Monitoring International Trends

February – March 2022

The NBA monitors international developments that may influence the management of blood and blood products in Australia including but not limited to:

- Potential new product developments and applications
- Global regulatory and blood practice trends
- Events that may have an impact on global supply, demand and pricing
- Emerging risks and relevant issues.

Some key topics that have appeared in news media, online publications, and industry and research updates have been included in this report, including:

- **Blood Supply:** March is Red Cross Month in the United States with the agency asking Americans to think about donating to support the organisation or help with the on-going blood needs. The Australian Red Cross Lifeblood (Lifeblood) has confirmed that close to 100,000 donors were unable to donate blood due to Omicron infection or associated isolation protocols in the past few months.
- **Blood Disorders:** The US Food & Drug Administration has approved multiple medications for the treatment of haemolytic anaemia. In the European Union, a new treatment for sickle cell disease has gained approval for treatment.
- **Transfusion:** Limited supplies of blood products has resulted in a focus on product administration to determine if reducing transfusion events or lowering transfusion volumes has negative impacts on patient health. A study conducted by the International Society of Blood Transfusion found that during the COVID-19 pandemic, blood donations have dropped in 70.6% of collecting facilities. Operational challenges include loss of staff, increased workloads and delays in reagent supplies.
- **Gene Therapy**: Gene therapies for haemophilia are returning positive results in trials. CSL Behring made a marketing authorisation application for its product, EtranaDez, to the European Medicines Agency (EMA). The EMA have agreed to review the results of their research with possibility of approval in the next five months.
- **COVID-19:** The Omicron subvariant BA.2 is the dominant variant of COVID-19 worldwide. The Australian Technical Advisory Group on Immunisation (ATAGI) advised that three doses of a COVID-19 vaccine are required to be 'up to date'. The Australian Government announced that the Biosecurity Emergency Determination relating to COVID-19 will not be renewed when it lapses on 17 April 2022.
- **Other items of interest:** A survey conducted by the World Health Organisation found that disruptions in basic health services such as vaccination programs and treatment of diseases like AIDS were reported in 92% of 129 participating countries.

Contents

1 Blood supply

This section contains news articles and government agency statements on blood supply, changes to donation criteria, and a report from the UK Infected Blood inquiry.

1.1 Blood supply – Australia

The flood crisis in Southern Queensland and the East Coast of New South Wales affected blood services. Lifeblood confirmed that the flooding, evacuation orders, road closures and disruptions to public transport resulted in a shortfall of 3,000 donations. Lifeblood also confirmed that close to 100,000 donors were unable to donate blood due to Omicron infection or associated isolation protocols in the past few months. Lifeblood provided a submission to the Therapeutic Goods Administration to have this restriction reviewed. Meanwhile, changing distribution of blood types in Australia has highlighted declining proportions of RhD-negative blood donors.

- Blood donors urgently needed as flooding hits supplies
- Omicron sidelines 100,000 blood donors
- Call to loosen restrictions for UK blood donors as Omicron takes donation toll
- Increasing challenges of finding blood donors highlighted
- Blood supply faces challenges due to decline in RhD negative blood donors

1.2 Blood supply – North America

March is Red Cross Month in the United States with the agency asking Americans to think about donating to support the organisation or help with the ongoing blood needs. They advised that they will temporarily resume testing for COVID-19 through March for the purpose of identifying blood supplies that have high levels of antibodies which may be used for convalescent plasma. Community blood centres are joining together to ensure supplies.

- American Red Cross: Red Cross Month
- Bloodlines: How the pandemic created a nationwide blood shortage
- Majority of U.S. blood centers now part of nation's first emergency blood reserve
- AABB launches new alliance to support the U.S. blood supply
- Red Cross testing blood donations for COVID-19 antibodies

1.3 Blood supply – World news

The UK has repealed a law that required African donors to report if their partner had ever had sex in areas where HIV is endemic. The Ukrainian conflict has seen local queues to donate blood for the treatment of injury. Studies have been released on the safety of blood donation practices and donor health reporting in Nigeria and Cameroon. The deferral period for men who have had sex with men to donate blood reduced from 12 months to four in the Republic of Ireland.

