PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile: A Québec-based plasma donor biobank to study COVID-19 immunity (PlasCoV)
AUTHORS	Germain, Marc; Lewin, Antoine; Bazin, Renée; Dieudé, Mélanie; Perreault, Josée; Boivin, Amélie; Grégoire, Yves; Renaud, Christian

VERSION 1 – REVIEW

REVIEWER	Gottschick, Cornelia Martin-Luther-Universitat Halle-Wittenberg
REVIEW RETURNED	13-Dec-2022

GENERAL COMMENTS	Thank you for asking me to review the manuscript „Cohort profile: A Québec-based plasma donor biobank to study COVID-19 immunity (PlasCoV)". The manuscript is well structured and written comprehensibly. I only have one comment: It would be nice to add more information on sample handling, i.e. number and volume of aliquots. As I understand, there is only one aliquot per donation available, so that may be a limitation as well.

REVIEWER	Stærke, Nina Breinholt Aarhus University Hospital, Infectious Diseases
REVIEW RETURNED	14-Dec-2022

GENERAL COMMENTS	This is a cohort profile study presenting a longitudinal cohort of plasma donors where plasma samples are collected for SARS-CoV-2 serology at each donation. Serology data is combined with registry data on vaccination and test results. The cohort is large and quite well described and has potential to answer important questions about vaccine response, hybrid immunity etc. The cohort is overall well presented and I mainly have minor comments and questions: 1) Minor: The section "strenghts and limitations" should be placed in the end of the article. Additionally, right after the abstract should be a bullet-point section with a shorter description of strenghts and limitations. This is described in the author guidelines for cohort profile papers. 2) I would like the section "future plans" to not only be in the abstract but also in the main text, if possible with elaboration of any planned studies. 3) To me it was not quite clear how and when participants were asked to participate - Did they receive a letter, are they asked when they come in for donation or?. Are/has all plasma donors

	been asked to participate? This should be described more clearly in the text. This also includes mentioning the informed consent process. 4) Is the study still recruting participants? Would be nice to understand the process of inclusion a little better. 5) It would make sense to also report the median age of the participants and not only the proportion in each age-group. 6) Registry data: I think the registries should be described in a bit more detail (vaccine information and information about SARS-CoV2 testing). How complete are these registries? Will all vaccine information be captured? Which tests are included in the registry of infection data(PCR/quick-test/serology)? A little background information on the testing frequency/strategy in Canada in the study period could also be usefull for the reader. Another thing, mostly technical, is that it would be easier for the reader if the collection of data from registries was described earlier in the text. Currently it is placed in the very end of the cohort description, after mentioning the vaccine and infection data several times. 7) I was surprised to read that only 131 donors had an infection between two samples, it seems like very few. How many donors had infection overall? 8) Samples are taken when donors come in for donation; which makes participation easy for donors, but I believe it introduces a limitation that the samples are not taken systematically in relation to vaccination. This should be mentioned.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comments to the Authors
Comment 1.1: Thank you for asking me to review the manuscript „Cohort profile: A Québec-based plasma donor biobank to study COVID-19 immunity (PlasCoV)".
The manuscript is well structured and written comprehensibly. I only have one comment:
It would be nice to add more information on sample handling, i.e. number and volume of aliquots. As I understand, there is only one aliquot per donation available, so that may be a limitation as well.
Response: We thank the Reviewer for the opportunity to clarify this point. A 3 ml are collected and frozen for biobanking, and ~200 µL or 500 µL of the thawed, biobanked sample can be provided upon request. We have clarified as follows (underlined parts highlight additions):
Cohort description, Cohort establishment and overview, 3rd paragraph: "*A 3 ml sample is collected from the plasma bag and frozen for biobanking, and aliquots of ~200 µL to 500 µL of the thawed, biobanked sample can be provided upon request (so that each sample can be used to prepare at least 6 aliquots upon thawing)*."

