

HOW DO I ?

# How we secured a COVID-19 convalescent plasma procurement scheme in Japan

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**Abstract**

**Background:** In order to tackle the COVID-19 pandemic, a COVID-19 convalescent plasma (CCP) procurement program was initiated in Japan in April 2020. The program was a collaboration between a government-managed national hospital, an infectious disease research institute, and a blood banking organization. Each party assumed different responsibilities: recruitment, SARS-CoV-2 antibody profiling, and plasmapheresis; conduction of screening tests; and SARS-CoV-2 blood testing, respectively.

**Methods:** We adopted a two-point screening approach before the collected CCP was labeled as a CCP product for investigational use, for which we mainly

tested anti-SARS-CoV-2 antibody eligibility and blood product eligibility. Anti-SARS-CoV-2 spike protein titer was measured using enzyme-linked immunosorbent assay, and the IC<sub>50</sub> value was denoted as the neutralizing activity. Blood donor eligibility was extended beyond the normal blood donation guidelines to include a broader range of participants. After both eligibility criteria were confirmed, participants were asked to revisit the hospital for blood donation, which is a unique aspect of the Japanese CCP program, as most donations are taking place in normal blood donation venues in other countries. Some donors were re-scheduled for repeat plasma donations. As public interest in anti-SARS-CoV-2 antibodies increased, test results were given to the participants.

**Results:** As of September 17, 2020, our collection of CCP products was sufficient to treat more than 100 patients. As a result, projects for administration and distribution are also being conducted.

**Conclusions:** We successfully implemented a CCP procurement scheme with the goal to expand to other parts of the country to improve treatment options for COVID-19.

#### KEYWORDS

antibody, blood donation, convalescent plasma, COVID-19, plasmapheresis, SARS-CoV-2

Since the discovery in Wuhan, China, in December 2019, the coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), as of August 9, 2020, has affected nearly 20 million people in over 200 countries worldwide.<sup>1</sup> Japan seemed to have averted a massive pandemic by May 2020; however, there was a resurgence in July 2020, with a record number of new cases nearly every week. To date, COVID-19 treatment options have been limited; remdesivir is the only antiviral treatment officially approved in Japan. Corticosteroids are widely used along with remdesivir, as recommended in the guidelines<sup>2</sup> and evidenced by various studies.<sup>3-5</sup> The Japanese Association for Infectious Diseases recommends additional antivirals based on limited evidence.<sup>6</sup>

Historically, convalescent plasma therapy has been utilized to treat emerging infectious diseases for which treatments are limited or unavailable. For instance, it has been used to treat diseases such as SARS, Middle East respiratory syndrome, and Ebola.<sup>7,8</sup> COVID-19 is not an exception for this therapy, and has been implemented in countries such as China,<sup>9</sup> India,<sup>10</sup> Italy,<sup>11</sup> Turkey,<sup>12</sup> and the United States of America.<sup>13</sup>

COVID-19 convalescent plasma (CCP) procurement began in Japan in April 2020. Our hospital, the National Center for Global Health and Medicine (NCGM), developed the CCP donation scheme in collaboration with the Japanese Red Cross (JRC) Society and the National

Institute of Infectious Disease (NIID). NCGM and NIID are pivotal institutions in the Japanese COVID-19 pandemic. The former is a government-managed national hospital and the latter is a governmental research institute; COVID-19 treatments and infection control measures are being investigated at both. JRC, the sole blood banking organization in Japan, was also indispensable in the development of the donation scheme. This article outlines the entire CCP procurement process developed and implemented in Japan by NCGM with support from JRC and NIID.

## 1 | INITIATION AND ROLES

All three institutes assumed different roles/responsibilities in the CCP procurement program. The program was initiated by NCGM, which is a complex organization of hospitals and research institutes. This organizational structure allowed us to both access COVID-19 convalescent individuals and perform anti-SARS-CoV-2 antibody tests. Hence, our responsibility was to recruit participants, determine their antibody profiles, and confirm CCP donor eligibility. To ensure that the quality and type of screening tests performed on participants and CCP products are equivalent to those performed for regular blood donation, we sought support from JRC to test for infectious diseases, irregular antibodies, and anti-Human