- Ireland: New criteria for gay men to donate blood in effect
- United Kingdom: Landmark donation eligibility change for Black African heritage donors
- Nigeria: Lagos tasks blood logistics firms on quality service
- Kenya: State piloting secure digital system to curb blood theft
- Ukraine: Worried Ukrainians queue out the door to donate their blood for war casualties

1.4 Regulatory and donation criteria changes

Blood donor deferrals have increased significantly during the COVID-19 pandemic, with ongoing effects on supply around the world. The United States Red Cross declared a Blood Crisis, which has affected other consumers of US blood products such as Europe and Australia. Canadian and UK Blood Services made appeals for more donors. Reports suggest that objections to a new eligibility form have resulted in a boycott of the Israeli blood service by some religious groups.

- Red Cross declares first ever blood crisis amid Omicron surge
- New and returning donors needed to support patients through Omicron
- Impact of COVID-19 on blood donor deferral patterns during the COVID-19 pandemic
- Israel sees blood donation shortage amid Omicron
- Plasma donor compensation still an 'open wound' in EU's blood directive revision

1.5 Blood donor characteristics and donation effects

The relationship between glycosylated haemoglobin level and red blood cell storage lesion in blood donors

Glycosylated haemoglobin (the amount of glucose in the blood) is associated with various abnormalities of red blood cells (RBCs) and with enhanced oxidative stress. This Chinese study aimed to explore glycosylated haemoglobin levels in 875 potential blood donors and the effect on red blood cell storage. The researchers found a relatively high percentage of eligible blood donors showed glycosylated haemoglobin levels in diabetes and prediabetes ranges, with age, BMI, smoking, and alcohol consumption being the main factors influencing these levels.

1.6 Other items

The Association for the Advancement of Blood & Biotherapies has released the latest edition of its publication *Standards for Blood Banks and Transfusion Services.* The ongoing conflict in Yemen has impacted the safety and availability of blood transfusion, in particular the ability to meet demand while ensuring the safety of supply.

- Standards for Blood Banks and Transfusion Services, 33rd edition
- Donor blood procurement, safety, and clinical utilisation: A study of blood transfusion services in a tertiary care hospital in Nigeria
- Implementation of an Africa-specific donor health questionnaire for human immunodeficiency virus risk screening
- Baseline assessment findings of the Africa Society for Blood Transfusion Step-Wise Accreditation Programme in 10 sub-Saharan African countries, 2016–2018

2 Blood disorders and treatments

This section includes published new media, research and industry statements on the progress of blood disorder treatments across various conditions.

2.1 Thrombotic disorders

Thromboinflammation and antithrombotics in COVID-19: Accumulating evidence and current status

This editorial looks at studies available relating to thrombotic complications of COVID-19 infection. The authors note that there is limited evidence supporting the benefit of therapeutic-dose or intermediate-dose anticoagulation compared with standard prophylactic heparin in the treatment of severe COVID-19. However, in the specific prevention of venous thromboembolism, a complication of COVID-19, treatment was shown to be beneficial.

Elevated plasma levels of plasminogen activator inhibitor-1 are associated with risk of future incident venous thromboembolism

Researchers investigated the effect of elevated plasminogen activator inhibitor-1 (PAI-1), frequently elevated in obesity, on the risk of venous thromboembolism. PAI-1 is the main inhibitor of fibrinolysis. The authors' findings indicate that plasma PAI-1 is associated with increased risk of future venous thromboembolism and the potential to partially mediate the venous thromboembolism in obesity.

Impact of restrictive red blood cell transfusion strategy on thrombosis-related events: A meta-analysis and systematic review

Researchers conducted a meta-analysis of 30 randomised trials to compare thrombosis-related complications between restrictive and liberal transfusion strategies. They found that the incidence of thromboembolic events was relatively lower in the restrictive transfusion groups, but no difference in cerebrovascular accidents or myocardial infarction. The researchers suggested that a restrictive red blood cell transfusion strategy significantly reduced the risk of thromboembolic events, although the Grading of Recommendations Assessment, Development and Evaluation quality of evidence was very low.

2.2 Haemophilia

Laboratory coagulation tests and recombinant porcine factor VIII: A United Kingdom Haemophilia Centre Doctors' Organisation guideline

The United Kingdom Haemophilia Centre Doctors' Organisation conducted a review of the current literature relating to the use of Recombinant porcine factor VIII (rpFVIII) to develop a guideline for the treatment of patients with acquired haemophilia A.

