . 43,48 = 17609

To conclude, **this method is very easy to apply, which is why it is used extensively.** However, there could be errors if the reference data are not accurate or the multiplier is not correctly defined. Moreover, the estimator is not very reliable if the target population is heterogeneous.

1.2 CAPTURE-RECAPTURE METHOD

This method allows determining the prevalence of a population based on the resulting coincidences between two or more incomplete data sources.

The more data sources we have available, the better and more comprehensive the method. However, to simplify our explanation of this method, we will present an example in which only two data sources are used.

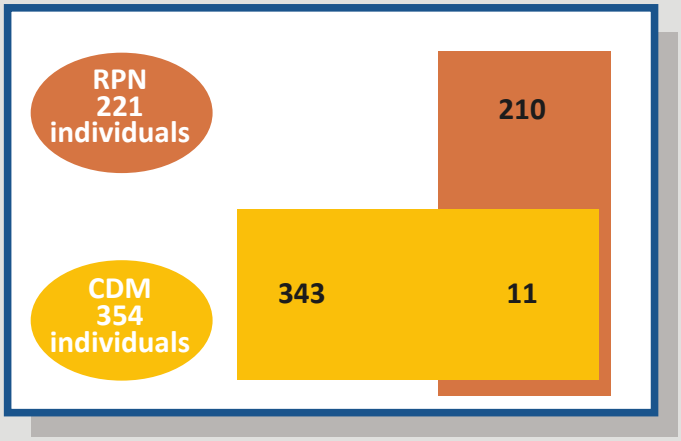
Continuing with the previous example, once again we want to estimate the number of opiate users in a certain country and for a certain year. To do so, we have two data sources that we know are incomplete. They include members of our population of interest, but we know that they only include a part of the population. One data source could be the register of a methadone clinic (CDM) and the other could be the national police records (RPN) of arrests related to opiate use. The users present in both sources would be called “m”, and the unknown population would be “N”, which we want to calculate. Thus, assuming that both data sources are independent and that the fact that someone may appear in one data source does not change the possibility of appearing in the other, the odds ratio would be equal to 1. (Figure 2). From there we can conclude that d = (b*c/a), and based on this data, we can calculate the total number of the population we want to know, which is N (N = a + b + c + d).

Figure 2: Formulation and example of the capture-recapture method.
Source: Own preparation.

$$\text{Odds Ratio (OR)} = \frac{a/b}{c/d} = 1$$

$$d = \frac{c*b}{a}$$

$$N = a+b+c+d$$



		RPN (Capture)		
		Yes	No	
CDM (Capture)	Yes	a=11	b=343	354
	No	c=210	d	
		221		N

CDM: Methadone Clinic
RPN: National Police Records
N: UNknown population
m:number of individuals that appear in both databases

Thus, if we had 354 registered users in a CDM and 221 in the RPN, and only 11 coincided in both databases, then the estimate of the population of opiate users would be 7,112 (Figure 2).

To calculate the confidence interval, we suggest using the formula offered on page 78 in the manual, "Estimating the Prevalence of Problem Drug Use in Europe", by Hartnoll et al., referring to the variance of N (our population of interest) (3).

This method also involves a series of requirements: 1) The population of reference must be closed (a fixed number of people), which is why it is advisable to use short study times of approximately one year (3); 2) the data sources must be independent (appearing in one of the sources must not mean that someone is predisposed to appear, or not, in the other) and must be representative of the population of study (3); and 3) each case in the population must have the same probability of being captured in each source (3, 5). These requirements are fairly comprehensive and difficult to achieve in their entirety. Therefore, depending on the greater or lesser extent to which they are met, we can estimate our prevalence with greater or lesser accuracy.

The possible biases to keep in mind when applying this methodology are clear: the degree of independence of the data sources and the lack of representativity. Regarding the independence of the data sources, it behoves us to point out that when working with three or more sources, we can evaluate this requirement through various data adjustment models, but this requirement cannot be assessed when working with only two sources.

After having checked for independence, if the data sources are not independent, then the fact that someone appears in one data source could represent a greater possibility of appearing in the other: this is called positive dependence, and it represents a risk of underestimating the population. Conversely, there is negative dependence when appearing in one data source decreases the possibility of appearing in the other, thereby involving an overestimation of our population (3). Regarding the representativity of data sources, it depends on the uniformity of the population under study. If our population were very heterogeneous, we could become subject to a major bias of underestimation, given that only one subgroup of this population could be represented in the data sources. This bias can be avoided by conducting an analysis according to those subgroups (3).

The capture-recapture method is also easy to apply and is used extensively in epidemiology. However, it involves some assumptions that are not always easy to achieve, and it is therefore not free from bias.

1.3 MULTIVARIATE INDICATOR METHOD

This method estimates of the size of a population by using information from populations for which there are data (calibration population) and extrapolating it to the population that we want to calculate (target population). And it does so through variables of interest that are in both populations (14). This is done through the relationship that exists between the study variable and other variables that are related to it.

To understand this better, we'll use an example, as in the preceding methods. If we would like to estimate the prevalence of drug users in a country, we would need to have information on a set of indicators related to drug use (for example, the number of people receiving treatment for drug addiction, the number of drug-related arrests, the number of drug-related deaths, etc.) in all the regions into which the country is divided. These indicators are called predictors. Moreover, we'll need to know the prevalence of drug use in some of these regions (calibration populations), which we will call anchor points (14, 15). Once this information is known, a relationship is established between the anchor points and the predictors using a least squares regression (14), thereby allowing us to estimate the prevalence of drug use in the regions where this information is deficient.

Finally, the prevalence of drug use in the entire country would be estimated by totalling the estimates of the regional prevalence (14).

Thus, if we have complete data on the prevalence of drug users in the community of Madrid, such as the number of people who are receiving treatment for this addiction or the number of arrests or of deaths related to substance use, then we could infer what is happening in other communities where we only have partial information.

The key point of this method, therefore, is making the correct association between the information we want to estimate (i.e. number of drug users), which would be our "dependent variable", and the predictors in our calibration sample (i.e. number of people receiving treatment for drug use, number of drug-related arrests, etc.), and this association must be transferable to all other areas (15, 16). In other words, if there is a relationship between the size of a population and several of its indicators, then whenever we don't know this size, we can use the indicators to infer it.

This method is not free from limitations. The assumption of the existence of a linear relationship between unobserved prevalence and observed indicators is the main component to be assessed (14). Moreover, other factors could be influencing the indicators and could invalidate the assumption of linearity. Continuing with the aforementioned example, we could think that an increase in the prevalence of drug users would lead to a growing number of addicts receiving treatment. However, the number of addicts receiving treatment could be restricted by the capacity of treatment services. For the best possible application of this method, the comparability of the indicators between the target population and the calibration population must be carefully analysed. In this same sense, the reliability and validity of the anchor points are crucially important to the estimate.

