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Preparedness and activities of the anti-SARS-CoV-2 convalescent plasma bank in the Veneto region (Italy): An organizational model for future emergencies

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ABSTRACT

Background: Convalescent plasma (CP) has been used in the past in various pandemics, in particular in H1N1, SARS and MERS infections. In Spring 2020, when ongoing the SARS-CoV-2 pandemics, the Veneto Region (V-R) has proposed setting-up an anti-SARS-CoV-2 CP (CCP) Bank, with the aim of preparing a supply of CCP immediately available in case of subsequest epidemic waves.
Materials and Methods: Key-points to be developed for a quick set-up of the V-R CCP Bank have been recruitment of donors recovered from COVID-19 infection, laboratory analysis for the biological qualification of the CCP units, including titre of neutralizing antibodies and reduction of pathogens, according to National Blood Centre (CNS) Directives, adaptation of the V-R Information Technology systems and cost analysis. Some activities, including diagnostic and viral inactivation processes, have been centralized in 2 or 3 sites. Laboratory analysis upon preliminary admission of the donor included all tests required by the Italian laws and the CNS directives.
Results: From April to August 2020, 3,298 people have contacted the V-R Blood Transfusion Services: of these, 1,632 have been evaluated and examined as first time donors and those found to be suitable have carried out 955 donations, from which 2,626 therapeutic fractions have been obtained, at a cost around 215,00 Euro. Since October 2020, the number of COVID-19 inpatients has had a surge with a heavy hospital overload. Moreover, the high request of CCP therapy by clinicians has been just as unexpected, showing a wide therapeutic use.
Conclusions: The organizational model here presented, which has allowed the rapid collection of a large amount of CCP, could be useful when facing new pandemic outbreaks, especially in low and middle income countries, with generally acceptable costs.

1. Introduction

Passive immunotherapy by using plasma from convalescent subjects ("convalescent plasma", CP) has been a widespread and effective anti-infective treatment in the pre-antibiotic era and one of the founding pillars of basic immunology [1]. For a very long time and even today, immunoprophylaxis using specific human immunoglobulins has been an irreplaceable tool for the post-exposure prevention of several viral infections, including measles, hepatitis B and rabies [2].

In recent times, therapy with CP has been revived during the SARS-

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CoV-1 (2002–2004) and Western Africa Ebola (2013–2016) epidemics, or when other more circumscribed viral outbreaks occurred, for which there were no effective immunoprophylaxis and other therapeutic tools (e.g., MERS epidemic, 2014–2015) [3]. For instance, in the case of SARS-CoV-1, a human respiratory disease caused by a Coronavirus, treatment with CP was associated with a 23 % reduction in mortality and provided best results when administered at the early stages of disease [4]. Moreover, the overall safety of treatment with CP has been recently confirmed [5], in keeping with the daily transfusion practice with plasma products [6].

On the basis of the first Chinese experiences on the use of anti-SARS-CoV-2 CP (CCP) [7], an Interventional Study Protocol on treatment of COVID-19 patients has been also proposed by the University Hospital of Padova in April 2020, with the aim of verifying whether the administration of CCP to patients at risk of serious complications could reduce their mortality or at least need for intensive care therapy. The Study Protocol, after the approval of the Padova Hospital Management Office, has been discussed with the Scientific Technical Committee (STC) of the Veneto Region (V-R), that endorsed it. Before starting, the Study Protocol has been approved by the Ethics Committee (EC) of the Padova University Hospital, and then by Hospital ECs of all provinces of the V-R. After recruiting first patients affected with COVID-19, preliminary clinical results has been immediately notified to the STC, that considered them very encouraging.

In the meantime, COVID-19 patients in the V-R were decreasing and overload on health facilities was slowing. At the same time, there was a large availability of recovered subjects suitable for CCP donation.

