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Methodological Problems and Solutions for Sampling in Epidemiological SARS-CoV-2 Research

Rainer Schnell
University of Duisburg-Essen

Menno Smid
infas, Bonn

Existing reporting systems and surveys give biased estimates of the true prevalence of SARS-CoV-2 infections and the development of these rates over time. Little is known on progression of the disease in persons who are already identified as infected. Finally, the number of deaths due to the infection (not during the infection) is also unknown. We describe data requirements for epidemiological and social research and give details of the sampling and fieldwork procedures required for different types of studies.

Keywords: COVID-19; Nonresponse; Selection Bias; Non-probability Samples

1 Introduction

Prevalence estimates are needed to evaluate political measures for controlling the spread of SARS-CoV-2 infections.

The data reported by the German federal government agency responsible for disease control and prevention (Robert Koch Institute, RKI) are based on officially reported infections. As in other countries, these figures are a function of the test activities. The resulting numbers are biased estimates of the point prevalence (i.e., the proportion of persons in a population with a specific condition at a specified point in time, Porta (2014)).

If the proportion of people in the population which is tested in a given country is high, higher prevalence estimates will be published in this country compared with a country in which a lower percentage of persons is tested, even though the actual prevalence is the same. Depending on the threshold used for the decision who is tested, different estimates will result. Since the test activity in Germany is higher than in other European countries, this will explain some of the differences between Germany and other countries with regard to the proportion of deaths among those infected (see Figure 1).[1]

People do not get tested randomly. They either experience the symptoms or their general practitioner identifies a potential infection. Considered as a sampling procedure, this is a self-selected sample, therefore a non-probability sample. The official number of infections thus yields a biased estimate.

The second official number is the number of COVID-19 related deaths. This is the number of people who died while having a SARS-CoV-2 infection. Without postmortem examination, it is not clear if a person actually died because of this infection. Since no random sample of autopsies (neither of deaths in general, nor of cases considered to be COVID-19 related) is available, the official data in Germany do not allow the calculation of a fatality rate.[2]

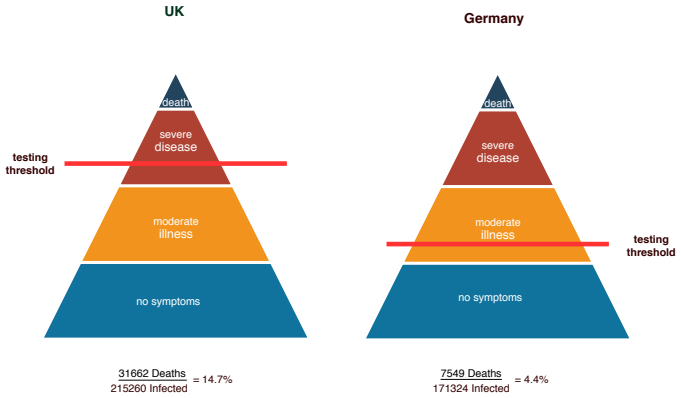

Figure 1. Percentage deaths of known infected persons. Data: Johns Hopkins University, 10.5.2020 10:32 GMT.

The procedures for determining official figures in Germany currently in use do not permit estimates of the number of asymptomatic cases. Furthermore, the amount of information collected on known positives is limited. Therefore, neither information on pre-existing medical conditions, nor social factors impacting the prevalence are available. Longitudinal data on known positives are either not collected or

Contact information: Rainer Schnell, Research Methodology Group, University of Duisburg-Essen (Email: Rainer.Schnell@uni-due.de)

[1] The idea for this plot is due to Prof. Debby Bogaert on Twitter, 13:48, 21.3.2020.

[2] The Case Fatality Rate is defined as the number of persons who died from a disease/number of persons with the disease, Porta (2014)).

at least not published. For example, the percentage of mild disease progressions is unknown. The available data cannot be extrapolated regionally or nationally. Finally, the identification of asymptomatic local infection clusters is at least difficult. Therefore, better population samples are needed.

2 Methodological criteria

To design a survey, specific target criteria are required. Different scientific and political purposes require different kinds of information:

1. Overall, unbiased estimates of prevalence are needed.
2. To reflect the disease progression of persons, a longitudinal study of known positives is required.
3. Information on social factors influencing the probability of infections should be available.

