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Cohort profile: A Québec-based plasma donor biobank to study COVID-19 immunity (PlasCoV)

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Abstract

Purpose

Long-term humoral immunity to COVID-19 is not well understood owing to the continuous emergence of new variants of concern, the evolving vaccine- and infection-induced immunity, and the limited follow-up of previous studies. As the blood service in Québec (Canada), we established in April 2021 a COVID-19-focused biobank.

Participants

As of January 2022, included 86,229 plasma samples from 15,502 regular donors (age range=18-84 years, female %=49.7%), for an average of 5.6 donations per donor. Nearly two thirds (65.6%) of biobank donors made at least 2 donations, with many donors having provided samples pre- and post-vaccination (3061 [19.75%]) or pre- and post-infection (131 [0.85%]), thus allowing longitudinal studies on vaccine- and infection-induced immunity.

Findings to date

Comparative analysis of the immune response after the first and second dose of the BNT162b2 COVID-19 vaccine among SARS-CoV-2 naïve and previously infected individuals revealed that a single vaccine dose administered to previously infected individuals yields a maximal immune response. In contrast, SARS-CoV-2 naïve individuals required two vaccine doses to produce a maximal immune response. Furthermore, the results of a four-phase seroprevalence study indicate that the anti-N

antibody response wanes quite rapidly, so that up to one third of previously infected donors were seronegative for anti-N.

Future plans

This plasma biobank from frequent and motivated donors, and the longitudinal nature of the biobank, will provide valuable insights into the anti-SARS-CoV-2 immune response and its persistence in time, and the effect of vaccination and of viral variants on the specificity of the antiSARS-CoV-2 immune response.

Strengths and Limitations

The herein described biobank has several strengths. To the best of our knowledge, this would be the largest biobank of plasma samples dedicated to COVID-19 research, with >80,000 samples from >15,000 donors and new samples continually being added until at least December 2022. Furthermore, the large subset of donors with ≥2 samples (65.6%) – along with the high frequency of donations in this subset (i.e., median: once every 29.0 days) – enables the conduct of longitudinal analyses on COVID-19 immunity. Another strength is that donors provided a broad consent, which allows researchers to recontact them for other projects (e.g., supplemental questionnaire). Lastly, the cost of establishing the biobank was minimized since the infrastructure and personnel required for sample collection were already in place at our blood collection sites. Given these strengths, our biobank may serve as a model for other blood operators and government partners who would be interested in reproducing our initiative elsewhere.

Certain limitations should nonetheless be considered when using our biobank samples. First, only plasma samples are available, such that the biobank cannot be used to study cell-

based immunity. Researchers interested in studying cell-based immunity may want to contact BCQ19, which routinely collects peripheral blood mononuclear cells.[1] Second, despite the large sample, the plasma donor population is not fully representative of the overall Québec population, as expected since plasma donors are typically more representative of the healthy adult population. All exclusion criteria for plasma donations were also exclusion criteria for the biobank including immunodeficiencies, active infection, recent cancer among other chronic diseases. Third, the database associated with our biobank does not include information on disease severity, such as hospitalization or intensive care unit admission. Fourth, the database does not include information on socioeconomic status, such as income and education. However, the six-digit zip code can be used to generate a proxy index for socioeconomic status.

Introduction

Despite remarkable progress, our understanding of the long-term, humoral immunity to COVID-19 is incomplete owing to a number of challenges. The emergence of new variants of concern, such as Omicron, continuously challenges prior assumptions and data on the effectiveness and persistence of COVID-19 immunity.[2,3] Furthermore, amid mass vaccination, disentangling infection and vaccine-induced humoral response to SARS-CoV-2 has become increasingly difficult to inform public health authorities.[4–6] Notably, the vast majority of published serological studies used a cross-sectional design, and hence do not provide individual-level data on COVID-19 immunity.[7] The more limited number of longitudinal studies that have been conducted had follow-up periods <12 months[8–19] and lacked long-term funding commitment. Clearly, new initiatives are needed to overcome these barriers.

Historically, biobanks have spurred research efforts on novel or rare diseases[20] and would likely help address the aforementioned challenges for COVID-19 research. They do so using highly standardized, quality-controlled processes to analyze a large number of biological specimens which are made available to the research community. In addition, biobanks are subject to regulatory oversight to protect donors' rights. Virtually all biobanks collect a "broad" consent that allows for samples to be used for multiple research purposes.[21] For researchers, this practice (while controversial)[22] alleviates the burden associated with seeking consent.

Existing COVID-19-focused biobanks are suboptimal to longitudinally study COVID-19 immunity. The *Biobanque québécoise de la COVID-19* (BCQ19) is a biobanking initiative

in Québec (Canada) that includes blood samples from individuals with a negative (controls) or positive COVID-19 PCR test result, with samples collected at several fixed time points for up to 24 months post-diagnosis (for non-hospitalized individuals) or post-hospitalization (for hospitalized individuals).[1] However, BCQ19 is limited in terms of sample size and population representativeness. Furthermore, the unavailability of samples prior to diagnosis or hospitalization hinders the study of the early immune response to COVID-19.

Blood services such as our institution (Héma-Québec – the only blood service operating in Québec) are ideally positioned to establish a biobank that would complement BCQ19 or other COVID-19-focused biobanks and better address researchers' needs. Indeed, blood services routinely collect biological specimens from donors in the general population, thereby substantially alleviating the high cost normally associated with the establishment of a biobank. Blood services have been key partners in conducting COVID-19 research since the beginning of the pandemic;[23] involving them in biobanking efforts is therefore a sound approach to fuel additional research on COVID-19 immunity.

Here, we report on the establishment of a new biobank dedicated to COVID-19 research to inform public health in the province of Québec (Canada). The biobank consists of regular plasma donations collected throughout Québec, hence the name 'PlasCoV'. Because plasma donors can donate every 6 days at our institution, the biobank includes a large number of repeat donors for whom longitudinal analyses are feasible.

Cohort Description

The project was initiated on February 23, 2021. A pilot phase was launched in March 2021, and the project was expanded to all of our fixed collection centers in April 2021. At that time, the majority of the Québec general population was unvaccinated,[24] which enabled us to collect samples both pre- and post-vaccination obtained from many donors.

Ten fixed blood centers –all located in large or medium size (≥100.000 population) areas were designated to collect biobank-dedicated samples (**Table 1**). The resulting donor cohort is therefore broadly representative of plasma donors living in urban and suburban areas throughout Québec.

Table 1. Number of samples collected by each blood center

Center name	Metropolitan area	Health region (#-name)	Samples collected, N (%)[1]
Globule - Centre Laval	Montréal	13-Laval	3909 (4.1)
Globule - Kirkland	Montréal	06-Montréal	2574 (2.7)
Globule - Quartier Dix30	Montréal	16-Montérégie	5134 (5.4)
Globule - Place Versailles	Montréal	06-Montréal	3205 (3.3)
Globule - Quartier Lebourgneuf	Québec city	03-Capitale Nationale	11260 (11.7)
Globule - Sainte-Foy	Québec city	03-Capitale Nationale	11391 (11.9)
Plasmavie - Gatineau	Gatineau	08-Outaouais	11878 (12.4)
Plasmavie - Saguenay	Saguenay	02-Saguenay-Lac-St-Jean	17325 (18.1)
Plasmavie - Sherbrooke	Sherbrooke	05-Estrie	16669 (17.4)
Plasmavie - Trois-Rivières	Trois-Rivières	04-Mauricie et Centre du Québec	12627 (13.2)

[1]As of 01/24/2022

The project is entirely funded by the COVID-19 Immunity Task Force (CITF), a government-funded working group dedicated to advancing knowledge and research on COVID-19 in Canada and to inform public health authorities. CITF has provided a long-term funding commitment (2 years) for this biobank project, which will enable the conduct of long-term studies on infection- and vaccine-induced immunity to COVID-19.

The biobank includes samples from a population-based cohort of healthy voluntary, non-remunerated donors of plasma for fractionation who consented that their samples be used for research purposes. As of 01/24/2022, 15,502 out of 17,070 (90.8%) donors consented to have a small aliquot of their donations used for research on COVID-19. No donor recruitment campaign was specifically undertaken for this research initiative.

Donor characteristics were assessed as of 01/24/2022. Among consenting donors, the most common age group was 18-29 years (28.4%; **Table 2**). The six health regions where donors most often lived were Capitale-Nationale (18.1%), Estrie (14.7%), Saguenay-Lac-Saint-Jean (14.4%), Mauricie et Centre-du-Québec (11.4%), Outaouais (11.2%), and Montréal (9.8%). The cohort predominantly included donors who self-identified as white (93.6%). Relative to non-consenting donors, consenting donors tended to be younger (e.g., 18-29 years: 28.4% vs. 24.1% for the biobank and non-consenting donors respectively); and included slightly more female donors (i.e., 49.7% vs. 46.3%) and more residents of urban areas (e.g., Montreal-Laval region: 12.1% vs. 8.1%). Relative to the Québec general population, consenting donors had a similar age and sex distribution, but the densely populated region of Montreal-Laval was underrepresented (12.1% vs. 24.4%).

The cohort includes 3061 donors with samples collected pre- and post-vaccination, thereby enabling the study of vaccine-induced immunity in a real-world population of vaccine-naïve individuals. The cohort also includes 10,551 donors with samples collected only post-vaccination. Finally, the cohort include 1326 donors with sample collected only pre-vaccination and 564 donors with no vaccination history or missing information. Another (more limited) subset consists of 131 donors with available data before and after a documented infection.