Development of factor IX inhibitor in an adult with severe haemophilia B following COVID-19 vaccination: A case report

Researchers have reported a case of FIX inhibitor in a patient with haemophilia B developing after receiving a COVID-19 Pfizer vaccination. Association with the Pfizer vaccine is speculative as researchers were unable to determine whether the vaccine caused the FIX inhibitor or whether the vaccination hyperstimulated a pre-existing immune response to a previous COVID-19 infection.

Four cases of acquired haemophilia A following immunisation with COVID-19 vaccine

In the province of Reggio Emilia in Italy, scientists observed four cases of acquired haemophilia following immunisation with the Pfizer COVID-19 vaccine during the first eight months from the beginning of the region's COVID-19 vaccination campaign. The authors do not conclude that the Pfizer vaccine is the cause of acquired haemophilia in the four observed patients and note that three of the four patients had autoimmune disorders or cancer, which could have heightened susceptibility to this acquired haemophilia.

Regression analysis to estimate the Factor VIII activity of patients with haemophilia A without inhibitor who received emicizumab therapy

This study looked at the effect of emicizumab (Hemlibra) on coagulation assay regression models to estimate FVIII activity and determine the appropriate dosing of FVIII concentrates during bleeding emergencies. Researchers concluded that the regression models can estimate the FVIII levels in patients with haemophilia A receiving emicizumab and would be useful in a bleeding emergency.

Improvement in pain-related quality of life in patients with haemophilia A treated with rFVIIIFc individualised prophylaxis: post hoc analysis from the A-LONG study

Pain is a common symptom of haemophilia primarily due to joint bleeding, which adversely affects patients' physical functioning and can impact their quality of life. This study looked at the effect of prophylactic treatment with recombinant factor VIII Fc fusion protein (rFVIIIFc), an extended half-life clotting factor, on patient-reported measures of pain with severe haemophilia A. Results showed improvements in pain across the length of the study with a greater proportion of patients reporting no pain/discomfort at the end of the study.

Impact of first COVID-19 lockdown on paediatric and adult haemophilia patients treated in a French Haemophilia Comprehensive Care Centre

The study investigated the impact of the first French COVID-19 lockdown on haemophilia patients in terms of symptoms, management, medication adherence, mental health and lifestyle behaviours. Researchers found that bleeding episodes remained unchanged as did adherence to medication plans for haemophilia patients. However, there were significant changes in lifestyle behaviours including large increases in screen time, decreases in physical activity and weight gain, all factors which can impact on overall patient health.

Risk factors for increased perioperative blood loss during total knee arthroplasty in patients with haemophilia

This study aimed to identify the risk factors for increased blood loss during surgery following total knee arthroplasty in patients with haemophilic arthropathy. The authors found that approximately 540 mL of blood loss occurs in patients with haemophilia during total knee arthroplasty. They found that blood loss during surgery is increased when haematocrit and coagulation factor levels are low on the operation day, concluding that a coagulation factor level of <93.5% or haematocrit level of <38.2% may be a significant risk factor for increasing perioperative blood loss.

Sanofi, with positive data in hand, to ask for approval of longer-lasting haemophilia therapy

Drug companies Sanofi and Sobi plan to submit an experimental, longer-lasting haemophilia treatment for US Food and Drug Administration (FDA) approval. According to a company statement, patients that received the once-weekly preventive treatment 'Efanesoctocog alfa' ended up having, on average, less than one bleeding event over the course of a year.

Aerobic exercise in patients with haemophilia: A systematic review on safety, feasibility and health effects

Researchers investigated the safety and feasibility of aerobic exercise in people with haemophilia. The researchers looked at seven studies that investigated the effects of aquatic exercise, walking, treadmill running, bicycle riding and swimming on the health of people with haemophilia. The researchers found that exercise can be considered as a safe and feasible option when supervised, supporting current recommendations from aerobic exercise experts and general health guidelines.

Recombinant single-chain factor VIII in severe haemophilia: Long-term safety and efficacy in previously treated patients in the AFFINITY extension study

This study investigated the long-term safety and efficacy of single-chain factor VIII prophylaxis in previously treated haemophilia A patients. Researchers found that most patients maintained or reduced the frequency of prophylaxis regimens with rVIII-SingleChain. The treatment showed a favourable safety profile and was not associated with inhibitor development.

