How did we rapidly implement a convalescent plasma program?

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Since the beginning of the COVID-19 pandemic, the use of convalescent plasma as a possible treatment has been explored. Here we describe our experience as the first U.S. organization creating a COVID-19 convalescent plasma program to support its use through the single-patient emergency investigational new drug, the National Expanded Access Program, and multiple randomized controlled trials. Within weeks, we were able to distribute more than 8000 products, scale up collections to more than 4000 units per week, meet hospital demand, and support randomized controlled trials to evaluate the efficacy of convalescent plasma treatment. This was through strategic planning; redeployment of staff; and active engagement of hospital, community, and public health partners. Our partners helped with donor recruitment, testing, patient advocacy, and patient availability. The program will continue to evolve as we learn more about optimizing the product. Remaining issues to be resolved are antibody titers, dose, and at what stage of disease to transfuse.

The coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), pandemic, has resulted in 1.2 million cases and more than 70,000 deaths in the United States alone.[1] New York City is the center of the U.S. epidemic: more than 325,000 cases and 25,000 deaths have occurred in New York State, more than half (56%) of which have been reported in New York City as of May 5, 2020.[2] New York Blood Center Enterprises (NYBCe), which includes New York Blood Center (NYBC) and its operating divisions Community Blood Center of Kansas City, Missouri, Innovative Blood Resources, Blood Bank of Delmarva, and Rhode Island Blood Center, is headquartered and is the primarily blood supplier of New York City. We developed a COVID-19 convalescent plasma (CCP) program in partnership with our hospitals given plausible benefit to prevent and treat COVID-19.

COVID-19 convalescent plasma is postulated to be effective through process of passive immunization, specifically transfer of neutralizing antibodies from a recovered individual to someone at risk of COVID-19 after exposure to SARS-COV-2 or treatment if already manifesting symptoms. Interest in CCP emerged early in the pandemic, given the prior application of CCP to treat other coronavirus diseases (i.e., SARS and Middle Eastern Respiratory Syndrome);[3] early examples of use of CCP during the COVID-19 epidemic in China

ABBREVIATIONS: CCP = COVID-19 convalescent plasma; eIND = emergency investigational new drug; EAP = Expanded Access Program; NYBC = New York Blood Center; NYBCe = New York Blood Center Enterprises; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

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demonstrated that CCP was safe and potentially beneficial in treatment of severe COVID-19.[4-6] Furthermore, CCP represents a virus-specific approach that can be implemented rapidly, while other disease specific therapies are still being developed.

Being at the center of the COVID-19 pandemic, NYBCe and our partners took a leading role in the provision and transfusion of CCP. Our blood centers had the facilities and capabilities necessary to collect, test, and distribute CCP. Our goal is that every patient receives CCP upon hospital arrival. Here we describe our evolving work with CCP to meet that goal (Fig. 1).

PHASE I: HOSPITAL PARTNERS RECRUIT DONORS

New York Blood Center Enterprises initiated a CCP program with engagement of our hospitals in early March 2020. The hospitals assumed a major role in recruitment, given their ability to identify and test SARS-CoV-2–positive individuals. The program was conceived and designed before the launch of the FDA's guidelines for use of CCP under a single-patient emergency investigational new drug (eIND) pathway to access CCP on March 24, 2020.[7] The eIND provided criteria for donor eligibility that included a prior diagnosis of COVID-19 as documented by laboratory test, complete resolution of symptoms for at least 14 days, a negative COVID-19 test result by nasopharyngeal swab or blood by molecular diagnostic test, and defined SARS-CoV-2–specific neutralizing antibody titers (>1:320), if able to perform testing[7] (Table 1). The criteria also specified the compassionate use of CCP in COVID-19 patients with severe or immediately life-threatening disease.

Our hospital partners had access to recovered COVID-19 patients, along with the capability to perform molecular and antibody testing for SARS-CoV-2. Therefore, a system of direct referral from hospitals was established. Hospitals recruited and qualified donors; consequently, all CCP units that were collected from those donors were returned to that referring hospital.

Recruitment

Identification and recruitment of eligible individuals was undertaken through a variety of mechanisms. Approaches included social media, direct referral of patients after discharge for COVID-19–related care, and mining of electronic medical records for individuals who had had positive test results for SARS-CoV-2, under a HIPPA waiver. Hospitals had institutional review board (IRB)-approved protocols to conduct recruitment and screening of CCP donors.

