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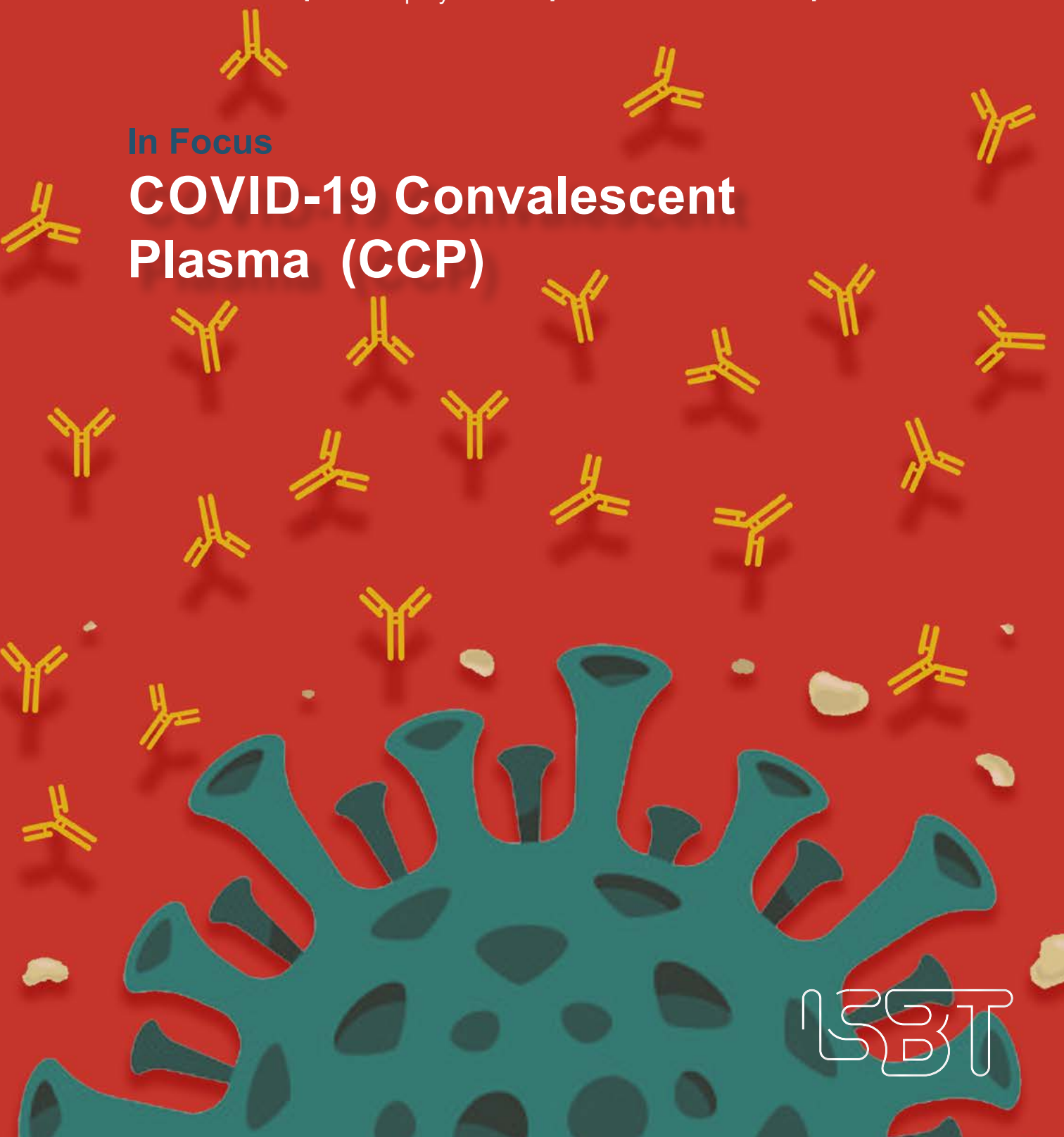
Clinical Effectiveness of CCP | New Blood Group Systems | Nobel Prize in Medicine | SARS-CoV-2 antibodies



In Focus

COVID-19 Convalescent Plasma (CCP)

Editorial

This edition of Transfusion Today has a focus on COVID-19 Convalescent Plasma (CCP) and highlights the many ways that blood services and researchers are working together globally to develop antibody based therapies. Effective testing is an important aspect of this, in identifying suitable CPP donors. In addition to this, blood centres are also in a good position to utilise their expertise in testing and existing organizational systems to monitor seroprevalence in healthy populations. The possibility of vaccination against SARS-CoV-2 is coming ever closer which is, of course, the best news for us all. However, it is interesting to consider the impact on transfusion medicine, and the excellent article by Mike Busch and Roger Dodd on this topic makes a thought provoking read.

With no opportunity to meet in person, the central office is assisting ISBT Working Party (WP) Chairs to hold Zoom business meetings incorporating as many of the features of a face to face meeting as possible, including voting. The Working Party on Red Cell Immunogenetics and Blood Group Terminology pioneered this approach - with success and the exceptional acceptance of three new blood group systems, as described in this edition by the Co-Chairs Catherine Hyland and Christoph Gassner.

Thanks to the support of so many presenters, moderators and sponsors ISBT2020 has a full programme of scientific sessions, e-posters, workshops, social events such as the Young Professional Breakfast and even a virtual fun run! By the time this is published ISBT2020 will have taken place, and I hope we will have been able to bring as much as possible of the congress experience to everyone taking part. All scientific content will be available for registered delegates to watch on demand until the end of March 2021, and if you missed ISBT2020 it is still possible to register to take advantage of this after the live event. ISBT2020 also saw the launch of an update to the perennially popular 2008 book "Introduction to Blood Transfusion Technology" more on this in the next edition of Transfusion Today which will be dedicated to education in transfusion medicine. Meanwhile, I wish you all the very best for the festive season, and a happy and healthy 2021.

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Clinical use and effectiveness of CCP

COVID-19, caused by the SARS-CoV-2 virus, has resulted in over 39.4 million infections and 1.11 million deaths worldwide with no established specific therapy or prophylaxis to date. Convalescent Plasma (CP), collected from patients who have recovered from an infection and made neutralizing antibodies, has been used effectively and safely as a form of immediate passive-immunity to treat previous novel viruses [1] including H1N1, SARS-CoV and MERS-CoV. The lack of proven treatments for COVID-19 and historical successes of CP have placed COVID-19 Convalescent Plasma (CCP) on the potential therapy list. But whether it is effective and if so at what antibody titer, plasma volume and number of doses; for which patients and at what stage of the infection are yet to be established.

CP works by inducing viral clearance, phagocytosis and antibody-dependent cell-mediated cytotoxicity of infected cells as well as dampening the overactive immune response and cytokine storm [2]. Initial CCP publications were encouraging [3-5], reporting improved radiological features [3, 4], reduced viral load [3-5] and oxygen requirements and increased survival [3, 4] but were critically limited in study design, patient numbers and study methodology. CCP use in the setting of clinical trials, specifically large Randomized Controlled Trials (RCT) was recommended and over 160 CCP trials are currently registered. Performing RCTs during a pandemic is challenging with administrative requirements delaying commencement early on and waning patient numbers hindering recruitment later on.
CCP appears to be most beneficial early in the disease by inducing viral clearance prior to the development of a cytokine storm and the need for ventilation [5-7]. Some non-randomised studies showed positive trend [6, 8] regarding oxygenation [6], radiological and laboratory features [8] and survival [6]. However published RCT results are less encouraging: one RCT of 103 patients that was terminated early due to slow enrolment, did not show a statistically significant improvement in patient outcome with CCP [9], another was terminated early due to efficacy concerns with 53 of 66 recipients demonstrating SARS-CoV-2 antibodies at baseline [10] and a third including 464 patients, did not measure CCP donor Sars-CoV-2 antibody levels but found no reduction in mortality in the CCP arm [11]. Significantly, a Cochrane review reported uncertainty as to whether CCP has any effect on mortality and duration of hospitalization and ambiguity regarding optimal dose and timing as a result of inconsistent reporting across studies [12]. Interestingly, CCP use has shown promising results in patients with B-cell immunodeficiency and prolonged COVID-19 symptoms [13]. Potential safety risks of CCP include transfusion transmissible infections, transfusion related associated lung injury, transfusion associated circulatory overload, antibody dependant cellular toxicity and exacerbation of an underlying coagulopathy. However, a safety study of 20 000 patients [7] confirmed overall safety of CCP with <1% incidence of serious adverse events and 0.3% mortality in the first four hours after transfusion.
Multiple trials across various settings investigating both the prophylactic as well as the therapeutic use of CCP are underway; the results of which are eagerly awaited to inform evidence-based therapy decisions.

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Antibody measurements in CCP to define the best units for patients with SARS-CoV-2

Different therapeutic approaches were proposed at the moment for treating COVID-19, caused by SARS-CoV-2; except for dexamethasone 1,2, all have failed in RCTs 3,4,5. COVID-19 convalescent plasma (CCP) transfusions are regarded as safe, but still under study as therapy for severe cases 6. Unfortunately, the CCP source is limited and not all donors qualify for donation. It is important that CCP collection centers establish appropriate strategies and guidance to provide adequate, safe and available CCP units.

One of the main points for CCP collection defined by the ISBT Working Party on Global Blood Safety 1 is that "Key ethical, quality, and safety guidance for the selection of donors, the collection and processing of blood, and the transfusion of COVID-19 convalescent plasma should be followed"

CCP donors must undergo a series of screening tests to be qualified, based on:

1) General tests: intended to screen any blood donor (blood grouping, infectious disease markers, etc), according to each country´s legislation.

2) Absence of SARS CoV-2 infection: by use of virologic tests (e.g. nucleic acid test - NAT, by nasopharyngeal swab). Some countries advocate that donors are allowed to donate without additional testing for SARS-CoV-2 at >14 days after full recovery, although it would be more prudent to consider CCP collections between 14 to 28 days after full recovery from symptoms.