The vast majority (i.e., 96.4%) of donors had received ≥1 vaccine dose, and 95.7% had received ≥2 doses; only 1.6% were unvaccinated. In Québec, the second vaccine dose was delayed for up to 16 weeks to optimize population-level immunity amid concerns over limited vaccine supply. As a result, a large proportion of plasma donors (14.6%) received their second dose 85-112 days after their first dose, but some received it within the □3 week gap recommended by the manufacturer (i.e., 1.9% within 4 weeks). This notable feature of our biobank may be used to study the impact of vaccine dose intervals on the immune response, as done by Tauzin et al.[25] (described in more details further down).

The following vaccines have been administered in Québec: ChAdOx1-S, BNT162b2, and mRNA-1273. Some individuals have received combinations of these vaccines, which was allowed by public health authorities to help fast-track the vaccination campaign.

As previously mentioned, a key feature of this biobank is the availability of multiple, longitudinal plasma samples and data collected for a large proportion of the cohort. As of 01/24/2022, the biobank had collected 86,229 samples from 15,502 donors, for an average of 5.6 donations per donor.

Table 2. Donor characteristics (as of 01/24/2022)

	Consenting donors (N=15,502)		Non-consenting donors (N=1568)		General, adult population[1]
	N	(%)	N	(%)	(%)
Sex[2]					
Female	7709	(49.7)	831	(46.3)	(50.2)
Age (years)[2,3]					
18-29	4399	(28.4)	433	(24.1)	(17.1)
30-39	2556	(16.5)	269	(15)	(16.0)
40-49	2287	(14.8)	251	(14)	(16.1)
50-59	2440	(15.7)	335	(18.7)	(16.1)
60-70	3178	(20.5)	408	(22.7)	(18.3)
≥71	642	(4.1)	100	(5.6)	(16.4)
Self-reported race/ethnicity[2,4]					
White	14517	(93.6)	1667	(92.8)	NA
Other	985	(6.4)	129	(7.2)	NA
Health region (#-name)[2,3]					
02-Saguenay-Lac-Saint-Jean	2234	(14.4)	299	(16.6)	(3.3)
03-Capitale-Nationale	2811	(18.1)	351	(19.5)	(9.0)
04-Mauricie et Centre-du-Québec	1771	(11.4)	213	(11.9)	(6.2)
05-Estrie	2282	(14.7)	277	(15.4)	(5.8)
06-Montréal	1518	(9.8)	103	(5.7)	(24.4)
07-Outaouais	1729	(11.2)	263	(14.6)	(4.6)
12-Chaudière-Appalaches	744	(4.8)	100	(5.6)	(5.0)
13-Laval	353	(2.3)	24	(1.3)	(5.1)
14-Lanaudière	252	(1.6)	18	(1)	(6.0)
15-Laurentides	333	(2.1)	22	(1.2)	(7.4)
16-Montérégie	1259	(8.1)	108	(6)	(16.6)
Regions without fixed centers[4]	126	(0.8)	<11	(<0.70)[5]	(6.4)
Unknown or outside Québec	90	(0.6)	<11	(<0.70)[5]	NA
Number of vaccine doses received[2,6]					
0	254	(1.6)	NA	NA	
1	103	(0.7)	NA	NA	(91.6)
2	5275	(34.0)	NA	NA	(88.7)
>2	9561	(61.7)	NA	NA	(47.1)
Missing data[7]	309	(2.0)	NA	NA	NA
Prior documented COVID-19 infection[2,6,8]					
Yes	1662	(10.7)	NA	NA	(5.6)
No	13531	(87.3)	NA	NA	(94.4)
Missing data[7]	309	(2.0)	NA	NA	NA

Abbreviation: COVID-19 = coronavirus disease-19

Notes:

1. For the general population of Québec, various data sources were used to capture variables of interest
2. Demographics (i.e., sex, age, self-reported ethnicity, and health region) are reported as of 01-24-2022. Data on prior vaccination and documented infection are reported as of 01-24-2022.
3. For the general population, data come from the following: Ministère de la Santé et des Services sociaux du Québec. Estimations et projections de population par territoire sociosanitaire. Available from: https://publications.msss.gouv.qc.ca/msss/document-001617/. Accessed on August 10, 2022.
4. Includes (01-Bas-Saint-Laurent, 08-Abitibi-Témiscamingue, 09-Côte-Nord, 10-Nord-du-Québec, 11-Gaspésie-Îles-de-la-Madeleine, 17-Nunavik)
5. Exact number is lower than 11, and is thus not reported to preserve donor anonymity
6. For the general population, data come from the following: Institut national de santé publique du Québec. Données COVID-19 par âge et sexe - Évolution des cas. Available from: https://www.inspq.qc.ca/covid-19/donnees/age-sexe/evolution-cas. Accessed on 03-01-2022."
7. Missing data are due to mismatches between donor information recorded in our institution's database and that recorded in governmental databases (N=309),)
8. Data for the general population are underestimated since the age groups used in publically available data (see footnote 7) exclude individuals aged 18-19 years.

At least two donations are available for nearly two thirds of the cohort (i.e., 65.6%), thereby enabling the conduct of longitudinal analyses (**Figure 1**). Most of these repeat donors appeared to donate regularly, with a median gap between donations ranging from 51.0 days for those with 2 donations to 11.8 days for those with ≥15 donations (median=29 days among those with ≥2 donations; **Figure 1**).

Of note, loss to follow-up is not applicable to this cohort. 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.

Several variables are collected as part of routine donor screening. These variables include demographic characteristics (e.g., age, sex) and clinical characteristics (e.g., blood type, recent blood-borne infections, diabetes; see **Table 3** for detailed list of measurements), which (except for blood type) are all self-reported by the donor. Other variables related to

prior COVID-19 vaccination and infection were obtained by linking in-house donor data with the *Système d'information pour la protection des maladies infectieuses* (SI-PMI), a government vaccination registry Infection data was obtained through the government platform (Trajectoire de Santé Publique – TSP). This information was added to carry out a mandate given by the Ministère de la santé et des services sociaux for the seroprevalence study only. Of note, data on mortality and other comorbidities that are not relevant for plasma donation are not available in the dataset.

Table 3 Summary of the principal* variables collected or derived from the cohort

Variables	Baseline before vaccination/infection	After vaccination/infection information	Follow-up information
Internal Data			
Questionnaire			
Demographics: Age/Sexe/Area RSS/Ethnicity	✓	✓	✓
BMI calculated with	✓	✓	✓
Height	✓	✓	✓
Weight	✓	✓	✓
Medication use			
Tobacco use			✓
Blood pressure[1]	✓		
Diabetes profile and treatment (without insulin)[2]	✓	✓	✓
Occupational Status			✓
COVID-19 vaccination status[3]	✓	✓	✓
History of PCR-detected infection[4]	✓	✓	✓
Laboratory tests			
Hemoglobin level	✓	✓	✓
Blood type (ABO Rh genotype phenotype)	✓	✓	✓
External Data			
COVID-19 vaccination status[5]	✓	✓	✓
History of PCR-detected infection[6]	✓	✓	✓

Note:

* Several other variables such as donor interdictions, infectious state, etc. are routinely collected but not presented in this table

1. Available only for a subset of blood donor before COVIC-19 pandemic period
2. Diabetes treated with insulin is an exclusion criterion for blood donation
3. Reported by the donor

4. Reported by the donor
5. Provincial vaccination registry, Système d'information pour la protection des maladies infectieuses (SI-PMI)
6. Provincial COVID-19 infection registry, Trajectoire de Santé Publique – TSP

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Findings to Date

Longitudinal assessment of COVID-19 immunity

A study by Tauzin et al. used samples from our biobank to study the immune response to the mRNA vaccine BNT162b2 among SARS-CoV-2-naïve and previously infected (PI) individuals.[25] Specifically, anti-RBD titers, antibody binding, antibody-dependent cell-mediated cytotoxicity (ADCC), neutralization activity, and antibody avidity were assessed in the two groups after their first and second dose of vaccine. The impact of an extended interval (16 weeks vs 4 weeks) between the two doses of vaccine was also studied.

They observed that the levels of anti-RBD and anti-Spike antibodies as well as the capacity to recognize and neutralize different SARS-CoV-2 variants of PI individuals was increased after the first dose of vaccine and only minimally declined thereafter. Administration of the second dose to some PI individuals did not further increase the strength of the immune response compared to PI individuals vaccinated with only one dose.

In contrast, whereas the levels of SARS-CoV-2-specific antibodies as well as their functional activities increased in naïve individuals after the first dose of vaccine, the decline in antibody titers and functional activity was more pronounced compared to PI individuals. Administration of the second dose of vaccine permitted to reach much higher

antibody levels than after their first dose. These levels were similar to those observed in PI individuals after their first or second dose of vaccine.

Tauzin et al. additionally investigated the impact of an extended vaccine interval among SARS-CoV-2-naïve individuals. With the exception of ADCC, all assays (antibody levels, variant recognition and neutralization) were consistent with a better immune response among individuals with an extended interval of ~16 weeks compared with those with an interval of ~4 weeks between the two doses.

Serosurvey

A publicly available report from our institution used biobank samples to estimate the seroprevalence of anti-SARS-CoV-2 antibodies in Québec from June 2021 – July 2021.[4] This was the third phase of a serosurvey initiated in May 2020. Phases 1 (May-June 2020) and 2 (January-March 2021) only included whole blood donors rather than plasma donors from the biobank, since the PlasCoV project had not yet been launched. Phase 3 assessed both anti-RBD and anti-N seroprevalence, since >80% of the population had received at least one vaccine dose at the time of the serosurvey.[24]

The anti-RBD seroprevalence was 89.61%, consistent with the widespread vaccination coverage during phase 3. However, the anti-N seroprevalence was only 6.43%, which was lower than the anti-RBD seroprevalence among unvaccinated blood donors included in phase 2 (i.e., 10.52%).