Qualification

Donor eligibility for CCP, included a previous diagnosis of COVID-19, lack of symptoms for at least 14 days, a negative molecular test, and high SARS-CoV-2–specific neutralizing antibody titers. Additionally, standard donor eligibility criteria needed to be met for CCP donation. Hospital recruiters discussed common blood donor deferral criteria with potential CCP donors.

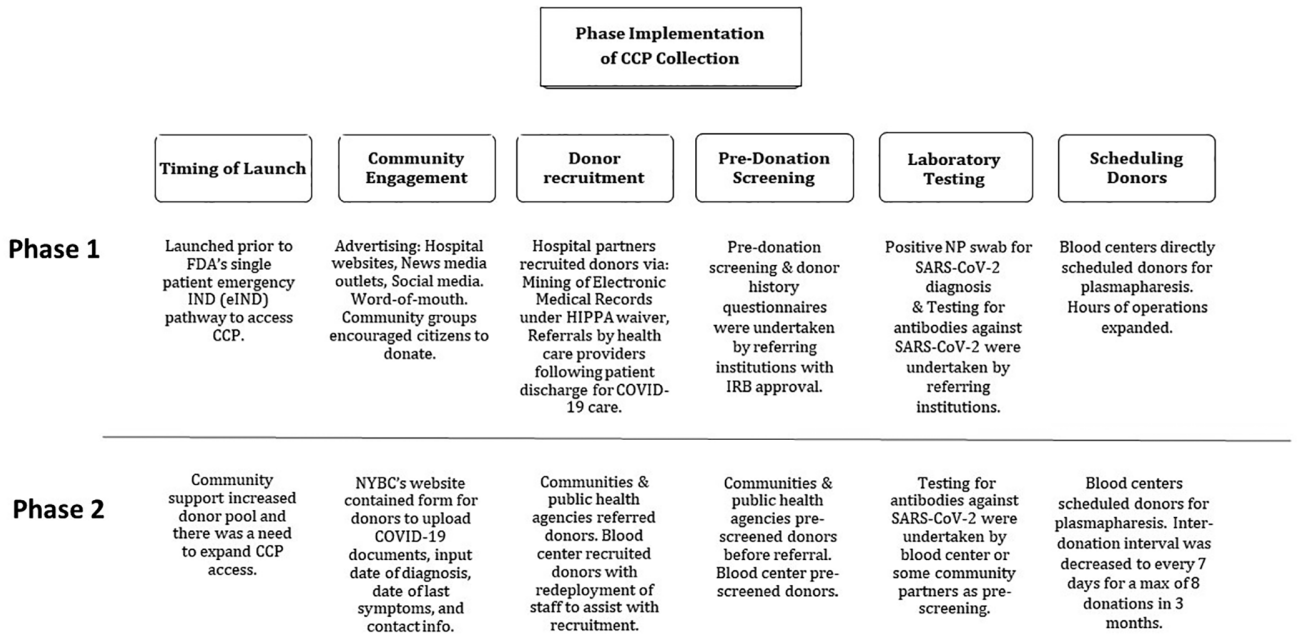

Fig. 1. Phase implementation of CCP collection. Figure shows the differences between Phase I and Phase II processes.