Already then, a second COVID-19 wave was being foreseen. While considering the large supply of CCP collected and stored until then, it was necessary questioning whether to continue collection when epidemics were slowing down, in the face of a large number of recovered patients after the first epidemic wave. The V-R proposed the project of setting-up a CCP Bank, with the aim of completing the study and, above all, of preparing a supply of plasma immediately available in case of subsequent epidemic waves. Therefore, on the basis of the operative model promoted for the implementation of the preliminary Study Protocol, the organization of the V-R CCP Bank has been put in place.

This project involved all the V-R Transfusion Medicine network, which is organized on the provincial territory through the Departments of Transfusion Medicine (DIMTs), referring to the Regional Centre for the Coordination of Transfusion Activities (CRAT).

Aim of this report is to describe the organizational model for developing a quick set-up of a CCP Bank, as performed by the V-R, including the following key-points:

1) recruitment of donors recovered from COVID-19 infection;
2) laboratory analysis, in addition to testing required for donor screening and biological qualification of blood transfusion products;
3) implementation of pathogen reduction procedures in the collected CCP units;
4) administrative management of all test sampling intended for other V-R laboratories, out of the competence of Blood Transfusion Services;
5) adaptation of the Information Technology systems to tracing new activities and data management;
6) cost analysis of the newly introduced tests and its proper management.

In fact, a detailed analysis of an operating model for this purpose could be useful for the organization of a CCP Bank, when occurring future emergencies, also in other countries.

2. Methods

2.1. Recruitment of donors recovered from COVID-19 infection

Recruitment criteria for recovered subjects have been equally applied in all DIMTs of the V-R. Enrollment has been on a voluntary basis, and required that all donors had to fulfill eligibility criteria for plasma donation, according to the current Italian laws, besides a recent SARS-CoV-2 infection. First, a list of recovered, previously hospitalized subjects, has supplied by the Clinical Department where patients had been admitted. Then, the DIMT personnel has set an appointment to evaluate eligibility for donation. At each hospital, promotion of CCP donation has been primarily forwarded to health workers who had fallen ill with COVID-19, as many of them shared this initiative. Moreover, the V-R has authorized access to the Regional Database of SARS-CoV-2 positive population, thus allowing data extraction of age and sex, in order to identify quickly suitable subjects for CCP donation. Furthermore, the V-R have sent a nominal letter to all recovered people to invite them to contact the Blood Transfusion Unit closest to their home for a possible CCP donation. Finally, as a public appeal to donate, a video spot has been created and broadcasted on the website of the V-R and through local TV.

The CRAT has shared with all DIMTs and the V-R Health Offices the online monitoring of the activities, updating daily the number of recovered individuals by contacting Blood Collection Units, those eligible for donation after a telephone triage, donors undergoing medical examination for donation and preliminary sampling for the determination of the presence of anti-SARS-CoV-2 antibodies (Abs), number of CCP donations, units collected and therapeutic fractions (TFs) frozen and stored per blood group and neutralizing anti-SARS-CoV-2 Abs, TFs transfused per blood group, as shown in Table 1.

To ensure an organized flow of the analytical and production process throughout the V-R, some activities, including diagnostic and viral inactivation processes, have been centralized in 2 or 3 DIMTs, in order not to waste technological and personnel resources, according to effectiveness and efficacy criteria (Table 2).

Recruitment of CCP donors has been carried out in all DIMTs and, within these ones, in several Blood Collection Units pertaining to the provincial Department. Thus, access of donors has been facilitated, avoiding long tranfers, as well as any prolonged absence from workplace.

Additional tests required by the Italian National Blood Center (CNS) for the biological qualification of the collected CCP units (HEV, HAV, Parvovirus B19, SARS-CoV-2-NAT), have been carried out in two laboratories, i.e., Institute of Microbiology and Virology of the University Hospital of Padova and DIMT of Vicenza. At the laboratory of the Institute of Microbiology and Virology Laboratory of the University Hospital of Padova, determination of the anti-SARS-CoV-2 neutralizing Abs titre has been performed for all regional activity.