This unexpected result was likely driven by seroreversion, which occurs faster for anti-N than anti-S (or anti-RBD) antibodies.[26–28] Indeed, nearly 40% of PI donors in phase 3 tested seronegative for anti-N, likely because of seroreversion. This apparent rapid waning

of anti-N antibodies was also observed in a separate cohort of 54 PI donors who donated convalescent plasma used in the CONCOR-1 clinical trial.[29] After >200 days of follow-up, anti-N seroreversion occurred in 33.3% of donors, whereas anti-RBD seroreversion occurred in only 11.1% of donors. Taken together, these results suggest anti-N seroprevalence may only be adequate to capture relatively recent infections, thereby questioning its usefulness in serosurveys.[6] At the time of writing this manuscript, a fourth seroprevalence study is ongoing with PlasCoV samples, in which we are comparing anti-N responses pre- and post-infection to estimate the incidence of recent infections in the context of the Omicron wave.

Collaboration

All researchers in Canada or elsewhere may apply to access the PlasCoV biobank. Researchers will be asked to fill a form with high-level information on their project's objectives, methods, novelty, and relevance to the biobank's objectives. They will also be asked to justify the sample size needed and any particular inclusion criteria, and obtain ethics approval for their project.

Data Sharing Statement

Details on the PlasCoV biobank and the application process can be obtained through Héma-Québec's website at https://www.hema-quebec.qc.ca/coronavirus/hema-quebec-en-contexte-de-pandemie/etude-plascov.en.html. Enquiries can be sent by e-mail to BiobanqueCOVID@hema-quebec.qc.ca, or alternately to Dr. Marc Germain (Marc.Germain@hema-quebec.qc.ca), the biobank director.

Funding Declaration

The project is entirely funded by the COVID-19 Immunity Task Force (CITF), which is supported by the Public Health Agency of Canada (PHAC). The views expressed herein do not necessarily reflect the views of the PHAC.

Contributorship Statement

MG, AL, RB and CR conceived and designed the study. AL, AB, JP, and YG collected the data. AL and YG analyzed the data, with input from MG, RB, MD and CR. MG, AL, YG and RB drafted the manuscript and MD, AB, CR and JP critically revised it for important intellectual content. All authors approved the final version to be published.

Ethics Approval

This study was approved by Héma-Québec Institutional review board. Individual informed consent was obtained from participants at the time of registration in the PlasCoV Biobank.

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Conflicts of interest:

None.

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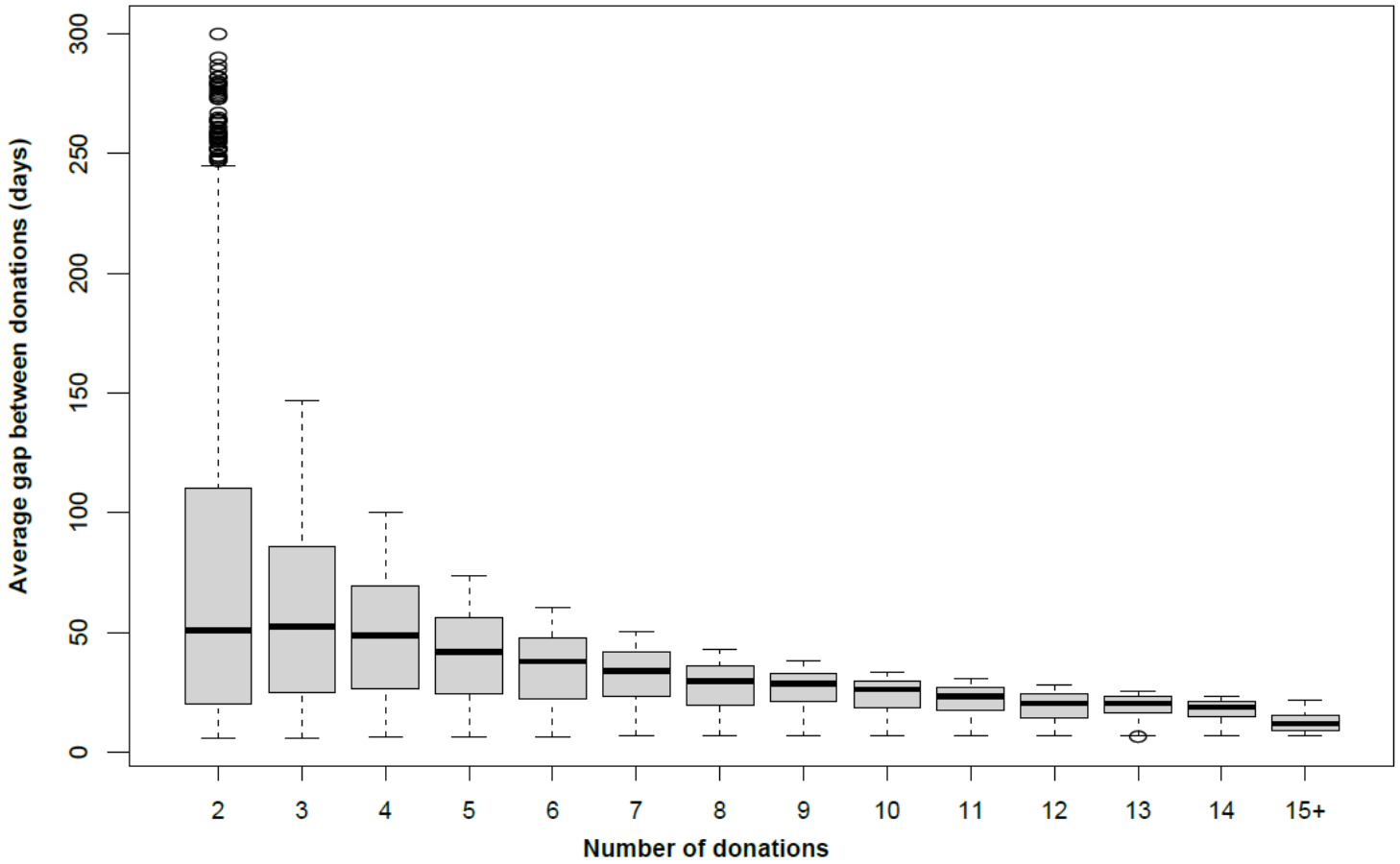
Figure 1. Average number of days between donations as function of the number of donations in PlasCoV



Donors (N)	2,498	1,505	1,045	758	567	441	344	355	274	209	177	187	165	1,631
Proportion (%)	16.1	9.7	6.7	4.9	3.7	2.8	2.2	2.3	1.8	1.3	1.1	1.2	1.1	10.5

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Cohort profile: A Québec-based plasma donor biobank to study COVID-19 immunity (PlasCoV)

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Cohort profile: A Québec-based plasma donor biobank to study COVID-19 immunity (PlasCoV)

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Abstract

Purpose

The long-term humoral immunity to COVID-19 is not well understood owing to the continuous emergence of new variants of concern, the evolving vaccine- and infection-induced immunity, and the limited duration of follow-up in previous studies. As the sole blood service in Québec (Canada), we established a COVID-19-focused biobank ("PlasCoV") in April 2021.

Participants

As of January 2022, the biobank included 86,229 plasma samples from 15,502 regular donors (age range=18–84 years, females=49.7%), for an average of 5.6 donations per donor. Nearly two thirds (65.6%) of biobank donors made at least two donations, with many donors having provided samples pre- and post-vaccination (3061 [19.8%]) or pre- and post-infection (131 [0.9%]), thus allowing for longitudinal studies on vaccine- and infection-induced immunity.

Findings to date

A study that used PlasCoV samples revealed that previously infected individuals who received a single dose of the BNT162b2 COVID-19 vaccine exhibited the strongest immune response. By contrast, SARS-CoV-2-naïve individuals required two vaccine doses to produce a maximal immune response. Furthermore, the results of a four-phase seroprevalence study indicated that the anti-nucleocapsid (N) response wanes rapidly, so that up to one third of previously infected donors were seronegative for anti-N.

Future plans

This plasma biobank will facilitate the conduct of longitudinal studies on COVID-19 immunity, thus helping to provide valuable insights into the anti-SARS-CoV-2 immune response and its persistence, and the effects of vaccination and variants on the specificity of the anti-SARS-CoV-2 immune response.

Strengths and limitations

- To the best of our knowledge, this would be the largest biobank of plasma samples dedicated to COVID-19 research, with >80,000 samples from >15,000 donors; new samples will continue to be added until March 2023.
- Furthermore, the large subset of donors with ≥2 samples (i.e., 65.6%) — along with the high frequency of donations in this subset (i.e., median: once every 29.0 days) — enables the conduct of longitudinal analyses on COVID-19 immunity.
- The cost of establishing the biobank was minimized since the infrastructure and personnel required for sample collection were already in place at our blood collection sites.
- Only plasma samples are available, such that the biobank cannot be used to study cell-mediated immunity.
- Despite the large sample, the plasma donor population is not fully representative of the overall Québec population, as expected since plasma donors typically reflect the healthy adult population.

Introduction

Despite remarkable progress, our understanding of the long-term, humoral immunity to COVID-19 is incomplete owing to a number of challenges. The emergence of new variants of concern, such as Omicron, continuously challenges prior assumptions and data on the effectiveness and persistence of COVID-19 immunity [1,2]. Furthermore, amid mass vaccination, disentangling infection from vaccine-induced antibodies to SARS-CoV-2 has become increasingly difficult to inform public health authorities [3–5]. Notably, the vast majority of published serological studies used a cross-sectional design, and hence do not provide longitudinally collected data on COVID-19 immunity [6]. Lastly, the more limited number of longitudinal studies that have been conducted had follow-up periods <12 months [7–18] and lacked long-term funding commitment. Clearly, new initiatives are needed to overcome these barriers.

Historically, biobanks have spurred research efforts on novel or rare diseases [19] and would likely help address the aforementioned challenges for COVID-19 research. They do so using highly standardized, quality-controlled processes to analyze a large number of biological specimens which are made available to the research community. In addition, biobanks are subject to regulatory oversight to protect donors' rights. Virtually all biobanks collect a "broad" consent that allows for samples to be used for multiple research purposes [20]. For researchers, this practice (while controversial [21]) alleviates the burden associated with seeking consent.