Reviewer 2

This is a cohort profile study presenting a longitudinal cohort of plasma donors where plasma samples are collected for SARS-CoV-2 serology at each donation. Serology data is combined with registry data on vaccination and test results. The cohort is large and quite well described and has potential to answer important questions about vaccine response, hybrid immunity etc. The cohort is overall well presented and I mainly have minor comments and questions:

Comment 2.1: Minor: The section "strenghts and limitations" should be placed in the end of the article. Additionally, right after the abstract should be a bullet-point section with a shorter description of strenghts and limitations. This is described in the author guidelines for cohort profile papers.

Response: We thank the Reviewer for bringing this point to our attention. We have moved the detailed section on the strengths and limitations at the end of our manuscript. We have also added bullet points describing the main strengths and limitations of our cohort after the abstract.

Comment 2.2: I would like the section "future plans" to not only be in the abstract but also in the main text, if possible with elaboration of any planned studies.

Response: We have added such section towards the end of our manuscript, after “Findings to date”.
Comment 2.3: To me it was not quite clear how and when participants were asked to participate - Did they receive a letter, are they asked when they come in for donation or?. Are/has all plasma donors been asked to participate? This should be described more clearly in the text. This also includes mentioning the informed consent process.

Response: We have clarified as follows (underlined parts highlight additions):
Cohort description, Cohort establishment and overview, 3rd paragraph: “*Specifically, the pre-donation questionnaire asks donors if they are willing to give part of their regular donation for research purposes. A donor’s consent is considered valid for all donations, and so those who consent are not asked this question at subsequent donations. A donor can decide at any time, simply by giving verbal notice, to withdraw his/her consent for the use of his/her samples and data*”
Furthermore, please note that biobank participants were free to donate plasma if and whenever they wanted, as part of routine plasma donation. This is described in the following paragraph:
Cohort description, Participant characteristics, 8h paragraph: “*Donors were free to donate plasma if and whenever they wanted: They did not consent to a strict protocol involving regular, scheduled visits at specific time points.*”

Comment 2.4: Is the study still recruting participants? Would be nice to understand the process of inclusion a little better.

Response: We have clarified as follows (underlined portions highlight additions):

Cohort description, Participant characteristics, 1st paragraph: “*The recruitment of new donors ended on October 1, 2022; however, donations from individuals who consented to participate before October 1, 2022 will be collected up until March 31, 2023.*”

Comment 2.5: It would make sense to also report the median age of the participants and not only the proportion in each age-group.

Response: We have added the mean and median age of the participants in Table 1 and have revised the following sentences (strikethrough highlights deletions, underlined parts highlight additions):
Cohort description, Participant characteristics, 2nd paragraph: “*Among consenting donors, the most common age group was 18-29 yearsmedian age was 43.0 years (28.4%; **Table 23**).”*
Cohort description, Participant characteristics, 2nd paragraph: “*Relative to non-consenting donors, consenting donors tended to be younger (i.e., e.g., 18-29 years: 28.4% vs. 24.1% for the biobank and non-consenting donors respectivelymedian age: 43.0 vs. 48.0 years);), […]*”

Comment 2.6: Registry data: I think the registries should be described in a bit more detail (vaccine information and information about SARS-CoV2 testing). How complete are these registries? Will all vaccine information be captured? Which tests are included in the registry of infection data(PCR/quick-

test/serology)? A little background information on the testing frequency/strategy in Canada in the study period could also be usefull for the reader. Another thing, mostly technical, is that it would be easier for the reader if the collection of data from registries was described earlier in the text. Currently it is placed in the very end of the cohort description, after mentioning the vaccine and infection data several times.