Administrative acceptance of all additional outsourced services was carried out at the Blood Transfusion Unit of the University Hospital of Padova, which also provided for the reporting and sending of results to each DIMT.

In 3 out of the 7 DIMTs (Padova, Verona and Vicenza) plasma viral inactivation process treatment has been carried out, for all CCP units collected throughout the V-R.

The CRAT has provided for the adaptation of the Information Technology System extended to all the V-R Blood Transfusion network. The Healthcare Centre of the V-R (Azienda Zero) has proceeded to purchase of all consumable materials needed for analytical process of the laboratory samples, and to acquire new equipments, including a sufficient number of freezers for CCP storage.

Each DIMT have provided for the transport of blood samples and, if possible, of the CCP units, after performing and validating laboratory tests required by the Italian laws for the biological qualification of blood products.

CCP units have been stored in dedicated freezers, separated from all other plasma units for clinical use or plasma-derived industry.

As regards storage and distribution of CCP units, centralization of stocks at the Blood Transfusion Unit of the University Hospital of Padova had been first hypothesized. This option, however, besides impractical

Table 1
Model of monitoring file of the CCP collection and therapeutic use shared between the Veneto Region CRAT and DIMTs.

N° contacts between recovered patients and DIMTs								N° potential subjects eligible for CCP donation							
	DIMTs								DIMTs						
Date	BL	PD	RO	TV	VE	VI	VR	Date	BL	PD	RO	TV	VE	VI	VR
N° subjects undergoing CCP donation								N° collected CCP units							
	DIMTs								DIMTs						
Date	BL	PD	RO	TV	VE	VI	VR	Date	BL	PD	RO	TV	VE	VI	VR
N° stored TFs								N° transfused TFs and treated patients							
	DIMTs							DIMTs	N° transfused TFs			N° treated patients			
Date	BL	PD	RO	TV	VE	VI	VR	BL							
								PD							
								RO							
								TV							
								VE							
								VI							
								VR							

N° stored TFs (site, ABO grouping, neutralizing Abs titre)													
Blood grouping	O			A			B			AB			
Neutralizing Abs titre	80	160	320	80	160	320	80	160	320	80	160	320	
BL													
PD													
RO													
TV													
VE													
VI													
VR													

BL: Belluno.
PD: Padova.
RO: Rovigo.
TV: Treviso.
VE: Venice.
VI: Vicenza.
VR: Verona.

Table 2
Sites of performing the CCP qualification tests and plasma viral inactivation process.

DIMT	Qualification tests (Italian laws)	NAT SARS-CoV-2 test	anti-SARS CoV-2 IgG Abs test	anti-SARS CoV-2 neutralizing Abs test	Plasma viral inactivation process
Belluno	Belluno DIMT	Institute of Microbiology and Virology - Padova	Institute of Microbiology and Virology - Padova	Institute of Microbiology and Virology - Padova	Padova DIMT
Treviso	Treviso DIMT	Institute of Microbiology and Virology - Padova	Institute of Microbiology and Virology - Padova	Institute of Microbiology and Virology - Padova	Padova DIMT
Verona	Verona DIMT	Institute of Microbiology and Virology - Padova	Institute of Microbiology and Virology - Padova	Institute of Microbiology and Virology - Padova	Verona DIMT
Vicenza	Vicenza DIMT	Vicenza DIMT	Institute of Microbiology and Virology - Padova	Institute of Microbiology and Virology - Padova	Vicenza DIMT
Venezia	Venice DIMT	Vicenza DIMT	Institute of Microbiology and Virology - Padova	Institute of Microbiology and Virology - Padova	Vicenza DIMT
Rovigo	Rovigo DIMT	Institute of Microbiology and Virology - Padova	Institute of Microbiology and Virology - Padova	Institute of Microbiology and Virology - Padova	Padova DIMT

owing to the need for large available spaces, would have resulted in difficulties in the management and, particularly, in the distribution of CCP units to various hospitals of the V-R. For this reason, it has been agreed to set up a "diffuse" CCP Bank and each DIMT has become the reference site for its own territory. In case of difficulty or lack of promptly available CCP units, the V-R Transfusion Medicine network has guaranteed the support of what was necessary, as happens daily also for any other blood component.