However, existing COVID-19-focused biobanks are suboptimal to longitudinally study COVID-19 immunity. The *Biobanque québécoise de la COVID-19* (BCQ19) is a

biobanking initiative in Québec (Canada) that includes blood samples from individuals with a negative (controls) or positive SARS-CoV-2 PCR test result, with samples collected at several fixed time points for up to 24 months post-diagnosis (for non-hospitalized individuals) or post-hospitalization (for hospitalized individuals) [22]. However, BCQ19 is limited in terms of sample size and population representativeness. Furthermore, the unavailability of samples prior to diagnosis or hospitalization hinders the study of the early immune response to COVID-19.

Blood services such as our institution (Héma-Québec – the only blood service operating in Québec) are ideally positioned to establish a biobank that would complement BCQ19 or other COVID-19-focused biobanks and better address researchers' needs. Indeed, blood services routinely collect biological specimens from donors in the general population, thereby substantially alleviating the high cost normally associated with the establishment of a biobank. Blood services have been key partners in conducting COVID-19 research since the beginning of the pandemic [23]; involving them in biobanking efforts is therefore a sound approach to fuel additional research on COVID-19 immunity.

Here, we report on the establishment of a new biobank dedicated to COVID-19 research to inform public health in the province of Québec (Canada). The biobank consists of regular plasma donations collected throughout Québec, hence the name 'PlasCoV'. Because plasma donors can donate every 6 days at our institution, the biobank includes a large number of repeat donors for whom longitudinal analyses are feasible.

Cohort description

Cohort establishment and overview

The project was initiated on February 23, 2021. A pilot phase was launched in March 2021, and the project was expanded to all of our fixed collection centers in April 2021. At that time, the majority of the Québec general population was unvaccinated [24], which enabled us to collect samples pre- and post-vaccination for many donors.

Ten fixed blood centers — all located in large or medium size (≥100,000 population) areas — were designated to collect biobank-dedicated samples (**Table 1**). The resulting donor cohort is therefore broadly representative of plasma donors living in urban and suburban areas throughout Québec.

Table 1. Number of samples collected by each blood center as of January 24, 2022.

Center name	Metropolitan area	Health region (#-name)	Samples collected, N (%)	
Globule - Centre Laval	Montréal	13-Laval	3909	(4.1)
Globule - Kirkland	Montréal	06-Montréal	2574	(2.7)
Globule - Quartier Dix30	Montréal	16-Montérégie	5134	(5.4)
Globule - Place Versailles	Montréal	06-Montréal	3205	(3.3)
Globule - Quartier Lebourgneuf	Québec city	03-Capitale Nationale	11260	(11.7)
Globule - Sainte-Foy	Québec city	03-Capitale Nationale	11391	(11.9)
Plasmavie - Gatineau	Gatineau	08-Outaouais	11878	(12.4)
Plasmavie - Saguenay	Saguenay	02-Saguenay-Lac-St-Jean	17325	(18.1)
Plasmavie - Sherbrooke	Sherbrooke	05-Estrie	16669	(17.4)
Plasmavie - Trois-Rivières	Trois-Rivières	04-Mauricie et Centre du Québec	12627	(13.2)

The biobank includes samples from a population-based cohort of healthy, voluntary, non-remunerated donors of plasma for fractionation who consented that their samples be used for research purposes. Specifically, the pre-donation questionnaire asks donors if they are willing to give part of their routine 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. 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).

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., as tobacco use, medication use, and occupational status) can be obtained through a supplemental questionnaire filled by donors during their donation.

Table 2. Summary of the main variables* collected or derived from the cohort.

Variables	Information collected before vaccination/infection	Information collected after vaccination/infection	Information routinely collected at pre-donation screening
Internal Data			
Donor questionnaire			
Demographics: Age/Sex/Health region/Ethnicity	X	X	X
BMI calculated with	X	X	X
Height	X	X	X
Weight	X	X	X
Blood pressure[1]	X		
Diabetes profile and treatment (without insulin)[2]	X	X	X
COVID-19 vaccination status[3]	X	X	X
History of PCR-confirmed infection[4]	X	X	X
Laboratory tests			
Hemoglobin level	X	X	X
Blood type (ABO and Rh genotype or phenotype)	X	X	X
External Data			
COVID-19 vaccination status[5]	X	X	X
History of PCR-detected infection[6]	X	X	X

Abbreviation: COVID-19 = coronavirus disease-19

Notes:

* Several other variables such as donor deferrals, infectious state, etc. are routinely collected but are not presented in this table.

1. Available only for a subset of blood donor before the COVID-19 pandemic.
2. Diabetes treated with insulin is an exclusion criterion for blood donation.
3. Reported by the donor.
4. Reported by the donor.

5. From the provincial vaccination registry *Système d'information pour la protection des maladies infectieuses (SI-PMI)*.
6. From the provincial COVID-19 infection registry *Trajectoire de Santé Publique – TSP*.

Participant characteristics

As of January 24, 2022, 15,502 out of 17,070 (90.8%) donors consented to have a small volume of their donations used for research on COVID-19 (**Table 3**). No donor recruitment campaign was specifically undertaken for this research initiative. 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.

Donor characteristics were assessed as of January 24, 2022. Among consenting donors, median age was 43.0 years (**Table 3**). The six health regions where donors most often lived were Capitale-Nationale (18.1%), Estrie (14.7%), Saguenay-Lac-Saint-Jean (14.4%), Mauricie et Centre-du-Québec (11.4%), Outaouais (11.2%), and Montréal (9.8%). The cohort predominantly included donors who self-identified as white (93.6%). Relative to non-consenting donors, consenting donors tended to be younger (i.e., median age: 43.0 vs. 48.0 years), and included slightly more female donors (i.e., 49.7% vs. 46.3%) and more residents of urban areas (e.g., Montreal-Laval region: 12.1% vs. 8.1%). Relative to the Québec general population, consenting donors had a similar age and sex distribution, but the densely populated region of Montreal-Laval was underrepresented (12.1% vs. 29.5%).

A key feature of this biobank is the availability of multiple, longitudinally collected plasma samples and associated data. As of January 24, 2022, the biobank had collected 86,229 samples from 15,502 donors, for an average of 5.6 donations per donor. At least two donations are available for nearly two thirds of the cohort (i.e., 65.6%), thereby enabling the conduct of longitudinal analyses (**Figure 1**). Most of these repeat donors appeared to donate regularly, with a median gap between donations ranging from 51.0 days for those

with 2 donations to 11.8 days for those with ≥15 donations (median=29.0 days among those with ≥2 donations; **Figure 1**).

The cohort includes 3061 donors with samples collected pre- and post-vaccination, thereby enabling the study of vaccine-induced immunity in a real-world population of vaccine-naïve individuals. The cohort also includes 10,551 donors with samples collected only post-vaccination. Finally, the cohort includes 1326 donors with sample collected only pre-vaccination and 564 donors with no vaccination history or missing information.

The vast majority (i.e., 96.4%) of donors had received ≥1 vaccine dose, and 95.7% had received ≥2 doses; only 1.6% were unvaccinated. In Québec, the second vaccine dose was delayed for up to 16 weeks to optimize population-level immunity amid concerns over limited vaccine supply. As a result, a large proportion of plasma donors (i.e., 14.6%) received their second dose 85-112 days after their first dose, but some received it within the □3-week gap recommended by the manufacturer (i.e., 1.9% within 4 weeks). This notable feature of our biobank may be used to study the impact of vaccine dose intervals on the immune response, as done by Tauzin et al. [25] (described in more details further down).

The following vaccines have been administered in Québec: ChAdOx1-S, BNT162b2, and mRNA-1273. Some individuals have received combinations of these vaccines, which was allowed by public health authorities to help fast-track the vaccination campaign.

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).

Table 3. Donor characteristics as of January 24, 2022.	Consenting donors (N=15,502)		Non-consenting donors (N=1568)		General, adult population[1]
Sex,[2] n (%)					
Female	7709	(49.7)	831	(46.3)	(50.2)
Age (years),[2,3] mean ± SD (median)	43.9 ± 16.8 (43.0)		46.1 ± 16.7 (48.0)		50.2 ± 18.8 (50.0)
Age (years),[2,3], n (%)					
18-29	4399	(28.4)	433	(24.1)	(17.1)
30-39	2556	(16.5)	269	(15)	(16.0)
40-49	2287	(14.8)	251	(14)	(16.1)
50-59	2440	(15.7)	335	(18.7)	(16.1)
60-70	3178	(20.5)	408	(22.7)	(18.3)
≥71	642	(4.1)	100	(5.6)	(16.4)
Self-reported race/ethnicity,[2,4] n (%)					
White	14517	(93.6)	1667	(92.8)	NA
Other	985	(6.4)	129	(7.2)	NA
Health region (#-name),[2,3] n (%)					
02-Saguenay-Lac-Saint-Jean	2234	(14.4)	299	(16.6)	(3.3)
03-Capitale-Nationale	2811	(18.1)	351	(19.5)	(9.0)
04-Mauricie et Centre-du-Québec	1771	(11.4)	213	(11.9)	(6.2)
05-Estrie	2282	(14.7)	277	(15.4)	(5.8)
06-Montréal	1518	(9.8)	103	(5.7)	(24.4)
07-Outaouais	1729	(11.2)	263	(14.6)	(4.6)
12-Chaudière-Appalaches	744	(4.8)	100	(5.6)	(5.0)
13-Laval	353	(2.3)	24	(1.3)	(5.1)
14-Lanaudière	252	(1.6)	18	(1)	(6.0)
15-Laurentides	333	(2.1)	22	(1.2)	(7.4)
16-Montérégie	1259	(8.1)	108	(6)	(16.6)
Regions without fixed centers[4]	126	(0.8)	<11	(<0.70)[5]	(6.4)
Unknown or outside Québec	90	(0.6)	<11	(<0.70)[5]	NA
Number of vaccine doses received,[2,6] n (%)					
0	254	(1.6)	NA	NA	
1	103	(0.7)	NA	NA	(91.6)
2	5275	(34.0)	NA	NA	(88.7)
>2	9561	(61.7)	NA	NA	(47.1)
Missing data[7]	309	(2.0)	NA	NA	NA