3) Specific serological assays – The main purpose of CCP therapy it to provide passive antibodies to recipients to control the infection, using two different strategies:

a. Neutralizing antibodies (nAb) - Directed against the spike protein; this test has not a standardized, uniform definition of acceptable levels, being recommended to accept donors with minimum nAb titer ≥80, though ≥160 is more advisable. Testing for nAbs requires viral cultures, being cumbersome, expensive and demanding a biosafety level 3 laboratory (BSL3). To circumvent this, an alternative is to use a laboratory-engineered pseudovirus test, which is reliable, sensitive and more available, requiring a BSL2. Although testing for nAbs is still considered as the "gold standard" for CCP donor screening, its applicability is considered difficult to be implemented worldwide, particularly in regions/countries with less technical or economical resources.

b. Binding antibodies – These tests could be developed in house, being gradually replaced by commercial, licensed tests, directed either against spike (S) or nucleocapsid (N) proteins. There are good evidences correlating high reactive tests, either by the signal cut-off ratio (S/CO) or area under curve (AUC) with nAb titer 8,9. This alternative seems appropriate and should be further validated globally.

Regardless of which screening tests are adopted, there are also evidences that correlate higher nAb titers with severity of disease, age, weight and number of days after the onset of disease. Thus, not all convalescent donors will bear high nAbs at the moment of their first interview/collection and most nAb levels tend to decline with time. So, it is important to recognize that there is a "golden period" for high titer nAb CCP collection, usually lasting no more than 100 days after onset of disease, leading BTS to develop strategies for recruitment, screening and collection of the best appropriate CCP donors, complying both with donor and recipient´s safety, providing CCP components that are most adequate for patient´s needs.

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Collecting COVID-19 CCP: supply and demand considerations

This year brought a unique challenge for blood organizations around the world: collecting COVID-19 Convalescent Plasma (CCP), a brand-new product, as a highly uncertain epidemic unfolds. Against a backdrop of movement control orders, social distancing measures and other non-pharmaceutical interventions that put blood supplies under pressure as loyal repeat donors remained at home, blood organizations had to recruit an entirely new kind of donor: those who have recovered from SARS-CoV-2 infection. While the regulatory environment and operational practices continue to evolve in many countries, and evidence on clinical efficacy and optimal dosing regimens is still emerging, some key considerations for CCP supply and demand have become evident.

The driving force of epidemic trajectory

The manner in which the epidemic trajectory shapes CCP supply and demand creates a challenge for blood organizations. Early in an outbreak, there are no or few potential CCP donors. Demand for CCP grows as people are infected and hospitalized, but the supply of potential donors (individuals who have recovered and have been symptom free for a minimal period) lags behind. This can make it challenging to meet CCP demand during early surges in cases and hospitalizations. Countries that have been most successful in controlling early waves of the epidemic may be more poorly positioned to meet CCP demand in future outbreaks. An expected 'winter wave' of COVID-19 in the northern hemisphere is of immediate concern.

Donor recruitment and qualification

Blood collection organizations in the United States have used a variety of mechanisms to recruit and qualify donors. Partnering with clinicians in the hospitals served was an important early strategy to identify potential CCP donors. Providers are in daily contact with current COVID-19 patients who become potential CCP donors after recovery and have a strong motivation to ensure CCP therapy is available for their future patients. Conventional marketing campaigns targeting potential donors directly have also been important.

In the US and other countries, blood centers began offering universal SARS-CoV-2 antibody testing in the second half of 2020 to incentivize donation and relieve pressure on the blood supply. These programs have also proved useful for infection surveillance purposes [1,2]. In some cases, blood organizations are labeling convalescent plasma with sufficient SARS-CoV-2 antibodies derived from whole blood donations. The volume of plasma derived from a whole blood donation is small, however, and most organizations rely on plasmapheresis collection.

It is believed that convalescent plasma with high neutralizing antibody titers are most likely to be clinically efficacious. Under the U.S. FDA's Emergency Use Authorization for CCP, collectors will be required to label all units as high or low titer from December. Other jurisdictions may introduce similar requirements. During early 2020, CCP products were frequently released without any antibody screening results, and in recent months mere positivity on a binding antibody (bAb) assay has sufficed. Since neutralization assays are cumbersome and expensive, identifying high-titer units is a formidable challenge, and thresholds on bAb assays as proxy measures of neutralization titers are being evaluated.

Insights from a simulation model

We developed an open source demand, production, and supply simulation model designed to inform CCP programs. In an analysis of a variety of epidemic trajectories from eleven U.S. states with large COVID-19 epidemics, and by varying uncertain parameters over wide ranges in over 100,000 simulation runs, we gained insights into factors that influence blood collectors' ability to utilize apheresis capacity and meet demand for CCP [3].

In our simulations, epidemic trajectories with early, sharp increases in COVID-19 hospitalizations, like those observed in New York and New Jersey, saw significant unmet demand for CCP units. More gradual increases in hospitalizations, as seen in California, increased the likelihood that blood agencies would be able to keep pace with demand. Another key insight was that for epidemic trajectories that included two peaks in hospitalizations, ability to meet demand was greatly enhanced during the second wave because the plateau and downswing of the first epidemic peak afforded blood agencies time to amass a CCP stockpile for use in later waves. This observation has another implication: sharing inventory across geographic areas that are at different stages of the epidemic could greatly decrease the risk of shortage.

COVID-19 convalescent plasma is likely to remain a critical healthcare resource until more effective antiviral therapies are available or widespread vaccination checks the global pandemic. By learning from experience and sharing information, blood agencies can strengthen their ability to meet demand, and perhaps be better equipped to collect convalescent plasma for future disease outbreaks.

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COVID-19 Vaccines and Transfusion Medicine

An enormous amount of work is currently being focused on developing vaccines for COVID-19 and their availability is anxiously awaited.(1) It is reasonable to expect that approved vaccines will be widely implemented to reduce SARS-CoV-2 infections and/or COVID-19 disease, and we want to discuss the extent to which these vaccines might impact our own field.

In many countries, the COVID-19 pandemic has resulted in enormous stress on blood supplies, because of the necessity to motivate donations during periods of movement control orders and social distancing, and the overwhelming need to assure safety from infection among donors and staff. It is easy to think that the availability and use of vaccines will eliminate, or minimize these precautions. However, it must be remembered that even the best vaccines are not completely effective and that currently we have no clear measures of the efficacy of any of the vaccines under development. Some of the clinical trials under way are basing success on efficacy for prevention of COVID-19 disease of 50% or more, with secondary endpoints for prevention of acquisition and shedding of SARS-CoV-2. The longevity of protection is unknown, and multiple inoculations may be needed to sustain immunity. In other words, even when vaccines are widely available, the possibility of person-to-person infection will continue for an unpredictable amount of time. Where and while infections continue, we will not be able to relax our safety measures vis-à-vis donor and staff protection.

It is widely accepted that SARS-CoV-2 is almost certainly not transmitted by transfusion, so it may be surprising to find that it may be necessary to consider the safety of blood collected from recent vaccinees. In broad terms, it is likely that many vaccines will be distributed before full regulatory approval (e.g., Emergency Use Authorizations from the US FDA) and will thus be experimental and may need to be managed as such. Many of the vaccines that are being developed for COVID-19 rely on technologies that have not yet been used in humans, and consequently there may not be adequate information about possible adverse effects. It is reasonable to expect that vaccines from inactivated viruses and those using recombinant antigens will not pose any risk. A brief post-inoculation deferral should probably be considered for vaccines based on live, attenuated viruses. It is unlikely (but unknown) whether novel RNA and DNA vaccines would be a problem, as these vaccines have not yet been used in humans, but regulatory agencies have signaled that nucleic acid-based vaccines will not likely require donor deferral. Finally, some use adenovirus, lentivirus, or other vectors, which may or may not be replicative.

Again, this is unknown territory but temporary deferral following receipt of replicating vector vaccines is likely. It is to be hoped that manufacturers and regulators will provide appropriate advice for each distributed vaccine. Of note, the WHO maintains a listing of all COVID vaccines under development or trial, identifying the technology and status of trials and regulatory review: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.

In addition to donor eligibility and donor and staff safety, introduction of SARS-CoV-2 vaccines will impact test selection for serosurveillance studies based on blood donor populations. In many countries blood donor samples are being accessed and tested for SARS-CoV-2 antibodies to contribute to public health efforts to track incidence of infection and the impact of interventions to reduce transmission.(2) Many of these antibody assays are based on the spike protein or receptor binding domain of SARS-CoV-2 which are the immunogens in most vaccines. Vaccine-induced seropositivity (VISP) will confound donor based serosurveillance testing algorithms and necessitate use of nucleocapsid based antibody assays as either the primary screening tests or in multi-test algorithms. Blood donor surveillance may also contribute to detection of reinfections and vaccine breakthrough infections based on appropriately designed studies and test algorithms.

Finally vaccines may be employed to enhance SARS-CoV-2 antibodies in donors of COVID-19 Convalescent Plasma (CCP) and hyperimmune globulins (HIgG). Large scale implementation of CCP under EUA has occurred in the US and some other countries, and randomized trials of CCP and HIgG are in progress. Although current CCP and HIgG products are derived from donors who have recovered from COVID-19 disease or detected by antibody screening of healthy donors, the titers of neutralizing antibodies in these donors are variable and wane over time. Many of the vaccines in development induce higher titer neutralizing antibodies and cellular immune responses than occur following natural infection, and most vaccine trials include both previously infected and naive participants. Based on the impact of vaccines on immune parameters in convalescent donors, there may be a role for vaccination of CCP and HIgG donors to increase the potency of these passive immune therapies.

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Status of development of hyperimmune globulin therapies

Hyperimmune immunoglobulin (H-Ig) is a plasma derivative that is manufactured from plasma by chromatographic and fractionation procedures. It is currently being investigated as a potential treatment option for coronavirus disease 2019 (COVID-19).

H-Ig is prepared from human or animal plasma with high titres of pathogen-specific antibodies made in response to exposure to these pathogens or immunisation. H-Ig typically contains highly purified and concentrated antibodies at consistently higher levels than those found in convalescent plasma. By neutralising the specific pathogen, early treatment is postulated to increase clearance of the initial inoculum which may reduce mortality and disease severity [1]. Other postulated mechanisms include antibody-dependent cellular cytotoxicity and phagocytosis.