TABLE 1. Summary of FDA recommendations for CCP donor eligibility

Updates in FDA recommendations by date	March 24, 2020	April 13, 2020	May 1, 2020
COVID-19 diagnosis	Prior diagnosis of COVID-19 documented by a laboratory test.	Evidence of COVID-19 documented by a laboratory test either by: 1. A diagnostic test (e.g., nasopharyngeal swab) at the time of illness **OR** **2. A positive serologic test for SARS-CoV-2 antibodies after recovery, if prior diagnostic testing was not performed at the time COVID-19 was suspected.**	Evidence of COVID-19 documented by a laboratory test **either** by: 1. A diagnostic test (e.g., nasopharyngeal swab) at the time of illness **OR** 2. A positive serologic test for SARS-CoV-2 antibodies after recovery, if prior diagnostic testing was not performed at the time COVID-19 was suspected.
Time from last symptoms	Complete resolution of symptoms at least 14 days before donation.	Either one of the following: **1. Complete resolution of symptoms at least 28 days before donation** **OR** **2. Complete resolution of symptoms at least 14 days before donation, AND** **negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood.**	**Complete resolution of symptoms at least 14 days before the donation.**
COVID-19 retesting criteria	Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood.	**Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood if 14-28 days from last symptoms.**	**A negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor.**
HLA testing	Female donors negative for HLA antibodies or male donors.	Male donors, female donors who have not been pregnant, **or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.**	Male donors, female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.
Antibody titers	Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., optimally greater than 320).	Defined SARS-CoV-2 neutralizing antibody titers **We recommend neutralizing antibody titers of at least 160. A titer of 80 may be considered acceptable if an alternative matched unit is not available.** **NOTE: If neutralizing antibody titers cannot be obtained in advance, consider storing a retention sample from the convalescent plasma donation for determining antibody titers at a later date.**	SARS-CoV-2 neutralizing antibody titers, if available. When measurement of neutralizing antibody titers is available, we recommend neutralizing antibody titers of at least **160**. A titer of 80 may be considered acceptable if an alternative matched unit is not available. When measurement of neutralizing antibody titers is not available, consider storing a retention sample from the convalescent plasma donation for determining antibody titers at a later date. **Although optional for all IND pathways, storing samples for single-patient eINDs is not recommended.**

* Changes to each preceding document in **bold.**

Scheduling

For all donors who were deemed qualified by a hospital partner, donor information was communicated through an order form to the blood center along with attestation that CCP-specific criteria were met. Upon receipt, donor center schedulers contacted the potential donor, confirmed donor eligibility, and scheduled the donor for plasmapheresis at a conveniently located fixed donation site. Appointments were available 7 days a week, and the centers' hours of operation were expanded for donor convenience and to increase capacity.

TRANSITION: CHANGES IN FDA RECOMMENDATIONS

On April 7 (updated on April 13), the FDA released the "Investigational COVID-19 Convalescent Plasma: Guidance for Industry."[8] The donor eligibility recommendations

changed to diagnosis of COVID-19 documented by laboratory test (nasopharyngeal swab polymerase chain reaction [PCR] or positive serologic test for SARS-CoV-2 antibodies if diagnostic testing was not performed when disease was suspected), complete resolution of symptoms for at least 28 days or complete resolutions of symptoms for at least 14 days and negative COVID-19 test results by nasopharyngeal swab or blood by molecular diagnostic test, defined SARS-CoV-2–specific neutralizing antibody titers, if available (160 or 80), and transfusion-related acute lung injury (TRALI) mitigated (Table 1). With incorporation of regulatory supporting data from our partners, and after consultation with infectious disease experts, NYBCe submitted an alternate procedure to the Food and Drug Administration (FDA) so as not to require further PCR testing if the donors had at least 14 days without symptoms (April 10, 2020). Our alternate procedure was supported by 1) lack of infectious viral isolates after 14 days of being asymptomatic although individuals may still be PCR positive, 2) lack of blood PCR positivity after 14 days of being asymptomatic, 3) both donors and collection staff wearing masks with other environmental and personal protections to mitigate disease spread, 4) limited testing and personal protective equipment in our community, and 5) urgent need for CCP in our community. On May 1, the updated amendment of the FDA guidance, formally supported our policy, that is, a negative result for COVID-19 by a molecular test was no longer necessary.[9]

On April 3, 2020, the FDA also announced the National Expanded Access Program (EAP).[10] The EAP is a partnership between FDA, Mayo Clinic (who holds the IND, IRB, and patient data), American Red Cross, and Biomedical Advanced Research and Development Authority. In the future, Biomedical Advanced Research and Development Authority may provide funding for the CCP units provided under the EAP; however, to date NYBCe is supplying CCP as it would charge for any blood product. NYBCe can supply CCP to patients enrolled in the EAP, single-patient eIND, or IND-approved clinical trial. The EAP expanded patient eligibility to adults who were severely or critically ill and also at high risk of becoming severely or critically ill. The EAP was designed to make it easy for hospitals and physicians to enroll patients as it involves limited data collection.