2.2. Assessment of eligibility for CCP donation procedure

In the V-R, deferred donation has been adopted for many years as an additional safety criterion. Indeed, all donors, before admission to the donation, are clinically evaluated by a complete medical history and are subjected to a preliminary laboratory test profile. In the case of CCP, donors had to show the same eligibility conditions as plasma donors, according to the current directives of the Italian laws [8]. In addition, CNS, with its own directives [9,10], has made mandatory some additional validation tests, i.e., testing for HEV, HAV, Parvovirus B19-NAT, as well as for a pathogen reduction treatment, assimilating the qualification of CCP to plasma-derived products. To access the donation, a titre of neutralizing antibodies $>$ 1:160 has been required. From an operational point of view, donors for whom confirmation of the neutralizing titre gave a lower value have not been considered to be unconditionally discarded: CCP units with 1:40 or 1:80 titre were used in double dose, or as a supplementary dose in high weight patients.

Laboratory analysis upon preliminary admission of the donor included all tests required by the Italian laws and the CNS directives for the collection of CCP, according to the position paper promoted by the Italian Society for Transfusion Medicine and Immunohaematology (SIMTI) and the Italian Society for Haemapheresis and Cell Manipulation (SIdEM) [11], as indicated in Table 3.

All donors had to sign informed consent, on admission and at donation. After checking laboratory analysis, donors have been asked to donate within 15 days of tests being performed. A plasma donation by apheresis by using the blood cell separator AURORA (Fresenius Kabi, Italy, srl) has been then performed, collecting about 600 mL of plasma (excluding ACD-A as anticoagulant agent), at each donation (Table 4).

Examination profiles of CCP donors have been based on the definition of "recovered patient" and "patient who eliminated the virus", according to the document of the Italian Ministry of Health, issued on 28 February 2020 [12]. In fact, recovered patient has been defined as a subject resolving symptoms of COVID-19 and negative in two consecutive tests, carried out 24 h apart, for the search for SARS-CoV-2 on a nasopharyngeal swab. The definition of virus clearance indicated the disappearance of SARS-CoV-2 RNA detectable in body fluids, both in people who had signs/symptoms of disease and during asymptomatic phase without signs of disease.

Recently a correlation between the presence of viral RNA in the circulating blood and the severity of the disease [13,14] has been demonstrated, but all tested donors have been negative on plasma SARS-COV-2 NAT testing. Both serological and NAT tests for SARS-COV-2 detection have been carried out with commercial kits. On the other hand, the determination of neutralizing Abs has been performed by an in-house assay. As previously described [15], a microneutralization method has been used, by evaluating the cytopathic effect of the virus on VERO6 cells, in the presence of diluted serum samples. After incubation at 37 °C for 72 h, the highest serum dilution reducing the cytopathic effect by 90 % has been considered to determine the titre of neutralizing Abs.

Execution of the in-house test for neutralizing Abs has been maintained from April to May 2020.

Subsequently, donor selection for anti-SARS-CoV-2 Abs has been carried out with the LIAISON® CLIA SARS-CoV-2 S1/S2 IgG (DiaSorin SpA, Saluggia, Italy) system, that determines IgG antibodies directed against the S1/S2 antigens. The test has high sensitivity (97.4 %) and specificity (98.5 %) and a positive agreement of 94.4 % on the Plaque Reduction Neutralization Test (PRNT). A value of 80 AU/mL has been correlated to a neutralizing antibodies (PRNT) 1:160 titre [16]. Based on the data declared by the manufacturer and some literature reports data, an internal check of correlation between the CLIA and the microneutralization test has been also made. It has been so possible to establish a 50 AU/mL is equivalent in 80 % of cases at 1:80 titre, while the threshold of 120 AU/ mL corresponds in 80 % of cases to 1:160 (Tab. IV). Beyond these values, the correlation between the two tests has resulted to be reduced.

