HOW DO WE DECIDE HOW REPRESENTATIVE OUR DONORS ARE FOR PUBLIC HEALTH SURVEILLANCE?

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Manuscript type: HOW DO I….

Source of Support: Canadian Blood Services
Conflicts of Interest: The authors declare that they have no conflicts of interest.
Word Count: 2386 words
Number of Figures 3
Number of Tables 1
Number of References 21

Acknowledgements: We thank Jennifer Delorme for preparing figures and tables.

Running Head: Donor Representativeness for Public Health

Key words: Public health, surveillance, blood donors

Abstract

Background: Surveillance of blood donors is fundamental to safety of the blood supply. Such data can also be useful for public health policy but tend to be under-utilized. When the COVID-19 pandemic arrived, blood centers around the world measured blood donor SARS-CoV-2 seroprevalence to inform public health policy. There is now a movement towards blood centers becoming more involved in public health research and surveillance post-pandemic. However, blood donors are a healthy population and not representative of all segments of the general population. In this article we explain how blood centers can evaluate their donor base to understand which part of the general population they are representative of.

Study Design and Methods: Methodologic approaches for evaluating samples relative to the target population were reviewed. Blood donor data that are available to most blood centers were identified and application to assessing representativeness of blood donors were evaluated.

Results: Key aspects of blood donor data to compare with general population data include donor selection criteria, health indicators, geography and demographics. In some cases, statistical adjustment can improve representativeness.

Discussion: Comparing key blood donor data with corresponding general population data can define the subset of the general population for which a particular blood center's donors may be representative of. We suggest that donors are an ideal convenience population for surveillance of infectious agents which are frequently asymptomatic and main routes of transmission are not deferrable, for studying the natural history of disease in an initially well population, and for vaccination serology surveillance.

Introduction

Testing and monitoring blood donations for markers of infectious disease is a pillar of blood safety. It also contributes to public health surveillance in a number of ways. For example, in many countries there are legal requirements to report positive tests for certain infections to public health authorities. When new blood borne pathogens emerge, testing of blood donors often makes a valuable contribution to public health surveillance. A good example is West Nile Virus, which emerged in the United States and Canada in 2002 [1]. In Sweden and Denmark, the Scandat database has been in place for a number of years utilizing health records and donor data to understand blood transmissibility [2]. However, blood services have not typically recruited donors to participate in studies unrelated to blood safety or donor selection criteria. A notable exception is the Danish Blood Donor Study which aims to understand why donors are healthy, and to monitor development of disease in an initially healthy population [3]. Donors are invited to complete questionnaires, provide additional samples and permit their information to be linked to administrative databases for hospital admissions and registries of various chronic diseases and deaths [3].

Since late 2019 the SARS-CoV-2 pandemic brought an unprecedented need for public health surveillance data to inform predictive modelling on the progression of the pandemic and validate models. Blood services around the world carried out seroprevalence studies, capitalizing on already recruited donors and blood collection infrastructure [4,5]. Many countries are now interested in exploring ways in which previously under-utilized blood donors and donor data can contribute to public health research/surveillance [6]. In the United States the Centers for Disease Control and Prevention and the Recipient Epidemiology and Donor Evaluation Study (REDS -IV-P) team are collaborating on a national SARS-CoV-2 seroprevalence program among regular donors with a view towards transforming their study into a surveillance system for emerging pathogens [7,8].

The purpose of studying a sample of blood donors will always be to understand something about the wider population from which the sample was drawn. For blood safety it is fairly straightforward: results from a random sample of blood donors can be extrapolated to all blood donors. In other words, the sample is representative of blood donors as a whole. What about for public health purposes? Blood donors may not be representative of the whole general population. They are in general a healthy subset, but how do you define that subset?

In this article we describe a stepwise approach to assess the characteristics of donors relative to the general population. We provide examples and include "how-to" tips. We discuss how this assessment can be used to define the donor population and decide which types of blood donor research to do.

Donor selection criteria

Every blood center has elaborate donor screening procedures to ensure donor and recipient safety and vein-to-vein traceability of a product back to a given donor. These include donor registration, a health assessment questionnaire, a standard set of donor eligibility criteria, a mini-physical assessment (blood pressure, pulse, and temperature – these vary by blood center), and a hemoglobin screening test.