Another development was the FDA clearance of several IND applications in support of planned clinical trials to evaluate safety and efficacy of CCP. These protocols expanded the number of patients who were eligible for CCP treatment. The clinical trials, which should provide more definitive efficacy data, include other patient subsets such as pediatric patients and adults with mild and/or moderate disease. Trials were also cleared for use of CCP as prophylaxis for heavily exposed or at-risk individuals.[11]

PHASE II: NYBCE RECRUITS DONORS

Recruitment

Availability of recovered individuals in New York City and State was initially an obstacle for the CCP program. After the changes to donor eligibility and indications of use, NYBCe initiated its own donor recruitment. This decision was supported by the increased number of eligible donors after the tremendous support from the community to help with recruitment. Other recruitment methods included public appeals for donors, advertising through the blood center website, hospital partner sites, professional organizations (e.g., ccpp19.org, covidplasma.org), news outlets, social media (e.g., Facebook), and active community and governmental engagement.

To facilitate recruitment, NYBC's website was updated with information for donors, health care providers, and patient advocates (https://www.nybc.org/donate-blood/covid-19-and-blood-donation-copy/convalescent-plasma/?utm_source=web&utm_medium=banner&utm_campaign=covid). A Web-based form enabled donors to upload COVID-19 testing documentation and provide date of diagnosis, date of last symptoms, and their contact information. NYBC vastly increased the number of staff available to contact and schedule the potential donors. NYBC also received lists of potential donors from communities and public health agencies to contact for donation. Some of the community groups and public health agencies prescreened donors for CCP donor eligibility and common blood donation deferrals. Some partners also performed antibody testing as part of their prescreening.

Eligibility

Using information provided on the NYBC website and the lists of prescreened donors, NYBC staff members evaluated each potential donor before making an appointment for donation. Staff evaluated uploaded documentation of COVID-19 testing and reviewed information with the potential donor regarding donor symptoms and resolution. They also prescreened potential donors for major deferrals from blood donation. To assist with the training of new staff, we created a fact sheet that answered the most frequent questions (https://www.nybc.org/donate-blood/covid-19-and-blood-donation-copy/convalescent-plasma-donor-faq/).

Decreasing donation interval

To better meet the needs of patients by increasing the number of products available, NYBC decreased the donation interval between plasmapheresis collections. Normally, donors could donate every 28 days in infrequent plasma collection programs. Considering the plasma loss of platelet (PLT) donors, who may donate every 7 days (up to 24 times a year), as well as the unknown time frame in which SARS-CoV-2 antibodies would be circulating, NYBC requested an alternate procedure to shorten the interval between donations for CCP donors without performing all the requirements unique to frequent source plasma programs. The FDA indicated that it did not object to our approach if there was medical oversight. CCP donors were allowed to donate as frequently as every 7 days, but not more than eight times

TABLE 2. CCP donor demographics*

	O−	O+	A−	A+	B−	B+	AB−	AB+	Total
Female	**69**	**459**	**59**	**426**	**20**	**179**	**11**	**58**	**1281**
Alaskan Native/American Indian		1							1
Asian		11		3		9		3	26
Black or African American	1	9		6	1	4		2	23
Hispanic or Latino	6	68	3	33		19		2	131
Multiracial/other		9	1	10	1	5	1	1	28
White	32	217	37	244	10	90	6	22	658
No answer/not sure	30	144	18	130	8	52	4	28	414
Male	**64**	**509**	**70**	**499**	**25**	**220**	**7**	**89**	**1483**
Alaskan Native/American Indian		1							1
Asian		17		11	1	17		7	53
Black or African American	1	11		5	1	2			20
Hispanic or Latino	4	44	2	23		3		3	79
Multiracial/other	5	12		18	1	4	1	2	43
White	35	258	43	271	15	105	4	50	781
No answer/not sure	19	166	25	171	7	89	2	27	506
Total	**133**	**968**	**129**	**925**	**45**	**399**	**18**	**147**	**2764**

* Data up to May 4, 2020.

in a 3-month period. A decision on donations past 3 months was delayed until data on antibody persistence were available. In addition after the 3-month period, donors will need to undergo a medical evaluation to determine further donation.