Documented COVID-19 infection,[2,6,8] n (%)					
Yes	1662	(10.7)	NA	NA	(5.6)
No	13531	(87.3)	NA	NA	(94.4)
Missing data[7]	309	(2.0)	NA	NA	NA

Abbreviations: COVID-19 = coronavirus disease-19; SD = standard deviation

Notes:

1. For the general population of Québec, various data sources were used to capture variables of interest.
2. Demographics (i.e., sex, age, self-reported ethnicity, and health region) are reported as of 01-24-2022. Data on prior vaccination and documented infection are reported as of 01-24-2022.
3. For the general population, data come from the following: Ministère de la Santé et des Services sociaux du Québec. Estimations et projections de population par territoire sociosanitaire. Available from: https://publications.msss.gouv.qc.ca/msss/document-001617/. Accessed on August 10, 2022.
4. Includes (01-Bas-Saint-Laurent, 08-Abitibi-Témiscamingue, 09-Côte-Nord, 10-Nord-du-Québec, 11-Gaspésie-Îles-de-la-Madeleine, 17-Nunavik).
5. The exact number is lower than 11 and is thus not reported to preserve donor anonymity.
6. For the general population, data come from the following: Institut national de santé publique du Québec. Données COVID-19 par âge et sexe - Évolution des cas. Available from: https://www.inspq.qc.ca/covid-19/donnees/age-sexe/evolution-cas. Accessed on 03-01-2022."
7. Missing data are due to mismatches between donor information recorded in our institution's database and that recorded in governmental databases (N=309).
8. Data for the general population are underestimated since the age groups used in publicly available data (see footnote 7) exclude individuals aged 18-19 years.

Funding

The project is entirely funded by the COVID-19 Immunity Task Force (CITF), a government-funded working group dedicated to advancing knowledge and research on COVID-19 in Canada and to inform public health authorities. CITF has provided a long-term funding commitment (i.e., 2 years) for this biobank project, which will enable the conduct of long-term studies on infection- and vaccine-induced immunity to COVID-19.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Findings to Date

Longitudinal assessment of COVID-19 immunity

A study by Tauzin et al. used samples from our biobank to study the immune response to the mRNA vaccine BNT162b2 among SARS-CoV-2-naïve and previously infected individuals [25]. The authors found that, in previously infected individuals, the immune response was strengthened after the first dose of vaccine and minimally declined thereafter. The administration of a second dose did not further increase the strength of the immune response. By contrast, in SARS-CoV-2-naïve individuals, the administration of a second dose further strengthened the immune response (except for antibody-mediated cell cytotoxicity [ADCC], which appeared more transient).

Tauzin et al. additionally investigated the impact of using an extended interval between the two vaccine doses in SARS-CoV-2-naïve individuals. With the exception of ADCC, all assays were consistent with a better immune response when administering the two doses ~16 weeks apart compared with ~4 weeks apart.

Serosurvey

A publicly available report from our institution used biobank samples to estimate the seroprevalence of anti-SARS-CoV-2 antibodies in Québec from June 2021 – July 2021 [3]. This was the third phase of a serosurvey initiated in May 2020. Phases 1 (May–June 2020) and 2 (January–March 2021) only included whole blood donors rather than plasma donors from the biobank, since the PlasCoV project had not yet been launched. Phase 3 assessed both anti-receptor binding domain (RBD) and anti-nucleocapsid (N) seroprevalence, since

>80% of the population had received at least one vaccine dose at the time of the serosurvey [24].

The anti-RBD seroprevalence was 89.6%, consistent with the widespread vaccination coverage during phase 3. However, the anti-N seroprevalence was only 6.4%, which was lower than the anti-RBD seroprevalence among unvaccinated blood donors included in phase 2 (i.e., 10.5%). This unexpected result was likely driven by seroreversion, which occurs faster for anti-N than anti-spike (or anti-RBD) antibodies [26–28]. Indeed, nearly 40% of previously infected donors in phase 3 were seronegative for anti-N, likely because of seroreversion. This apparent rapid waning of anti-N antibodies was also observed in a separate cohort of 54 previously infected donors of convalescent plasma used in the CONCOR-1 clinical trial [29]. After more than 200 days of follow-up, anti-N seroreversion occurred in 33.3% of these donors, whereas anti-RBD seroreversion occurred in only 11.1% of donors.

Taken together, these results suggest anti-N seroprevalence may only be adequate to capture relatively recent infections, thereby questioning its usefulness in serosurveys analyzed using conventional analytical approaches (i.e., using a hard threshold applied at a single time point to determine seropositivity) [5]. At the time of writing this manuscript, the fourth phase of this study is underway and uses PlasCoV samples to compare anti-N responses pre- and post-infection — a new approach to estimate the incidence of recent infections in the context of the Omicron wave.

Future plans

The herein described plasma biobank will help conduct longitudinal studies on COVID-19 immunity. The resulting evidence will provide valuable insights on several aspects of the immune response to COVID-19, including its persistence, its specificity against variants, and the effects of vaccination.

Future studies using this biobank are already planned or underway. Our organization will continue using PlasCoV samples for an ongoing anti-SARS-CoV-2 serosurvey up until March, 2023 (see above description). The biobank will also prove useful to address other research questions in public health such as hybrid immunity, response to emerging variants or new vaccine formulations. For example, another study will soon be conducted to estimate the impact of post-COVID-19 syndrome (a.k.a., long COVID) in a healthy, adult population using this large, prospective longitudinal cohort.

Strengths and limitations

The herein described biobank has several strengths. To the best of our knowledge, this would be the largest biobank of plasma samples dedicated to COVID-19 research, with >80,000 samples from >15,000 donors and new samples continually being added until March 2023. Furthermore, the large subset of donors with ≥2 samples (65.6%) — along with the high frequency of donations in this subset (i.e., median: once every 29.0 days) — enables the conduct of longitudinal analyses on COVID-19 immunity. Another strength is that donors provided a broad consent, which allows researchers to recontact them for other projects (e.g., supplemental questionnaire). Lastly, the cost of establishing the biobank was minimized since the infrastructure and personnel required for sample collection were

already in place at our blood collection sites. Given these strengths, our biobank may serve as a model for other blood operators and government partners who would be interested in reproducing our initiative elsewhere.

Certain limitations should nonetheless be considered when using our biobank samples. 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. Furthermore, only plasma samples are available, so that the biobank cannot be used to study cell-mediated immunity. Researchers interested in studying cell-mediated immunity may want to contact BCQ19, which routinely collects peripheral blood mononuclear cells [22]. Moreover, despite the large sample, the plasma donor population is not fully representative of the overall Québec population, as expected since plasma donors are typically more representative of the healthy adult population. All exclusion criteria for plasma donations were also exclusion criteria for the biobank, including immunodeficiencies, active infection, and recent cancer among other chronic diseases. In addition, the database associated with our biobank does not include information on disease severity, such as hospitalization or intensive care unit admission, mortality, and comorbidities. Lastly, the database does not include information on socioeconomic status, such as income and education. However, the six-digit zip code can be used to generate a proxy index for socioeconomic status.

Collaboration

All researchers in Canada or elsewhere may apply to access the PlasCoV biobank. Researchers will be asked to fill a form with high-level information on their project's objectives, methods, novelty, and relevance to the biobank's objectives. They will also be asked to justify the sample size needed and any particular inclusion criteria, and to obtain ethics approval for their project.

Data sharing statement

Details on the PlasCoV biobank and the application process can be obtained through Héma-Québec's website at https://www.hema-quebec.qc.ca/coronavirus/hema-quebec-en-contexte-de-pandemie/etude-plascov.en.html. Enquiries can be sent by e-mail to BiobanqueCOVID@hema-quebec.qc.ca, or alternately to Dr. Marc Germain (Marc.Germain@hema-quebec.qc.ca), the biobank director.

Funding declaration

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Contributorship statement

MG, AL, RB and CR conceived and designed the study. AL, AB, JP, and YG collected the data. AL and YG analyzed the data, with input from MG, RB, MD and CR. MG, AL, YG and RB drafted the manuscript and MD, AB, CR and JP critically revised it for important intellectual content. All authors approved the final version to be published.

Ethics approval

This study was approved by Héma-Québec Institutional review board. Individual informed consent was obtained from participants at the time of registration in the PlasCoV Biobank.

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Competing interest

No competing interest.