Donors must present some form of identification and have a fixed address and must be sufficiently mobile to present at a donation site and transfer on and off the donation chair. The questionnaire is usually available in one, or at most two languages. These pre-requirements would lead to the deferral of people with precarious housing arrangements, mobility problems, illiteracy, or poor fluency in the required language.

Table 1 lists some common deferral categories. These may vary considerably in different countries, based on epidemiology of infectious agents and regulatory requirements [9]. In most countries, gay and

bisexual men are deferred for a given period of time after having sex with another man. In general, European regulations, based on the EU directive of 2004 are more stringent regarding deferrals for medical conditions, while these conditions are not covered in US FDA regulations, resulting in more liberal practices [10]. This would result in a healthier donor population in European countries compared to the US and Canada.

Deferrals based on specific criteria or findings on exam or hemoglobin screening may be temporary (such as a 3-month deferral for travel to a malaria-risk area) or permanent (such as type 1 diabetes on insulin). However, even temporary deferrals may result in longer term donor loss, either because of recurrence of the behavior or discouragement of the donor. For example, people who travel frequently to deferrable destinations may find that they are rarely eligible to donate and decide not to donate. On site donor deferral rates provide little idea of the impact of criteria since many people who are eligible in theory may self-defer, in part due to public misconceptions about eligibility [11,12].

Careful review of donor selection criteria is a critical step in understanding the segment of the population donors may be representative of (See Table 1). Models to estimate the eligible population have been published [13,14] but they likely over-estimate the proportion ineligible because population data on health conditions are less specific than many donor criteria. It is possible to make a more qualitative judgement in a simpler way (See Figure 1). Start by dividing the deferral reasons into permanent and temporary, and then sort by the expected frequency in the general population. (Note that not all countries will have a published expected frequency and may need to estimate). This will identify the deferrals likely to have the greatest impact because they will affect the most people. Take note of criteria that are likely to capture the same person. For example, people with deferrable cardiovascular risk may also be older so if there is an upper age limit, it would capture the same individual. Using population data, you can gain an idea of the proportion of people who would be deferred permanently. For the temporary deferrals you can use population data to see how many people could have that

reason for deferral, but also make a judgement as to how likely it is that someone who had that reason at some point, but then became eligible would not donate because of it (e.g. perceived ineligibility). There is currently some data defining the impact of temporary deferral on donor self-selection; temporary deferrals have the greatest impact on return rates of donors at the start of their donation careers [15].

Health indicators in donors

The healthy donor effect has been described in European countries such as Denmark [16] and the Netherlands [17]. It is a selection bias in which people who choose to become blood donors perceive themselves as healthy. Likewise, people who perceive themselves as less healthy are less likely to donate. People who continue to donate do so because they are in good health. The healthy donor effect will be impacted by a combination of the donor selection criteria and perceived health. However perceived health will be different in different cultures and environments. Populations with poorer general health may be expected to have donors with poorer general health. This appears to be the case. In Denmark, known for a health-conscious general population, about 35% of women and about half of men were overweight [18]. In a study in southern US, where there is an epidemic of obesity, about half of young donors and nearly three quarters of donors over 23 years old were overweight [19].

This example highlights the importance of evaluating health indicators in donors and, ideally, comparing them with a random selection of individuals from the general population (see Figure 2). As general population samples may be difficult to obtain, an alternative could be comparing donor results to population statistics, albeit less robust. Some health indicators may be collected routinely by the blood center such as blood pressure and body weight or hemoglobin concentration in first time donors. Comparing these with population statistics would provide insight into how similar donors are to the general population. European blood centers and those in some other countries such as Canada often

document all medications that donors are taking. The proportion of donors taking different classes of medications would be informative as to the health status of donors. More detailed comparison could be done by surveying donors for health indicators and comparing with general population surveys.

Demographics

Demographic variables such as age, sex, and residential location are very informative of the donor base (See Figure 2). How similar are they to the general population? Mobile collection sites expand the collection area of fixed donation sites, but not all locations/neighborhoods are served. In addition, people in a given area may be more or less likely to donate. Indeed, minority groups tend to be under-represented [20]. General population summary data are available from government websites in many countries. A simple first step is to sort data from the donor base by different variables and then compare with similarly sorted or stratified data from the general population. Some blood services collect data on racial group which is useful for comparing the donor base with the general population. Socio-economic status is an important characteristic that is often not captured in donor data; however, neighborhood-level indices can be used as a proxy.