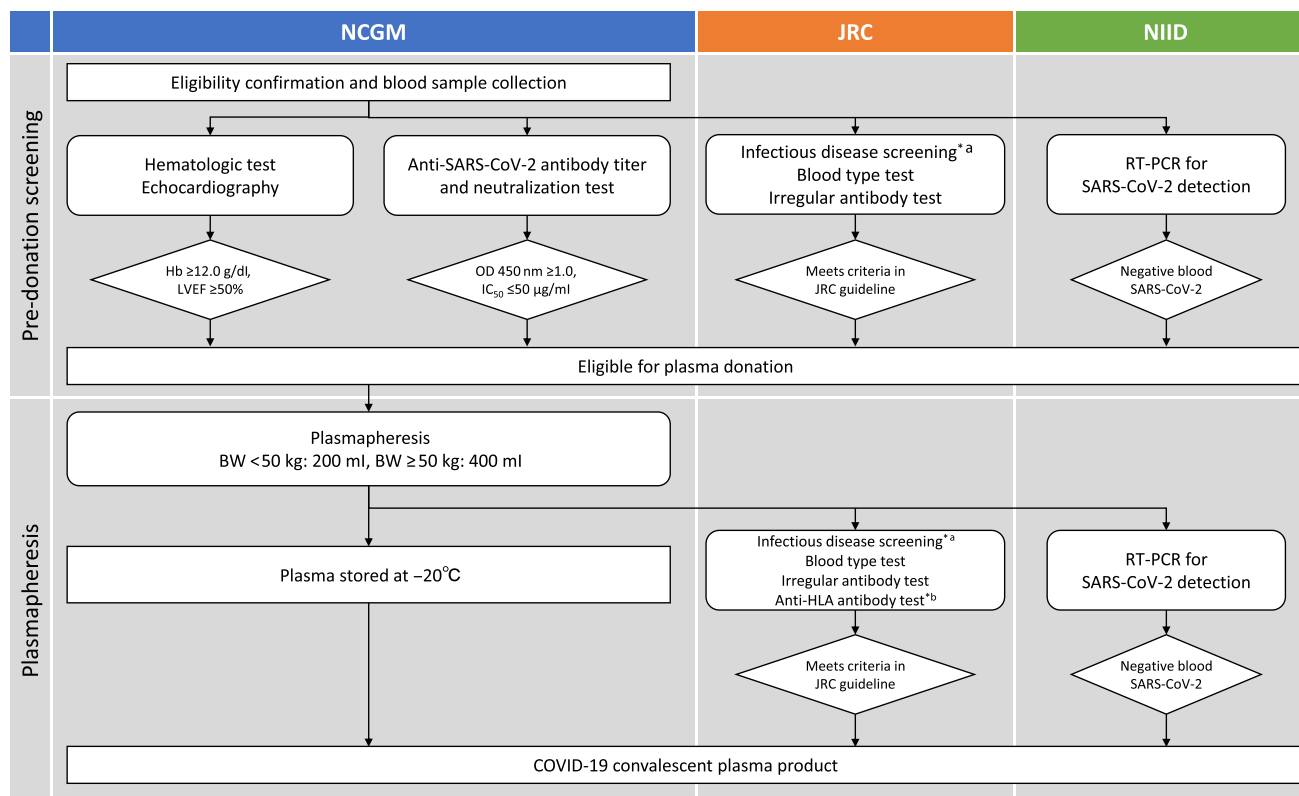
Leukocyte Antigen (anti-HLA) antibodies. NIID also collaborated with us on quantitative reverse transcription polymerase chain reaction (qRT-PCR) testing for SARS-CoV-2 detection in blood samples to exclude viremic patients, and solicit NIID expertise in case viremia was detected.

Plasmapheresis was conducted in the NCGM hospital by a team of hematologists, clinical engineers, and nurses. A maximum of two donors were subjected to simultaneous plasmapheresis. Even in cases of simultaneous plasmapheresis, at least one nurse per donor was attending each bedside. One hematologist and a clinical engineer monitored two donors simultaneously. Although JRC has multiple blood donation centers nationwide, we concluded that these centers could not be utilized for CCP donation alongside regular blood donations for infection control because the infectivity of recovered patients was in question at the initiation of the project. Considering that CCP donations in other countries take place at normal blood donation venues, this is a unique feature of the Japanese program.

## 2 | OVERVIEW

We adopted a two-point screening approach before the collected CCP was labeled as a CCP product for investigational use. The entire CCP procurement process is depicted in Figure 1. The first point is a pre-donation screening process for a participant, involving SARS-CoV-2 antibody testing. Other mandatory blood tests are hemoglobin (Hb) level, blood type, SARS-CoV-2, irregular antibody, and infectious disease screening. Hb levels  $\geq 12.0$  g/dl were required according to Japanese blood donation guidelines. Owing to circulatory issues in some donors, due to their recent recovery from COVID-19, we included echocardiography in the pre-donation screening to evaluate cardiac function, which is not a component of the routine blood donation scheme.