If estimates are obtained using different techniques or they refer to different time periods, then they can represent different populations of drug users, and this would have an influence on the validity of the national estimate (14). This validity can be improved by increasing the number of anchor points (15), which is also useful considering that the number of anchor points must be higher than the number of indicators because otherwise it wouldn't be possible to establish a regression between them (15).

We must attempt to minimise all these limitations when applying this method, given that, even though we are dealing with inferences and estimates, which always implicitly involve a margin of error, our objective is to make that error as small as possible so that we can have an approximation that is as close as possible to reality.

All these aspects must be taken into account if we decide to use this method. The method is easy to apply if we have the necessary data, but we must assess the suitability and accuracy of the method so that any possible biases are minimised and we thus obtain a valid and comprehensive estimate.

There are a number of practical examples in which this methodology has been applied, which can help to better understand it (14, 15).

1.4 TRUNCATED POISSON METHOD

This method allows making an estimate based on a single source of data that we know is incomplete. In this source, we'll know the individuals who have had contact with a certain service (such as a needle exchange program or a sexually transmitted disease clinic) and the number of times that they have had contact. The Truncated Poisson model allows inferring the population that has never had contact with that service based on the data on individuals who have had contact. In other words, through the number of individuals who have had contact once, the number who have had contract twice, the number who have had contact three times and so on, it is possible to estimate the number of individuals who have not had contact on any occasion (7, 8).

The Truncated Poisson method has several variants, although the one used the most is the Zelterman equation (9). (Figure 3). In our example, we use the database of a unit that dispenses sterile syringes and needles, which is composed of 403 heroin users and a total of 721 contacts over the course of 1 year. Of the 403 individuals, 247 have gone only once, 90 have gone twice and the remainder have gone three or more times. By replacing the parameters in the main equation (Figure 3), we can estimate a total population of 779 injected heroin users. (Figure 4).

To calculate the confidence interval for this method, we refer to other works (10, 11).

The requirements of this method are the following: 1) The probability of contacting with the data source is the same for all individuals; 2) that probability is independent from the number of times that there was previous contact; and 3) the population is uniform (7, 8).

Figure 3: Formulation of the Truncated Poisson method.
Source: Own preparation.

$$\check{N} = \frac{S}{1 - e\ xp\ (-\ 2f_2 / f_1)}$$

$$\check{N} = \frac{721}{1 - e\ xp\ (-\ 2x90 / 247)}$$

$$\check{N} = \frac{721}{1 - 0\ ,483}$$

$$\check{N} = 1395$$

ZELTERMAN EQUATION

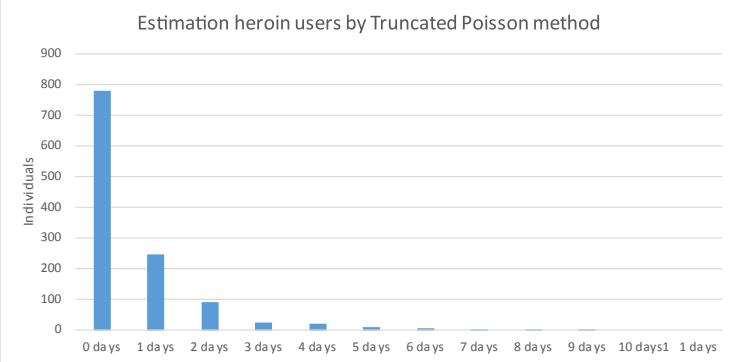
Ň = Hidden population size

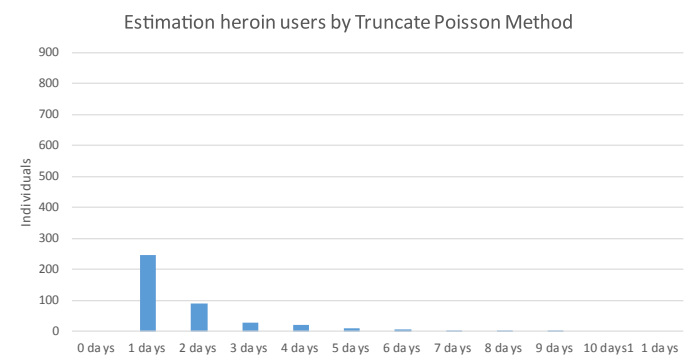
S = summation of all frequencies (events)

f2 = number of individuals who are registered twice

f1 = number of individuals who are registered once

Figure 4: Example of the Truncated Poisson method.
Source: Own preparation.





1.5 ADAPTIVE SAMPLING DESIGNS

Adaptive methods are those that, after an initial random sample, progressively include respondents according to their responses and the information compiled during a study. In this particular case, adaptation is based on location, given that researchers use geographic relationships between people to find others to be included in the sample.

There are several adaptive sampling designs.

Adaptive assignment method: the starting point is a sample obtained using a conventional design, such as simple or stratified random sampling. Subsequently, the sample is examined to search for evidence that some geographic areas show more behaviours of

