Peer Review File

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Reviewer A

Making Every Question Count

The authors have put together a nice example of providing an evidence-base for removing a pre-donation question. The question asks donors "In the last 12-months have you had an illness with swollen glands and a rash, with or without a fever?" which leads to further questioning and potential for a 12-month deferral. The question was originally used to identify donors who may have had HIV infection before testing was available but now superseded by HIV NAT testing. They used data up to 2016 and have been transparent about the various sources of data and the limitations of the study, the main one being that they do not know if the deferred donors who did not return are actually HIV positive. Their findings are that in their setting of low HIV incidence and sensitive HIV NAT testing, the question on symptoms does not appear effective.

On reading this I had some questions that I think it would be useful for the authors to address:

1. The authors mention the non-specificity of the symptoms asked about and give some examples of other infections Epstein-Barr virus, cytomegalovirus (CMV). However, they do not say whether, on further questioning, if these were suspected the donors would still be deferred for 12 months or given a shorter deferral or no deferral.

Response:

This is an excellent question. As is mentioned currently (line 86, page 4) any potential donor that declares 'ARS symptoms' is counselled by a medical officer and the deferral is applied at their discretion. Of the 90 donors who declared symptoms, only 59 were deferred after further questioning. On review of reasons for allowing donation in the remaining donors, a clear source of symptomatology (i.e. recent EBV infection) in the patient history was flagged in some cases. We have added information to the results section to reflect this (line 208 – 213, page 10).

2. Given that mpox symptoms also include rash and swollen glands could the authors say whether the question would have any utility for other infections, or if other pre-donation questions are likely to cover it. Is there a more general question on recent infection for example?

Response:

This is a very good point – the Lifeblood Donor History questionnaire in its current format is quite extensive and does include a more general question on whether the prospective donor has been unwell, seen a doctor, undergone investigation, had an STI, or used medication since last donation

for existing donors or in the past 12 months for new donors. A diagnosis of mpox or other infectious illness including STIs would be detected by these questions. The ARS question's inclusion in the questionnaire is purely to screen for ARS symptoms.

3. Did the authors consider any other options for the question eg a shorter time frame for asking about symptoms and/or a shorter time frame for deferral if symptoms were thought to be related to acute resolving infection or were the only options to keep or omit the question.

Response:

It is true that if the question was to be retained that shortening the time frame would logically result in less unnecessary donor deferrals. However, there are currently other questions on the Donor History Questionnaire that relate to recent infections and donors are deferred if they have been recently unwell – see response to 2 above. Further, given that we found that no donors who declared possible ARS symptoms and subsequently donated tested HIV-positive; and no donor testing HIV-positive who experienced ARS symptoms reported rash and lymphadenopathy in combination the question itself does not seem to be helpful for detecting HIV and could be entirely omitted without consequence.

4. Could the authors comment on whether the question would retain any utility in the era of increasing PrEP use? Or if in their setting, screening is still expected to detect infection. It would be useful to say how HIV is screened for by ARC Lifeblood.

Response:

Ensuring donations do not transmit infectious diseases is a key priority of Lifeblood and blood donors must complete a questionnaire every time they donate to assess their risk. In Australia, any behaviour that would necessitate a prospective donor to use PrEP would result in deferral from blood donation for 12 months, rendering the ARS question unnecessary. In addition, other questions and deferrals for HIV risk exposure include needlestick, blood/body fluid exposure / splash and MSM to name a few. The screening would therefore be expected to detect infection as no prospective donors should be on PrEP if they have truthfully answered the questionnaire.

We have included a statement on the testing for HIV by ARC Lifeblood in the methodology section (line 179 – 190, page 8).

5. In table 1, why is the MSM deferral not grouped with the other sexual deferrals?

Response:

We thank the reviewer for their comment and have now grouped the MSM deferral with other sexual deferrals.

6. In table 2, I think the order should be switched so number of returns shown first and then timing of those returns.

Response:

We thank the reviewer for their comment and have switched the ordering in this table.

7. Could authors provide rationale for the timeframes used – why only up to 2016 (apologies if I missed it!) Were the MSM and other partner deferrals reduced after this point for example. Are authors able to say whether the question has since been excluded?

Response:

The ARS question is very much still included in the Donor History Questionnaire to this day, as are the MSM and partner deferrals. The data is unfortunately only available until 2016 as this was data available to us for analysis at the time the study was conducted.

Reviewer B

The authors show that deferring donors based on self-reported ARS symptoms is not effective for identifying potentially HIV positive donors, and show that this leads to unnecessary donor loss. However, it is unclear from the manuscript how these results are applicable or even useful to other international blood banks as information on use of these deferral criteria in a more international context is missing. Additionally, important details are missing from the methods and results section, such as information on the setting of the study and a table concerning baseline information of the population. Authors should consider submitting this manuscript as a letter or short report.