The second screening point determines whether the CCP products qualify as blood products. Participants who passed the first screening point became donors and underwent plasmapheresis. The collected CCP products were tested for safety, namely, for infectious diseases,



**FIGURE 1** Overall image of convalescent plasma procurement. <sup>a</sup>HBs Ag, HBc Ab, HBs Ab, HCV Ab, HIV-1 Ab, HIV-2 Ab, HBV NAT, HCV NAT, HEV NAT (from August 6, 2020), HIV-1 NAT, HIV-2 NAT, Syphilis Ab, HTLV-1 Ab, HTLV-2 Ab, HumanparvovirusB19 Ag. <sup>b</sup>Only in females with past pregnancy or both sexes with a history of blood transfusion. Hb, hemoglobin; JRC, Japanese Red Cross; LVEF, left ventricle ejection fraction; NCGM, National Center for Global Health and Medicine; NIID, National Institute of Infectious Disease; RT-PCR, reverse transcription polymerase chain reaction [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

irregular antibodies, SARS-CoV-2, and, if necessary, anti-HLA antibodies. Anti-SARS-CoV-2 antibodies were retested to confirm that the titer and neutralization had not changed since the screening.

### 3 | RECRUITMENT

Initially, participants were recruited from prior hospital admissions; recruitment was then extended to the general public via social media platforms. In the early phase, patients admitted to NCGM were recruited, as they were the most approachable. However, the number of such patients was limited, and we soon ran out of participants. External participants were recruited in the next phase, wherein social network services (SNSs), including Twitter and Facebook, were utilized. SNS posts included a link to the website where the eligibility criteria were outlined. We also asked medical institutes cooperating with NCGM to put up posters or hand out leaflets calling for donation. Our project was also featured in a Japanese television news program, which also contributed to recruitment.

CCP applicants from external recruitment could apply either by phone or via an internet-based form. We started with a phone-based application and later created an internet-based form that allowed potential applicants to apply 24/7, which enabled more applications. We mandated applicants to enter their name, birth date, sex, date of onset, contact information, retention of COVID-19 testing documents, and whether they had checked the eligibility criteria beforehand. Hospital recruitment staff contacted the applicants by phone or e-mail to confirm the date of their screening.

### 4 | ANTIBODY MEASUREMENT

An enzyme-linked immunosorbent assay (ELISA) system was developed to measure the anti-spike antibody titer in convalescent serum/plasma. The SARS-CoV-2 spike protein is critical for cellular entry into host cells and is the main target of neutralizing antibodies. Recombinant spike protein was expressed with an Expi293 expression system (Thermo Fisher Scientific, Waltham, MA), and used as an antigen for anti-spike antibodies. Briefly, Expi293 cells were maintained in Expi293 expression medium at 37°C under 5% CO<sub>2</sub> with agitation at 125 rpm. Plasmid DNA encoding full-length SARS-CoV-2 spike protein<sup>14</sup> was transfected using ExpiFectamine™ 293 Reagent (Thermo Fisher Scientific), according to the manufacturer's protocol. Cells were harvested after 3 days, suspended in lysis buffer (20 mM Tris-HCl

[pH 8.0], 500 mM NaCl, 1 mM EDTA, 10 mM β-mercaptoethanol, 0.1% NP-40, and 5% glycerol), sonicated, and centrifuged for 30 min at 10,000 rpm. The supernatant was incubated with Strep-Tactin® Superflow™ Agarose beads (Merck Millipore, Burlington, MA) for 3 h at 4°C. After washing with lysis buffer, the protein was eluted using Strep-Tactin® Elution Buffer with desthiobiotin (IBA). Protein purity was validated via SDS polyacrylamide gel electrophoresis, and concentration was estimated using a standard curve obtained with pre-measured bovine serum albumin. The purified protein (2.5 μg/ml) was coated on a MaxiSoap 96-well ELISA plate (Thermo Fisher Scientific), incubated overnight at 4°C, blocked with 1% BlockAce (KAC, Kyoto, Japan) for 1 h at 37°C, and washed six times with phosphate-buffered saline (PBS, pH 7.4). Each diluted (1/800) convalescent serum/plasma sample (100 μl) was incubated for 1 h at 37°C. The plate was washed six times with PBS-T (PBS containing 0.2% Tween 20) and incubated with anti-human IgG conjugated with horseradish peroxidase (GeneTex, Irvine, CA) for 30 min at 37°C. Then, the captured anti-spike antibodies were detected with 3,3',5,5'-tetramethylbenzidine substrate solution (Nacalai Tesque, Kyoto, Japan), and absorbance at 450 nm wavelength (OD450) was measured using a microplate reader (Bio-Rad, Irvine, CA). Samples derived from healthy volunteers with no previous SARS-CoV-2 infection acted as negative controls, whereas those from infected patients, who had high amounts of anti-spike antibodies, were used as positive controls. Each sample was assayed in triplicate, and all measurements were normalized to positive control values. The positive and negative cut-off values of the antibody titer were set to a value of mean plus six times the standard deviation of the negative control.