H-Ig has been proven to be effective as prophylaxis in a range of clinical settings, especially where no vaccine is available or patients are unable to receive or have not yet received a vaccine. Current indications for use include infantile botulism, prevention of hepatitis B infection in liver transplantation, prevention of varicella zoster infection in immunosuppressed states, and prevention of cytomegalovirus infections in patients undergoing organ transplantation [2]. However, evidence for its effectiveness in previous respiratory outbreaks, such as H1N1 influenza, is mixed [3, 4] and there is no clinical data for its use in severe acute respiratory syndrome or Middle East respiratory syndrome.

Due to complex manufacturing process, H-Ig takes longer to develop than convalescent plasma. The fractionation process can affect plasma IgG-subclass composition and hence product efficacy, so extensive preclinical and clinical evaluation is required [2]. Pathogen inactivation is a component of the manufacturing process, which leads to lower risk of transfusion-transmitted infections, small volume and longer shelf-life allowing for ease of storage and transport. Safety profile is likely to be similar to those of standard immunoglobulin and theoretical risks include antibody-dependent enhancement of infection, although there have been no reports of this in convalescent plasma use to date [1].

In the case of COVID-19, an umbrella "Plasma Alliance" have been formed by a group of major plasma industry companies to maximise development of an H-Ig product [2]. Several trials are underway evaluating the efficacy and safety of H-Ig in the treatment of COVID-19 and prophylaxis in patients exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Of these, the ITAC study has commenced recruitment of its first patient in October 2020, and plans to enrol 500 hospitalised patients with COVID-19 internationally utilising the National Institutes of Health INSIGHT network, randomising participants to receive H-Ig with or without remdesivir (as standard of care) with the primary outcome of clinical improvement at day seven [5]. The other following trials evaluating H-Ig have been registered as "not yet recruiting" and are listed in Table 1.

Efficacy and safety of convalescent plasma in the treatment of patients with COVID-19 has not yet been established [1]. If efficacy of convalescent plasma is demonstrated in future studies, clear and transparent policies need to be developed to ensure ongoing measured collection of convalescent plasma in parallel with facilitated development of a validated and safe H-Ig product. This can allow for longer shelf-life and stability of transport, and equitable distribution should then be established. Until then, we await the continued progress of both convalescent plasma and H-Ig studies with interest.

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Table 1:

Registered studies evaluating hyperimmune immunoglobulin in COVID-19			
Title and URL	Design	Participants	Planned Completion Date
Inpatient Treatment With Anti-Coronavirus Immunoglobulin (ITAC) clinicaltrials.gov/ct2/show/NCT04546581	RCT	500	July 2021
Treatment with Anti-SARS-CoV-2 Immunoglobulin in patients with COVID-19 clinicaltrials.gov/ct2/show/NCT04573855	RCT	41	March 31, 2021
Convalescent Plasma and Human Intravenous Anti-COVID-19 Immunoglobulin in Patients Hospitalized for COVID-19 (Colombia) clinicaltrials.gov/show/NCT04395170	RCT	75	June 2021
Clinical Study for Efficacy of Anti-Corona VS2 Immunoglobulins Prepared From COVID19 Convalescent Plasma Prepared by VIPS Mini-Pool IVIG Medical Devices in Prevention of SARS-CoV-2 Infection in High Risk Groups as Well as Treatment of Early Cases of COVID19 Patient (Egypt) clinicaltrials.gov/ct2/show/NCT04383548	Single-arm interventional study	100	January 1, 2021
Treatment of Acute Severe 2019-nCoV Pneumonia With Immunoglobulin From Cured Patients (China) clinicaltrials.gov/ct2/show/NCT04264858	Non-randomised interventional study	10	May 31, 2020 (no update since March 2020)

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COVID-19: Blood centers rise to the occasion and lead seroprevalence studies

The World Health Organization (WHO) declared the COVID-19 pandemic on March 11, 2020. Since then, more than 43 million cases have been reported worldwide. Yet, the true prevalence is likely significantly higher, when 80% of people infected with SARS-CoV-2 (the virus that causes COVID-19) experience either mild or no symptoms. In contrast to diagnostic testing, which detects the virus at the time of infection, serological tests identify SARS-CoV-2 specific antibodies after exposure, regardless of clinical symptoms. The aim of seroprevalence studies is to determine the proportion of a population already infected and potentially immune to future infections. As the pandemic continues, these studies will play a pivotal role in helping public health authorities assess policies to contain and mitigate outbreaks, determine healthcare capacity, and coordinate vaccine distribution.

Blood services have risen to the occasion, leveraging their operational capacity and access to a representative healthy adult population, to lead SARS-CoV-2 seroprevalence studies worldwide. Within the first six months of the pandemic, 32/48 (73%) of blood services surveyed globally had already or planned to conduct seroprevalence studies (Figure 1) [1]. While SARS-CoV-2 has not been reported to be transfusion-transmissible [2], the speed in which partnerships were formed was unprecedented. This was a marked departure from usual practice as the primary aim of these studies was to inform public health policies, rather than donor policies. Seventeen countries, from North America (2), South America (1), Europe (8), Africa (2) and Asia (4) have published their preliminary seroprevalence findings among blood donors, ranging from as high as 66% in parts of Brazil to as low as 0.03% in Jordan [3,4]. All serological studies are systematically monitored by the live dashboard, SeroTracker (https://serotracker.com) [5]. This dashboard allows users to visualize country-specific estimates and compare between regions, population groups, and types of serological tests.

In theory, calculating seroprevalence is straightforward, but amid the shifting sands of the pandemic, challenges exist. Conclusions drawn from these studies are limited to; the populations studied, the study design and timing, and the accuracy of the tests used to identify antibodies (Figure 2).

Population – The WHO endorses seroprevalence studies of blood donors since they are a convenient sample of healthy adult population. But care should be taken when generalizing the results beyond the target population. There is also a potential for selection bias as donors are a self-selected group of people. Additionally, since infection rates are likely different by socioeconomic status, age and ethnic/racial minorities in regions within a country, grouping prevalence rates into a single summary may miss significant differences.

Study design & timing – Typically, seroprevalence studies occur at either single or multiple (serial) snapshots in time (cross-sectional). Unfortunately, nothing about this pandemic is still, and the timing of studies becomes very important. When pathogens attack, the body creates antibodies to neutralize the invader. From the time of infection, on average, it takes 10-28 days to develop specific immunoglobulin G (IgG) antibodies to SARS-CoV-2. And by approximately 100 days, the level of these antibodies detectable in the blood begins to decrease (wane) [6]. How waning antibodies affect an individual's immunity to future infections remains unknown. If sampling occurs outside this window of detection, people both early and later in their infection will be missed. Additionally, seroprevalence can be influenced by changing population-level trends, defined as surges of new cases followed by a downturn (epidemic waves).

Accuracy of Tests – Multiple commercial and in-house antibody tests are used by blood services globally. These various tests use one or more viral antigens (i.e. spike (S) or nucleocapsid (N) proteins) to detect SARS-CoV-2-specific antibodies by different technologies (i.e. ELISA, Lateral Flow, High Throughput CLIA). Test performance is measured by the percentage of people who are accurately identified as having antibodies "sensitivity" and not having antibodies "specificity", at a given threshold (signal-to-cut off ratio). While most assays have very high specificity, sensitivity varies, and at the population-level this will affect seroprevalence rates in high prevalence settings.

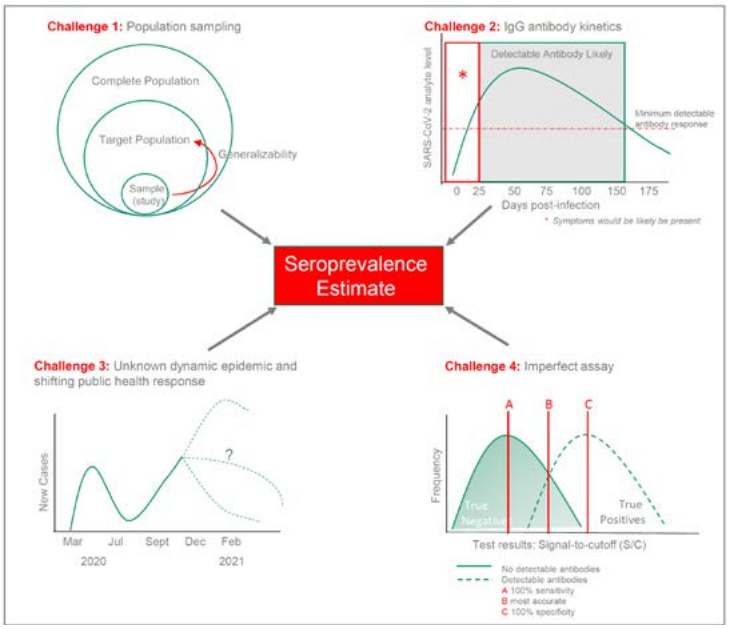
The COVID-19 pandemic has accelerated partnerships between public health and blood services. Blood donors continue to play a vital role in facilitating seroprevalence studies to assess and monitor the disease burden. We briefly identified challenges when conducting seroprevalence studies in this article. Moving forward, the ISBT Transfusion Transmitted Infectious Diseases Working Party plans to leverage expertise and data between blood services worldwide to continue to inform public health policy.

Sahar Saeed
Canadian Blood Services
Canada

Antoine Lewin
Héma-Québec
Canada

Figure 1: Countries surveyed for COVID-19 seroprevalence studies (until June 2020)1

Figure 2. Graphical depiction of the challenges of seroprevalence studies



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From the President

Dear ISBT members,

This edition of Transfusion Today focusses on convalescent plasma, particularly on its use for patients with COVID-19 disease caused by SARS-CoV-2 infection. The interesting and educational articles in this issue cover different aspects of COVID convalescent plasma (CCP): what it is, what is known about how to use it – either as plasma, or for further manufacture into hyperimmune immunoglobulin preparations – and, importantly, what we still need to know.

The pandemic has upended the world this year – at the time of writing, more than 40 million people were reported to be infected, and more than a million reported to have died (see updates from the World Health Organization [WHO] COVID dashboard: covid19.who.int).