Statistical adjustments

What if donors are demographically different from the general population? It depends on how different they are. If the difference is only by a few percent (e.g. 51% of donors are male vs 49 % in the general population), it may not be very important. Start by comparing the proportion of relevant characteristics such as age, sex, and race in your blood donor sample with general population estimates.

Statistical adjustments use characteristics measured in the sample for which the distribution in the general population is reliably estimated. (e.g., using demographics measured in a census). Many

adjustment methods re-weight outcome measures so individuals with under-sampled characteristics are more strongly considered (e.g., calibration weighting, a process known as raking, See Figure 3). Other methods use regression to predict the outcome of interest for non-sampled individuals (e.g., multilevel regression with poststratification). Studies comparing statistically adjusted non-random samples to random samples have found that adjustment does not always eliminate bias, and that multilevel regression and poststratification often outperforms weight-based methods [20-22]. Statistical adjustment methods have not been systematically assessed using blood donor data, but their reliability likely varies depending on the adjustment method, and characteristics used. Importantly, these methods can adjust for unbalanced representation, but they cannot correct for systematic exclusion of large swaths of the target population. For example, donor data cannot reliably estimate prevalence in a target population that includes age groups that cannot donate blood. Despite these limitations, statistical adjustments can improve the generalizability of blood donor data, and using statistical adjustment is certainly preferred over naively assuming blood donors are representative.

Donor suitability for infectious disease surveillance

Because every effort is made to defer donors at risk of blood borne infections such as HIV, donor HIV rates are several fold lower than general population estimates [23]. Clearly donors are not suitable for estimating the HIV prevalence and incidence of the general population. However, because donors have been carefully screened for risk factors, and generally believe that their blood is safe for recipients, they may provide a good indicator of the infection rates in the subset of the population considered low-risk who are not targeted by physicians and public health campaigns for diagnosis and treatment.

Some infections do not have obvious risk factors or have risk factors that are not a reason for donor deferral, such as spending time outdoors in rural areas. Good examples are vector borne infections such

as *Babesia microti* (carried by ticks) and West Nile Virus (carried by mosquitos). Cases reported to public health are most often from symptomatic individuals who seek medical care. Blood donor surveillance can provide data on the unseen proportion of cases which are often more numerous than those that are reported. For both of these infections people often do not have symptoms and would be eligible to donate blood. Data on the true proportion of cases is important for estimating the incidence of symptomatic illness *1* and risk of future outbreaks. For example monitoring of mosquito borne viruses (Zika virus, Chkungunya virus and Dengue virus) infections in donors in Brazil showed that infection rates are not always aligned with annual outbreak seasons in different regions [24].

Infections that are not transmissible by blood, or by risk behaviors that often lead to donor deferral (high risk sexual behaviors, injection drug use) are potentially appropriate, with the caveat that people who are unwell would not be able to donate. SARS-CoV-2 antibody studies are a good example [5].

Donor suitability for health surveillance

As described above, donors must meet screening criteria to ensure that they are in good health at the time of donating. They may have underlying health conditions which will vary depending on a country's specific health criteria and the underlying health status of the general population. With this in mind, there are a number of areas for which donors could be suitable for health surveillance.

Some health measurements are part of the donation process. Hemoglobin or hematocrit is measured in all donors before donating, and if recorded electronically can provide a snapshot of the hemoglobin status of the apparently healthy population. This is best done in first time donors because prior donations will reduce iron status and eventually hemoglobin levels. Longitudinal monitoring of donors could be done to understand risk factors of health conditions in an initially healthy population. Additional data collection would be needed such as questionnaire, extra testing of samples and linkage

with administrative databases (e.g. hospital diagnostic data). A good example is the Danish Blood Donor Study [3]. Donors are a good population for sero-surveys of vaccine preventable infections. These are important for the evaluation of national vaccination programs.