Response: We have provided more background information on these registries and moved this information earlier in the text:
Cohort description, Variables: *"In addition to plasma samples, the biobank offers access to several variables that are collected as part of routine donor screening or linked to government registries. Variables collected as part of routine blood donation include demographic characteristics (e.g., age, sex) and clinical characteristics (e.g., blood type, recent blood-borne infections, diabetes), which (except for blood type) are all self-reported by the donor (Table 2). Data on COVID-19 vaccination were obtained by linking in-house donor data with the Système d'information pour la protection des maladies infectieuses (SI-PMI) — a government registry that captures all COVID-19 vaccinations covered by the universal, public health insurance in Québec (i.e., by the Régie* de *l'assurance maladie du Québec). Similarly, data on COVID-19 infections were obtained by linking in-house data with the Trajectoire de Santé Publique (TSP) — a government registry that captures data on SARS-CoV-2 infections detected by PCR tests performed on nasopharyngeal swabs. These tests were freely available to anyone experiencing COVID-19-related symptoms at the beginning of the pandemic, but have been restricted to priority groups (i.e., primarily health care workers and individuals aged ≥70) since January 5, 2022. If needed, additional variables (e.g., tobacco use, medication use, and occupational status) can be obtained through a supplemental questionnaire filled by donors during their donation."*

Comment 2.7: I was surprised to read that only 131 donors had an infection between two samples, it seems like very few. How many donors had infection overall?

Response: As reported in Table 1, 1662 (10.7%) consenting donors had at least one documented infection as of January 24, 2022. Of these, 712 (42.8%) had donated only one sample, leaving only 950 (57.2%) donors who had donated at least two samples and were thus at risk of experiencing an infection between the two donations. Furthermore, 1011 (60.8%) donors were infected in December 2021 or January 2022, leaving little time for a subsequent donation before the cut-off used to analyze our cohort (i.e., January 24, 2022). The seemingly low number of participants who contracted an infection between two donations is therefore largely due to the low number of at-risk patients. We have clarified as follows (underlined parts highlight additions):
Cohort description, Participant characteristics, 7th paragraph: "*Overall, 1662 (10.7%) donors had a documented infection as of January 24, 2022 (Table 3), including 131 (7.9%) donors with available samples before and after a documented infection. This seemingly low number of donors who contracted SARS-CoV-2 between two donations is largely driven by the low number of at-risk patients (i.e., either because they donated only once [N=712 (42.8%)], or because the timing of their infection left little time for a donation before January 24, 2022).*"

For the benefit of the Reviewer, another element that explains this seemingly low figure is that only *documented* infections were captured, i.e., PCR-confirmed infections that were detected by public health authorities and recorded in the registry *Trajectoire de Santé Publique (TSP)*. According to seroprevalence studies [1,2], these registries underestimate by at least 1-2 folds the proportion of the population with a history of infection, which partially explains the low proportion of previously infected donors. Notably, this underreporting was further compounded during the omicron wave, as testing resources were overwhelmed by the number of cases.
References:

[1] Lewin et al. Seroprevalence of SARS-CoV-2 antibodies among blood donors in Québec: an update from a serial cross-sectional study. Can J Public Health. 2022 Jun;113(3):385-393.
[2] Lewin et al. SARS-CoV-2 seroprevalence among blood donors in Québec, and analysis of symptoms associated with seropositivity: a nested case-control study. Can J Public Health. 2021 Aug;112(4):576-586.

Comment 2.8: Samples are taken when donors come in for donation; which makes participation easy for donors, but I believe it introduces a limitation that the samples are not taken systematically in relation to vaccination. This should be mentioned.

Response: We thank the Reviewer for the opportunity to clarify this important point. We have added the following limitation (underlined parts highlight additions):

Strengths and limitations, 2nd paragraph: "*To begin, the large number of samples is made possible in part because donors are free to donate whenever they want, i.e., they did not agree to participate in a research that involves a rigid protocol with scheduled visits. As a result, samples are not collected systematically after an event of interest, such as vaccination or infection, although the large number of samples as well as the participation of frequent donors who provide samples on a regular basis thereby increasing the likelihood of having samples within a reasonable time frame relative to vaccination or infection , mitigate this limitation."*