Managing severe haemophilia A in children

Researchers reviewed the history and current options for the treatment of paediatric patients with haemophilia A. The authors note the importance of FVIII concentrate products and emicizumab as suitable options for primary prophylaxis in paediatric haemophilia A, as much more data now exists to help with the safe and efficient care of children. As new therapy options come to light, further research will be needed to establish ideal use of and safety of treatment options for children.

Digital haemophilia: Insights into the use of social media for haemophilia care, research and advocacy

Researchers looked at the haemophilia community's use of the social media platform Twitter to determine how the community was interacting and assess the information available on Twitter for people with haemophilia. They found the largest categories of users were support and advocacy groups, people with bleeding disorders and healthcare providers. The results demonstrate patterns of effective Twitter usage for patient care, research and advocacy purposes among the haemophilia community.

DNA extracellular traps as potential biomarker of chronic haemophilic synovitis and therapeutic perspective in patients treated with PRP: A pilot study

Haemarthrosis in haemophiliacs (bleeding in the joint cavity) can cause serious complications including chronic haemophilic synovitis (CHS). Neutrophils are a type of immune cell that infiltrates joints that are bleeding. They release extracellular DNA traps (ETs) which are structures of DNA bound by enzymes that are associated with tissue damage. This study evaluated the presence of ETs as a mark of joint damage, and the protective effect of injection of platelet-rich plasma (PRP). The study found that joint and plasma levels of ET indicators correlated with worse joint health and bleeding episodes, suggesting that ETs formation could be a biomarker and potential therapeutic target for CHS.

The views of women with bleeding disorders

The aim of this study was to document the experience of women with a diagnosed bleeding disorder and to improve understanding of their needs. Two hundred and eighty women in the United Kingdom completed a survey, of which 13 participated in a focus group or individual interview. The authors found that women with bleeding disorders had similar positive experiences of healthcare, regardless of symptoms, treatment or whether if their disorder was acquired or inherited.

Reduced cardiovascular morbidity in patients with haemophilia: results of a 5-year multinational prospective study

The life expectancy of people with haemophilia has increased with the availability of clotting factor concentrates (VIII and IX). With longer life expectancy, there has also been an increase in the occurrence of cardiovascular disease (CVD) among haemophilia patients. Researchers in the UK and Europe looked at the relationship between the severity of haemophilia and cardiovascular disease, finding there was no statistically significant relationship between severity of haemophilia and incidence of CVD. The authors found in those with haemophilia, there was a lower-than-predicted incidence of cardiovascular disease.

The impact of improving haemophilia A management within the Spanish National Healthcare System

Researchers looked at the model of service delivery for haemophilia A patients in Spain and suggested possible improvements to services, including some methods already present in the Australia delivery model.

Combination of genetic factors and ABO O genotypes may predict faster decay of FVIII infused in haemophilia A patients

Researchers suggest that there is substantially faster FVIII decay associated with the ABO O genotypes, which has potential implications for genetically tailored substitutive haemophilia treatment.

Report of surgeries, their outcome and the thrombin generation assay in patients with Factor XI deficiency

This study confirmed that patients with factor XI deficiency cannot be used as a reliable predictor of bleeding in surgeries.

Time is Blood: The impact of diagnostic delays on Acquired Haemophilia A

In a retrospective study at a single hospital system in the US between 1 March 2010, and 17 January 2017, researchers looked at the result of six patients meeting the criteria for acquired haemophilia A and propose an algorithm to aid in early diagnosis and treatment in emergency and non-specialised settings.

Efficient and safe correction of haemophilia A by lentiviral vector-transduced BOECs in an implantable device: Molecular Therapy

This study looked at the long-term expression of FVIII in endothelial cells through lentiviral vector (LV)-mediated gene transfer holds the promise of a one-time treatment for haemophilia A. Researchers sought to determine whether LV-corrected blood outgrowth endothelial cells (BOECs) implanted through a prevascularised medical device (Cell Pouch) would rescue the bleeding phenotype of mice.