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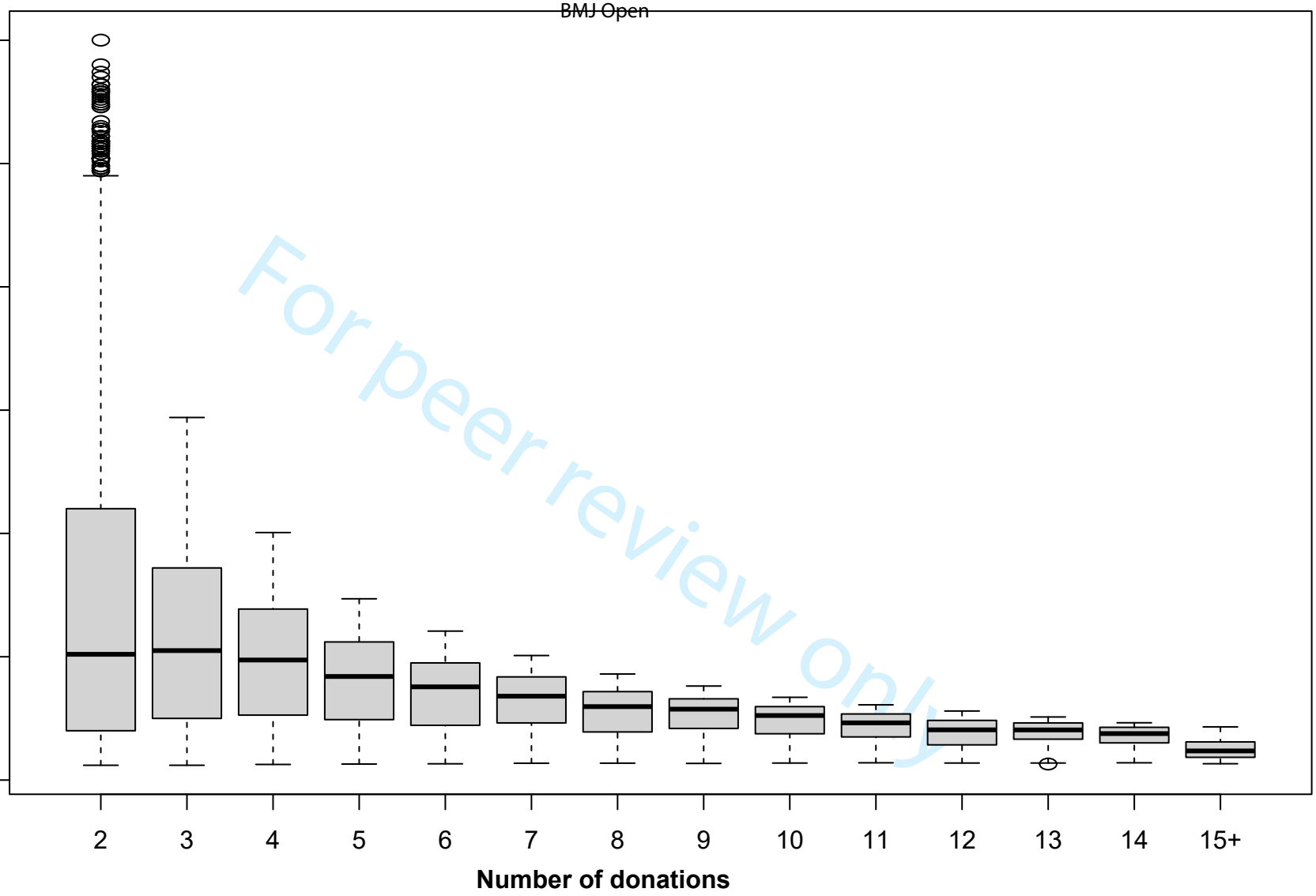
Figure caption

Figure 1. Average number of days between donations as a function of the number of donations in PlasCoV.



Donors (N)	2,498	1,505	1,045	758	567	441	344	355	274	209	177	187	165	1,631
Proportion (%)	16.1	9.7	6.7	4.9	3.7	2.8	2.2	2.3	1.8	1.3	1.1	1.2	1.1	10.5

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Cohort profile: A Québec-based plasma donor biobank to study COVID-19 immunity (PlasCoV)

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Cohort profile: A Québec-based plasma donor biobank to study COVID-19 immunity (PlasCoV)

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Abstract

Purpose

The long-term humoral immunity to COVID-19 is not well understood owing to the continuous emergence of new variants of concern, the evolving vaccine- and infection-induced immunity, and the limited duration of follow-up in previous studies. As the sole blood service in Québec (Canada), we established a COVID-19-focused biobank ("PlasCoV") in April 2021.

Participants

As of January 2022, the biobank included 86,229 plasma samples from 15,502 regular donors (age range=18–84 years, females=49.7%), for an average of 5.6 donations per donor. Nearly two thirds (65.6%) of biobank donors made at least two donations, with many donors having provided samples pre- and post-vaccination (3061 [19.8%]) or pre- and post-infection (131 [0.9%]), thus allowing for longitudinal studies on vaccine- and infection-induced immunity.

Findings to date

A study that used PlasCoV samples revealed that previously infected individuals who received a single dose of the BNT162b2 COVID-19 vaccine exhibited the strongest immune response. By contrast, SARS-CoV-2-naïve individuals required two vaccine doses to produce a maximal immune response. Furthermore, the results of a four-phase seroprevalence study indicated that the anti-nucleocapsid (N) response wanes rapidly, so that up to one third of previously infected donors were seronegative for anti-N.

Future plans

Donations from individuals who consented to participate before October 1, 2022 will be collected up until March 31, 2023. This plasma biobank will facilitate the conduct of longitudinal studies on COVID-19 immunity, thus helping to provide valuable insights into the anti-SARS-CoV-2 immune response and its persistence, and the effects of vaccination and variants on the specificity of the anti-SARS-CoV-2 immune response.

Strengths and limitations

- To the best of our knowledge, this would be the largest biobank of plasma samples dedicated to COVID-19 research, with >80,000 samples from >15,000 donors; new samples will continue to be added until March 2023.
- Furthermore, the large subset of donors with ≥2 samples (i.e., 65.6%) — along with the high frequency of donations in this subset (i.e., median: once every 29.0 days) — enables the conduct of longitudinal analyses on COVID-19 immunity.
- The cost of establishing the biobank was minimized since the infrastructure and personnel required for sample collection were already in place at our blood collection sites.
- Only plasma samples are available, such that the biobank cannot be used to study cell-mediated immunity.
- Despite the large sample, the plasma donor population is not fully representative of the overall Québec population, as expected since plasma donors typically reflect the healthy adult population.

Introduction

Despite remarkable progress, our understanding of the long-term, humoral immunity to COVID-19 is incomplete owing to a number of challenges. The emergence of new variants of concern, such as Omicron, continuously challenges prior assumptions and data on the effectiveness and persistence of COVID-19 immunity [1,2]. Furthermore, amid mass vaccination, disentangling infection from vaccine-induced antibodies to SARS-CoV-2 has become increasingly difficult to inform public health authorities [3–5]. Notably, the vast majority of published serological studies used a cross-sectional design, and hence do not provide longitudinally collected data on COVID-19 immunity [6]. Lastly, the more limited number of longitudinal studies that have been conducted had follow-up periods <12 months [7–18] and lacked long-term funding commitment. Clearly, new initiatives are needed to overcome these barriers.

Historically, biobanks have spurred research efforts on novel or rare diseases [19] and would likely help address the aforementioned challenges for COVID-19 research. They do so using highly standardized, quality-controlled processes to analyze a large number of biological specimens which are made available to the research community. In addition, biobanks are subject to regulatory oversight to protect donors' rights. Virtually all biobanks collect a "broad" consent that allows for samples to be used for multiple research purposes [20]. For researchers, this practice (while controversial [21]) alleviates the burden associated with seeking consent.

However, existing COVID-19-focused biobanks are suboptimal to longitudinally study COVID-19 immunity. The *Biobanque québécoise de la COVID-19* (BCQ19) is a

biobanking initiative in Québec (Canada) that includes blood samples from individuals with a negative (controls) or positive SARS-CoV-2 PCR test result, with samples collected at several fixed time points for up to 24 months post-diagnosis (for non-hospitalized individuals) or post-hospitalization (for hospitalized individuals) [22]. However, BCQ19 is limited in terms of sample size and population representativeness. Furthermore, the unavailability of samples prior to diagnosis or hospitalization hinders the study of the early immune response to COVID-19.

Blood services such as our institution (Héma-Québec – the only blood service operating in Québec) are ideally positioned to establish a biobank that would complement BCQ19 or other COVID-19-focused biobanks and better address researchers' needs. Indeed, blood services routinely collect biological specimens from donors in the general population, thereby substantially alleviating the high cost normally associated with the establishment of a biobank. Blood services have been key partners in conducting COVID-19 research since the beginning of the pandemic [23]; involving them in biobanking efforts is therefore a sound approach to fuel additional research on COVID-19 immunity.

Here, we report on the establishment of a new biobank dedicated to COVID-19 research to inform public health in the province of Québec (Canada). The biobank consists of regular plasma donations collected throughout Québec, hence the name 'PlasCoV'. Because plasma donors can donate every 6 days at our institution, the biobank includes a large number of repeat donors for whom longitudinal analyses are feasible.

Cohort description

Cohort establishment and overview

The project was initiated on February 23, 2021. A pilot phase was launched in March 2021, and the project was expanded to all of our fixed collection centers in April 2021. At that time, the majority of the Québec general population was unvaccinated [24], which enabled us to collect samples pre- and post-vaccination for many donors.

Ten fixed blood centers — all located in large or medium size (≥100,000 population) areas — were designated to collect biobank-dedicated samples (**Table 1**). The resulting donor cohort is therefore broadly representative of plasma donors living in urban and suburban areas throughout Québec.

Table 1. Number of samples collected by each blood center as of January 24, 2022.

Center name	Metropolitan area	Health region (#-name)	Samples collected, N (%)	
Globule - Centre Laval	Montréal	13-Laval	3909	(4.1)
Globule - Kirkland	Montréal	06-Montréal	2574	(2.7)
Globule - Quartier Dix30	Montréal	16-Montérégie	5134	(5.4)
Globule - Place Versailles	Montréal	06-Montréal	3205	(3.3)
Globule - Quartier Lebourgneuf	Québec city	03-Capitale Nationale	11260	(11.7)
Globule - Sainte-Foy	Québec city	03-Capitale Nationale	11391	(11.9)
Plasmavie - Gatineau	Gatineau	08-Outaouais	11878	(12.4)
Plasmavie - Saguenay	Saguenay	02-Saguenay-Lac-St-Jean	17325	(18.1)
Plasmavie - Sherbrooke	Sherbrooke	05-Estrie	16669	(17.4)
Plasmavie - Trois-Rivières	Trois-Rivières	04-Mauricie et Centre du Québec	12627	(13.2)

The biobank includes samples from a population-based cohort of healthy, voluntary, non-remunerated donors of plasma for fractionation who consented that their samples be used for research purposes. Specifically, the pre-donation questionnaire asks donors if they are willing to give part of their routine 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. 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).