To detect neutralizing activity, IgG fractions were obtained from the sera of all participants, using a column-based technique. The activity of the isolated IgG fractions was determined using an *in vitro* antiviral assay. For the assay, TMPRSS2-overexpressing VeroE6 (VeroE6TMPRSS2) cells were seeded in a 96-well plate. The following day, a virus (SARS-CoV-205-2N), isolated from a COVID-19-patient treated at NCGM, was inoculated into the cells in the presence of purified IgG fraction, and cultured for 3 days. After the culture, the cytopathic effect in SARS-CoV-2-exposed cells with and without the IgG fraction was determined, and the neutralizing activity of the IgG fraction was expressed as the half-maximal inhibitory concentration (IC<sub>50</sub>) value.<sup>15</sup> Participant plasma containing IgG fraction with IC<sub>50</sub> ≤ 50 μg/ml was considered to have neutralizing activity.

## 5 | ELIGIBILITY

Eligibility was evaluated twice, for participants before the pre-donation screening and for donors before plasmapheresis. A complete list of inclusion and exclusion criteria for participants and donors are listed in Tables 1 and 2.

### 5.1 | Pre-donation screening eligibility

Inclusion criteria for pre-donation screening were set according to the JRC blood donation guidelines and CCP-specific requirements. The CCP-specific inclusion criteria were “having a previous COVID-19 diagnosis” and “at least three weeks from symptom onset at screening.” No restrictions were set for COVID-19 severity, and recovered patients of all severities were included. As eligible participants were cleared from isolation or hospitalization under the latest policy, we did not collect nasopharyngeal swab specimens for qRT-PCR. Criteria for age and body weight were set according to the JRC guidelines.

Exclusion criteria, on the other hand, were modified from those stipulated in the JRC blood donation guidelines, to include a broader range of participants. Persons with a history of blood transfusion or organ transplants are generally excluded by the JRC guidelines; however, severe COVID-19 cases may have had a blood transfusion, and hence, we mitigated this criterion by testing for anti-HLA antibodies. Criteria for comorbidity were also modified to allow persons with diseases stipulated in exclusion criteria (1) to participate if the disease had resolved or was not exacerbated. Individual eligibility by comorbidity was assessed by a physician after a comprehensive physical examination.

### 5.2 | Donor eligibility

We determined donor eligibility for the SARS-CoV-2 antibody after testing an adequate number of samples from pre-donation screening. These data were used to establish the antibody-level criteria. Analysis of 40 pre-donation screening samples revealed that samples exhibiting more than 1.0 OD of absorbance at 450 nm were positive for high neutralizing activity (Figure 2A); we selected participants whose samples exhibited OD values greater than 1.0 as CCP donors. For 199 samples, the OD values ranged from 0.072 to 3.725. Antibody titers and neutralizing antibodies were highly correlated (Figure 2B,  $p < .0001$ ).

SARS-CoV-2 antibody-specific criteria are described elsewhere in detail. Left ventricle ejection fraction

TABLE 1 Pre-donation screening eligibility

Inclusion criteria
Candidates must satisfy all the following items to undergo pre-donation screening.
1. Written consent obtained from the candidate
2. Cleared from isolation or hospitalization under latest policy
3. Male or female aged 20–69 years
4. Weighs $\geq 45$ kg for male or $\geq 40$ kg for female
5. Previous COVID-19 diagnosis confirmed by official documentation
6. At least 3 weeks from onset
Exclusion criteria
Candidates must be excluded from pre-donation screening if they meet any of the following.
1. Current or past history of cardiovascular disease, malignant tumor, hematologic disease, convulsive disorders, asthmatic disease, or cerebral apoplexy, and considered inappropriate for blood donation by a physician
2. Past history of blood transfusion or organ transplant and considered inappropriate for blood donation by a physician
3. Had or plan to have any of the following vaccinations or treatments within the specified period from plasmapheresis
i. HBV vaccination within 2 weeks
ii. Anti-HBs human immunoglobulin within 6 months
iii. Post-animal bite rabies vaccination within 1 year
iv. Smallpox vaccination within 2 months
v. Antiserum (tetanus, snake venom, gas gangrene, botulinum) within 3 months
vi. Other inactivated vaccines or toxoids within 24 h
vii. Other live vaccines within 4 weeks
4. Pierced or tattooed within 6 months
5. Within 3 or 6 months from animal or human bite, respectively
6. Known or suspected infection of HIV, HBV, or HCV
7. Has had any of the following overseas stay or residence
i. Within a year from $<1$ year stay or within 3 years from $\geq 1$ year stay in malaria endemic area
ii. Candidate, his/her mother or maternal grandmother grown up in Latin America
iii. $\geq 4$ week continuous stay or residence in Latin America
8. History of African trypanosomiasis or Babesiosis
9. Has a risk of vCJD judged from past overseas stay or residence
10. Diagnosed with or has a risk of Creutzfeldt-Jacob disease
11. Pregnant or breastfeeding female
12. Does not meet any of the above but considered inappropriate for plasmapheresis or blood donation by a physician