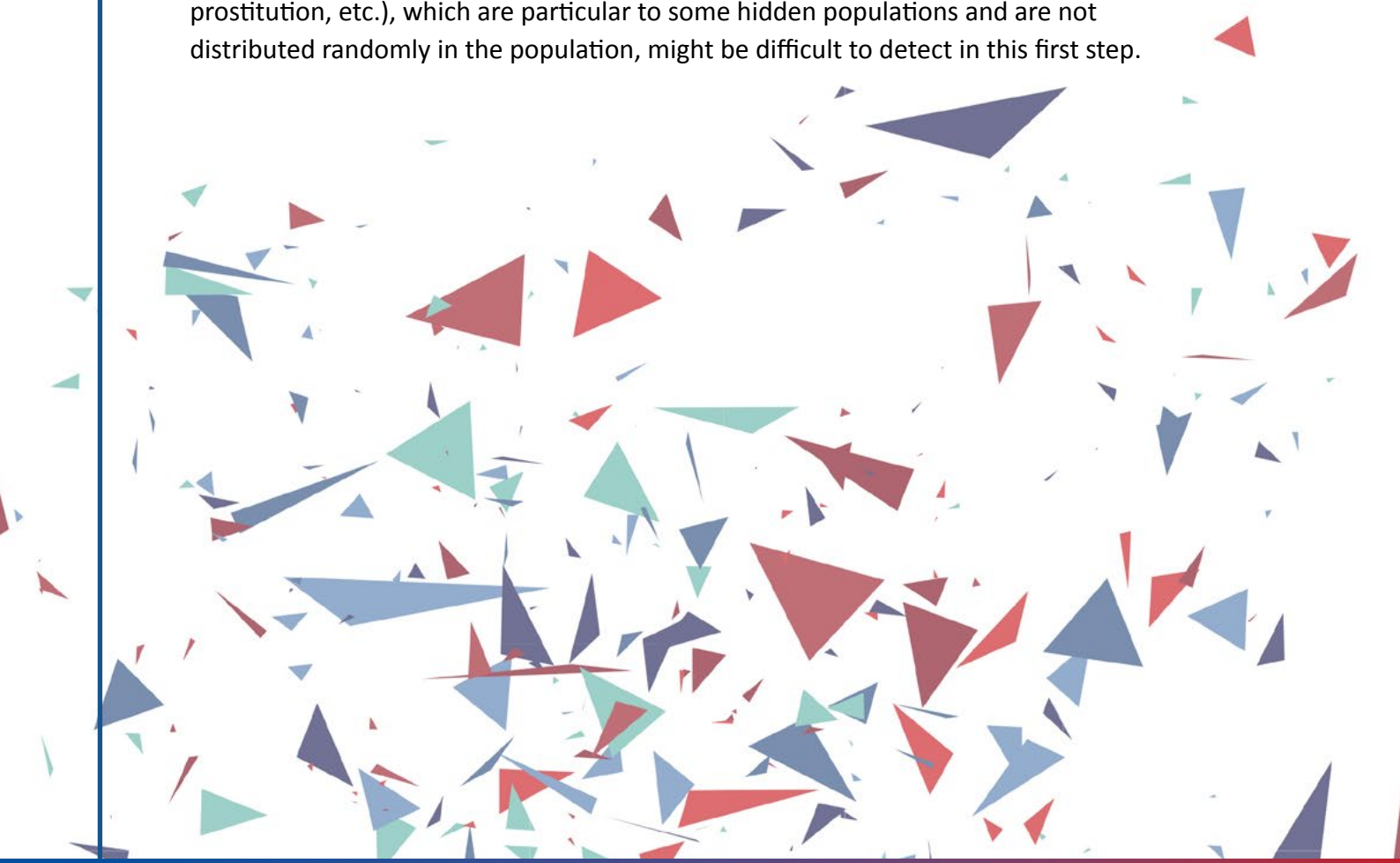
interest than others, depending on the observed values in some key variables. Sampling then continues by concentrating on those areas (24).

Once again following the example used in the preceding methodologies, if we want to know the number of youths who are at risk of becoming drug users, an initial stratified random sample can be taken, which measures the key variables that are known to indicate the risk of onset of drug use (first contact with "soft" drugs, beliefs about the regulatory levels of drugs, etc.). Then, in geographic areas where a high concentration of risk appears, more sampling resources are assigned, and a larger sample is taken to continue with the study (24).

Adaptive cluster sampling: as with the preceding model, an initial sample is selected using a conventional sampling design. When we find an individual who shows our variable of interest, the units (house, school, family, etc.) of the neighbourhood of that individual are added to the sample. In turn, if an individual of any of the added units satisfies the condition, then even more units are added, and so on (24).

For example, a study on people who use drugs could begin with a random sample of homes. Whenever a home contains a person who uses drugs, then samples of the neighbouring houses will be taken. If, in turn, any of these houses contains a person who is a drug user, then samples of their neighbouring houses will be taken, and so on.

However, **these methods have a major limitation: they both begin with a random sampling.** We could therefore find that the variables of interest (drug use, HIV, prostitution, etc.), which are particular to some hidden populations and are not distributed randomly in the population, might be difficult to detect in this first step.

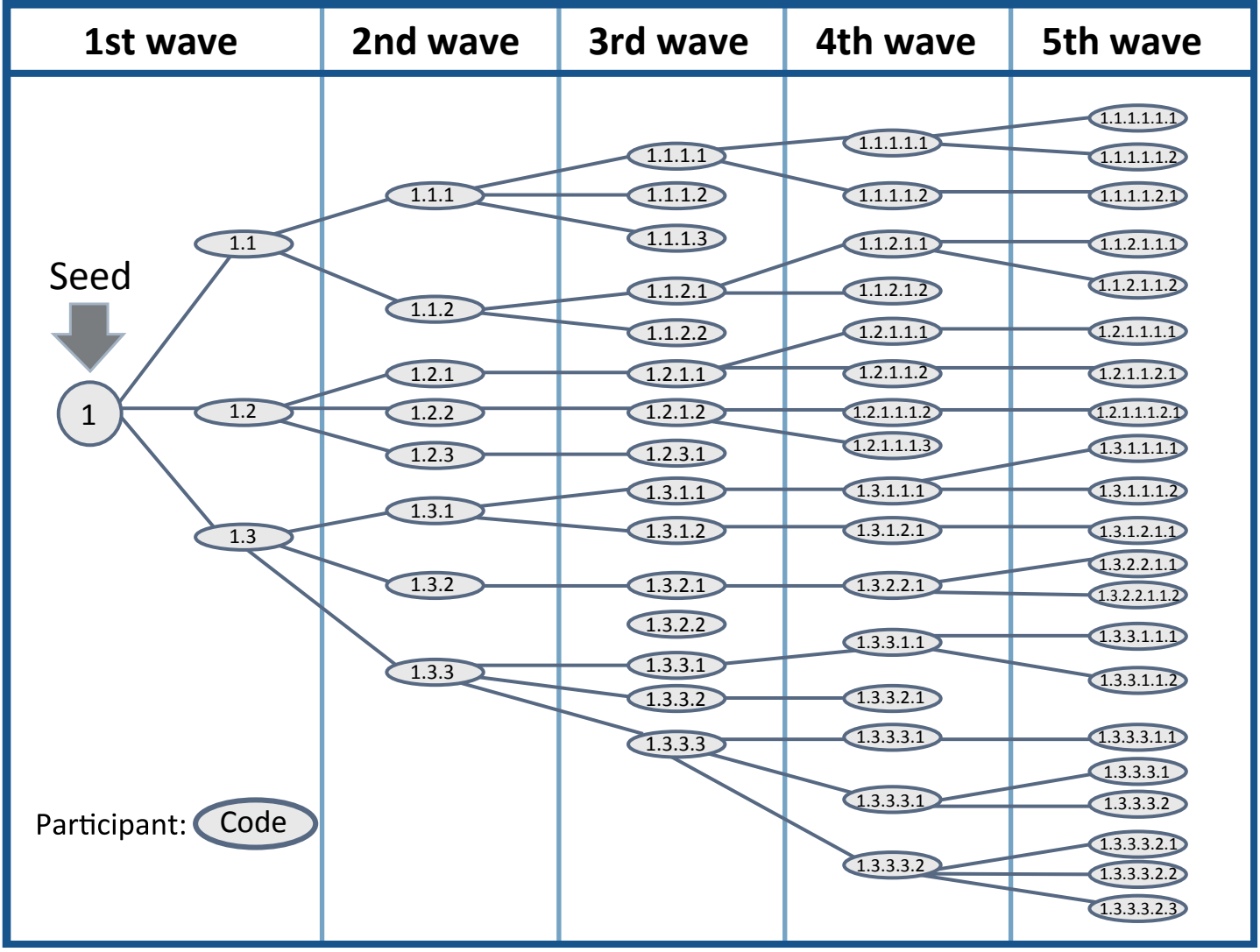


2. METHODS BASED ON SOCIAL NETWORKS

2.1 RESPONDENT-DRIVEN SAMPLING (RDS) METHOD

This is a variant of chain or snowball sampling. This model attempts to establish a protocol for the sampling and obtain non-biased estimators that can be generalised to the population as a whole. The sampling begins with a selection of initial informants (seeds), similarly to the snowball method, who will not be included in the subsequent analysis. These seeds, in turn, select a limited number of new respondents, and so on. Each group of respondents derived from a seed is a chain, and the recruited group of each stage is a wave (figure 5). A sufficient number of waves will be generated so that the different variables that could lead to confusion are stabilised and the sample obtained is representative of the population (1, 2).