As a governmental agency, the RKI does not only operate according to rules and criteria of scientific research, but, first and foremost, it is the RKI's main task to control the infection by identifying, tracking and curbing of cases.

For scientific research including prevalence estimates, different procedures and criteria are needed. In the absence of a tested statistical model, only design-based statistical inference will give unbiased estimates for the required information. Therefore, random samples of the general population are required. As epidemiological, political and economic decisions rely on the estimated parameters, the sampling has to be done according to proven methodological standards. This implies a national sample with known selection probabilities. The design has to be published and discussed in any detail before sampling begins.

Furthermore, fieldwork has to be done according to professional standards in survey methodology. Finally, all fieldwork techniques and results including non-response, follow-ups and weighting have to be documented and the data set should be made available for researchers according to international privacy standards.[3]

3 Different samples for different purposes

We recommend to use four different kinds of samples for COVID-19 related epidemiological and social surveys:

1. Prevalence Sample: proportion of infected persons in the population,
2. Panel Study: progression of the disease within persons,
3. Postmortem Sample: causes of death,
4. Social Research Survey: attitudes and social impact.

Each of the proposed samples will be discussed below.

3.1 Randomly selected general population seroprevalence survey

To obtain prevalence estimates of a population regardless of the diagnostic status, general population surveys are needed (ECDC, 2020). For SARS-CoV-2, different tests are in use. Serologic testing for SARS-CoV-2 antibodies is considered as the best available method for prevalence estimates (Bendavid et al., 2020). Roche claims a specificity of 99.8% and 100% sensitivity for its recently FDA-approved Elecsys-Anti-SARS-CoV-2-test (Roche, 2020). For this kind of test, venous blood has to be collected. Collecting a national sample of venous blood is challenging. We begin by considering the sample selection and sample size.

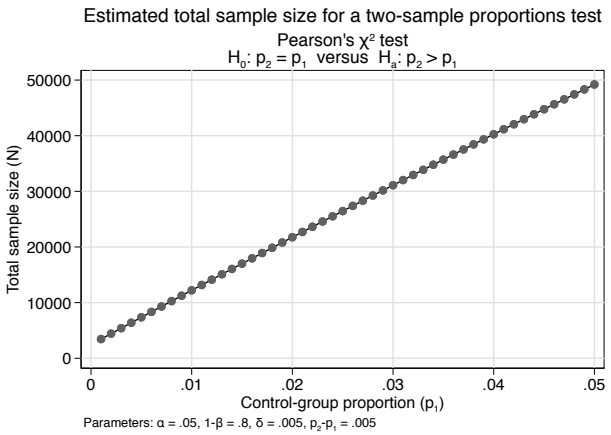

Figure 2. Required sample size for independent samples (cross sections)

Germany consists of sixteen federal states. Therefore, most surveys use state as sampling stratum. Within each state, municipalities are sampled proportional to size. Within the selected municipalities, the register of citizens is used as the sampling frame. 140 to 250 primary sampling units (PSUs, here: municipalities) are used for most national research projects in Germany. For SARS-CoV-2 research, larger numbers of sampling points are desirable. Furthermore, it is essential that the PSUs are selected at random.[4]

Obtaining the lists of persons from independent registries usually takes up to six months, but given the current public interest, a deadline two months seem to be possible. However, to account for municipalities responding too slowly, an initial increase in the number of municipalities is necessary.

To be useful for estimating trends, such a seroprevalence

[3] An example would be the 'five-safes' in official statistics (Desai, Ritchie, & Welpton, 2016). Therefore, a research data centre independent from a governmental agency and the research group conducting the study is needed at the moment the data processing (not the analysis) is completed.

[4] Convenience sampling of PSUs as done in the largest medical study in Germany (NAKO, see Schipf (2020)) is unsuitable for unbiased population estimates. In the NAKO study, the PSUs are selected in the proximity of the involved research units, therefore some states are missing entirely, and rural areas are neglected. The effort required by respondents to participate adds a second layer of sampling bias.