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; vCJD, variant Creutzfeldt-Jacob disease.

(LVEF)  $\geq 50\%$  was also a CCP donor-specific criterion. Considering recent recovery from COVID-19, LVEF  $\geq 50\%$  was set in addition to selecting donors with normal cardiac function, and echocardiography was conducted at the pre-donation screening. Other criteria were determined according to the blood donation guidelines.

**TABLE 2** COVID-19 convalescent plasma donor eligibility

Inclusion criteria
Candidates must satisfy all the following items to undergo plasmapheresis.
1. Male or female aged 20–69 years
2. Within 90 days from documented informed consent
3. Weighs $\geq 45$ kg for male or $\geq 40$ kg for female
4. Systolic blood pressure $\geq 90$ mmHg and hemoglobin $\geq 12.0$ g/dl
5. Has sufficient anti-SARS-CoV-2 antibody titer and half-maximal inhibitory concentration ( $IC_{50}$ ) at pre-donation screening
6. LVEF $\geq 50\%$ by echocardiography
7. No problematic infectious disease, antigen, or antibody detected in the pre-donation screening blood sample <sup>a</sup>
Exclusion criteria
Candidates must be excluded from blood donation if they meet any of the following on the day of plasmapheresis.
1. Febrile or poor overall condition
2. Underwent hemorrhagic dental treatment within 3 days
3. Has an ongoing injury or trauma
4. Traveled overseas within 4 weeks
5. Had any of the following vaccinations or treatments within the specified period
i. HBV vaccination within 2 weeks
ii. Anti-HBs human immunoglobulin within 6 months
iii. Post-animal bite rabies vaccination within 1 year
iv. Smallpox vaccination within 2 months
v. Antiserum (tetanus, snake venom, gas gangrene, botulinum) within 3 months
vi. Other inactivated vaccines or toxoids within 24 h
vii. Other live vaccines within 4 weeks
6. Pierced or tattooed within 6 months
7. Within 3 or 6 months from animal or human bite, respectively <sup>b</sup>
8. Pregnant or breastfeeding female <sup>b</sup>
9. Does not meet any of the above but considered inappropriate for blood donation by a physician <sup>b</sup>

Abbreviations: HBV, hepatitis B virus; LVEF, left ventricle ejection fraction.

<sup>a</sup>Irregular antibody, hepatitis B virus, hepatitis C virus, hepatitis E virus, human immunodeficiency virus, human T-lymphotropic virus, parvovirus B19, and syphilis.

<sup>b</sup>Also evaluated at pre-donation screening.

## 6 | PRE-DONATION SCREENING

Pre-donation screening took place at the Infectious Disease Department outpatient clinic at NCGM. Pre-donation screening took about 90 min for COVID-19 diagnosis confirmation, eligibility confirmation, blood collection, and echocardiography. Approximately 40 ml of blood was drawn and delivered to the NCGM laboratory, NCGM hospital laboratory, JRC, and NIID. These blood samples were enclosed in triple packaging and delivered to JRC and NIID the next day via the

refrigerated courier service of a local company. The NCGM laboratory and hospital laboratory received the samples directly by intramural delivery on the same day of collection. The results of echocardiography, hematologic tests, and blood type were available on an electronic health record system implemented in NCGM. Other test results were reported in the form of a PDF scan of a manually signed report, qRT-PCR curve, or measurements entered in an Excel file.