Figure 5: Schematic presentation of the respondent-drive sampling method



Source: Sordo L, Pérez-Vicente S, Rodríguez del Águila MM, Bravo MJ. Respondent-driven sampling for the study of difficult access populations Med Clin (Barc) [Internet]. 2013;140(2):83–7.
Available from: http://linkinghub.elsevier.com/retrieve/pii/S0025775312007087

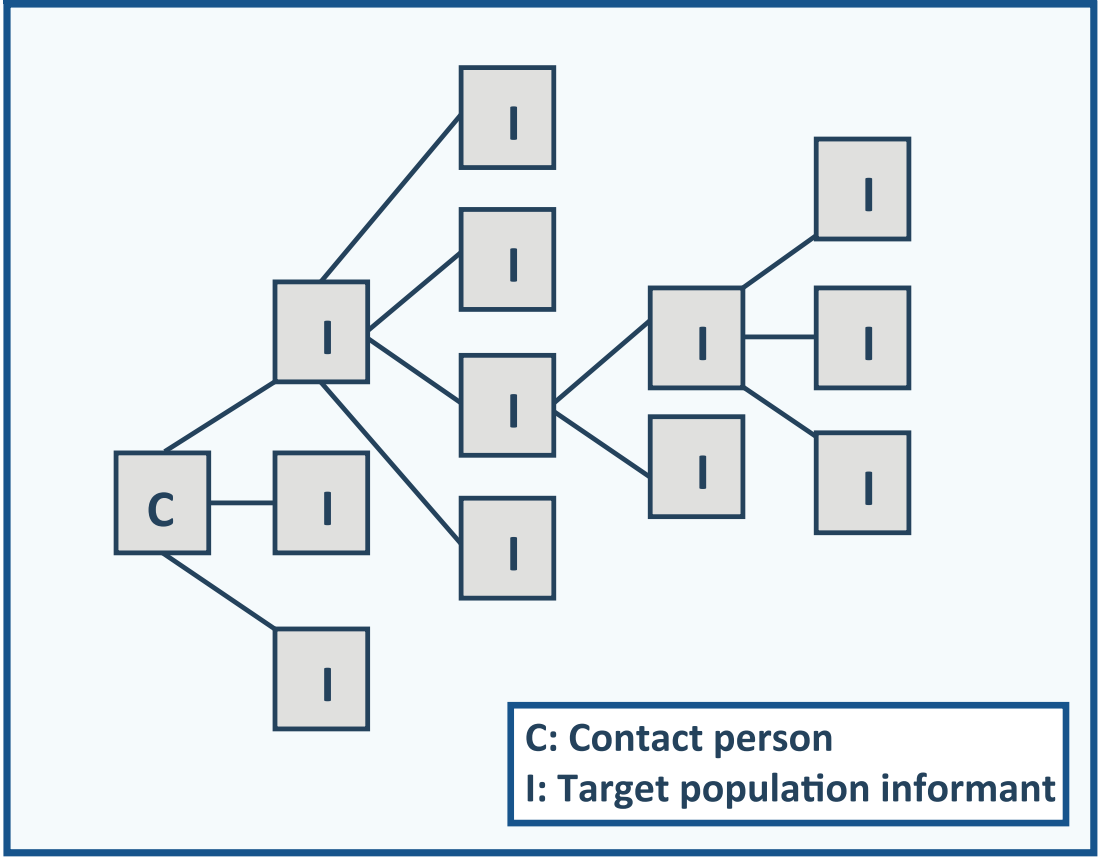
The main advantage of this method with respect to other nomination techniques (those that directly contact respondents, who provide access to other users or to certain information) is precisely the systematization of the process and the balance reached by the possible confounding variables upon completion of the process.

Like all the preceding methods, nomination techniques must also meet certain requirements. 1) The data provided by the respondents must be highly reliable (3) and 2) the target population must be correctly defined (not segmented) and must be connected by dense social networks (1).

2.2 RANDOM-WALK METHOD

To calculate the size of a target population using this technique, it makes contact with the members of a population through nominations from their social contacts. Recruiters begin by selecting several people as informants (for example, drug users). These informants then offer a list of possible persons at risk, among whom the recruiters randomly select one, who once again offers a list of persons at risk from among their contacts, from which one is selected at random, who will then offer another list of persons at risk, and so on (Figure 6).

Figure 6: Design of a prevalence estimation study according to the Random-Walk method.



Source: Own preparation. Based on the model shown in Bell DC, Erbaugh EB, Serrano T, Dayton-Shotts CA, Montoya ID. A comparison of network sampling designs for a hidden population of drug users: Random walk vs. respondent-driven sampling. Soc Sci Res; 2017;62:350–61.

To the extent that Random-Walk is introduced in a population, every person of the target population has a statistically non-null probability of being selected (17).

This is a method included among those that are **based on social networks** (this latter term is understood as a set of individuals who have some type of personal relationship or common interest). It is very similar to the aforementioned RDS (Respondent-driven sampling). The main difference stems from the fact that, while in the RDS method the respondents themselves nominate the respondents of the next wave and they are compensated through various incentives, in the Random-Walk method the respondent provides a list of persons from their social network who meet the requirements to be chosen, and it is the actual researcher who randomly chooses the next respondent from among the people on that list.

If the Random-Walk method is implemented correctly, it can generate a highly representative sample of the target population (17). However, there is the possibility that sampling bias will appear if the population contains multiple networks that are not mutually connected (17). If all the members of the population were interconnected (ideal but unreal situation), they would all be reachable through a single seed. But since small, isolated groups exist, they escape the sampling framework. To reduce this bias, multiple "seeds" must be selected in various networks (17). In the stated example, to calculate the number of heroin users in a city, it wouldn't be enough to begin with just one user. Several would have to be sought, distributed throughout various zones of the city.