Unique aspects of conducting donor research

Due to the ever-present need for blood products the numbers of blood donors far exceed the number of samples and potentially questionnaire data available in stand-alone research studies, making them both a practical and low-cost option for research. Donors can be consented for public health or blood safety research in general as part of routine consent to donate. However, blood donor research generally must not interfere with the donation process or routine blood testing. It can be challenging to harmonize data collection across jurisdictions in areas such as Europe or the US where there are multiple independent blood services. Because the operational constraints of blood services often result in larger numbers of donors from certain geographic areas, sample selection procedures need to consider this potential bias.

Summary and Conclusion

Because people must be healthy and at low risk of transfusion transmissible infections to donate blood, donors will be a healthy subset of the general population. Central to interpreting donor surveillance is clearly defining the donor population. Important influencers of donor representativeness are donor demographics, geographic distribution, donor selection criteria, perceived eligibility and motivation to donate and background health status of the general population. These will vary by region, hence every country or region wishing to use donor data to inform public health policy should undertake their own assessment. In some cases, mathematical adjustments can help to reduce skewing of certain demographic groups. Based on the assessment, it will be possible to decide which types of surveillance donors in a particular region would be best suited to. We suggest that donors are an ideal convenience

population for surveillance of infectious agents for which many people are asymptomatic and where the main routes of transmission would not be a reason for deferral, for studying the natural history of disease in an initially well population, and for vaccination serology surveillance.

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Pre-requisites	- Literacy - Fluent in screening language - Have fixed address - Adequate physical mobility
Basic Criteria	- Minimum and maximum age - Minimum hemoglobin - Not pregnant or recently pregnant
Infectious risks Permanent and Temporary deferrals	- Known previous infection with TTIs - Risk factors for TTIs - High risk sexual behaviours - History of injection drug use - History of incarceration - Previous residence in malaria risk area - Previous residence in a vCJD risk area
Donor Health Permanent and Temporary deferrals	- Cardiac disease - Diabetes - History of cancer - Medication use
Eligible but may not donate	- Perceived ineligibility/health concerns - Blood donation not part of culture - Blood collection site not easily accessible for social or geographic reasons - Fear of needles

Table 1 Reasons specific to blood donation that may impact donor representativeness of the general population

There are numerous eligibility criteria that can exclude certain people from donating. Note that many criteria are temporary deferrals and individuals may be eligible at another time. There are also people who are eligible to donate but do not. The “opt-out” group may also be fluid.

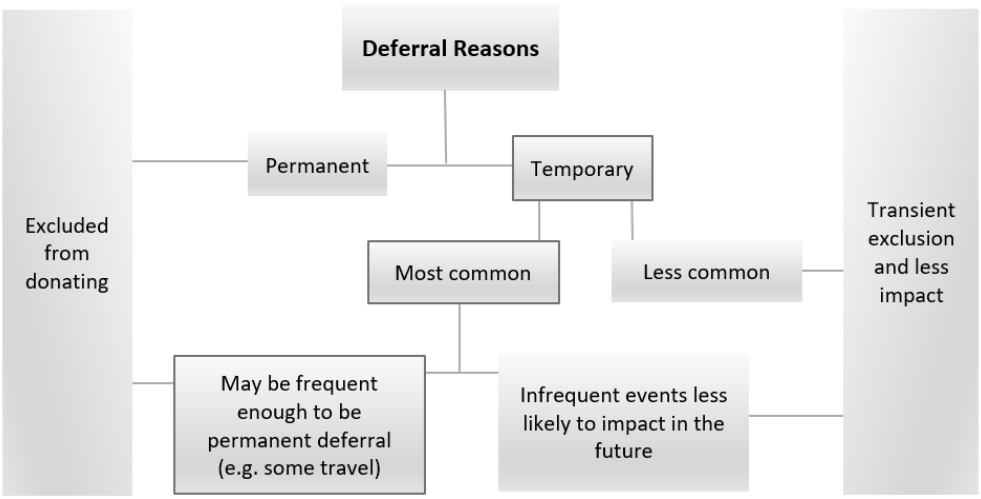

Figure 1 Schematic diagram for evaluating the impact of deferral

Permanent deferrals and temporary deferrals for repetitive behaviours will exclude individuals from donating. However, temporary reasons for deferral will only have an impact if the behaviour or risk is recent. Temporary deferral for rare events will have minimal impact.