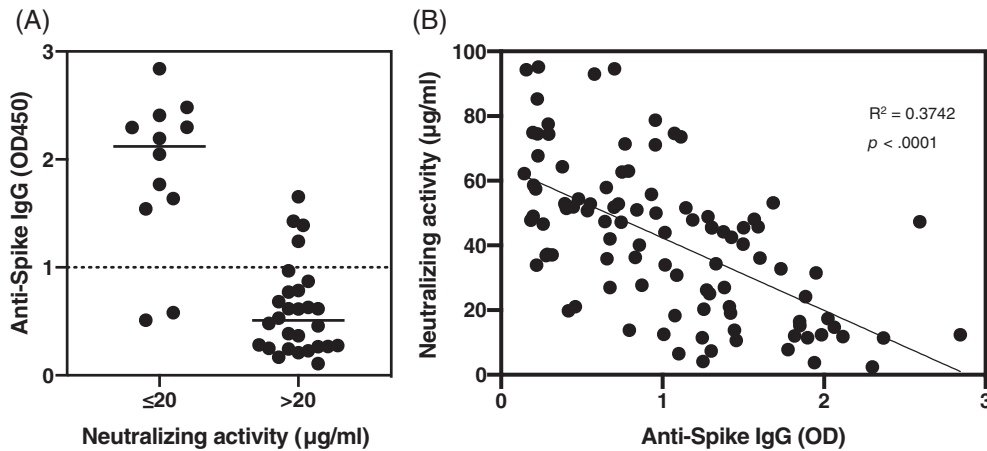
Screening was conducted on a maximum of five applicants per day from Monday to Thursday. As screening took place in the NCGM hospital alongside regular clinical practice, the maximum screening capacity was 20 persons per week. Friday screening is conducted irregularly, and on-demand as NIID cannot regularly conduct the test on Saturdays. Although the screening capacity was relatively small compared with that of CCP programs in other countries, it was sufficient for the Tokyo area because the pandemic range was also relatively small.

## 7 | SCHEDULING AND RE-SCHEDULING

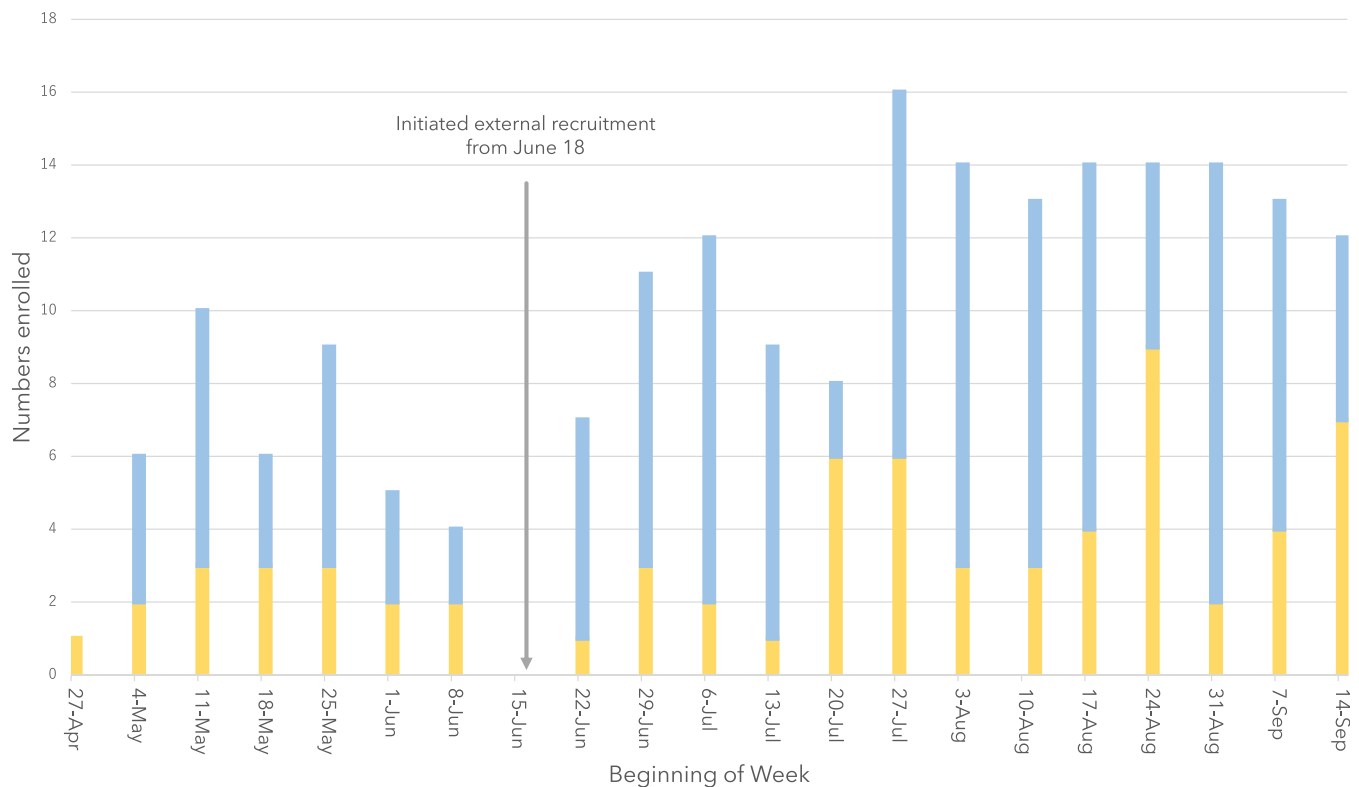
Participants who met the donor criteria were contacted through phone call or e-mail to schedule plasmapheresis for plasma donation. We provided brief results of their SARS-CoV-2 antibody test over the phone and asked them to return for plasmapheresis. Some donors were re-scheduled for another plasma donation; at least 14 days of interval, determined according to the JRC guidelines, was required between the donations. Antibody measurements were not repeated for consecutive donations.