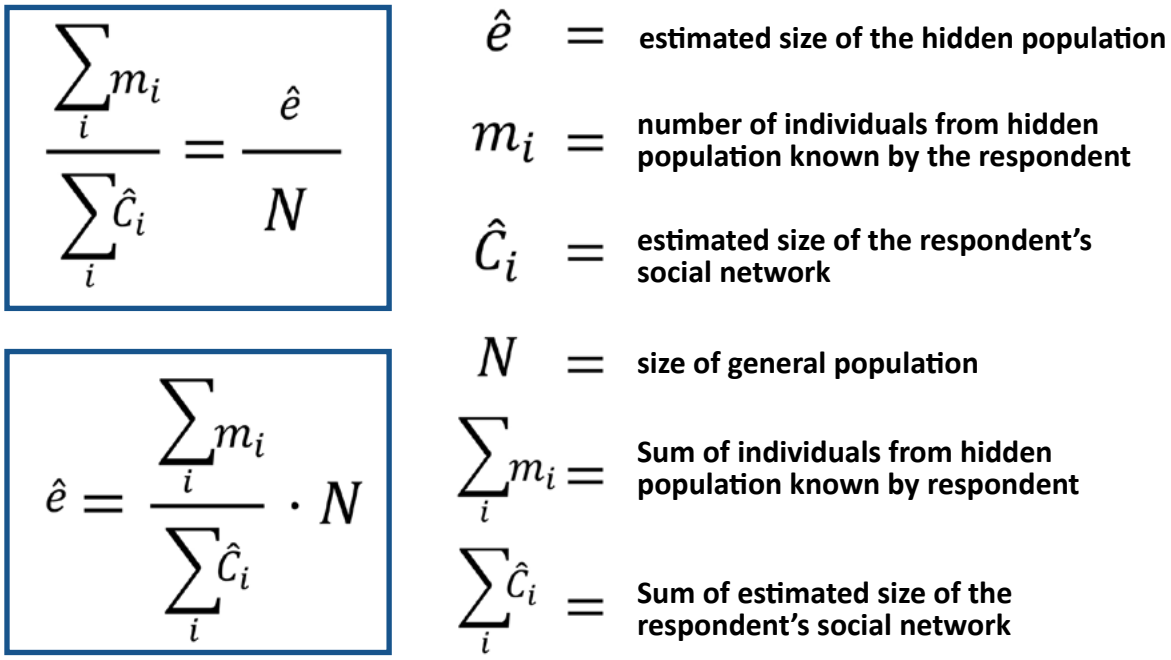
Other possible biases occur when an informant is unsure about disclosing information regarding the behaviours of their social networks or feels especially motivated to do so because of a certain circumstance, thus offering untrue information in either of the two cases. To minimise this bias, researchers must get involved with the subjects and recruit them personally, thereby increasing the trust that respondents place in the researchers, even though this means a greater investment in time and resources (17).

2.3 THE NETWORK SCALE-UP METHOD

This is another method based on social networks. The method assumes that the social networks of people are representative of the general population in which they live (18, 19). Based on this assumption, we observe the number of individuals who show a characteristic in the social network of a person, and this information is then extrapolated to the general population.

Continuing with the example of drug users, if an individual (whether or not they belong to the target population) knows 300 people and only two of them are drug users, then we assume that in the general population this proportion will remain consistent, meaning 2/300 people would be drug users (18). By combining information about the social networks of many people, we'll be able to determine the size of the hidden population by using a simple formula (see Figure 7). The formula basically consists in taking the sum of the people who are known by the surveyed subjects and who meet the criteria of the hidden population to be studied and dividing that number by the sum of their social networks, then multiplying that quotient by the size of the general population.

Figure 7: Formula used to estimate the size of the population through Network Scale-up.



Source: Own preparation, based on the model in the article by Bernard HR, Hallett T, Iovita A, Johnsen EC, Lyerla R, McCarty C, et al. Counting hard-to-count populations: the network scale-up method for public health. Sex Transm Infect [Internet]. 2010;86(Suppl 2):ii11-ii15.

The main difficulty lies in the ability to estimate the actual social network of each person (20). To do so there are **two methods:**

a) Known population method. This technique attempts to quantify the number of subjects known by a surveyed person from among several population groups whose size is known in advance, including populations other than the hidden population of interest (18, 20). For example, the number of subjects known by a respondent (their social network) could be estimated based on what is known about the population of diabetics over the age of 18 years in Spain. Using this technique, healthy subjects could be asked about how many subjects they know with this disease. If that person says that they know 22 diabetics, and we know that in Spain there are approximately 5.3 million diabetics over the age

of 18 years and that there is a total population of 38.2 million Spaniards over the age of 18 (10), then we can assume that, according to the simple "rule of three", the respondent knows 159 people (their social network). To reduce the variance of the estimate, it is recommendable to look into at least 20 different sub-populations (18).

b) Sum method. This technique attempts to quantify the number of people who meet the criteria of the population of study in each one of their social groups: family, friends, neighbours, work colleagues, etc. The sum of the persons referenced in these categories will provide us with an estimate of the size of their personal network (18, 20). This method is simpler, but it requires a good definition of the categories, while not overlooking any, otherwise the outcome would be subject to under-estimation. Also, the categories must be mutually exclusive so that the same acquaintance is not counted in two different categories, which would lead to over-estimation (18).

After having calculated the number of persons known by a respondent (denominator), we then ask about our variable of interest: the number of persons who are drug users in the respondent's social network (numerator). Continuing with the initial example, if the respondent knows 2 people who are drug users and their social network is comprised of 159 people (estimated using the known population method), we assume that 2/159 people in Spain are drug users. According to the INE (21), there are 46.5 million people in Spain, and therefore, according to this method there are 584,906 people who use drugs in Spain.

This calculation is repeated with numerous respondents, and by applying the formula in Figure 7, we can get an estimate of the size of the hidden population.

Just like with all other methods, this one is not free from bias. The main one is so-called transmission bias (18), in which the respondent does not know about all the life aspects of their contacts, which frequently occurs, and even more so in this particular case concerning socially stigmatised activities. Another is the so-called barrier effect (18): having contacts among the population of study could depend on physical or social barriers, such as race, ethnicity, occupation or place of residence. Another bias that we could encounter is the recall effect, in which the respondent cannot correctly recall the number of people they know in a sub-population or cannot do so within the time frame allowed by the study (20).

Nevertheless, the method also has numerous advantages: it does not ask respondents directly about their characteristics, rather it asks about the people they know who have those characteristics, thus providing an anonymous list of contacts. This causes a decrease of the burden of stigma in respondents (20). Second, since we do not need to directly interview the members of a hidden population, rather the general population, we can perform general sampling techniques that are less expensive and easier to implement (20). Another advantage is that the method can be used to generate estimates for various hidden populations simultaneously, and it can be easily applied to populations of known size, which would allow us to assess the validity of the method itself (22).

The Network scale-up method is efficient. Its capacity to generate accurate estimates of hidden populations using conventional sampling frameworks and survey techniques makes it a considerably less expensive but faster method than the techniques commonly used to study these populations (10). It is consequently being used in studies throughout the world, and this use is increasingly becoming more extensive (18, 19, 20, 22, 23).