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., as tobacco use, medication use, and occupational status) can be obtained through a supplemental questionnaire filled by donors during their donation.

Table 2. Summary of the main variables* collected or derived from the cohort.

Variables	Information collected before vaccination/infection	Information collected after vaccination/infection	Information routinely collected at pre-donation screening
Internal Data			
Donor questionnaire			
Demographics: Age/Sex/Health region/Ethnicity	X	X	X
BMI calculated with	X	X	X
Height	X	X	X
Weight	X	X	X
Blood pressure[1]	X		
Diabetes profile and treatment (without insulin)[2]	X	X	X
COVID-19 vaccination status[3]	X	X	X
History of PCR-confirmed infection[4]	X	X	X
Laboratory tests			
Hemoglobin level	X	X	X
Blood type (ABO and Rh genotype or phenotype)	X	X	X
External Data			
COVID-19 vaccination status[5]	X	X	X
History of PCR-detected infection[6]	X	X	X

Abbreviation: COVID-19 = coronavirus disease-19

Notes:

* Several other variables such as donor deferrals, infectious state, etc. are routinely collected but are not presented in this table.

1. Available only for a subset of blood donor before the COVID-19 pandemic.
2. Diabetes treated with insulin is an exclusion criterion for blood donation.
3. Reported by the donor.
4. Reported by the donor.

5. From the provincial vaccination registry *Système d'information pour la protection des maladies infectieuses (SI-PMI)*.
6. From the provincial COVID-19 infection registry *Trajectoire de Santé Publique – TSP*.

Participant characteristics

As of January 24, 2022, 15,502 out of 17,070 (90.8%) donors consented to have a small volume of their donations used for research on COVID-19 (**Table 3**). No donor recruitment campaign was specifically undertaken for this research initiative. 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.

Donor characteristics were assessed as of January 24, 2022. Among consenting donors, median age was 43.0 years (**Table 3**). The six health regions where donors most often lived were Capitale-Nationale (18.1%), Estrie (14.7%), Saguenay-Lac-Saint-Jean (14.4%), Mauricie et Centre-du-Québec (11.4%), Outaouais (11.2%), and Montréal (9.8%). The cohort predominantly included donors who self-identified as white (93.6%). Relative to non-consenting donors, consenting donors tended to be younger (i.e., median age: 43.0 vs. 48.0 years), and included slightly more female donors (i.e., 49.7% vs. 46.3%) and more residents of urban areas (e.g., Montreal-Laval region: 12.1% vs. 8.1%). Relative to the Québec general population, consenting donors had a similar age and sex distribution, but the densely populated region of Montreal-Laval was underrepresented (12.1% vs. 29.5%).

A key feature of this biobank is the availability of multiple, longitudinally collected plasma samples and associated data. As of January 24, 2022, the biobank had collected 86,229 samples from 15,502 donors, for an average of 5.6 donations per donor. At least two donations are available for nearly two thirds of the cohort (i.e., 65.6%), thereby enabling the conduct of longitudinal analyses (**Figure 1**). Most of these repeat donors appeared to donate regularly, with a median gap between donations ranging from 51.0 days for those

with 2 donations to 11.8 days for those with ≥15 donations (median=29.0 days among those with ≥2 donations; **Figure 1**).

The cohort includes 3061 donors with samples collected pre- and post-vaccination, thereby enabling the study of vaccine-induced immunity in a real-world population of vaccine-naïve individuals. The cohort also includes 10,551 donors with samples collected only post-vaccination. Finally, the cohort includes 1326 donors with sample collected only pre-vaccination and 564 donors with no vaccination history or missing information.

The vast majority (i.e., 96.4%) of donors had received ≥1 vaccine dose, and 95.7% had received ≥2 doses; only 1.6% were unvaccinated. In Québec, the second vaccine dose was delayed for up to 16 weeks to optimize population-level immunity amid concerns over limited vaccine supply. As a result, a large proportion of plasma donors (i.e., 14.6%) received their second dose 85-112 days after their first dose, but some received it within the □3-week gap recommended by the manufacturer (i.e., 1.9% within 4 weeks). This notable feature of our biobank may be used to study the impact of vaccine dose intervals on the immune response, as done by Tauzin et al. [25] (described in more details further down).

The following vaccines have been administered in Québec: ChAdOx1-S, BNT162b2, and mRNA-1273. Some individuals have received combinations of these vaccines, which was allowed by public health authorities to help fast-track the vaccination campaign.

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).

Table 3. Donor characteristics as of January 24, 2022.	Consenting donors (N=15,502)		Non-consenting donors (N=1568)		General, adult population[1]
Sex,[2] n (%)					
Female	7709	(49.7)	831	(46.3)	(50.2)
Age (years),[2,3] mean ± SD (median)	43.9 ± 16.8 (43.0)		46.1 ± 16.7 (48.0)		50.2 ± 18.8 (50.0)
Age (years),[2,3], n (%)					
18-29	4399	(28.4)	433	(24.1)	(17.1)
30-39	2556	(16.5)	269	(15)	(16.0)
40-49	2287	(14.8)	251	(14)	(16.1)
50-59	2440	(15.7)	335	(18.7)	(16.1)
60-70	3178	(20.5)	408	(22.7)	(18.3)
≥71	642	(4.1)	100	(5.6)	(16.4)
Self-reported race/ethnicity,[2,4] n (%)					
White	14517	(93.6)	1667	(92.8)	NA
Other	985	(6.4)	129	(7.2)	NA
Health region (#-name),[2,3] n (%)					
02-Saguenay-Lac-Saint-Jean	2234	(14.4)	299	(16.6)	(3.3)
03-Capitale-Nationale	2811	(18.1)	351	(19.5)	(9.0)
04-Mauricie et Centre-du-Québec	1771	(11.4)	213	(11.9)	(6.2)
05-Estrie	2282	(14.7)	277	(15.4)	(5.8)
06-Montréal	1518	(9.8)	103	(5.7)	(24.4)
07-Outaouais	1729	(11.2)	263	(14.6)	(4.6)
12-Chaudière-Appalaches	744	(4.8)	100	(5.6)	(5.0)
13-Laval	353	(2.3)	24	(1.3)	(5.1)
14-Lanaudière	252	(1.6)	18	(1)	(6.0)
15-Laurentides	333	(2.1)	22	(1.2)	(7.4)
16-Montérégie	1259	(8.1)	108	(6)	(16.6)
Regions without fixed centers[4]	126	(0.8)	<11	(<0.70)[5]	(6.4)
Unknown or outside Québec	90	(0.6)	<11	(<0.70)[5]	NA
Number of vaccine doses received,[2,6] n (%)					
0	254	(1.6)	NA	NA	
1	103	(0.7)	NA	NA	(91.6)
2	5275	(34.0)	NA	NA	(88.7)
>2	9561	(61.7)	NA	NA	(47.1)
Missing data[7]	309	(2.0)	NA	NA	NA

Documented COVID-19 infection,[2,6,8] n (%)					
Yes	1662	(10.7)	NA	NA	(5.6)
No	13531	(87.3)	NA	NA	(94.4)
Missing data[7]	309	(2.0)	NA	NA	NA

Abbreviations: COVID-19 = coronavirus disease-19; SD = standard deviation

Notes:

1. For the general population of Québec, various data sources were used to capture variables of interest.
2. Demographics (i.e., sex, age, self-reported ethnicity, and health region) are reported as of 01-24-2022. Data on prior vaccination and documented infection are reported as of 01-24-2022.
3. For the general population, data come from the following: Ministère de la Santé et des Services sociaux du Québec. Estimations et projections de population par territoire sociosanitaire. Available from: https://publications.msss.gouv.qc.ca/msss/document-001617/. Accessed on August 10, 2022.
4. Includes (01-Bas-Saint-Laurent, 08-Abitibi-Témiscamingue, 09-Côte-Nord, 10-Nord-du-Québec, 11-Gaspésie-Îles-de-la-Madeleine, 17-Nunavik).
5. The exact number is lower than 11 and is thus not reported to preserve donor anonymity.
6. For the general population, data come from the following: Institut national de santé publique du Québec. Données COVID-19 par âge et sexe - Évolution des cas. Available from: https://www.inspq.qc.ca/covid-19/donnees/age-sexe/evolution-cas. Accessed on 03-01-2022."
7. Missing data are due to mismatches between donor information recorded in our institution's database and that recorded in governmental databases (N=309).
8. Data for the general population are underestimated since the age groups used in publicly available data (see footnote 7) exclude individuals aged 18-19 years.

Funding

The project is entirely funded by the COVID-19 Immunity Task Force (CITF), a government-funded working group dedicated to advancing knowledge and research on COVID-19 in Canada and to inform public health authorities. CITF has provided a long-term funding commitment (i.e., 2 years) for this biobank project, which will enable the conduct of long-term studies on infection- and vaccine-induced immunity to COVID-19.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Findings to Date

Longitudinal assessment of COVID-19 immunity

A study by Tauzin et al. used samples from our biobank to study the immune response to the mRNA vaccine BNT162b2 among SARS-CoV-2-naïve and previously infected individuals [25]. The authors found that, in previously infected individuals, the immune response was strengthened after the first dose of vaccine and minimally declined thereafter. The administration of a second dose did not further increase the strength of the immune response. By contrast, in SARS-CoV-2-naïve individuals, the administration of a second dose further strengthened the immune response (except for antibody-mediated cell cytotoxicity [ADCC], which appeared more transient).