I am thinking of all in the ISBT community who have been ill, or caring for family or friends who have been affected by the virus. Many of you have had your personal or professional plans for 2020, and beyond, disrupted as we search for ways to manage the outbreak.

Treatment and prevention strategies for SARS-CoV-2 infection are high priorities, and CCP features prominently in the current global efforts. While CCP is already being widely used, one thing is for sure – we need more high-quality research to determine its efficacy and safety, so that we can answer the questions of whether CCP benefits (all, or some) patients with COVID-19. The best way to get these data is through rigorous randomised trials adequately powered to answer the questions on clinical outcomes, and collecting samples (from donors, products and patients) for analyses in correlative laboratory studies. Many ISBT members are participating in this work. In my own country, Australia, there are two trials currently underway: ASCOT (in hospitalised patients in Australia and New Zealand) and REMAP-CAP (an international platform trial for patients requiring intensive care support). It has been very interesting to participate in this research and to see the wonderful collaborations between different clinical specialties. Many other studies are in progress around the world, and we await the results of these efforts.

International collaborations will help us deliver the answers we need faster and more efficiently. To help in these efforts, ISBT has brought many people and resources together. We are sharing regulatory and other guidance information in a dedicated webpage on our website; hosting educational webinars (more than 10 already, which can be viewed via the website); and providing links to many useful publications and other resources, which are being updated continually. We also acknowledge the leadership of the WHO and our many other national and international partners. I hope there will be enduring benefits (such as harmonisation of protocols for collecting and testing convalescent plasma, agreement on key trial endpoints and definitions, and maintenance of trial platforms) established as part of this work, and with other clinical and research partners, that will be helpful in future research.

I thank the editors and contributors to this edition of Transfusion Today, and encourage you to read the articles. I hope you find them useful in your work and studies. We greatly value your feedback, so please let us know what you think.

In these difficult times, I thank everyone for their great work helping to save lives – including collecting, testing or preparing CCP, administering it in the hospital setting, or conducting research into its use. Of course, all our other important work needs to continue too, including maintaining regular blood supplies, and taking care of donors, patients – and each other.

Yours truly,

Erica Wood
ISBT President

Membership year 2021-2022

Thank you for your support of ISBT in 2020, which was an extraordinary year for all of us. We appreciate your belief in us, especially the new members who joined us during this time. With your continued support, nothing can keep us from our mission to share knowledge in blood transfusion and enhance transfusion practice!

The new membership year will run from **April 1, 2021** to **March 31, 2022**. You will be able to start renewing your membership from March 1, 2021. Be prepared for a new year full of Education!

Join us on ISBT Education, stay up to date with our quarterly magazine Transfusion Today and follow the latest posts on the ISBT Forum and our social media channels.

More information about membership can be found on the website: isbtweb.org/my-isbt/join/
or send an email to Mildred: membership@isbtweb.org.

"ISBT provides a great opportunity to interact with colleagues worldwide and to participate in relevant discussions pertaining to the future of transfusion medicine."
- Peter Horn, Germany

"I think ISBT is the main forum for translating science and networking into best practices"
- Morten Bagge Hansen, Denmark

Welcome to our new members

September 2020 - December 2020

Africa

Cameroon: Armelle Ariane Dongmo Tchemeza
Nigeria: Emmanuel Chinedu Onuoha, Ann Ogbenna
South Africa: Adriaan Meyer, Rochelle Smith, Candice Sinclair, faisal Hassen, Carmen Addinali, Kean Thompson, Michelle Vermeulen, Marike Gevers, Hayley Alie, Moonsamy Archery, Kim Strutt, Sybil Jacobs, Priscilla Sedibelwane, Deborah Smith, Reginald Valensky, Nomatembe Msi, Karen Dramat, Nadia Mundey, Eileen Rutherford, Caren Overall, Fuzlyn Riffel, Russell Cable, Lizela Mtebele, Claudia Fillander, Germain Rose, Michel Breuninger, Faieqa Adams, Delizia Montgomery, Duane Jacobs, Vivienne Taylor, Shaldine Sutton, Cecilia Adolph, Janine Wilschut, Hilton Marais, Anel Le Roux, Imtiaz Kaprey, Heather Stuurman, Ashleigh Button, Jacques Breslaw, Renier Myburgh, Vincent Erasmus, Garth Davids, Charlotte Ingram, Arthur Bird, Sharon Adriaanse
Uganda: Sandra Naluze

Americas

Brazil: Cecilia Lorea, Luciana Maria Barros Carlos, Carolina Bub
Canada: Aditi Khandelwal, Melanie Bodnar, Susanna Darnel
Chile : Paolo Rojas, Claudia Burgos, Paula Gonzalez
Colombia : Michel Garcia, Bernardo Armando Camacho Rodriguez
Costa Rica : Roger Soto Palma
Mexico : Mireya Leticia Portillo Garcia, Erik Alejandro Diaz Chuc, Juan Manuel Cisneros Carrasco, Luz Cristina Vital, Emmanuel Fernandez Sanchez
Peru : Oscar Alama, Roxana Regalado Rafael, Alejandro Bustamante
USA: Tina Ipe, Sara Bakhtary, Martin Ongkeko, Constantine Kanakis, Zhan Ye, Joseph Schwartz, Eduard Grebe, Allan Klompas, Jose Cancelas, John Birdsall

Eastern Mediterranean

Egypt: Dalia Ashour
Pakistan: Kanwal Shafiq, Humaira Rehman
Saudi Arabia: Hend AlHumaidan, Waseem Muhammad, Said Abdou, Abdulraheem Alshareef

Europe

Belgium: Philippe Anciaux, Marion Bareille
Cyprus: Socrates Menelaou
Czech Republic: Petr Papousek
Estonia: Astrid Pihlak
France: Laure Croisille, Richard Forde, Jean Baptiste Thibert
Germany: Richard Schafer, Ute Gravemann, Jose Francisco Villena Ossa
Greece: Virginia Voulgaridou, Athina Papadopoulou, Theano Karafoulidou, Maria Chouridi, Vasiliki Pliatsika, Anthippi Gafou, Fotini-Frangiski Sakellaridi
Ireland: Allison Waters
Israel: Ari Gargir
Italy: Simonetta Pupella, Chiara Bellia, Enrico Sorrentino
Netherlands: Jan Karregat
Poland: Monika Salwierz
Romania: Mirela Tianu
Sweden: Marja-Kaisa Auvinen
United Kingdom: Gregory Barber, Laura Williams, Kathryn Maguire, Wayne Miller

South East Asia

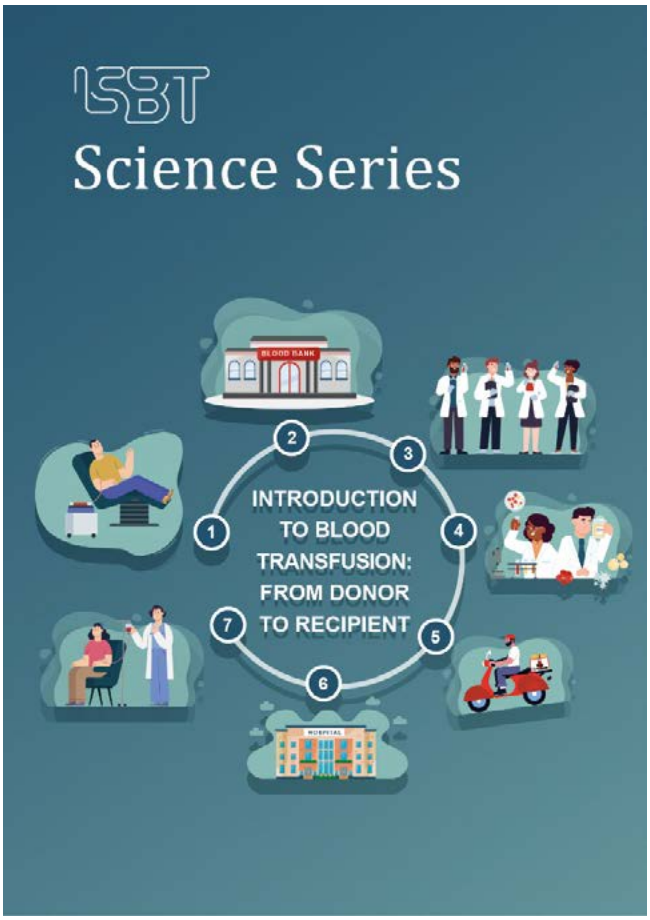
India: Dr. Shivkumar Kori, Arun M, Joyisa Deb, Hema Salam, Sanjeev Kumar Sawhney, Charumathy Arjunan, Isha Polavarapu, Sanooja Pinki
Thailand: Janejira Kittivorapart, Philaiphon Jongruamklang

Western Pacific

Australia: Rosemary Rasmussen, Kathryn Robinson, Dianne Evertdina Van der Wal, Leonardo Cavalli, Katie Gould, Rachel Thorpe, Luke Soo, Chun Lam James Ng, Xuan Bui
Hong Kong SAR of China: Nga Sze Wong, Wai Man Stacey Lam, Jennifer Leung
China: Chongzhi Guo, Binzhen Chen
Japan: Koji Miyazaki, Hatsue Tsuneyama
Malaysia: Dr Bavani Sandrakasan, Zalizah Khalid, Nadzirah Binti Yahya
Philippines: Kristine Joy Gacutno
Singapore: Niti Dawar
South Korea: Tae Hyun Um
Taiwan: I-Chien H[illegible]ch, Chang Chien Hung Hsu

ISBT 2020

By the time this edition of transfusion today is published, ISBT's very first virtual congress, ISBT2020 will have taken place. The virtual experience included a full scientific programme with state of the art lectures, educational sessions, e-posters and workshops, and of course the opportunity to interact with other speakers, delegates and exhibitors. Thank you! to everyone who made this possible and to those of you who joined us live.