BLOOD DONATION

Eligibility determination

On-site CCP donor evaluation was performed identically to regular blood donors. All donations at NYBCe now occur at fixed-site locations. Donors are screened before entering the donor room to make sure they are feeling well, are afebrile, and are wearing a mask. In addition, the donor rooms have been reconfigured to ensure adequate social distancing, staff are also wearing masks and gloves, and the environment is more frequently cleaned.

Donors were deferred if they did not meet all blood donation criteria. The on-site deferral rate for CCP donors was 9%.

Demographics

The demographics for CCP donors are shown in Table 2. The demographic distribution of CCP donors was similar to that of our regular donor pool. Determination of quantitative differences was difficult as there was a significantly larger pool of "unknown" ethnicity among CCP donors (32%) compared to the normal donor pool (9%).

Collection

Standard volumes of plasma (400-800 mL) were collected by apheresis from all eligible donors. A new phlebotomy code was created in our Blood Establishment Computer System to identify CCP products. In addition, it was necessary to train the collections team on the new process of identifying and qualifying CCP donors.

Testing

All standard donor testing was performed. This included infectious disease marker testing and HLA antibody screening. The latter was restricted to female donors who had been previously pregnant as is consistent with our standard TRALI mitigation strategy. Eight percent of donations were not eligible for transfusion due to positive infectious disease markers, HLA antibodies, or red blood cell (RBC) antibodies.

For the Phase I CCP donors, viral and SARS-CoV-2 antibody testing was undertaken during the predonation phase at the hospital or referral laboratory, in accordance with their study-specific protocols. For the Phase II donors, New York State's Wadsworth Laboratory performed a qualitative assay to detect SARS-CoV-2 antibodies. This microsphere immunoassay is against the nucleocapsid protein and detects total antibody. NYBCe has also implemented the Ortho (VITROS Immunodiagnostic Products Anti-SARS-CoV-2 total reagent pack) assay. Overall, antibodies were detected by either platform in 97% of donations.

When the CCP program started, product availability and testing availability lagged product demand. To ensure availability of CCP for severely and critically ill patients, CCP products were released before SARS-CoV-2 antibody testing results, as was the practice across the nation. Because now we have antibody testing availability and have more products than demand, we are now able to only release products that have reactive antibody test results. Donors who test negative for antibody testing will not be scheduled for CCP donation again but redirected to donate other products (whole blood, RBCs, or PLTs).

For all collections, samples are being saved for future testing, as required by the FDA for the EAP. In addition, units are being produced with a long tail segment to enable hospitals to test the units without breaching the main product.

PROCESSING AND LABELING

The CCP is collected and split into approximately 200-mL units. A request was submitted to the International Council for Commonality in Blood Banking Automation for a new ISBT product code for CCP with ACD as the anticoagulant (e.g., E9747V00, E9747VA0, E9747VB0, E9747VC0, E9747VD0). Our label looks a bit different because we were first to work with FDA/CBER/OBRR to create the label and used more traditional IND labeling approach.

New labels were created with the description "Convalescent Plasma Anti-SARS-CoV-2 Immune Plasma." In addition, an IND statement was required on the label (Fig. 2). Hospital contacts were amended to require patients to be transfused under IND only. This could be single-patient eIND, EAP, or study specific IND.

INVENTORY MANAGEMENT AND DISTRIBUTION

First-time collections that were procured during Phase I were distributed back to the referring hospitals. To tie the donation with the referring hospital, the NYBC applied our directed donor protocol in Blood Establishment Computer System to manage the product throughout the process. However, no true directed donations were considered due to multiple factors, including the inherent delay in getting a directed donation product to patient, ABO compatibility, eligibility, and the need to make products manufactured from one donation available to more than one patient. Subsequent donations by individuals originally recruited in Phase I are released into the Phase II inventory pool to allow for equitable access of CCP.

The Phase I process is also used for some clinical trials, which include certain donor eligibility criteria as well as linking donor and product characteristics with patient outcomes. Phase II donations are available to all hospitals, independent of whether they are existing NYBCe customers. Information is provided on our website, where health care providers are able to request CCP for their patients using an online form. The website provides important information on how to enroll patients into existing studies and how to order CCP.