Tauzin et al. additionally investigated the impact of using an extended interval between the two vaccine doses in SARS-CoV-2-naïve individuals. With the exception of ADCC, all assays were consistent with a better immune response when administering the two doses ~16 weeks apart compared with ~4 weeks apart.

Serosurvey

A publicly available report from our institution used biobank samples to estimate the seroprevalence of anti-SARS-CoV-2 antibodies in Québec from June 2021 – July 2021 [3]. This was the third phase of a serosurvey initiated in May 2020. Phases 1 (May–June 2020) and 2 (January–March 2021) only included whole blood donors rather than plasma donors from the biobank, since the PlasCoV project had not yet been launched. Phase 3 assessed both anti-receptor binding domain (RBD) and anti-nucleocapsid (N) seroprevalence, since

>80% of the population had received at least one vaccine dose at the time of the serosurvey [24].

The anti-RBD seroprevalence was 89.6%, consistent with the widespread vaccination coverage during phase 3. However, the anti-N seroprevalence was only 6.4%, which was lower than the anti-RBD seroprevalence among unvaccinated blood donors included in phase 2 (i.e., 10.5%). This unexpected result was likely driven by seroreversion, which occurs faster for anti-N than anti-spike (or anti-RBD) antibodies [26–28]. Indeed, nearly 40% of previously infected donors in phase 3 were seronegative for anti-N, likely because of seroreversion. This apparent rapid waning of anti-N antibodies was also observed in a separate cohort of 54 previously infected donors of convalescent plasma used in the CONCOR-1 clinical trial [29]. After more than 200 days of follow-up, anti-N seroreversion occurred in 33.3% of these donors, whereas anti-RBD seroreversion occurred in only 11.1% of donors.

Taken together, these results suggest anti-N seroprevalence may only be adequate to capture relatively recent infections, thereby questioning its usefulness in serosurveys analyzed using conventional analytical approaches (i.e., using a hard threshold applied at a single time point to determine seropositivity) [5]. At the time of writing this manuscript, the fourth phase of this study is underway and uses PlasCoV samples to compare anti-N responses pre- and post-infection — a new approach to estimate the incidence of recent infections in the context of the Omicron wave.

Future plans

The herein described plasma biobank will help conduct longitudinal studies on COVID-19 immunity. The resulting evidence will provide valuable insights on several aspects of the immune response to COVID-19, including its persistence, its specificity against variants, and the effects of vaccination.

Future studies using this biobank are already planned or underway. Our organization will continue using PlasCoV samples for an ongoing anti-SARS-CoV-2 serosurvey up until March, 2023 (see above description). The biobank will also prove useful to address other research questions in public health such as hybrid immunity, response to emerging variants or new vaccine formulations. For example, another study will soon be conducted to estimate the impact of post-COVID-19 syndrome (a.k.a., long COVID) in a healthy, adult population using this large, prospective longitudinal cohort.

Strengths and limitations

The herein described biobank has several strengths. To the best of our knowledge, this would be the largest biobank of plasma samples dedicated to COVID-19 research, with >80,000 samples from >15,000 donors and new samples continually being added until March 2023. Furthermore, the large subset of donors with ≥2 samples (65.6%) — along with the high frequency of donations in this subset (i.e., median: once every 29.0 days) — enables the conduct of longitudinal analyses on COVID-19 immunity. Another strength is that donors provided a broad consent, which allows researchers to recontact them for other projects (e.g., supplemental questionnaire). Lastly, the cost of establishing the biobank was minimized since the infrastructure and personnel required for sample collection were

already in place at our blood collection sites. Given these strengths, our biobank may serve as a model for other blood operators and government partners who would be interested in reproducing our initiative elsewhere.

Certain limitations should nonetheless be considered when using our biobank samples. 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. Furthermore, only plasma samples are available, so that the biobank cannot be used to study cell-mediated immunity. Researchers interested in studying cell-mediated immunity may want to contact BCQ19, which routinely collects peripheral blood mononuclear cells [22]. Moreover, despite the large sample, the plasma donor population is not fully representative of the overall Québec population, as expected since plasma donors are typically more representative of the healthy adult population. All exclusion criteria for plasma donations were also exclusion criteria for the biobank, including immunodeficiencies, active infection, and recent cancer among other chronic diseases. In addition, the database associated with our biobank does not include information on disease severity, such as hospitalization or intensive care unit admission, mortality, and comorbidities. Lastly, the database does not include information on socioeconomic status, such as income and education. However, the six-digit zip code can be used to generate a proxy index for socioeconomic status.

Collaboration

All researchers in Canada or elsewhere may apply to access the PlasCoV biobank. Researchers will be asked to fill a form with high-level information on their project's objectives, methods, novelty, and relevance to the biobank's objectives. They will also be asked to justify the sample size needed and any particular inclusion criteria, and to obtain ethics approval for their project.

Data sharing statement

Details on the PlasCoV biobank and the application process can be obtained through Héma-Québec's website at https://www.hema-quebec.qc.ca/coronavirus/hema-quebec-en-contexte-de-pandemie/etude-plascov.en.html. Enquiries can be sent by e-mail to BiobanqueCOVID@hema-quebec.qc.ca, or alternately to Dr. Marc Germain (Marc.Germain@hema-quebec.qc.ca), the biobank director.

Funding declaration

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Contributorship statement

MG, AL, RB and CR conceived and designed the study. AL, AB, JP, and YG collected the data. AL and YG analyzed the data, with input from MG, RB, MD and CR. MG, AL, YG and RB drafted the manuscript and MD, AB, CR and JP critically revised it for important intellectual content. All authors approved the final version to be published.

Ethics approval

This study was approved by Héma-Québec Institutional review board. Individual informed consent was obtained from participants at the time of registration in the PlasCoV Biobank.

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Competing interest

No competing interest.

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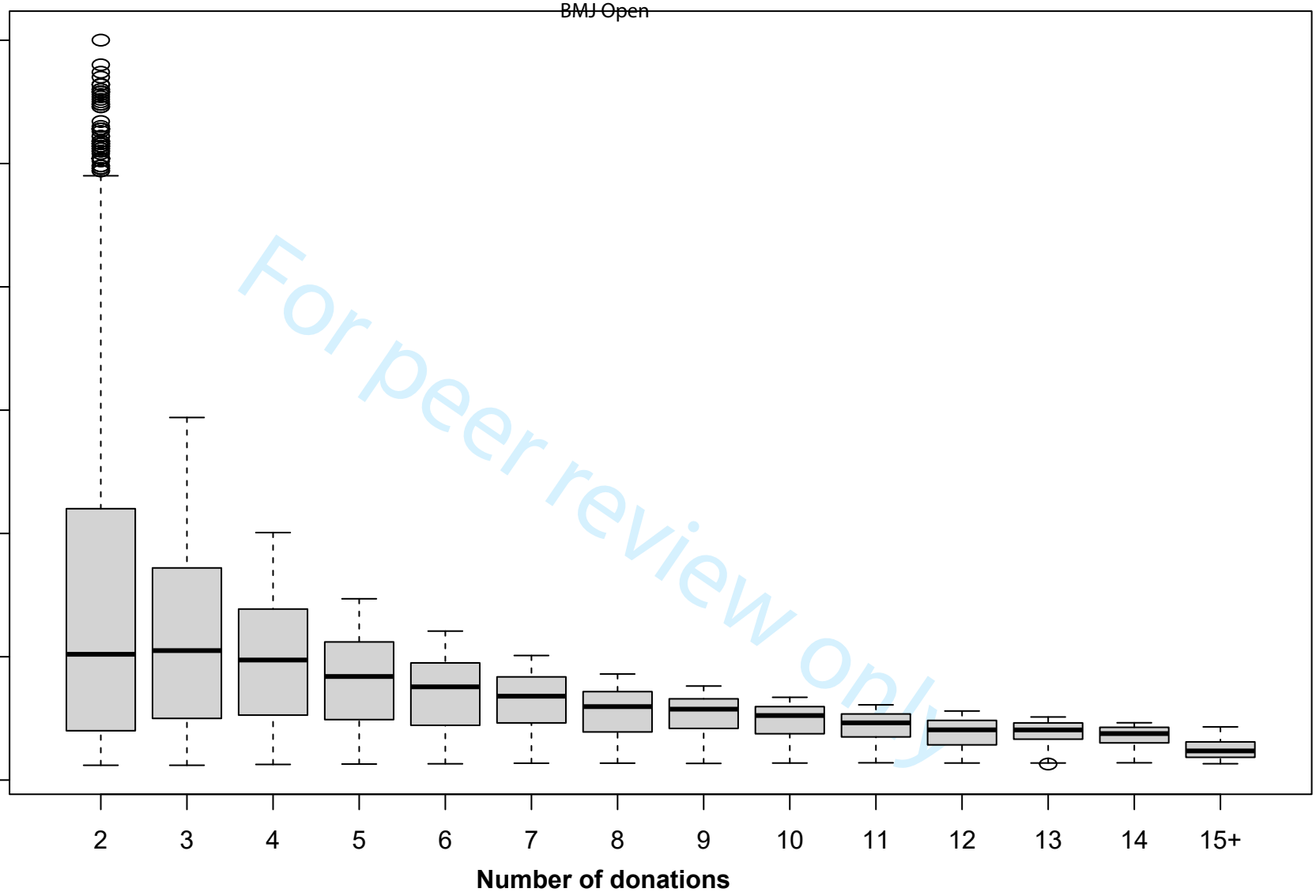
Figure caption

Figure 1. Average number of days between donations as a function of the number of donations in PlasCoV.



Donors (N)	2,498	1,505	1,045	758	567	441	344	355	274	209	177	187	165	1,631
Proportion (%)	16.1	9.7	6.7	4.9	3.7	2.8	2.2	2.3	1.8	1.3	1.1	1.2	1.1	10.5