OTHER METHODS

In addition to the described techniques, there are other, more specific techniques for estimating populations. We will merely mention them here because, due to being used less, they are not the object of this study.

These other methods are different variants of the aforementioned ones, such as the covariate model in the capture-recapture method (4), which allows checking the heterogeneity of the individuals in data sources and adjusting the data using stratification in subgroups. Another method that is occasionally used is the so-called back calculation method (4), according to which, knowing the incidence and the end-point of a certain process (use of drugs), we can estimate the starting point (onset of use) and thus calculate the prevalence of the process.

Table 3: Main indirect methods for calculating hard-to-reach populations (I).

METHOD	REQUIREMENTS	LIMITATIONS	EXAMPLE
Benchmark-Multiplier Based on using a known number of people from a data source (i.e. deaths among drug users) and multiplying it by a known rate (i.e. mortality rate among drug users).	· Comprehensive benchmark. · The sampling used to estimate the multiplier must be representative of the target population. · The case definition used for the benchmark and multiplier must match.	**· Possibility of bias if the requirements are not applied correctly.** **· Not applicable if the population is heterogeneous.**	
Capture-Recapture Based on comparing several data sources of the population of study, assessing the degree to which individuals are repeated and inferring the total number in the population.	· Closed population of reference. · There are no false positives. · Independent data sources. · Every case has the same probability of being captured in each list. · Databases are representative of the population.	**· Possibility of bias if the requirements are not applied correctly.** **· Negative dependence: over-estimation.** **· Positive dependence and heterogeneity: under-estimation.**	
Multivariate Indicator method It takes information from populations for which data are available (the calibration population) and extrapolates the information to populations for which data are not available (target population).	· Having indicators related to the behaviour of the population that we want to know about, in all areas where this population is distributed (province, community, country, etc.). · Knowing the prevalence of the population that we want to know about in some of these regions (calibration populations).	**· Assumed linearity between anchor points and predictors.** **· Comparability between indicators of various regions.** **· Validity of the anchor points.**	Estimating prevalence of problem drug use at national level in countries of the European Union and Norway. Addiction 2003;98 (0965–2140)
Truncated Poisson method By using the number of individuals who have had contact once, twice, three times, etc., the number of individuals who have never had contact is estimated.	· The number of contacts with the source must be recorded. · The probability of having contact with a register/record a certain number of times is constant for all individuals. · That probability is independent from the number of times that there was previous contact. · It requires that the variable follow a Poisson distribution.	**· More complicated calculations.** **· Requires a number of contacts with the source.**	

Table 3: Main indirect methods for calculating hard-to-reach populations (II).

METHOD	REQUIREMENTS	LIMITATIONS	EXAMPLE
Adaptive sampling designs Based on an initial random sampling, respondents are included according to their geographic location.	· The study population is not segmented and is not isolated geographically.	**· If the variables of interest are not distributed randomly in the population, it could be difficult to detect any individual who shows those variables in the first step.**	Adaptive sampling in research on risk-related behaviors. Drug Alcohol Depend. 2002;68:57–67. (Link-tracing adaptive design)
Respondent-Driven Sampling (RDS) Techniques based on direct contact with respondents. In turn, respondents provide access to and/or information about other users.	· Representative sample. · Reliable, self-reported data. · Correctly defined target population. · Study population is not segmented but connected by dense social networks.	**· It does not allow estimators that can be generalised to the population of reference (except RDS).** **· Sampling bias: Possibility that the respondents belong to a subgroup of the study population (except RDS).**	
Random-Walk method Through contact with informants, we obtain both information about and access to the hidden population. Differentiated from RDS by the randomisation prior to selecting the respondents.	· Representative sample of the study population. · Study population is not segmented but connected by dense social networks. · Reliable, self-reported data.	**· Sampling Bias: existence of networks that are not mutually connected. Some members of the population would escape our sampling.** **· Information bias: the informant offers untrue information.**	A comparison of network sampling designs for a hidden population of drug users: Random walk vs. respondent-driven sampling. Soc Sci Res. Elsevier Ltd; 2017;62:350–61.
Network Scale-up method The number of individuals who show a characteristic in the social network of a person is observed, and this information is extrapolated to the general population.	· Access to the general population through population surveys or other interview methods.	**· Transmission bias: the respondent does not know about all the aspects of their contacts.** **· Barrier effect: having contacts among the study population could depend on physical or social barriers.** **· Recall effect: the respondent does not recall the quantity of people they know in a sub-population.**	The application of network scale up method on estimating the prevalence of some disabilities in the Southeast of Iran. J Res Health Sci [Internet]. 2014;14(4):272-5.

PART II HARM REDUCTION COVERAGE

INTRODUCTION

After having focused on how to determine the number of people who inject drugs in a certain area, this guideline now moves ahead with a vision of public health and discusses the subject of the level of needs that are covered for those people. Injecting drug users are not only exposed to many health risks inherent in this method of use (transmission of diseases and increased infections), they are also exposed to drug addiction, which often goes hand in hand, and to the illegal nature that is almost always involved in obtaining drugs. This group is considered a disadvantaged population group that often lives at the margins of society, for which very specific actions must be taken to reach this population and minimise the risks of worsening the health conditions of its members. The approach that attempts to improve the health conditions of this population is framed under an overall designation called "harm reduction". This section of the guide attempts to provide an overall vision of how to determine, epidemiologically, if harm reduction is being applied effectively. It attempts to provide the basic tools to effectively design the monitoring of this harm reduction coverage.

While there is no unequivocal definition of the interventions that must be considered under the concept of harm reduction, there is an established common minimum. This guideline considers the definitions of the World Health Organization (WHO) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA):

"Harm reduction encompasses interventions, programmes and policies that seek to reduce the health, social and economic harms of drug use to individuals, communities and societies. (…) Harm reduction approaches neither exclude nor presume a treatment goal of abstinence, and this means that abstinence-oriented interventions can also fall within the hierarchy of harm reduction goals (28)."

The activities encompassed by the concept are varied and not always uniform, but they could include the following: opioid substitution treatment; needle and syringe programmes; supervised drug consumption facilities; drug overdose prevention; counselling services, outreach, peer education and health promotion; testing, vaccination and treatment of drug-related infectious diseases; interventions for stimulant users; and drug-related sexual risk reduction (28, 29, 34).

HR (Harm Reduction) is not merely a pragmatic response to an occasional problem arising in a specific population. It concerns a set of measures that have been evaluated, and their effectiveness in the population has been proved (28). However, there are many countries that have yet to establish the minimum required changes to their health policies regarding HR, especially when it is well known that such inaction involves negative health consequences as a result of unnecessarily exposing members of the population to unnecessary risks (30).

Various systematic reviews (31, 32) have shown that NSP and OST interventions work in different areas, especially with respect to reducing the incidence of infectious disease among IDUs and reducing overall mortality (33). Moreover, HR doesn't merely benefit the physical health of people. HR resources not only place users in contact with society, they also serve as a bridge for possible integration.