Table 4
Analysis of the correlation between anti-SARS-CoV-2 CLIA test (DiaSorin) and neutralizazion test (in-house method).

Test CLIA-DiaSorin	N° samples: 43	N° samples: 41	N° samples: 38
Mean	52.5	125.6	126.3
Standard deviation	26.2	52.6	18.7
Variation coefficient	50.0	41.9	14.8
Correlation with neutralization test	**50 AU → 1:80**	**120 AU → 1:160**	**>125 AU 1:320**

On the basis of these data, the CLIA test has been used for donor preselection, but all collected CCP units have been then analyzed with the traditional microneutralization test, as above described.

2.3. Biological qualification of CP units

All CCP units have been validated in accordance with current Italian laws. Diagnostic techniques have been the same for all DIMTs, according to the V-R indications. Serological HBsAg, anti-HCV, anti-HIV1/2 and syphilis testing has been performed with the ALINITY-Abbott Diagnostic System (Abbot Park, IL, USA), while the NAT-test for HBV-HCV-HIV1/2 with the GRIFOLS-Procleix Panther System (Grifols International S.A, Barcelona, Spain). NAT screening for HEV, HAV, Parvovirus B19 and SARS-CoV2 has been performed with the Grifols-Procleix Panther System (Grifols International S.A., Barcelona, Spain) at the DIMTs of Venice and Vicenza, while it was performed with the Cobas-Roche System (Roche Diagnostic SpA, Monza, Italy) at all other DIMTs.

2.4. Pathogen reduction treatment in CCP units

The Intercept-CERUS System, commercially promoted in Italy by Kedrion-Biopharma (Kedrion SpA, Castelvecchio Pascoli, Lucca, Italy), has been used throughout the V-R. The system is based on amatosalen hydrochloride, a synthetic psoralen compound, that interconnects reversibly in the helical regions of DNA and RNA. By exposing to UV-A light from 320 to 400 nm, amotosalen binds in a covalent way with pyrimidine bases of nucleic acids. Genomic sequences of pathogens and leukocytes, thus cross-linked, cannot longer function or replicate. No pharmacological effect of residual amotosalen is demonstrated, since this system involves a step of removing the residual molecule by filtration.

Coronavirus family is also considered susceptible to this tool of inactivation. Each CCP unit has been subsequently fractionated into

Table 3
Donor testing on admission and at donation.

Italian laws (*)		CNS Directives		Study protocol	
Admission	Donation	Admission	Donation	Admission	Donation
Full blood count	Full blood count PT/INR, APTT, Fibrinogen Protein electrophoresis		Full blood count PT/INR, APTT, Fibrinogen	Full blood count PT/INR, APTT, Fibrinogen Protein electrophoresis	Full blood count
HBsAg, anti-HCV Abs, anti-HIV1-2 Abs + HIV Ag, syphilis Abs	HBsAg, anti-HCV Abs, anti-HIV1-2 Abs + HIV Ag, syphilis Abs		HBsAg, anti-HCV Abs, anti-HIV1-2 Abs + HIV Ag, syphilis Abs	HBsAg, anti-HCV Abs, anti-HIV1-2 Abs + HIV Ag, syphilis Abs	HBsAg, anti-HCV Abs, anti-HIV1-2 Abs + HIV Ag, syphilis Abs
HCV, HBV, HIV1 NAT	HCV, HBV, HIV1 NAT		HCV, HBV, HIV1 NAT	HCV, HBV, HIV1 NAT	HCV, HBV, HIV1 NAT
Blood group, including ABO, Rh phenotype and Kell	Blood group, including ABO control		Blood group, including ABO, Rh phenotype and Kell	Blood group, including ABO, Rh phenotype and Kell	Blood group, including ABO control
Indirect Coombs test	Indirect Coombs test		Indirect Coombs test HEV, HAV, PV B19 NAT anti-SARS-CoV-2 neutralizing Abs	Direct and indirect Coombs test anti-SARS-CoV-2 neutralizing/ IgG Abs SARS-CoV-2 NAT	HEV, HAV, PV B19 NAT anti-SARS-CoV-2 neutralizing Abs SARS-CoV-2 NAT

(*) The Italian law does not provide for the figure of the “first time donor for deferred donation”, a choice that was instead made by the Veneto Region.

three about 200 mL subunits, each of which constituted a therapeutic fraction (TF).