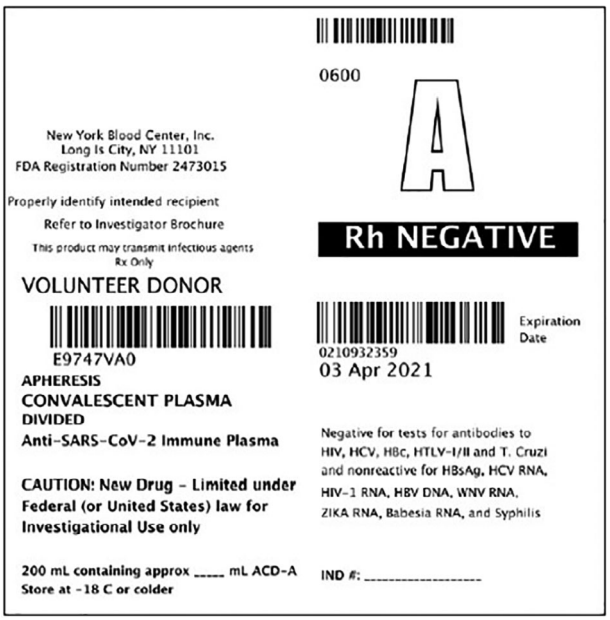

Fig. 2. Sample CCP label. In addition to general labeling requirements, CCP units are additionally labeled with "Convalescent Plasma Anti-SARS-CoV-2 Immune Plasma." An IND statement is also a requirement.

SCALE-UP

Both the CCP unit collection and the distribution experienced rapid growth over the first 6 weeks of the program (Fig. 3). By the third week of collection, the blood center had sufficient inventory of CCP units available to meet all local hospital requests, moving the status of CCP units from a scarce resource to a limited but available resource. By early May, CCP is now an available resource. NYBCe is also able to support emergency requests from regions of the country not directly served by NYBCe blood centers. Distribution of products nationally is primarily through Blood Centers of America.

COVID-19 convalescent plasma collections are currently performed at fixed sites on apheresis machines. We are expanding to include apheresis machines that can be used on mobile drives (Fig. 4).

NEXT STEPS

At this time, more than 10,000 CCP products have been collected. As processes continue to change and become more efficient, we hope to create a large enough inventory of CCP to help meet the demand in our region and continue to be a large contributor to the CCP supply throughout the nation. As other regions of the country become impacted by COVID-19, we will have the CCP products available to meet their needs. In the future, we intend to contribute to a national stockpile of CCP and eventually to the production of hyperimmune globulin.

Future changes are anticipated with the availability of clinical outcome data. If CCP is deemed safe and the clinical

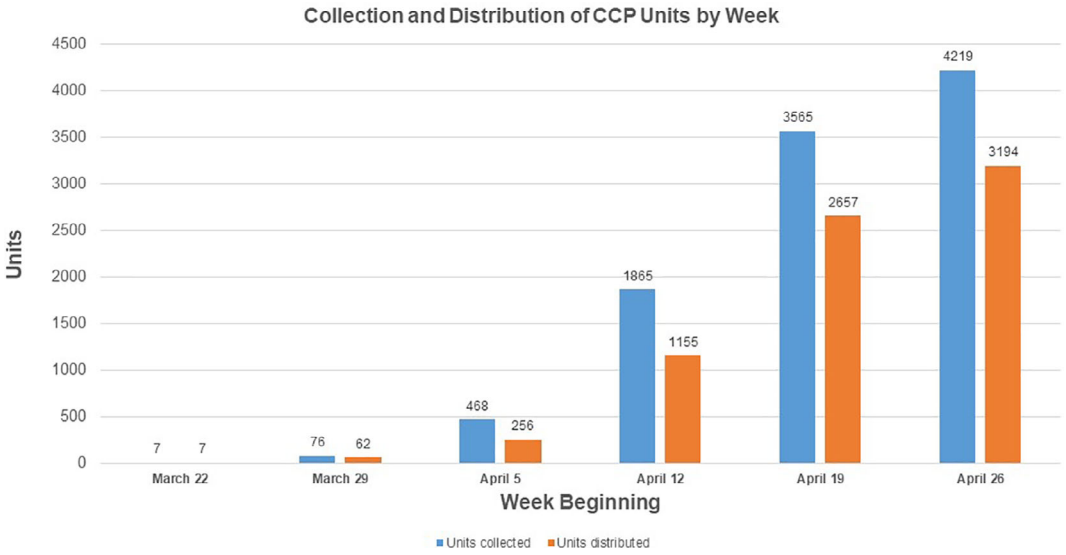

Fig. 3. Collection and distribution of CCP units over time. Bars represent the number of units collected (blue) and distributed (orange) by week. Differences in collection and distribution largely represent collected units that did not meet patient transfusion requirements (i.e., HLA antibodies detected, positive ID markers). Some represent units about to be distributed, but in house at time of data collection. [Color figure can be viewed at wileyonlinelibrary.com]