Coverage has been defined as the proportion of the population that is in need of and has actually received an effective intervention (29, 35). It was a concept whose importance started growing in the middle of last century, and it finally received definitive backing within the context of the Alma-Ata Declaration of 1978 (36). If we do not know the degree to which the needs of populations are covered (if we do not know the coverage), we will be hard pressed to come up with policy approaches that provide a solution.

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations and the application of this study to the control of health problems (37). If we apply this definition to HR coverage, we find that the utility of determining coverage is knowing the extent to which those in need of a health intervention actually get it (38). Unfortunately, there is a shortage of information about HR coverage: it may not be not generalised, but it is nonetheless considerable. And the absence of interventions is not always the reason. There are environments in which harm reduction measures actually do exist, but there isn't information about the reality of those measures: the level of implementation, the effectiveness, the equality, etc. In brief, we don't know the degree to which they fulfil the needs of different populations of drug users (30).

In many countries, there is more or less comprehensive knowledge of HR coverage. It is based on epidemiological studies and the collection of monitoring data. Yet there are countries where, even though harm reduction exists, data are barely compiled.

The objective of this section is to provide orientation regarding the basic foundations for determining the coverage of harm reduction.

THE DETERMINATION OF COVERAGE

Determining HR coverage involves establishing the indicators that define it, then compiling information adequately and finally analysing that information with the ultimate aim of continuous monitoring that allows us to see both the levels that are reached and any improvement opportunities. Data must be interpreted from both an internal and external perspective and must be compared with data from the surrounding environment. This guideline does not endeavour to go over how to collect information, although it is essential that information be collected appropriately, beginning at the service delivery level. If any of the links in the chain fail, the determination of coverage will fail, and often the weakest link from an epidemiological point of view is the collection of information, especially when it has to be done by services that are focused on healthcare. Therefore, even though we are not going to go into depth regarding this aspect, it is important to think about the most effective way of gathering information.

This guideline focuses on identifying what we must use as a "proxy" for coverage: the indicators. Coverage, like many other concepts in health, becomes something abstract that is embodied by that which shapes it. In this case, the indicators are what shape it. There are a number of indicators. They range from those that are proposed by the WHO (29) and that are widely used in various publications (40) (including availability, coverage, quality and outcome/impact), to other approaches that attempt to delve deeper into those indicators (30, 39). In this guideline, we will focus on the former and only in reference to coverage. The guideline attempts to provide orientation about the best way to determine the HR coverage of any country, yet it also clearly seeks to help those countries where there is barely any HR coverage. Consequently, below we focus on the minimum indicators that would have to be collected. This allows us to get an idea of the level of each country's HR situation and then compare that level with the surrounding countries.

2.1 CONSIDERATIONS ABOUT THE POPULATION WITH RESPECT TO COVERAGE AND CALCULATION OF INDICATORS (WHO)

Even before talking about indicators, there are a series of aspects about the population that we have to keep at the forefront so that we measure what we truly want to measure.

a) The target population: When measuring the level of coverage of any aspect of harm reduction, a frequent fault is forgetting about for whom that harm reduction is provided. It's not only a matter of ensuring that HR is available, rather it's also a matter of ensuring that HR reaches the target population. And to do so, we must remember that this population has many idiosyncrasies that must be kept in mind, although in this case there is one in particular: this population's use of and access to medical services is very different from

that of the general population. It is therefore necessary to be very cautious about what we are evaluating because even though everything may fit numerically, it may not be appropriate qualitatively. We will be discussing coverage, how to determine it, the indicators and the populations of reference. But we must never lose sight of the fact that, no matter how many syringes we have available, if we can't get them to the population, their presence won't be synonymous with an effective intervention.

b) Population of reference: The first half of this document discussed how to determine the number of PWIDs, although the indicated methodologies allow us to go well beyond that specific population. Therefore, we refer to that part for the actual calculation of the population of reference.

When determining HR coverage, we have to be especially careful about defining the population of reference, also called the "denominator population". Obviously, talking about drug users is not the same thing as talking about illegal drug users, what the EMCDDA calls High Risk Drug Users (HRDUs). In this sense, we must be careful when determining the denominators. Something that is often overlooked is the operational definition of each one of these concepts. **Who is a drug user?** Someone who uses daily, someone who used a short time ago or someone who has used occasionally? In the case of PWIDs, the WHO refers to within the last year, and the EMCDDA refers to within the last 4 weeks.

Once the denominator is clear, the key is ensuring that it corresponds to the nominator. However, just because these concepts may not be clear doesn't mean that we should stop collecting what we do have available. The WHO recommends the following: If a suitable population size estimate is not available to be used as a denominator, collecting and reporting the numerator data is still recommended (29).

2.2 THE INDICATORS

This guideline has already emphasized this point, and its intention is not to "create" new indicators. It also doesn't attempt to conduct a systematic and comprehensive review of existing indicators. What the guideline does endeavour is to provide a simplified answer to the question of **how to determine Harm Reduction coverage**, or at least provide information about the minimum that must be done for determining that coverage. Initially, the process will be related to a certain country, but it can be extrapolated to different geographic environments. As in the preceding chapters, we will be consistent with what has been determined by the WHO and the EMCDDA, and the indicators proposed by these two organizations are those that form the backbone of what is developed below.

Indicators perform a dual function: they allow us to have a better understanding of the reality of the countries where they are applied, and they allow us to compare that reality to other environments. Considering the former function, we could develop indicators

that attempt to cover everything that has already been stated and understood as harm reduction. But if we keep in mind the second function, it doesn't seem advisable to generate too many indicators. In many countries, indicators couldn't be completed, and the comparability of those indicators would be very limited. Moreover, even though the word "indicator" itself points out that it is used to "indicate", often these indicators are focused on what is prioritised in a country's policies. It's better to prioritise 6 or 7 aspects, rather than 30.

Consequently, when preparing the table of indicators suggested by this guideline, we have kept in mind both criteria. We have therefore differentiated between those indicators that are the minimum to be determined and another series of indicators that we could call "non-priority", but we mustn't fail to point them out in order to establish a good monitoring system of harm reduction. These indicators have been drawn from the WHO's recommendations (29) and from the indicators recorded by the EMCDDA. In addition to other consulted sources, the systematic review by Larney (40) warrants special mention. The review provided a coverage map of harm reduction globally, thereby making the effort to choose indicators that were both the most accurate and the most widely used.

As it was previously stated, harm reduction covers a multitude of areas, which are all legitimate. However, the ones we indicate in this guideline are the following: Needle and syringe programmes, opioid substitution therapy and other drug dependence treatment, HIV testing and counselling, antiretroviral therapy, condom programme, drug consumption rooms, Take Home Naloxone and Heroin Assistant treatment. For each of these areas, the set of globally recommended indicators has been indicated (second column) and those that we could call the minimum indicators (third column).