3. Results

3.1. Preliminary activities and creation of the CCP Bank of the Veneto region

Veneto is an Italian region with overall 4,906,000 inhabitants (data to 2020) divided into 7 provinces, with a population per province ranging from 201,972 (Belluno) to 939,672 inhabitants (Padova). As previously reported, each province has a DIMT that guarantees all transfusion activities.

Activity of CCP collection lasted until 31 July 2020 on an ongoing basis. However, more time passed from the Spring 2020 COVID-19 epidemic peak, lower was the amount of neutralizing antibodies detected in the CCP donors. Therefore, activity of CP collection has been slowed down, by completing exclusively lists of donors undergoing to preliminary tests and showing an adequate titre of neutralizing antibodies. Activity data, updated at 31 August 2020, are shown in Table 5.

At the end of August 2020, Rt contagion index in Italy, including the V-R, has begun to rise, exceeding 1.0 value. However, the features of the population affected by the new epidemic wave, were very different from those of the previous one. At this stage, recruitment activity was in fact at a standstill. On the other hand, there was a progressive increase in COVID-19 patients' hospitalization, so over time requests for CCP units by clinicians have increased. In particular, since October 2020, the number of COVID-19 inpatients has had a surge with a heavy hospital overload. Moreover, the high request of CCP therapy by clinicians was just as unexpected, when considering that, meanwhile, a definitive assessment on its effectiveness had not yet been obtained [17–19].

Within the V-R Blood Transfusion network, transfers of CCP units among various DIMTs have been arranged to try to guarantee a therapeutic support in a homogeneous manner throughout all the territory, considering that some areas presented an epidemic outbreak more than others, with a greater number of COVID-19 hospitalized patients.

3.2. Cost analysis

Cost analysis has been conducted using primarily the National Tariff of products and services for all activities, as codified in the V-R Tariff Directory (V-R-TD) of Services and in the National Tariff Directory (N-TD) of blood components. This choice has been carried out to made homogeneous data and to avoid distorting effects related to the simultaneous performance of the normal activities of the Blood Transfusion Services, thus avoiding bias in the allocation of the costs of human and technological resources used in the production of CCP.

For all activities not included in the Directories, analysis of the specific costs has been made, in particular for the preparatory activity before the CCP donation, consisting with the contact and triage of the recovered people, in the enrollment and clinical screening of potential donors, in their overall assessment and in defining eligibility for donation.

Table 6 shows the tariff values of the services codified by the V-R-TD and the N-TD of blood components provided by the State-Regions Conference, 20 October 2015 [20]. In addition, collection of CCP preliminarily has provided for dedicated and specific paths for recruitment and clinical evaluation of potential donors. These are non-coded activities, so a specific analysis of the time commitment of the staff and the consequent costs have been carried out. For the coded services related to the potential donor (laboratory tests for eligibility) standard rates have been applied.

According to this adjunctive cost analysis and costs of a standard plasma collection by apheresis, and when considering the activity of CCP collection in the period March-August 2020, overall cost has been about 912.540,2 Euro, namely 347,5 Euro per CCP TF.

It has to be noticed that new National directives, starting from October 2020, have modified the CCP collection protocol, by eliminating HEV, HAV, Parvovirus B19 NAT from the potential donor's profile, and more CRAT, according with the V-R DIMTs, has decided to eliminate SARS-CoV-2 NAT testing from the donation profile (until then, these tests had been always negative). This change has led to a reduction of working load, with a greater operational speed, as well as to a significant lowering in the CCP production costs. Thus, the cost of a single CCP TF can be at present estimated at around 215,00 Euro: all CCP units collected have been considered in the cost analysis, including those eliminated for any cause.