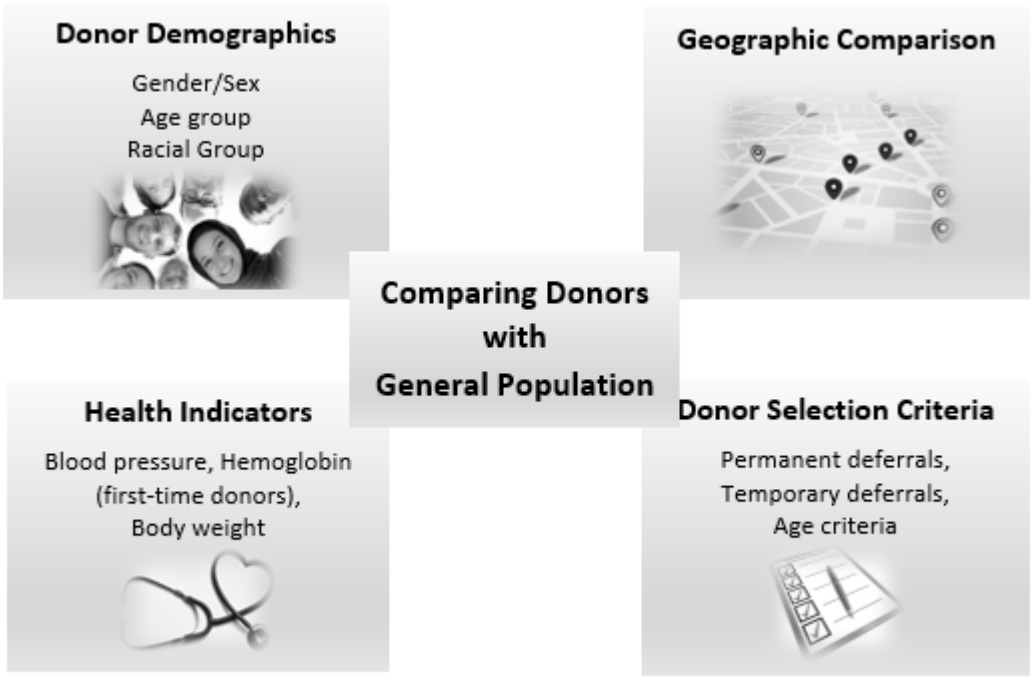

Figure 2 Comparing donors with the general population

There are four main areas which should each be evaluated to understand which subset of the general population donors may be representative. Note that every region or blood center may be different.

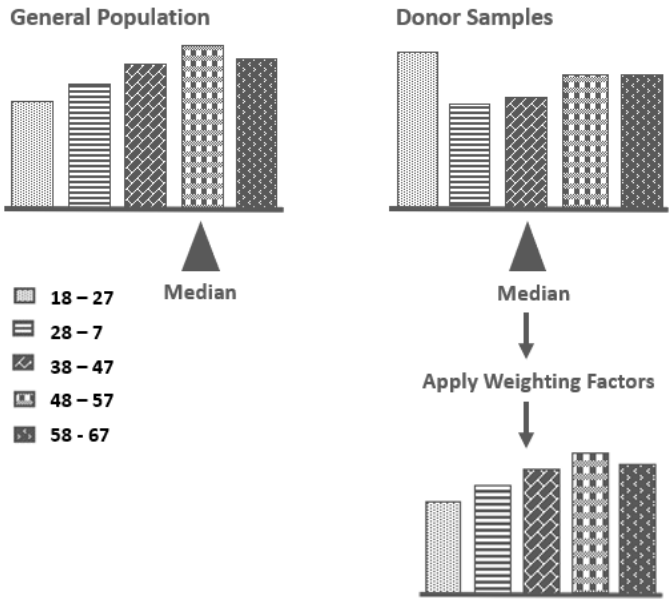

Figure 3 Weighting a donor sample to be demographically similar to the general population

In this example, the age distribution of donors differs from the target population; notice that a larger share of donors are in the youngest age group, and the target population tends to be older. Calibration weighting can correct for under- or over-representation of age groups when estimating parameters for the target population, which is particularly important when parameters may differ across age groups.