There will be a full report on ISBT2020 in the next issue of Transfusion Today. In the meantime, if you missed the live event, the good news is that there is still the opportunity to register! The entire scientific programme remains on the congress platform for delegates and new registrants to watch at any time until March 31, 2020. This is a great opportunity to enjoy the congress programme at your leisure and to earn CME credits which will also be available for those watching on-demand. www.isbtweb.org/isbt2020/registration

ISBT2020 was also the occasion of the exciting launch of an update to the hugely successful book "Introduction to Blood Transfusion Technology", first printed in 2008 and much downloaded from the ISBT website ever since. The book has been renamed "Introduction to blood Transfusion: from Donor to Recipient" to reflect that the content covers the entire blood transfusion chain.
This update has been made possible by the amazing work of two of the original authors Beryl Armstrong and Rob Wilkinson, and that of Mindy Goldman acting as editor of the new edition and coordinating a team of reviewers to include developments since the first edition.
This continues to be a valuable resource to all requiring a sound knowledge of the basic principles that underpin good practice in transfusion medicine, in all settings but particularly in low and medium income countries where specialist education in blood transfusion can be more difficult to access.
The next edition of Transfusion Today will be dedicated to "Transfusion Education" and will include a full feature on the book, to be published in hard copy during 2021.

Arwa Z. Al Riyami
ISBT Young Professional Council
Oman

Young Professional Involvement in the COVID-19 Pandemic

The Coronavirus Disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global health emergency since it was declared as a pandemic in March 11, 2020. COVID-19 has brought about immense challenges in the health care systems and economics globally, with the impact being higher in countries of the developing world.

Young people are some of those most affected by the pandemic's socio-economic impact, especially those working in healthcare. Little is known about the extent to which youth are socially distancing, what motivations underlie their social distancing, and the impact of COVID-19 on their mental and social health. The COVID-19 pandemic can impact young people in different ways. They are as likely as elderly people to become infected and contagious upon exposure. Inadequate personal protective equipment for health care workers, including young professionals during certain phases of the pandemic, increase their vulnerability. The consequences of burnout, anxiety, concerns from infecting family members, providing child-care while working under increased pressure in response to the pandemic need to be assessed. This would help to better define needed organizational and governmental support to the young workforce, and to mitigate the psychological effects of similar pandemics on the youth.

Young people are also affected by closures of face-to-face formal and non-formal education opportunities, which deprive them of social engagement with their peers and educators. Prolonged periods of closures and movement restrictions may lead to additional emotional unrest and anxieties. Nevertheless, the pandemic opened many opportunities to young learners such as e-learning, access to virtual courses, congresses and educational activities. It also opened free access to many publications and journal resources. Although this has its advantages in medical education and professional development, it has also brought issues of limited access to technology and alternate forms of education and information in some countries and certain groups of learners.

Young Professionals are among the most active individuals in global responses: not only are they on the frontlines as healthcare workers, but they are also advancing health and safety. Different ISBT Young professionals are currently enrolled in different tasks in relation to this pandemic.
This includes clinical bedside care of COVID-19 patients, performing immunohematology/biological tests for COVID-19 patients, blood bank inventory management during COVID-19 pandemic, development of COVID-19 tests and vaccines, and enrollment in programs in convalescent plasma production, testing and use. Moreover, young professionals can play a powerful role in disseminating accurate information on COVID-19, risk reduction, national preparedness and response efforts through different platforms including social media. In addition, involvement of young professional in the different research activities in relation to COVID-19, such as diagnosis, treatment and prevention, opens opportunities for sharing experiences and connection with professionals from around the world.

The ISBT Young Professional Council has designed an online survey to evaluate the degree to which young transfusion medicine professionals have been involved with the COVID-19 pandemic and related activities, and the impact that the pandemic on them. The survey was distributed to young professionals globally inviting young professional in transfusion medicine aged 40 years or under to participate. The council aims to publish the results of this survey to help the community to address Young Professionals' needs in similar pandemics in the future.

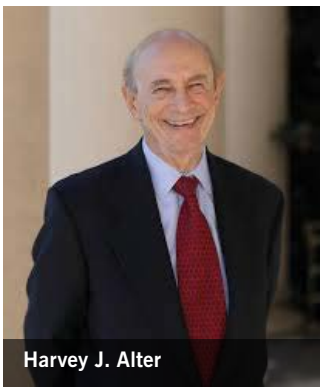
Share with us through social media your journey in fighting COVID-19. Don't forget to use our hashtag #ISBTYoungBlood! We wish you to stay safe and look forward to meet you face to face in future ISBT congresses.

2020 Nobel Prize in Medicine

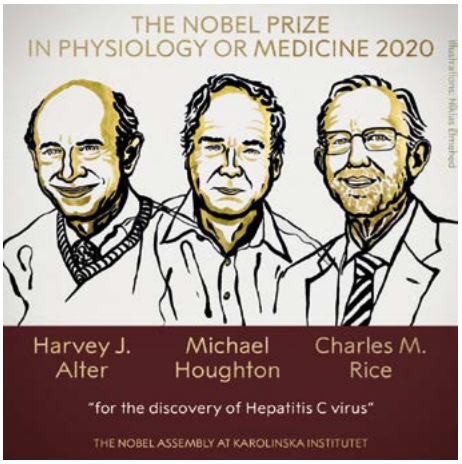
The prize was awarded to three scientists, Harvey J. Alter, Michael Houghton and Charles M. Rice for their contributions to the prevention and treatment of blood-borne hepatitis, a major global health problem that can cause cirrhosis and cancer of the liver.

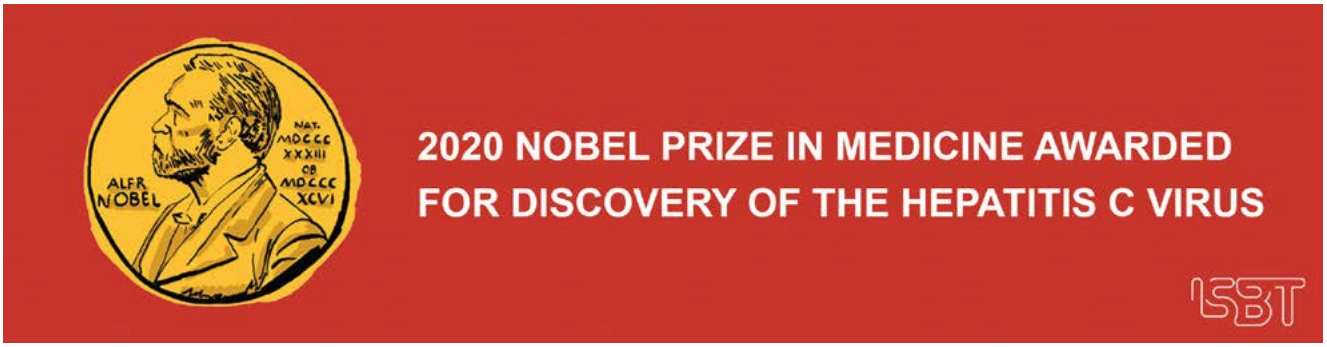
Harvey had focused on viral hepatitis for many years and in the 1960s co-discovered the Australia antigen, a key to detecting Hepatitis B. In 1989 he reported a new form of transfusion transmissible viral hepatitis, initially named ''non-A non-B'', leading to the discovery of the Hepatitis C virus (HCV). Development of tests for HCV allowed for donor screening and the opportunity to prevent previously unexplained cases of blood-borne hepatitis. The discovery of HCV also enabled development of new treatments such as direct acting antivirals (DAAs) that achieve a very high cure rate. This work, in the words of the Nobel Prize awarding committee, has "saved millions of lives."

Harvey received the ISBT Presidential Award in 2002 for his contributions to science and blood safety. Congratulations, Harvey, from the ISBT, on being awarded the Nobel Prize in Medicine!


Harvey J. Alter

ISBT Presidential Award 2002





Christoph Gassner
Private University in the Principality of Liechtenstein
Liechtenstein

Catherine Hyland
Australian Red Cross Lifeblood
Australia

ISBT Working Party on Red Cell Immunogenetics and Blood Group Terminology

Summary - new blood group systems
The RCI & BGT Working Party (WP) held its first virtual business meeting via Zoom on Tuesday September 29, 2020. It was an exceptional event with the WP formally recognising three new blood group systems, bringing the total number of systems to 41.

Background to the WP

It is forty years since the ISBT Working Party (WP) for Terminology for Red Cell Surface Antigens met at the ISBT International Congress in Montreal, Canada in 1980. The WP, now called Red Cell Immunogenetics and Blood Group Terminology (RCI & BGT), determines acceptance criteria, ratifies, names and catalogues blood group systems, antigens, and associated alleles. WP business meetings have till now been held during ISBT Congress gatherings. This year marks the first virtual business meeting connecting 35 people, including 24 WP members, across different time zones.

Highlights from the meeting

Thierry Peyrard and Nicole Thornton presented compelling scientific evidence to show the genes that 'specify blood group systems': CTL2 and PEL (by Thierry) and MAM (by Nicole). The vote by members to accept and register these systems was unanimous. CTL2, PEL and MAM will be registered as ISBT 039, 040 and 041. The respective genes giving rise to these BGs, as defined under the International HUGO Nomenclature, are *SLC44A2*, *ABCC4* and *EMP3*.

CTL2 assigned ISBT 039

The first study presented by Thierry was triggered by a pregnant woman of Moroccan ancestry who presented with an antibody reacting against a high frequency antigen (HFA) on red cells. Compatibility testing showed five unrelated subjects, also from Morocco, and one female patient from Europe lacked this HFA.

Thierry reported that a whole exome sequencing approach combined with expression studies (transfections, knockout mice and immunoprecipitation) and knowledge from a study by other researchers on the human red cell proteome identified a variant in the *SLC44A2* as the candidate gene in the Moroccan subset.

The variant on this gene is a c.1192C>A change which causes an amino acid change (p.Pro398Thr) on the third extracellular loop of the protein. In vitro studies using transfected cells showed the loss of the high frequency antigen associated with this amino acid change.

Finally, the European subject exhibited a very large deletion of the *SLC44A2* gene. An antibody in the European proband was directed against the total wild type protein in the red cell membrane. This *SLC44A2* null phenotype is associated with hearing impairment in the upper frequency range.

This represents the 39th blood group system, designated ISBT 039. The SLC44A2 protein is also called CTL-2 for Choline Transporter-like Protein 2.