Table 6
Cost-analysis: Rates of tests and activities performed according to the Study Protocol, and additional activities performed cost.

Tests and activities	Unit rate (€)
Anti-SARS-CoV-2 serology (IgG titre)	14.45
Anti-SARS-CoV-2 neutralization test (titre)	75.60
HEV NAT	61.70
HAV NAT	61.70
Parvovirus B19 NAT	56.05
SARS-CoV-2 NAT	61.70
Productive plasmapheresis (including biological qualification)	172.00
Pathogen inactivation session (per single CCP unit)	60.00

Additional activities performed

Activity	Profession	Time (min) for single activity	Cost for single activity (€)
Call for donation	administrative operator or nurse	15	5,25
Medical examination for donor suitability	physician	30	36,00
Blood sampling	nurse	15	7,05
Donor data management	administrative operator or nurse	10	3,50
CCP unit data management	biologist	10	12,00
CCP Bank management	physician	10	12,00

Table 5
The CCP Bank of the Veneto Region: updating at 2020, 31th August.

DIMT	BELLUNO	PADOVA	ROVIGO	TREVISO	VENICE	VERONA	VICENZA	TOTAL
N° inhabitants	201,972	939,672	233,386	888,309	851,663	930,339	862,363	4,907,704
N° contacted patients after recovery	131	761	59	331	682	789	545	3,298
N° donors at admission	29	606	29	199	248	262	259	1,632
N° active donors	6	210	4	63	114	130	114	720
N° CCP donations	6	394	8	74	114	181	178	966
N° CCP therapeutic units (TUs)	18	957	21	219	342	535	534	2,626
N° transfused patients	0	37	0	36	26	1	6	106
N° transfused CCP TUs	0	156	0	116	147	3	21	443
N° avalaible CCP TUs								2,183

4. Discussion

Passive immunotherapy belongs to the history of transfusion medicine. In fact, it represents a recurrent condition, when a new infectious agent appears, not having effective tools to fight it or what is available is not sufficient to resolve public health emergency [21]. Spanish flu pandemic (1918–1920) is traditionally reported as the first experience of passive immunotherapy extended to large sections of the population [22]. However, therapeutic use of convalescent plasma was already used some years earlier, during two epidemic waves of measles in a rural area of Central Italy, by using serum from recovered people in some patients with severe disease [23].

From March 2020 onwards, with the outbreak of the SARS-CoV-2 pandemic, CCP has been once again of great interest, after the first published Chinese experiences [7], since several study protocols have been launched, whose results to date have not given a definitive response on the efficacy of this treatment [24]. Nevertheless, when considering the uncertain results of clinical trials on the use of some initially promising treatments [25–27] and, in the face of persistent uncertainty or unavailability of other drugs [28,29], therapy with CCP maintains at present its relevance. The high levels of safety by transfusion therapy with blood components [30] constitute today a further element for which CCP has been until now and will be probably requested in the next times.

Setting up of the V-R CCP Bank has represented an important commitment and a great challenge, revealing itself as a resource when the pandemic wave returned in Autumn 2020.

Literature data on the organization of a CP for previous viral epidemics in other countries are not so numerous [31–35], that it has been proposed to describe here in detail the stages of the establishment of the CCP Bank in the V-R.