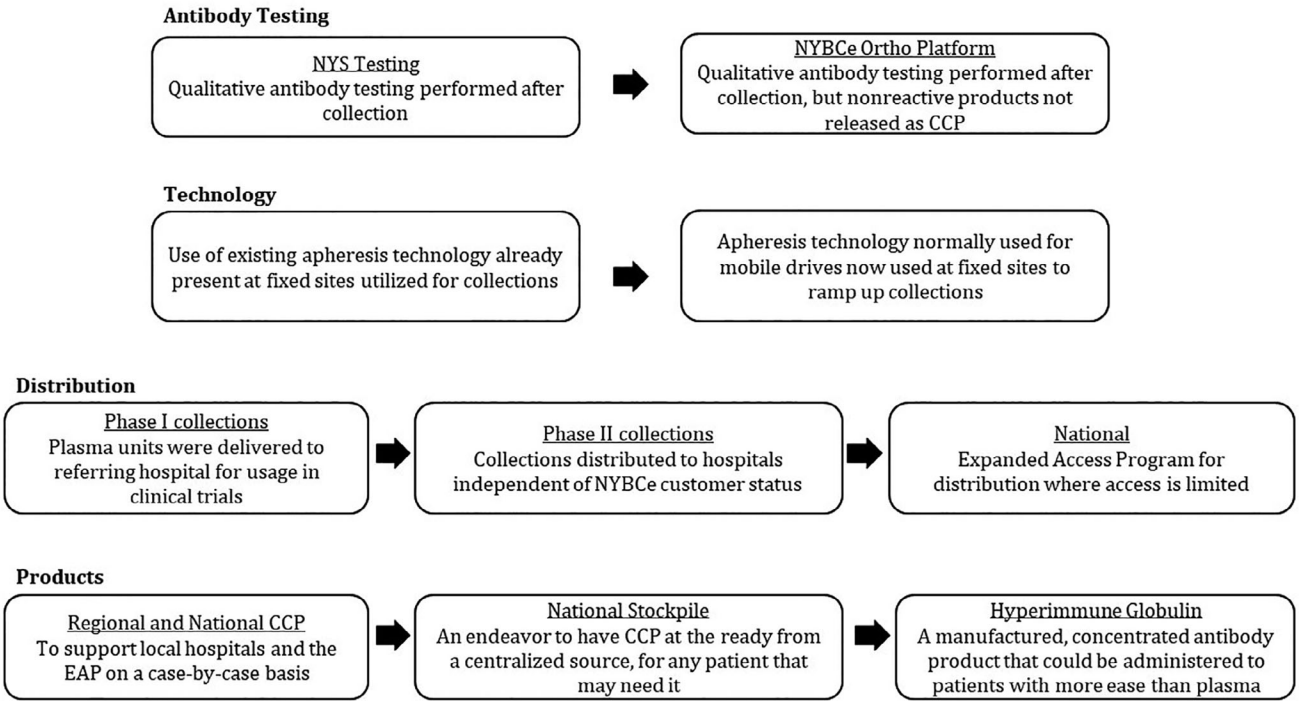

Fig. 4. Scale up of CCP collection. Figure highlights improvements in the process to greatly increase the supply of CCP.

outcomes are positive, then CCP may become an FDA approved product given without need for IND. If trials showing CCP is beneficial early in disease course or for prophylaxis, demand may significantly increase. If donor antibody testing data is correlated with patient outcome, then we can optimize CCP products.

In conclusion, we provided the framework for how NYBCe worked with hospitals, public health, and community partners to ramp up CCP collections with the goal that CCP would become available to every patient. We continue to modify the CCP program as more data and testing become available.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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