## 8 | PLASMAPHERESIS

A maximum of 400 ml plasma per person was collected for each plasmapheresis. For donors weighing  $< 50$  kg, 200 ml was the maximum. A centrifugal plasma exchange device (COM.TEC, Fresenius SE & Co. KGaA, Germany) was used for plasma collection. To compensate for possible health damages, we contracted clinical research insurance. The regular blood donation program led by JRC includes compensation for health damage that may occur due to donations. Insurance was contracted to equalize the aid provided to donors. We also supplied a bottle of water and a sports drink after plasmapheresis to minimize adverse events due to dehydration.



**FIGURE 2** Analyses of antibody titer and neutralizing activity in pre-donation screening samples. Antibody titers are presented as OD values (absorbance at 450 nm) and neutralizing activities as half-maximal inhibitory concentration ( $IC_{50}$ ) values. (A) Values of antibody titer and neutralizing activity in 40 pre-donation screening samples. (B) Values and correlation of antibody titer and neutralizing activity in 199 pre-donation screening samples



**FIGURE 3** Number of study enrollments per week and eligibility for COVID-19 convalescent plasma (CCP) donors. Blue and yellow bars represent participants who were ineligible and those who were eligible as CCP donors, respectively [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

## 9 | PLASMA STORAGE

The collected CCP products were separated into units (bags) of 200 or 100 ml. These bags are intended for safety studies and Randomized Controlled Trial (RCTs), which we are currently conducting and planning,

respectively. Collected plasma was tested for safety, namely, for infectious diseases, irregular antibodies, SARS-CoV-2, and, if necessary, anti-HLA antibodies, before being stored for administration. All CCP products were allocated a lot number and stored in an exclusive freezer.

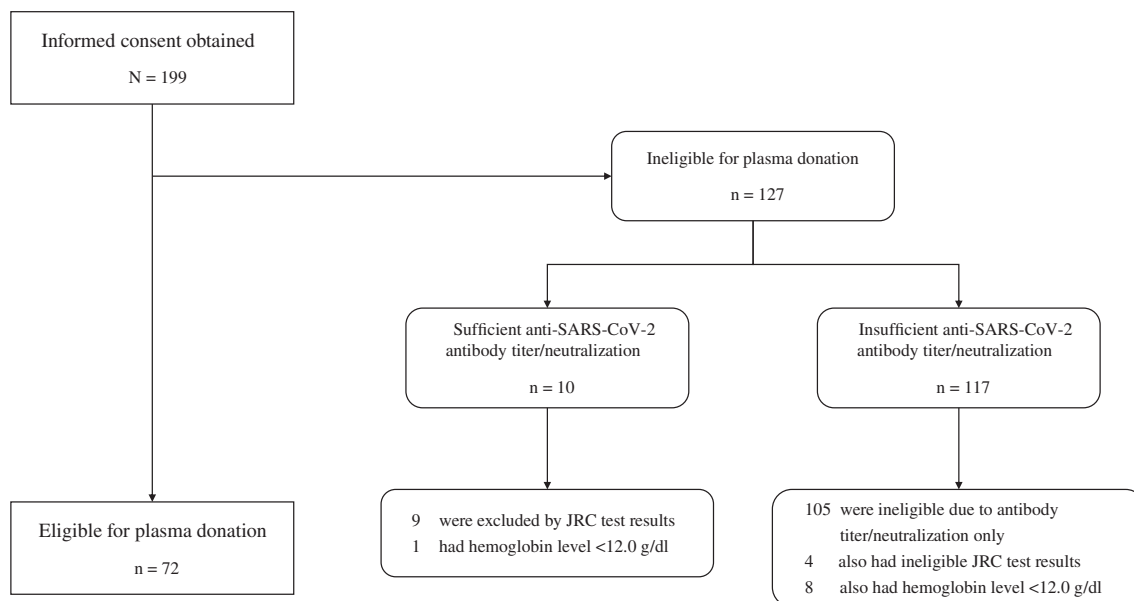


FIGURE 4 Flowchart of eligible and ineligible participants and reasons for ineligibility. JRC, Japanese Red Cross