PEL assigned ISBT 040

The high frequency PEL antigen was first described in 1980. However, the genetic locus for this antigen was never defined. PEL negative red cells, a rare type, have been found in four unrelated French Canadian families from the province of Quebec. Thierry reported how a comparative global proteomic analysis of the red cells pinpointed the ABCC4 as the likely candidate protein for the PEL antigen expression.

Review of whole exome sequence then showed a large deletion on the *ABCC4* gene in all PEL negative cases, even though unrelated. Sanger sequencing confirmed the breakpoint with the same location defined for all PEL negative cases. Subsequent molecular and cellular studies included western blot and transfection studies. These all confirmed that the ABCC4 protein carries the PEL blood group and that homozygosity for a large deletion in the *ABCC4* gene is responsible for the rare PEL-negative phenotype.

This represents the 40th blood group system, designated ISBT 040 The ABCC4 protein is a member of the superfamily of ATP-binding cassette transporters. Two other blood group systems are members of this superfamily: JR and LAN. The PEL-negative phenotype is associated with a moderate impaired platelet aggregation.

MAM assigned ISBT 041

The MAM-negative phenotype was first described in 1993 in a pregnant woman (M.A.M) who presented with an antibody to a high frequency red cell antigen. Severe or even fatal HDFN has since been reported in such cases. Nicole presented on a collaborative study that included six members of the Working Party and a number of research teams. Ten MAM-negative samples from around the globe were investigated.

Whole exome sequencing with filtering strategy on five subjects showed the only candidate gene was *EMP3*, encoding Epithelial Membrane Protein 3; Sanger sequencing of this one candidate gene *EMP3* confirmed mutations were present in this gene for all 10 MAM-negative samples. Four different allelic variants were defined amongst the 10 MAM-negative samples. Expression studies further confirmed a causal relationship between *EMP3* gene and MAM antigen.

This represents the 41st blood group system, designated ISBT 041. EMP3 has been reported to be a tumour suppressor gene. Further studies showed marked increase in reticulocyte proliferation of MAM-negative in-vitro cultures suggesting *EMP3* acts as a suppressor of proliferation in normal erythropoiesis. It may also have a function in regulating the level and stabilising CD44 at the cell surface of erythroid progenitors.

Conclusion: Blood Group Discoveries and the Genomic/Omic wave

The discovery of blood group systems seems to occur in waves. This current wave includes KANNO (ISBT 037) and SID (ISBT 038) reported last year. Genomic whole exome sequencing and, in some cases, red cell proteomic analysis, facilitated these discoveries.

For an antigen to be assigned to a blood group system the gene encoding it must be known. PEL and MAM antigens have remained without a genetic home since last century and until now have been assigned to the series of antigens in the ISBT "901" series. Four antigens remain in the 901 series – the challenge is on to find their genetic home(s).

Congratulations

To all the Research Teams involved in these recent Blood Group System discoveries, which represent significant milestones in Transfusion Medicine.

"Australian governments fund Australian Red Cross Lifeblood to provide blood, blood products and services to the Australian community"

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Educational page

The content of the ISBT Summer Highlights virtual meeting is now available online!

Why not watch one (or all!) of these excellent presentations and associated discussions on ISBT Education and take the opportunity to do some reflective learning, starting with the questions below. https://bit.ly/ISBTSummerHighlights2020

Day 1: Immunohaematology

Advances in genomics in the study of rare blood groups

Jill story

Blood group discovery is increasingly dependent on molecular testing, and now also bioinformatics. Simultaneously, single nucleotide variant arrays and whole exome sequencing have been used successfully for the resolution of previously unresolved blood groups such as JR, VEL, P1PK, AUG, SID, and mapping of selected genes and gene families. Whole exome sequence analysis has also been used in large collaborative studies targeting blood donor genetics not only for blood group phenotype prediction but also for predictors of blood donor health.

How can we utilise the data from whole exome sequencing to improve knowledge and transfusion safety?

Serological techniques for solving problems in immunohaematology

Nicole Thorton

There are many tools for solving difficult antibody identification problems, and looking for clues to guide their application based on an understanding of the characteristics of blood groups antigens and antibodies is key. So much can be achieved using basic serology, but supplementary tools may also be needed, requiring additional resources and expert knowledge to reveal a complex mixture of antibodies, or identify an antibody to a high frequency antigen.

Before you start testing your sample, what kind of data do you need regarding the patient?

Phenotype and allele matching - how far should we go?

Masja de Haas

Sickle cell disease patients can experience delayed transfusion reactions and have increased risk for hyperhaemolysis. When there is an emergency situation, increased delay of finding compatible units can be very stressful. Providing patients with donations matched for common red cell antigens, and with donors of similar ethnic background can lower the risk of alloimmunisation, but further studies are needed, e.g. to establish which Rh variants pose an immunisation risk and which antibodies are clinically relevant.

In which cases do you think genotyping and fully matched red cells are needed?

Day 2: Clinical Transfusion

An update on patient blood management

Katerina Pavenski

Patient Blood Management should be personalized, multidisciplinary and proactive. The "one size fits all" approach doesn't work in medicine and it is especially true in patient blood management where an individualised approach is key. Another significant consideration is ensuring that patient blood management plans are patient-centered. Any individualized plan should be developed with involvement of the patient and take into account their specific comorbidities, their preferences, their values and their specific risks and benefits when considering transfusion of red cells versus exposure to alternatives.

What do you think are the main barriers to implementation of PBM?

Management of haemolytic transfusion reactions and hyperhaemolysis syndrome

Sara Trompeter

In case of Delayed haemolytic transfusion reactions (DHTR) we often expect fever and other symptoms of haemolysis more than 24 hours after transfusion. However, hyperhaemolysis is a rare complication of transfusion where there is haemolysis of both donor and recipient red cells leading to post transfusion Haemoglobin level falling below the pre transfusion level, and is notoriously difficult to control. The causes are not fully understood and each case requires careful individual management.

Would you continue to transfuse a patient with hyperhaemolysis?

Learning from transfusion 'never events' - review of unintentional abo incompatible transfusions reported to serious hazards of transfusion (shot)

Shruthi Narayan

TACO and delays in provision of transfusion were prevalent causes of transfusion-related deaths in the UK in recent years. For the right component to go to the right person at the right time administered correctly, everything should fall in place throughout the transfusion chain. The coordination between clinical as well as laboratory staff with accurate patient identification is critical for safe transfusions.

What do you think is worse? Not reporting an error or not learning from one?

Day 3: COVID-19 immunology

Biology of corona viruses and how SARS-CoV-2 is unique

John Semple

Coronaviruses have been with us for some time, but understanding of the specific biology of SARS-CoV-2 is vital to inform strategies to produce vaccines against SARs-CoV-2. It also gives insights into the immune response such as antibody production and T-cell activation. SARS-CoV-2 give rise to a wide range of symptoms involving multiple organs, and carries a thrombotic risk, the mechanism for which is as yet not well understood. Severe COVID-19 infection in Caucasians is associated with significant coagulopathy.

Is blood (component) transfusion a suitable treatment in COVID-19 patients?

SARS-CoV-2 testing: applications and findings relevant to blood safety, donor screening and surveillance, and qualification of convalescent plasma and hyperimmune globulin

Mike Busch

There is rapid ongoing development of both antigen and antibody tests for SARS- Cov-2. Antibody testing can be used to identify potential COVID-19 convalescent plasma donors. Up until now, there has not been a transfusion transmission case of SARS-CoV-2 (or of other respiratory pathogens such as SARS-1 or MERS), although testing can detect low levels RNA in blood after recovery. The transient nature of antibodies to SARS-CoV-2 raises the possibility of reinfection and questions on the role of antibody testing in monitoring for previous exposure in individuals and populations.

What do you think are the benefits and limitations of testing for SARS-CoV-2?

Passive antibody therapy for COVID-19 - emphasison convalescent plasma

Arturo Casadevall

Convalescent plasma has long been a proven therapy for viral diseases in the absence of a vaccine. However, COVID-19 is a new and complex disease and CP is a highly heterogeneous product where every unit is different with a combination of active agents. Antibodies do lot of things as well as neutralising the virus; they activate complement, promote ADCC, crosslink Fc receptors and modulate immune responses. Rapid acceleration of clinical trials has been required to meet the challenge of the pandemic and to establish safety and efficacy. COVID-19 CP has been shown to be as safe as plasma used for other indications; fears of antibody dependent enhancement have not materialised. Studies on efficacy are positive, and trials are ongoing regarding the optimum time to start CP therapy and whether hospital admissions can be avoided.

In which patient groups would you use convalescent plasma to treat COVID-19?

https://bit.ly/ISBTSummerHighlights2020

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Start of EU twinning project strenghtening blood safety system in Georgia

Last February the EU Twinning project Strengthening Blood Safety System in Georgia officially started. This project is funded by the EU and a collaboration between EU member states Lithuania and The Netherlands. The project supports public health policies and programs in Georgia and aims to build a blood transfusion system that complies with EU directives.

In this project experts from the National Blood Center of Lithuania and Sanquin Blood Supply share their experience with their counterparts from the Ministry and the National Center for Disease Control (NCDC) to find solutions that comply with the EU directives and at the same time fit within the Georgian situation.

In the project four result areas are defined:

1. **Legislation**
   Translation of the EU directives in National Legislation
2. **Organization**
   Organization of the blood system (government oversight and blood supply)
3. **Voluntary donors**
   Change to voluntary non-remunerated donor system
4. **Human capacity**
   Capacity building for state authorities and key stakeholders needed for the blood system

The first consultation visit took place early February. During the visit a schedule for project activities was developed. Usually thereafter experts would come to Georgia to execute the activities in collaboration with the local counterparts. But as of March the COVID-19 pandemic affected the project and the situation changed when travel became impossible. With support from the EU Delegation and the flexibility of all project partners the activities started online via videoconferencing. With this alternative approach it was possible to successfully initiate four planned activities as well a steering meeting committee.

In September the delayed Kick-Off meeting took place in Tbilisi and experts from The Netherlands were welcomed for the occasion. Also an assessment visit was paid to a number of blood banks. Because of travel limitations the Lithuanian partners had to contribute to the meeting via videoconference.