Introduction: Is there any information on DQ-questions regarding HIV risk factors in other countries? How useful is this information in a more international context?

Response:

The AABB Full Length Donor Questionnaire (available at Blood Donor History Questionnaires (aabb.org)) does not contain a question equivalent to the Lifeblood ARS question and we are not aware of any blood service which does include such a question in their DQ, so this issue is primarily relevant to Lifeblood.

Authors should include information on the HIV prevalence in Australia, to illustrate how big of a threat HIV might be to blood safety.

Response:

HIV prevalence in Australia has since been included in the introduction section (line 77, page 4). Whilst HIV prevalence is low in Australia, Lifeblood considers donation safety a key priority and continues to question donors at every donation for risks of HIV.

The methods sections should contain a description of the blood establishment, including their area of service, amount of donors/locations, general eligibility criteria etc. Additionally, a short description of the study design should be given. It is unclear how donors are invited for a donation. Do they receive an invitation? Are there blood drives? Are deferred donors notified when they can donate again? This is essential information to be able to interpret and compare return rates.

Response:

This information has since been included in the methods section (line 111 – 118, page 6).

Line 77: What are the criteria for being deferred after ARS? The author could consider describing this in more detail in the method section.

Response:

There are no strict criteria and the deferral is ultimately at the discretion of a medical officer. A statement to reflect this has been included in the methods section (line 123 – 125, page 6).

Line 102: Could the author provide a clear overview (maybe in table form) on the main contents of each used database.

Response:

We have since incorporated this information into a table (Table 1, page 16) and hope this helps to provide a clear overview.

Methods: The methods-section would benefit from a flowchart which describes how many donors and which information were included from which database. Such an overview is now lacking which negatively impact the readability of this section.

Response:

We agree that the multiple databases can be difficult to follow and have since created a flowchart (Figure 1, page 22) to help assist with this respect.

122: What is the definition of a return? Donation attempt within 1 year, or 2 years? What if donors were deferred just prior to May 2016, were they counted as not returned?

Response:

We have since added some text to the methodology section to clarify this (lines 144 – 146, page 7). Whole blood donors are automatically excluded from donation for 12-weeks after successful donation. Day 1 was started after this period (line 150, page 7). The maximum follow up period was up to 579 days so some donors subsequently had a longer follow up period than others (with a minimum follow up period of 12 months).

126: What does the 579 days of follow-up entail? This seems quite a random number.

Response:

This was the maximum length of time the data-set allowed and hence this follow-up time was used. A shorter follow up time could have been selected (i.e. 12 months) however there was more data available and hence this time was used.

Line 135: This is unclear, did you use a Mann-Whitney U test or a t-test? As one is non-parametric and one is parametric. When using a Mann-Whitney U test, you automatically assume your data was not normally distributed. If that is the case the author should state that here.

Response:

Thank you for this feedback, this has been updated.

Line 138: "Data were collected regarding a selection of 12-month deferrals." What were the inclusion criteria for this selection?

Response:

All 12-month deferrals were compared (line 163, page 7). This has since been updated.

Line 147: See previous comment, please mention here that your data was not normally distributed.

Response:

Thank you for this feedback, this has been updated.

158: What does the author mean by de-identified? Anonymized or pseudonymized?

Response:

The data was completely anonymized.

Results: A table 1 is missing with the baseline characteristics of the studied population

Response:

Could the reviewer please clarify what baseline characteristics would be useful to include in table format? The Lifeblood Databases only include information regarding BMI, gender and age of donors as well as specific answers to donor questionnaire questions regarding risk factors.

Line 162: 90 donors of how many?

Response:

Unfortunately, this data was not captured by the dataset and is not available for inclusion.

Table 2: It is unclear what the column No. entails. It seems like it is the amount of donors that returns to donate, but then it is already stated in the column "No. returning, %, 95% CI". I would consider removing the No. column and moving the "No. returning" to the left.

Response:

This has since been updated

Table 3 uses the terms "new donors" and "repeat donors", however, these terms were not used before in the manuscript. Please define them in the methods section.

Response:

We have deleted the terms new and repeat donors to aid in clarity.

Discussion: As the data from MODB encompasses only for 2 years, authors should reflect on the fact they might overestimate the non-return of donors that were not deferred for ARS.

Response:

This is true – we have added a comment into the discussion section (line 293, page 12). However, we note that this group had higher return even with this limitation compared to those that were deferred which is a key finding.