TABLE 3 Demographics and clinical characteristics of participants ( $n = 199$ )

	All participants	Eligible (donors)	Ineligible
<i>N</i> (%)	199 (100%)	72 (36.2)	127 (63.8)
Age, median (range)	46 (20–69)	52.5 (20–69)	44 (22–69)
Sex, <i>n</i> (%)			
Male	102 (51.3)	46 (63.9)	56 (44.1)
Female	97 (48.7)	26 (36.1)	71 (55.9)
Blood type, <i>n</i> (%)			
A+	90 (45.2)	32 (44.4)	58 (45.7)
B+	36 (18.1)	15 (20.8)	21 (16.5)
AB+	18 (9.04)	8 (11.1)	10 (7.9)
O+	53 (26.6)	17 (23.6)	36 (28.3)
A–	1 (0.50)	0 (0)	1 (0.8)
Not tested	1 (0.50)	0 (0)	1 (0.8)
Recruitment, <i>n</i> (%) <sup>a</sup>			
Internal	51 (25.6)	22 (30.6)	29 (22.8)
External	148 (74.4)	50 (69.4)	98 (77.2)
Days from onset to screening, median (range)	54 (21–167)	50 (21–163)	56 (21–167)
Days from screening to donation, median (range)	—	21 (7–91) <sup>b</sup>	—
Days from onset to donation, median (range)	—	74 (32–177) <sup>b</sup>	—

<sup>a</sup>Internal participants were recruited from National Center for Global Health and Medicine-admitted patients. External participants were recruited from other sources.

<sup>b</sup>Median and range were derived from 69 participants for their first donation. Three were not scheduled for plasmapheresis when the manuscript was written, and eight were re-scheduled for their second donation.



## 10 | ANTIBODY TEST RESULTS FEEDBACK

As public interest increased, participants who underwent pre-donation screening requested the results of SARS-CoV-2 antibody tests. We developed a patient manual on how to interpret the results and distributed them to the participants along with their results.

The velocity of SARS-CoV-2 antibody decay is reported to be rapid or varies greatly among individuals.<sup>16,17</sup> This fact stimulated public interest in testing for SARS-CoV-2 antibodies. Accordingly, various SARS-CoV-2 antibody tests have become commercially available, but are often expensive. In this study, participants were not charged for antibody tests. The provision of results may have motivated participants who were willing to take the test but hesitated to procure commercially available tests due to the price.

## 11 | PROGRESS AND OUR NEXT GOAL

A total of 199 participants were screened by September 17, 2020; 72 (36.2%) met the donor eligibility criteria and have either donated CCP or been contacted for plasmapheresis. The median age was 46 (interquartile range [IQR] 36.5–55), 52.5 (IQR 43–59), and 44 (IQR 32.5–51.5) years for all, eligible, and ineligible participants, respectively. The median number of days from symptom onset to screening was 54 (IQR 34.5–96), 50 (IQR 33–96), and 56 (IQR 35–96) for all, eligible, and ineligible participants, respectively. Donors returned to the hospital for plasmapheresis in a median of 21 days (IQR 15–27), which was 74 days (IQR 60–108) from symptom onset. Our supply of CCP products is now sufficient to treat more than 100 patients. Figure 3 shows the number of enrolments per week. The first peak indicates NCGM-admitted enrollment. After starting recruitment using social media, the number of participants seems to have stabilized.

Donor eligibility, demographics, and clinical characteristics of the participants are shown in Figure 4 and Table 3. Of the 199 participants enrolled, 127 (63.8%) were ineligible for plasma donation. Most ineligible participants failed to meet the criteria owing to insufficient antibody titer/neutralization ( $n = 117$ , 58.1%). Other failures were due to JRC guidelines ( $n = 10$ , 5.0%), including past syphilis infection, HBV risk, human parvovirus B19 infection, and elevated ALT levels.

This article has described the CCP procurement scheme of Japan; projects for administration and distribution have also commenced. Our next objectives are to

complete the safety study, shift to RCT, and expand this treatment option to other parts of the country.

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## CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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