In summary, in this EU funded Twinning project (GE 18 ENI HE 01 19) Strengthening Blood Safety System Georgia key stakeholders and experts from Lithuania and The Netherlands collaborate in order to strengthen the Georgian blood supply system to comply with the EU directives.

Project Georgia kick-off meeting.

Project Georgia kick-off meeting.

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Tshering Yangdon
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Turnaround Time for Urgent Blood Needs at Tertiary Care Hospital, Bhutan: Internal assessment of a single center

The turnaround time (TAT) is an important quality indicator for Blood Transfusion (BT) which is one of the most common medical procedures performed in hospitals as a lifesaving intervention. The urgency of the blood required is defined based on the clinical assessment and requesting physician's order to blood bank.

Jigme Dorji Wangchuck, National Referral Hospital (JDWNRH) being the apex and the only tertiary care facility in Bhutan with bed strength of 380 requires 5000 blood units annually from its supplier the National Blood Bank (NBB) housed in the same hospital. Although there are various steps from collection of blood to issue for which TAT should be analyzed, the most crucial is the time taken for blood to be made available at bed-side when urgent blood requests are made for emergency transfusion cases. Hence a survey was conducted by the Quality Assurance and Standardization Division of the hospital with support from NBB.

Objective:
This survey aimed to assess the baseline TAT for urgent blood needs with reference to various degrees of urgency defined and the standard set for each category (Table 1). The request was received by NBB in the form of a filled blood request form (BRF) or telephonic calls by treating physicians in dire situations.

Table 1: Definitions and degrees of urgency

Interventional radiology guided procedures or Bedside procedures[6]			
Sr. No.	Degrees of Urgency /Types of Blood Availability for transfusion	Defenitions	Standard TAT for blood release against each degree of urgency
1	'Immediate'/ Group 'O' Rh Positive packed red cell (PRC)	Time interval between telephonic call received by NBB and un-crossmatched 'O' blood unit made ready for issue to the wards. Neither a blood sample nor BRF is awaited by NBB.	5 minutes
2	'Emergency' /Group Specific un-crossmatched whole blood or PRC	Time interval between receipt of patient's pre-transfusion sample and BRF and uncrossmatched blood unit made ready for issue.	10-15 minutes
3	'Urgent' /abbreviated Crossmatched whole blood or PRC/	Time interval between receipt of patient's pre-transfusion sample and BRF and an abbreviated (immediate spin) cross-matched blood made ready for issue.	15 -20 minutes
4	'Urgent'/Crossmatched whole blood or PRC	Time interval between receipt of patient's pre-transfusion sample and BRF and a fully cross-matched blood made ready for issue.	45-60 minutes

*NBB uses column agglutination technology routinely for all immune-hematological tests.

Methodology:
The survey was conducted at NBB from August 3 - 9, 2020 using a standard "Assessment form" (Table 2).

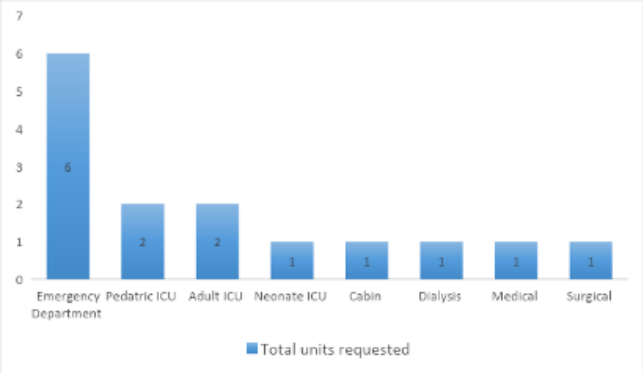
Table 2: Assessment Form (SAMPLE ONLY)

Interventional radiology guided procedures or Bedside procedures[6]					
Sl. No.	Patient ID no.	Degree of urgent blood need	Date and time when BRF /call received	Date and time when blood is ready for issue	Remarks

The staff on duty at NBB reception area was responsible for entering the details in the Assessment Form on a daily basis 24x7. An Excel sheet was used for data entry and analysis of the TAT.

Results:
A total of 15 'urgent crossmatched' whole /PRC blood requests were received. Of these, the Emergency Department had the most maximum with 6 requests followed by pediatric ICU and adult ICU and with 2 respectively (Table 3).

Table 3:



The average TAT was 44.6 minutes which was within the standard of 45-60 minutes

Limitations:
- It was only a 7 day short survey;
- TAT of other categories of urgency could not be assessed as no requests were received during the survey period.

Conclusion:
It was found that NBB was able to maintain the set TAT for urgent blood needs demonstrating availability of stocks at all times, staff efficiency and team work. However another survey with longer time period is recommended to validate this data. Such subsequent surveys also need to assess the time taken between pick up of blood and start of administration to the patient to actually assess patient outcomes and reduce any types of delays, after all BT is a lifesaving procedure.

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Canada's MSM Research Program - producing and mobilizing knowledge

In 2017, Canadian Blood Services and Héma-Québec launched the MSM (men who have sex with men) Research Program [1] (the Program) to address evidence gaps and advance the MSM blood donor deferral policy. The aim of this commentary is to describe the Program's knowledge production and mobilization activities and reflect on challenges and lessons learned. While the Program is one of many competitive research programs administered by Canadian Blood Services' Centre for Innovation (C4I), the complexities of the MSM blood donor deferral policy and changes under consideration required an innovative tailored approach.

1. Co-creating the research agenda

From the beginning, a priority of the Program was to engage stakeholders in defining the research agenda. This was facilitated by the existing relationships developed over many years between Canada's blood operators and LGTBQ+ communities, patient groups, and regulators. Research priorities were identified during a multidisciplinary meeting in 2017 with diverse stakeholders, [2] and subsequently used to guide the Program's knowledge production and dissemination activities. Following the meeting, C4I continued to engage academic researchers by leveraging its existing network to attract scholars with relevant expertise to apply for the Program's competitive grants. In total, the Program funded 15 research projects and brought together, for the first time, multidisciplinary teams comprising experts in the social and behavioural sciences, public health, and epidemiology, and collaborators from LGBTQ+ and patient communities.

2. Networking and knowledge mobilization

Since a key aim of the Program was to generate evidence in a coordinated fashion, whereby results from one project would inform others, C4I built into the design of the Program various networking and knowledge mobilization activities. These included: reviewing progress bi-annually, holding annual teleconferences, establishing a collaborative web portal, sharing lay research summaries with stakeholders, and organizing the Knowledge Synthesis Forum in 2019. At the Forum, researchers, blood operators' staff, regulators, LGBTQ+ and patient groups, and international experts reflected on the findings to date and identified additional evidence gaps. [3, 4] With many projects now in their final stages, targeted funding has been provided to facilitate knowledge dissemination. In addition to peer-reviewed publications and presentations, research teams are developing videos and pamphlets to make findings accessible to research participants and community stakeholders.

3. Challenges and lessons learned

Although still underway, C4I's knowledge mobilization approach is proving effective, as evidenced by engagement from research and stakeholder communities, participation in meetings, and surveys. However, facilitating knowledge transfer among the various groups, who may have different perspectives and uses for the knowledge, has been challenging. Ongoing efforts to share knowledge regarding relevant operational and regulatory processes is necessary to support research projects aimed at having operational impact. Managing different timelines and divergent expectations has also been challenging. To promote trust and collaborative relationships with researchers and stakeholders, communicating operational timelines and transparency is vital.

To conclude, the MSM Research Program highlights the role blood operators may play in facilitating multidisciplinary research that addresses complex donor policy. As increasing attention is paid to donor experiences, issues of diversity and inclusion, and the important role blood operators play in health and social systems, multidisciplinary teams that address complex questions from different vantage points is increasingly necessary. Developing safe, equitable, and feasible donor policy requires blood operators to think "outside the box" and support collaborative projects that enable the co-creation of knowledge across the scientific, medical, and social domains. With the Program, Canada's blood operators have leveraged their expertise in research and program administration, and their strong engagement with LGBTQ+ organizations, patient groups, and researchers, to implement an initiative that aims to address complex donor policy through multidisciplinary collaboration.

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The History and Challengers of the Fiji National Blood Services

The Fiji National Blood Services is part of the service provided by the Fiji Ministry of Health and Medical services. Initially the Fiji Red Cross Society was responsible for the donor recruitment and while the Pathology department looked after the collection of blood. In 2005 the Fiji Ministry of Health and Medical services took over the overall operations through the establishment of the Fiji National Blood Services.

The Fiji National blood services was established within the confines of the three major divisional hospitals in Fiji, namely the Colonial War Memorial Hospital which is located in Suva the capital of Fiji and looks after the Central and Eastern Division, The Lautoka Hospital which caters for the Western Division and the Labasa Hospital which caters for the Northern division.

The main role of the blood services was to recruit and collect blood from volunteer donors and also raise awareness the need for blood donation with the aim of achieving a 100% voluntary Non Renumerated Donors.

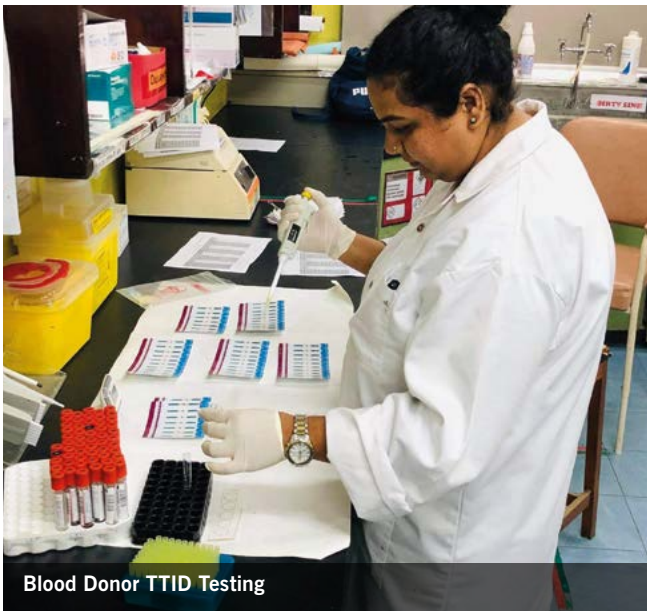
In 2012 the Fiji National Blood Services reviewed their strategic plan and endeavoured to expand its role through:

1. Testing for transfusion transmitted infection.
2. Blood group typing.
3. Blood Products Production.
4. Endeavouring on a more centralised blood services.