Quality of life in a large multinational haemophilia B cohort

An international study of 224 people living with haemophilia B was undertaken to understand their quality of life. Results were stratified by severity to understand the impacts of disease in an individual context and the development or history of inhibitors. Researchers found that in all severity groups (mild to severe), a proportion of subjects showed 'less than optimal' quality of life. However, the majority of mild and moderate participants reported a normal health profile, while half of the severe participants and only 13% of the patients with inhibitors reported the same quality of life.

Osteoporosis management and falls prevention in patients with haemophilia

Australian researchers investigated the management guidelines for haemophilia patients with osteoporosis as a result of low bone mineral density. The researchers looked at the British and Australian and World Federation guidelines for haemophilia regarding osteoporosis prevention, screening, diagnosis and management. They found that haemophilia guidelines did not adequately address osteoporosis management and fall prevention due to a lack of evidence in the literature.

Long-term efficacy and safety of subcutaneous concizumab prophylaxis in haemophilia A and haemophilia A/B with inhibitors

Novo Nordisk has released results of an extension study as part of it Phase 3 trial of the prophylaxis treatment concizumab, to determine the effect of the treatment on annualised bleeding rate, adverse events, and anti-drug antibody occurrence. Researchers reported that adverse events were mild, with no deaths or events leading to withdrawal or thromboembolic events. Anti-drug antibody occurrence developed in 25% of patients but were transient with no observed clinical effect in most cases.

BAFF gene polymorphism and the risk of the development of inhibitors in children with severe haemophilia A

This cohort study was carried out on 100 newly diagnosed boys with severe haemophilia A who had not previously been treated FVIII concentrate. Assessment of the patients' serum levels of BAFF and BAFF rs9514828 genotyping was performed at diagnosis and again at 50 days after exposure or the development of inhibitors, whichever occurred first. The patients were divided as positive or negative according to the presence or absence of inhibitors. The risk allele for BAFF rs9514828 was significantly more frequent in the inhibitor positive patients than the inhibitor negative patients.

Life-threatening bleeding in patients with haemophilia: a 10-year cohort study in Dakar, Senegal

This was an observational study with the aim of describing the characteristics of life-threatening bleeding events in 274 patients with haemophilia at the Dakar Hemophilia Treatment Center (HTC) during the last 10 years (2012–2021). Within the study group, 241 patients had haemophilia A (87.9%) and 33 had haemophilia B (12.1%). Researchers identified 31 life-threatening bleeding episodes over the specified period. The authors noted that as a resource-limited country, life-threatening bleeding events remains a real challenge in Senegal, when compared with better resourced countries.

Haemostatic efficacy of marstacimab alone or in combination with bypassing agents in haemophilia plasmas and a mouse bleeding model

Researchers aimed to assess the efficacy of combining the trial monoclonal antibody marstacimab with the bypassing agent recombinant factor FVIIa (rFVIIa) or activated prothrombin complex concentrate on blood clotting. Researchers wanted to determine if the combination of the treatments would result in excessive coagulation. The tests, conducted on mice, supported increased haemostasis through combined use of marstacimab and the bypassing agents rFVIIa or aPCC, without inducing excessive coagulation.

2.3 Anaemia

Treatment through a preoperative anaemia clinic is associated with a reduction in perioperative red blood cell transfusion in patients undergoing orthopedic and gynecologic surgery

Patients undergoing elective orthopaedic and gynaecologic surgery were screened for preoperative anaemia. Researchers then evaluated the results of 161 patients with preoperative anaemia who were treated through a preoperative anaemia clinic against patients who had not received treatment. Researchers found that treatment through a preoperative anaemia clinic was associated with a reduction in perioperative transfusion and possibly reduced the length of stay and readmission. Researchers also noted that treatment time before surgery correlated with a greater increase in haemoglobin up until 2 months prior to surgery.

Intravenous iron sucrose vs. blood transfusion in the management of moderate postpartum iron deficiency anaemia

Researchers compared the effect of intravenous iron sucrose against blood transfusion in increasing the blood cell counts and haemoglobin concentration in women suffering with moderate post-partum anaemia. Researchers found that intravenous iron sucrose was as effective as blood transfusion in replenishing the haemoglobin and iron storage status in haemodynamically stable women with moderate post-partum anaemia.

FDA approves treatment for anaemia in adults with rare inherited disorder

The US FDA has approved the use of Pyrukynd (mitapivat) tablets to treat haemolytic anaemia in adults with pyruvate kinase (PK) deficiency. Pyruvate kinase deficiency is an inherited disorder that causes premature red blood cell destruction, which leads to anaemia.