Table 4. Indicators of HR coverage

HR AREA	Complete list of indicators*	Priority indicators**
1. Needle and syringe programmes	· Types of NSPs (Number of cities and sites should be specified): Specialist agencies with NSP; Syringe vending/dispensing machines; Pharmacy-based NSPs; Prison-based NSPs; Outreach syringe provision sites serviced on a regular basis; Other (to specify). · Geographical spread of NSP-site in the country: Number of NSP sites per territorial unit. · Syringe provision at NSPs: Total number of syringes provided (and percentage of sites reporting). · Utilization of NSPs: Clients and contacts at NSPs; Number of all individual clients . · PWID regularly reached by NSPs.	· **Number of needle–syringes distributed by NSPs per year.** · Number of IDUs accessing NSPs in a year. · Proportion of IDUs accessing NSPs in a year, % (range).
2. Opioid substitution treatment	· Number of sites and forms of OST provided (methadone, buprenorphine, heroin or other). · Percentage of PWIDs accessing OST. · Number of OST clients.	· **Number of individuals receiving OST (including both IDUs and non-IDUs).** · Number of needle–syringes distributed per IDU per year (range). · Forms of OST available. · Number of OST recipients per 100 IDUs (range).
3. HIV Testing and Counselling	· Evidence of HIV testing programmes targeted to PWID. · Percentage of PWID receiving an HIV test in the previous 12 months (who know the result). · Number of PWID receiving an HIV test in the previous 12 months (who know the result).	· **Number of PWID receiving an HIV test in the past 12 months per 100 PWID.**
4. Antiretroviral treatment		· **Number of IDUs receiving ART.** Ratio of IDUs receiving ART: 100 IDUs living with HIV (range)
5. Condom programs	· Number of sites distributing condoms to PWIDs. · Number of PWIDs receiving condoms from targeted programmes. · Percentage of PWID receiving condoms from targeted programmes. · Number of condoms distributed by programmes targeting PWID.	· **Number of condoms distributed by PWID-targeted services per PWID.**
6. Drug consumption rooms	· Number of rooms. · Supervised injections. · All supervised consumptions.	
7. Take home naloxone	· Number of PWIDs receiving take home naloxone.	
8. Heroin assistant treat.	· Number of PWIDs receiving heroin assistant treatment.	

2.3 CALCULATING THE COVERAGE

Indicators are indispensable for determining HR coverage. But the process doesn't end there. The objective of this chapter is to determine if the needs of our population are being covered: if the population is being provided with what it needs. If we observe the indicators selected in the preceding chapter, we see that those that come the closest to coverage will give us percentage figures.

The closer we get to 100%, the closer we'll be to covering the population of people who inject. For example, regarding the indicator, "Proportion of IDUs accessing NSPs in a year, % (range)", 100% would mean that all IDUs have access to NSPs. But this does not strictly mean that coverage has been met in its entirety. There is a factor that we have to keep in mind: it could be that IDUs access this programme, but it could also be that they do not do so often enough or that they are not provided by adequate resources.

We faced a similar situation when we stopped to think about the suitability of having too many or too few indicators. And while there aren't many countries that endeavour this level of accuracy when determining HR coverage, in a guideline that summarises the most relevant aspects of this concept, we cannot ignore the fact that there are more elaborate ways to determine HR coverage.

a) Syringe Coverage

Syringe Coverage (SC) is the proportion Syringe Provision (SP) divided by what has become called Syringe Need (SN). SP is simply the quantity of syringes that are provided, which doesn't require much explanation. But we have to stop and look at the concept of SN. How many syringes do we think are needed? Beyond the fact that a user may contact certain services, we assume that users should have a new syringe every time they inject, and the calculation is made based on this assumption. And to determine the number of injections in question (to know how many syringes are needed), we have to consider the number of daily injections and the number of injection days, subsequently multiplying everything by the number of persons who are injecting. Thus, the figure for the number of needed syringes will come from the product of these three factors. SC will be SP/SN multiplied by 100 (see the coverage calculation table).

b) Opioid Substitution treatment (OST) Coverage

OST Coverage (OC) is the proportion of OST Provision (OP) divided by what is understood as OST Need (ON). We calculate ON as the sum of the OST already given, plus the number of persons to whom it is not given but who would benefit from OST. This last factor is what we have to look at. To calculate it, we begin by assuming that all persons who consume illegal opioids, especially injected opioids and heroine, would benefit from OST.

Thus, those opioid users not receiving OST would be the result of subtracting the number of opioid users who are in OST from the prevalence of opioid users. This can be seen more clearly in the calculation table.

c) HIV test coverage

In this case, the way to calculate the coverage is defined in the table of indicators. It will simply be necessary to determine the percentage of the estimated number of PWIDs in a certain period (which could be one year) to whom the test has been given. The formula can be seen in the calculation table.

d) ARV coverage

As in the preceding case, this calculation is simple and is already given. The percentage of users in ARV treatment will be determined, and this figure will be divided by the estimated number of PWIDs with HIV. To make this determination, we would refer back to the first part of this guideline (calculation in the table).

Table 5. Algorithms to calculate HR coverage

COVERAGE	ALGORITHMS
Syringe Coverage (SC)	$SC = \frac{\text{Syringe provision (SP)}}{\text{Syringe provision (SP)}} \times 100$ **Where:** SN=Injection prevalence x Mean number of injection days per year per IDU x Mean number of injections per day per user
OST Coverage (OC)	$OC = \frac{\text{OST provision (OP)}}{\text{OST need (ON)}} \times 100$ **Where:** ON= OP + opioid users not receiving OST (ONO) ONO= Opioid use prevalence – (Opioid use prevalence x proportion of opioid users in OST)
HIV Test coverage (HC)	$HC = \frac{\text{Number of PWIDs tested for HIV during a given time}}{\text{Estimated number of PWID (in this time)}} \times 100$
ARV coverage (AC)	$AC = \frac{\text{Number of ARV treatment among PWIDs}}{\text{Estimated number of HIV+ among PWIDs}} \times 100$

Source: Own preparation based on Barrio et al. (41)

CONCLUSIONS

This guideline provides a simple approach to the most basic concepts regarding the estimation of HR coverage.

It has a dual purpose: determining the basic minimums and providing for the possibility of furnishing data beyond those minimums. The guideline does not seek to replace the WHO's indicators, which are more or less widely used in various countries. Rather, **we summarise the indicators and provide the simplest possible approach** to not only improve the determination of coverage but also establish the basic principles for monitoring that coverage. This has been done without losing sight of the fact that all epidemiological monitoring is framed within public health, which, in addition to providing data, must also point out areas of improvement.

The idea is to monitor health so that we can determine how to improve it. And drug users, above all those who inject, critically need specific actions that not only improve their health but also prevent infections and keep them from being propagated in the population.

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