Challenges:

The budgetary allocation for Fiji national blood services is focused specifically on donor recruitment activities while donation consumables, TTID's testing and serological testing is incorporated in the budgetary allocation for the Pathology department. This has resulted in inconsistencies in supplies and a lack of donor education materials.

There is a great need for increase in manpower and training for the staff associated with donor recruitment, as lack of resources in this area limits management of voluntary donors and contributes to blood shortage.



Blood Donor TTID Testing

The Fiji National blood services set up as such that it is solely focused on donor recruitment; testing, storage is donor by the pathology department through the Transfusion section this has contributed to the lack of blood inventory management which is also a contributing factor to blood shortage. Unfortunately, lack of a National Blood Commission, a National Committee for Quality and hospital based Transfusion Committees to provide policy and standard operating procedure, has led to unnecessary blood transfusion requests which are not monitored. This, together with unavailability and delay of certain reagents, leads to a steady increase in difficult to transfuse patients, adding to the burden for local blood services.

TTID screening, if performed, is now through a rapid testing algorithm. Previous testing using an ELISA technique has been replaced by rapid testing due to funding constraints.

Despite the enormous challenge Fiji National Blood services faces, it continues to provide blood for the general population of Fiji through the dedicated staff finding innovative ways to work around the daily hurdles it faces.

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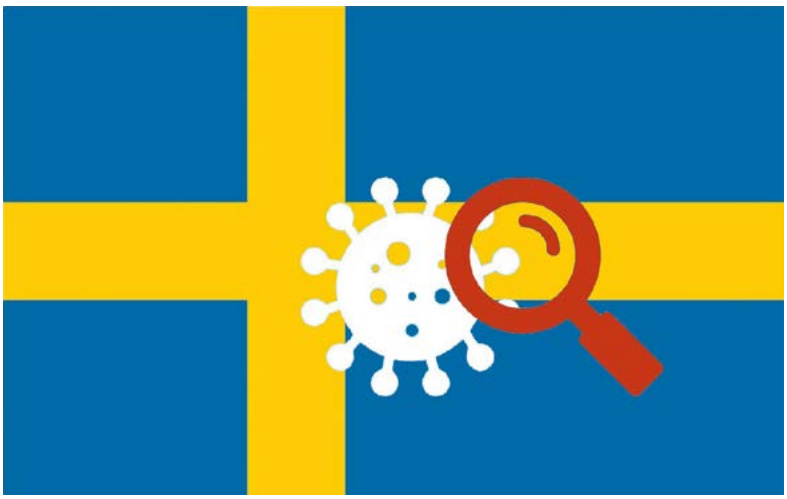
COVID-19 in Sweden

In Sweden there are 26 blood bank organizations in the 21 regions. The regions are independent but work together under the umbrella of the Swedish Blood Alliance (SweBa), a member of the European Blood Alliance (EBA). On February 1, the Government in Sweden classified COVID-19 as a disease that constitutes a danger to society, opening the possibility of extraordinary communicable disease control measures. The overall objective of the Government's efforts is to reduce the pace of the COVID-19 virus's spread: to 'flatten the curve' so that large numbers of people do not become ill at the same time, exceeding healthcare capacity. In addition, a high priority is to protect vulnerable groups, especially the elderly.

By October 6, 2020 over 94 000 persons have been infected with COVID-19 and over 2600 patients have been treated in the ICU. In all 5 895 have passed away, mainly in the elderly category, 89% were over 70 years of age. The worst affected areas were the large cities of Stockholm and Gothenburg. The epidemic started in Stockholm on the first week of March and lasted until the end of June. A peak was on June 24th, almost 1700 positive cases per day, not all of them needed hospital care. During the peaking week there were over 200 patients admitted to intensive care in Stockholm. For Gothenburg everything started about the same time. The second wave of new cases has started in September with around 2000 new cases per week mainly in the younger age groups and milder disease.

In the very early stage of covid-19 pandemics, SweBA organized weekly phone and webmeetings to cover all the issues blood banks might face during the pandemics. SweBA wanted to share the best practices among the member organizations as well as harmonize messages towards the donors. In Stockholm blood donations went down in periods with around 30% due to sickness and public health restrictions. This was partly matched with the reduction in demand for transfusions as elective operations and other blood demanding treatments were postponed. Periods of shortages in RBCs were managed with the help from other regions not so affected by the virus. General messages for donors were, keep coming, it is safe to give blood. As people were told to work from home if possible, it seriously affected the blood bus drives in Stockholm that had to be cancelled due to workplaces that were closed down. Some blood donation centers in Sweden introduced donation by appointment with good results. Until now no face masks or other protective equipment has been introduced at the blood donation sites in Sweden.

Staff members are told to stay home even with the slightest symptoms and we try to keep physical distancing of 2 meters between the donors at donation facilities. Some centers have started to collect convalescent plasma, but with decreasing levels of antibodies in recruited donors and satisfactory stock levels, most programs are paused.



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Patient Blood Management in Developing Countries

Patient Blood Management (PBM) is an evidence-based, multidisciplinary approach to optimizing the care of patients who might need transfusion. PBM is considered as an essential part of patient management in developed countries. The program should review patient blood management and utilization practices in a prospective, concurrent, and/or retrospective manner.

Developing countries still have many obstacles regarding clinical use of blood components. Unnecessary use and ordering of blood components is still a reality and needs strict policy, awareness, and training for all staff involved in blood transfusion chain. Patient Blood Management Program implementation is still far behind in Eastern Mediterranean Region, only few countries has adapted PBM program in their large hospitals as a new way for improvement of patients care. In Saudi Arabia only few large accredited hospitals start to adapt PBM protocol as for treatment of pre operative anaemias, use of transfusion alternatives and massive transfusion protocol. Although awareness and training on PBM has started, there are still no national policies or guidelines on PBM to be followed by all hospitals. Saudi Society of Transfusion Medicine is involved in awareness campaign and education and training on PBM through conducting workshops, presentations and brochures distribution.

At a King Abdulaziz University Hospital in Jeddah, a pilot study was conducted on blood transfusion for surgical patients. The study included 288 patients who received blood transfusion before surgery. This study shows that only (16%) of the patients had a hemoglobin level below 7 g/dL, whilst (43%) had a Hb level of 7 g/dL to 10 g/dL and (42%) a Hb level above 10g/dL. The authors reached a conclusion that PBM protocol should be in place and strategy should be initiated through the hospital transfusion committee to improve patient health and avoiding unnecessary blood transfusion at time of surgery. We should be very careful when taking decisions in ordering blood transfusion to avoid unnecessary transfusion, over-transfusion or under-transfusion.

Key Recommendation:
National policy and guidelines on PBM should be in place. Awareness and education among clinicians is to be conducted. Transfusion committees should be effective to review data and statistics of clinical use of blood and enforce policy and guidelines on PBM. Better communication and Multidisciplinary teamwork is needed. The use of alternatives to blood transfusion is highly recommended.

Future direction:
Introduction and implementation of a Patient Blood Management program in all hospitals will contribute a lot to patient safety, risk reduction, cost saving and improve quality of services provided to our patients in developing countries.

Initiation of personalized blood transfusion therapy through evaluation of individual patients for anaemia tolerance and the need for blood transfusion.

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Achieving a sustainable blood supply in Nigeria

The availability of blood for transfusion and the safety of blood supply remains a critical need in sub-Saharan Africa. In Nigeria, 2 million blood donations are estimated to be required to meet critical needs in 2019. However, data available for the 2019 first quarter, not up to 10% of the needed donations was achieved through voluntary blood donation. The prevalent blood sources in Nigerian public and private health facilities are family/replacement and paid donations while the contribution of non-remunerated voluntary donations to is negligible [1]. This is attributable in part to an inadequate coordinated regulatory supervision and funding, and perhaps a complacent attitude of stakeholders in the healthcare system.

Additionally, inadequate grasp of the demographic group(s) more likely to contribute significantly to the existing pool of voluntary blood donors and a lack of understanding of factors that will encourage or discourage a sustained behavioural change towards voluntary blood donation may have contributed to the short supply of voluntary donations. Students of tertiary institutions appear more interested in voluntary blood donations and they constitute a major proportion of voluntary blood donor pool in Nigeria. A recent investigation on how best to enhance the rate of repeat donations among tertiary students, enrolled 840 students by stratified random sampling from all six colleges of the University. The survey revealed that more than 60% of respondents demonstrated the willingness to donate blood. Though the proportion of previous donors was low, there was evidence that their willingness to donate was influenced by their knowledge of blood donation [2]. Unfortunately, due to the COVID-19 pandemic and implemented measures to prevent community spread in Nigeria, universities and all institutions of learning have been closed since March 2020. This has significantly affected the number of blood donations that otherwise would have been collected through institutional blood drives. On the other hand, the demand for blood which reduced at the start of lockdown measures in April 2020 began to increase gradually about a few weeks later putting a strain on the already low supply. Donor recruitment teams during the pandemic used electronic media advocacy and visited corporate organisations, e.g. banks, to create voluntary blood donation awareness.

Blood transfusion service, Nigeria.

Blood transfusion service, Nigeria.

The recruitment of family/replacement donors has been popular in Nigeria and the potential for converting this pool of donors to voluntary non-remunerated donors has been expressed [3]. However, the approach to achieving this without coercion remains unclear. Recently, a Nigerian High Court ruled against the prevalent practice of demanding blood donations from patients or their relatives as a prerequisite for accessing transfusion-related healthcare [4]. The judgment is correctly premised on the fact that the practice violates patients' fundamental human rights. When enforced it will technically restrain facilities from pursuing family/replacement donations. This will affect an already precarious blood supply and emphasizes the need for urgent translational research on the motivation and deterrents to regular voluntary blood donation in the Nigerian population.

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