Main strengths that have contributed to the realization of this project can be listed as follows:

a) full partecipation and sharing among the DIMTs of the V-R, which cover all transfusion needs of a territory of almost 5,000,000 inhabitants distributed over 18,000 km^2. Soon after early phases, when the collection and use of the CCP had been reserved for a Study Protocol set-up and applied exclusively in the Padova DIMT, such a project has been communicated to the CRAT and all other V-R DIMTs have been involved, with the preliminary agreement that, in the case of encouraging results, any activity of CCP collection and distribution would be extended to the entire V-R;
b) involvement of the STC of the V-R, a body of the Regional Government, that adopted the study protocol and promoted its funding by the Regional Treasury;
c) a precise distribution of tasks, being careful not to waste activities and resources, especially when considering healthcare personnel. When activities have been centralized, involving CCP units and test tubes transport, all contracts with external firms have been reviewed and supplemented.
d) an accurate cost analysis, which overall has been consistent with what is reported in the USA [36].

Role of the Direction Management of the various Hospitals of the V-R has been important, as it quickly enabled the acquisition of newly introduced instruments and equipments, both for the activities carried out within the DIMTs, as well as for those performed by other external laboratories. Moreover, role of Healthcare Centre of the V-R (Azienda Zero) has been also crucial in carrying out any administrative procedure for acquiring all that was needed for this project.

Furthermore, the V-R intervened with an advertising promotion campaign of CCP donation. Types of communication with the population represent a fundamental tool, whose management must be not only complete, but also appropriate and understandable by the common people to whom it is mainly directed. Results have been represented by the CCP donors' response, which has been exemplary, confirming the generosity and willingness of people to contribute anyway to overcome this emergency condition. All DIMT staff, for which collection, qualification and distribution of CCP units represented an additional workload more than standard transfusion activity, has been equally involved and fully active.

Regarding weaknesses, the main one has been (and it is still now) represented by testing all collected CCP units for the determination and titration of neutralizing antibodies by a microneutralization assay. It is a challenging laboratory analysis, in terms of personnel competence (and, consequently, training), safety of the environment in which has to be performed, owing to working in contact with a living virus. Moreover, execution times of such a laboratory test require a 72 -hs incubation, namely at least 4 days for the data availability. In addition, it allows a limited number of samples per session. Given these considerations, not all laboratories can have suitable facilities and staff, and to qualify a large amount of CCP units, adequate to the potential demand from clinicians, and loading times can be very long. Best option should be to apply other laboratory tests, even complementary one, but showing a good correlation with the neutralization test by a validation process, and mostly applicable to automatic instrumentation. Today some automation tests are commercially available, unlike March 2020, but none of these has been authorized to replace the functional test, according to National and European Directives [9,10,37]. As a matter of facts, FDA has recently issued guidance on alternative tests for the evaluation of neutralizing activity of CCP [38], so it is desirable that simpler and less time-consuming methods are adopted in the future.

With the recurrence of the pandemic outbreak in Autumn 2020, in the V-R most clinicians have requested the support by the CCP Bank for a wide therapeutic use, even those who during the first wave had expressed mistrust and had only resorted to drug and supportive therapy.

5. Conclusions

There are currently many doubts about the efficacy of CCP, especially on the basis of controlled studies [39–41], while some clinical experiences have shown a reduction in the mortality of patients with COVID-19 infection [42–46]. These discrepancies may be due to a quantity of bias when designing clinical studies on a disease for which there is still an incomplete knowledge [47]. In any case, CCP is a blood component with an excellent safety profile [5]. Pending the difficulties of a massive vaccination campaign [48] and the results of clinical trials on the efficacy of monoclonal antibodies [49], and considering the frequent appearance of variants of SARS-CoV-2 [50], it is possible that the collection and use of CCP will continue in many areas of the world. For this reason, the organizational model here presented, which has allowed the rapid collection of a large amount of CCPs, could be useful when facing new pandemic waves, especially in low and middle income countries, with generally acceptable costs.

Authorship contribution

GDS, GG[2], FF and GR contributed equally to this work. EB, AF, GG[6], AV contributed to contributed to the discussion of the project and to the local organization of activities; MP contributed to the development of laboratory tests; PM contributed to the revision of the manuscript; MC, MR, MR and FS contributed to the organization of activities and data collection.

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Declaration of Competing Interest

The authors declares no conflicts of interest.

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