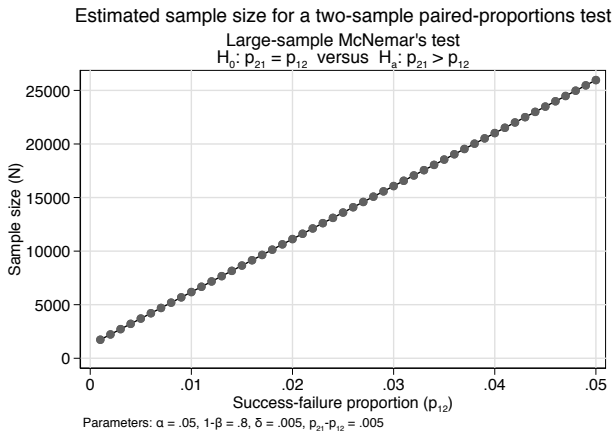

Figure 3. Required sample size for dependent samples (longitudinal survey)

survey can be designed as a longitudinal survey or as a repeated cross-sectional survey. We estimated the required sample size for both designs (see Figures 2 and 3).[5] For the calculations, design effects were neglected. In practice, design effects will increase the necessary sample size. Therefore, we consider the numbers provided as required minimum numbers. Since no actual seroprevalence estimates are known for Germany, we use a range of estimates, including the estimate given by Bendavid et al. (2020). Using conventional settings ($1 - \beta = 0.8$ and $\alpha = 0.05$), the resulting sample sizes are quite large. For example, a test of $p_1 = 0.01$ against $p_2 = 0.012$ would require two samples with $n = 33,629$ each.

The statistical gain by using a longitudinal design is small. As a panel study would increase the costs further and typically suffers from additional attrition problems, repeated cross-sections seem to be appropriate here. Although trivial, it should be noted that these numbers refer to national comparisons. If this level of precision has to be achieved on the state level, the same numbers are needed on state levels. The resulting sample sizes exceed the current capacities available for fieldwork in Germany. Therefore, lower levels of precision have to be accepted for national estimates if smaller samples are used.

For fieldwork, initial contact should be made by mail. Since venous blood is needed, a medical professional should take the blood sample (WHO, 2010). Different models seem to be possible. The selected citizen could be asked to visit

1. the general practitioner,
2. a geographically close general practitioner (preselected by the research team),
3. the municipal health department or
4. contact points of the mobile blood donation services of the Red Cross.

From an organisational point of view, the Red Cross would be optimal (as it has more than 4,000 mobile points and only a few regional organisations). Given the problems of involving large organisations, it seems more feasible to use a network of general practitioners. During previous large scale studies, such networks have been used by survey fieldwork organisations. Of course, financial incentives for the doctors involved are necessary. Considering the effort required by selected persons, financial incentives for the respondents seem to be appropriate. In any case, intensive non-response follow-ups are necessary. Every selected person has to be contacted repeatedly using different modes and by different organisations (for example, field-organisation, university and municipal health department). As missing responses could bias results due to non-random missingness (Little & Rubin, 2020), non-responding persons cannot be ignored. A final point of fieldwork should be mentioned: During a brief paper-and-pencil survey prior to the phlebotomy, permission should be obtained from the respondents for the follow-up. Given the large sample size, incentives, laboratory costs and organisational efforts required, we expect the total costs exceeding 100 € per case (and wave), excluding organisational overhead and academic staff. Considering the impact of the results, this seems to be justifiable.

3.2 Longitudinal study of disease progression

Very little is known about the disease progression of patients known to be infected but showing mild or no symptoms at all. Therefore, a longitudinal study of persons already diagnosed as infected is needed. The main purposes of the sample are (1) the estimation of the proportion of mild progressions and (2) the identification of symptom clusters. To meet these needs, a sample with $n < 5,000$ (giving a naive binomial confidence interval of about ± 0.014) will be sufficient. The sampling frame could be the lists of infected persons maintained at the municipal health departments for monitoring the quarantine. These lists do contain phone numbers, so recontacting and interviewing by phone (or asking by phone to take part in a web-survey) should be simple. During the initial contact, the permission of the patient to track them in hospitals and – in the worst case – in the municipal register of persons is essential. A daily follow-up, where simply the symptoms are checked until the quarantine ends, will limit respondent-burden and may even maintain cooperation rates. The costs for such a longitudinal study are minimal. As an academic project, we estimate the costs of about 100,000 €. Therefore, it is surprising that such studies have not been set up yet.

[5] The required sample sizes were computed with Stata 16.1 (StataCorp, 2019), based on equations given by Fleiss, Levin, and Paik (2003).

3.3 Postmortem sample

To clarify whether COVID-19 was the actual cause of death, autopsies are unavoidable. Both the Federal Association of German Pathologists (BDP) and the German Society for Pathology (DGP) recommended additional autopsies to identify the cause of death (BDP, 2020a). However, given the federal organisation of Germany, the jurisdiction concerning postmortem examinations is unclear. The infection control law (IfSG) seems to permit autopsies in case of infection diseases, although they are rarely done (Madea, Tag, Pollak, & Zollinger, 2014). A central register of all German autopsies on COVID-19 related deaths has been established (DeRegCOVID BDP (2020b)). As only the proportion of people who died of COVID-19 among those who were autopsied can be estimated, the statistical gain of DeRegCOVID is limited: Deaths due to COVID-19, which are not diagnosed, will be missed. Large-scale postmortem examinations of a random sample of persons deceased during a pandemic is needed. Most certainly, this will require new jurisdiction.

3.4 Social research on SARS-CoV-2 restrictions

To study the impact of social factors on attitudes relating to SARS-CoV-2 restrictions and their effect on behaviour as well as the social gradient on economic and social consequences, additional research is needed. This requires a random sample of the general population, including the elderly and economic disadvantaged. Therefore, access-panels or self-recruited samples are unsuitable for the aims of the study. As face-to-face interviews may be difficult for months, a mixed-mode survey after an initial mail contact by telephone, web or mail seems to be appropriate. The sampling frame should be based on local registers of citizens (which may be a subset of samples selected for other purposes as described above). Preparing the sampling frame will take at least two months. A sample size usual for social research ($n < 3,000$) may be sufficient for most purposes. Since the ongoing population panels in Germany (GSOEP, PASS, SHARE) will cover the topics mentioned soon, an additional panel study seems to be unnecessary. Therefore, compared to other samples, the cost of this study will be small. If done as an academic research project, we estimate about 250-300,000 € as required funding.

4 Summary

In the current situation in Germany, existing data does not permit the estimation of parameters of interest. Either the information is not available at all or most likely biased due to unsuitable sampling procedures. Therefore, we recommend four different samples:

1. Prevalence Sample: proportion of infected persons in the population,
2. Panel Study: progression of the disease within persons,
3. Postmortem Sample,
4. Social Research Survey: attitudes and social impact (not as a web survey).

To date, all available studies have been designed by medical experts or data analysts. Therefore, unusual designs with unknown selection probabilities prevail. However, with the possible exception of the postmortem sample, the design of all samples requires the expertise of survey methodologists during the initial stage.

Acknowledgement

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Commentary

The paper we were invited to review raises important points regarding the methodological requirements that are necessary to advance our knowledge about the spread of the Corona-pandemic in the population. It suggests relevant contributions to the investigation of crisis-related issues, such as the progression of the disease over time, the computation of mortality rates, surveying attitudes and the impact of the pandemic on society as a whole.

As the authors convincingly state, official estimates of infections and deaths are not trustworthy, because they do not rely on proper probability samples, but suffer heavily from various selection biases. We therefore fully agree with the authors' conclusion that the expertise of survey methodologists is sorely needed in the data collection for the proper estimation of health and other parameters, which eventually guide the political discussion on how to contain the pandemic. It is the major benefit of this paper that it provides exactly that: advice on methodological issues. Nevertheless, in the following, we would like to discuss some of the points put forward in the paper, especially regarding the purposes of COVID-19 research, the sampling strategy for the prevalence sample, the actual collection of blood samples, target persons' nonresponse and the sampling frame for a panel study on disease progression.

In the paper, the authors acknowledge early on that COVID-19 research serves scientific as well as political purposes, which is certainly true. The authors rightly state that "epidemiological, political and economic decisions will rely on the estimated parameters". However, we feel that different purposes have different implications for the design of studies and samples. While for some more purely scientific questions, such as the rate of asymptomatic to symptomatic infections overall, a one-shot, cross-sectional seroprevalence sample as described in the first part of the paper might suffice, for the political purpose of managing the pandemic (until a vaccine is ready for broader use in the general population) greater efforts will be needed. For example, in order to contain the pandemic, it might actually not be "unacceptable" to have large sample sizes implemented at the level of the 16 individual states. For government officials, information about the spread of the virus at the state level will allow more targeted responses to regional outbreaks. Testing capacities are sufficiently available by now, and financial resources should be as well, considering the alternative cost of halting large parts of the economy for several weeks in a row.

After this rather general observation, we turn to some more specific points of discussion. For example, the authors briefly mention the issue of local infection clusters, i.e., the fact that infections will most likely not be spread evenly across the whole population, but rather will concentrate locally in certain areas. Consequently, in many areas the number of infections will be very low, while in others, the density of infections will be high. This has implications for the sampling strategy of the prevalence sample for which the authors suggest a two-stage design (which is common practice for high quality, population-wide face-to-face surveys), where municipalities (the primary sampling units) are sampled first and citizens within municipalities are sampled second. While the authors state that "for COVID-research, larger numbers of sampling points are desirable" than for common population surveys, we find that the issue of local infection clusters warrants further discussion, because otherwise those clusters will be missed in the sample and the accuracy of estimates is likely to suffer. Maybe the rate of known positives per area (taken from administrative data) could be used as a stratum in the sampling procedure as a step to mitigate this problem.

The authors also claim that sampling from municipal registries, which usually takes up to six months or longer, could be accomplished within two months. In our view, based on previous experience with this kind of sampling procedure, this is a very ambitious goal and will only be possible if government agencies at the state and/or the federal level weigh in to emphasize the national urgency of this endeavor. As local administrations are already put under additional strain during the Corona-crisis, it is otherwise unlikely that scientific studies will be able to gather a complete gross sample within the time-span of two months from municipalities, even if the study were in the public interest. Hence, either the cooperation between scientific and government agencies can be

accomplished, or other, quicker sampling alternatives (such as a random route procedure) must be considered. This may not be as bad as it sounds. Arguably, the biggest problem of a random route procedure lies in the selection of respondents within a household. However, for COVID-19 research, it might be appropriate to sample all members in a selected household (in order to investigate transfer probabilities of the virus), omitting the necessity to rely on interviewers to choose individuals randomly within the household.

On the issue of fieldwork, the authors list different possibilities of how blood samples could be collected in the field (family doctors, municipal health departments, or the Red Cross). There is, however, the additional possibility of employing a team of trained nurse interviewers to collect blood samples directly from target persons. This is certainly not a standard practice in Germany, but fieldwork agencies in other countries have experience in collecting blood samples using qualified nurses (for example on the Health Survey for England). If it was decided to collect repeated cross-sections of the population on a regular basis, it could become an option to build up a team of qualified nurses specifically trained for this purpose.

The issue of nonresponse and the resulting problems of bias and increased fieldwork efforts deserve more attention overall. In general, surveying the prevalence of a disease may be problematic, as the parameter of interest in itself may be the cause of either non-contact or nonresponse (when the target person has fallen ill and cannot or does not want to respond). In addition, the suggested design is based on the willingness of people to participate in the survey, respectively to give their blood for the scientific and societal aim. Given that the willingness of people living in Germany for blood donations is usually low, we see the risk that the rate of refusals might be quite high. We think it is important to discuss how these issues of nonresponse threaten the aim for "unbiased estimates of prevalence" in more detail.

In addition to a prevalence sample of the general population, samples for certain sub-groups of society could also benefit political decision-makers. A case in point are schools, as there are ongoing debates about the benefits and drawbacks of school closures and their impact on the pandemic. It would, therefore, be desirable to know more about the infection rates among pupils. This could be accomplished through a study design where schools serve as primary sampling units, followed by classes and individual pupils. Similarly, samples of business establishments and employees could be drawn (potentially based on data from the Institute for Employment Research - IAB) to estimate the prevalence in the active workforce and the spread within establishments. Here, as suggested in the paper, the Red Cross might help, as they have experience in collecting blood (for blood banks) directly at establishments. Such an approach might also reduce nonresponse as it eases the response burden.

Finally, we wonder whether the suggested panel study of disease progression can yield the desired outcomes. In the introduction to the paper, the authors convincingly argue the difficulties in official estimates on the spread of the disease and that the decisions of those who get tested and who not are somewhat arbitrary. Therefore, we find the suggestion to use such administrative data on known positives as a sampling frame for this kind of study somewhat unconvincing.

In sum, we really enjoyed reading the paper and the formulation of appropriate research designs to investigate the spread of SARS-CoV-2. We hope that the points we raised in our commentary will stimulate a debate on these issues so that COVID-19 research will be able to make important contributions to the scientific understanding of this pandemic as well as the political management of the related public-health and economic crisis.

Michael Weinhardt
TU Berlin
Julia Bartosch
FU Berlin

Reply to Weinhardt and Bartosch

We wish to thank the editor for the opportunity to discuss some points raised by the commentators.

Although a national sample stratified by federal states would be desirable, the resulting sample size for state comparisons is beyond the capacities of existing fieldwork organisations. For example, the largest face-to-face survey outside official statistics is a readership survey (Media-Micro-Census GmbH, 2020)[6]. For this survey with about 33.000 CASI interviews, five institutes share the fieldwork. So the main argument is not financial, but organisational. Therefore, either new organisational structures have to be created, or the fieldwork has to be extended in time, making comparisons at least complicated. So we see currently no way to implement a timely national seroprevalence survey allowing for comparisons between states at the level of precision described in our contribution.

The use of nurses for collecting blood may be an option in many countries, but it is not in Germany. Drawing venous blood is in Germany a task, which may be delegated by a medical doctor, but only if the doctor is in physical proximity (Krull, 2015). Therefore, the suggestion to use a field of nurses is not compatible with German law.

Due to the lack of a central register, the use of municipal registries sampling is a tedious process in Germany. In the case of sampling for pandemic research, the public interest could be considered as given. The law covers sampling for scientific purposes from registers. Therefore only lack of resources could be a hindrance. Our estimate of the required

[6]Citations are listed in the references of the main article

time for a sample selection of two months was shared informally by the Association of German Municipality Statisticians (VDSt). However, some municipalities will miss the deadline. Therefore, it is common practice to contact more municipalities as needed. Late responding communities are replaced by communities in the same federal state and of the same size. If the duration of response is unrelated to the dependent variable, estimates will be unbiased.

The commentators recommend random-walks. They consider the selection of respondents within a household as the largest problem of this selection method. However, it has been shown that people living in nonstandard housing situations (non-housing buildings such as schools, industrial areas or administrative buildings) are likely to be missed by random-walks (Schnell, 1991). This under-coverage problem might add a more severe bias to estimates. Furthermore, a random-walk will, in most cases require that the interviewer has to convince the household to participate in a seroprevalence survey. That seems unlikely to be successful in the majority of cases. Since the random-walk will not yield a complete first name-last name combination for a selected address, nonresponse follow-ups will be difficult. Therefore, we consider random-walks for national seroprevalence surveys as unlikely to be successful.

Nonresponse in health surveys has the potential of missing data-generating mechanisms, which are not missing at random (NMAR). Sample selection suffering from NMAR can not be corrected by weighting procedures (Schnell, Noack, & Torregroza, 2017). Therefore, extensive fieldwork procedures to reduce the amount of nonresponse seems necessary. Details for fieldwork in Germany are described by Schnell (2019).

We suggested a panel study of disease progression. The aim of this study is not to estimate the proportions of cases without any symptoms. That requires a panel study of persons without regard to their diagnostic status. We discussed the problems of such a panel in our paper. However, we described as aim of the panel study of known positive cases as (1) the estimation of the proportion of mild progressions and (2) the identification of symptom clusters. Identifying correlating symptoms require a diagnosis of a disease. Cases without symptoms are unknown and can not be studied. If the seroprevalence survey yields a symptom-free patient, he will be included in the register of known cases. Therefore, aim (2) can be achieved by the suggested panel at low costs. The same applies to the purpose (1).

Finally, we consider the task of identifying unknown infections clusters as beyond the capabilities of population surveys with small sampling fractions. If no auxiliary information is available, no selection mechanism described in the sampling literature will yield estimates with smaller MSEs than an SRS respective a PPS sample. The only option we see is to abandon the idea of a point estimate at all and instead test if the prevalence exceeds a preset threshold. Lot quality assurance sampling (Levy & Lemeshow, 2008) (LQAS) is rarely used in the social sciences but may be useful here. However, we see no mathematical justification for sampling business establishments to improve prevalence estimates of the population as suggested by the commentators.

Rainer Schnell, and Menno Smid