FDA approves Enjaymo for treatment of Cold Agglutinin Disease

Cold agglutinin disease is a form of autoimmune haemolytic anaemia. The US Food & Drug Administration has approved Sanofi's sutimlimab-jome (Enjaymo), which works by inhibiting the destruction of red blood cells, to decrease the need for red blood cell transfusion because of haemolysis in adults with cold agglutinin disease.

Momelotinib: an emerging treatment for myelofibrosis patients with anaemia

Anaemia is present in approximately a third of myelofibrosis patients at diagnosis, eventually developing in nearly all patients. The need for red blood cell transfusions is an independent adverse risk factor for both overall survival and leukemic transformation. The authors of this study suggest that Momelotinib is one of the prime candidates to durably address the critical unmet needs of MF patients with moderate/severe anaemia.

Long-term eltrombopag for bone marrow failure depletes iron

Researchers conducted a retrospective review of patients treated at the National Institutes of Health comparing those treated with eltrombopag to a historical cohort treated with immunosuppression without eltrombopag. Researchers examined iron parameters, duration of therapy, response assessment, relapse rates, and common demographic parameters. The found eltrombopag efficiently chelates total body iron but prolonged use can deplete iron and ultimately lead to iron deficiency anaemia mimicking relapse, responsive to iron supplementation.

2.4 Post-partum haemorrhage

Assessment of post-partum haemorrhage risk among women with moderate thrombocytopenia

This study aimed to define whether moderate thrombocytopenia constitutes a risk factor for the development of post-partum haemorrhage and if any blood groups showed a stronger association with that risk. Researchers performed a multicentre retrospective cohort study, conducted in two obstetric departments in Milan and found that subjects with moderate thrombocytopenia had increased risk of post-partum haemorrhage when compared to a control group. They also confirmed that the risk of post-partum haemorrhage was stronger in blood group O patients.

2.5 Sickle cell disease

GEU approval for sickle cell drug Oxbryta

The European Commission has approved Oxbryta (voxelotor) for the treatment of haemolytic anaemia in patients with sickle cell disease over 12 years of age. Oxbryta prevents sickle haemoglobin polymerisation, the molecular basis of sickling and destruction of red blood cells in sickle cell disease.

Acute kidney injury in hospitalised children with sickle cell anaemia

Researchers evaluated the prevalence and risk factors associated with acute kidney injury in children admitted to a Ugandan hospital with sickle cell related vaso-occlusive crisis. Researchers found that 90 of the 185 children assessed had acute kidney injury with 61 of these children having acute kidney injury on admission to the hospital. The results demonstrated that acute kidney injury is a common complication in children with sickle cell anaemia who have experienced a vaso-occlusive crisis.

A systematic review on the management of transfusion related acute lung injury in transfusion dependent sickle cell disease

The onset of respiratory distress and acute lung injury following a blood transfusion is known as transfusion-related acute lung injury (TRALI). TRALI is an immune-mediated transfusion response that can result be life-threatening, but early detection and treatment increase the chances of survival. This study sought to investigate the current state of sickle cell disease (SCD) related TRALI care and therapy, suggesting that the current provision of supportive care falls short of that desired by haematologists and SCD patients.

Changes in the developmental status of pre-schoolers with sickle cell disease

This study examined the stability of developmental screening outcomes and factors influencing change in children with sickle cell disease. Researchers found that only two-thirds of children had stable outcomes between ages two and four years. The authors suggest that cerebrovascular complications are an important factor influencing developmental delays.

Sickle cell disease and COVID-19 in pregnant women

This study analysed the severity of COVID-19 infection in pregnant women with sickle cell disease and looked at the results of 82 women who were infected between March 2020 – February 2021. The study found that COVID-19 had typical presentation and rarely triggered a sickle cell crisis or other complications. Fetal outcomes were good and did not seem to be directly influenced by COVID-19.

Voxelotor for haemolytic anaemia treatment gains positive opinion

The Medicines and Healthcare products Regulatory Agency in the United Kingdom has issued a positive opinion of the treatment voxelotor. The positive opinion means that patients living with sickle cell disease and meeting the eligibility criteria can gain early-pre-license access to voxelotor.

Microcytic Anaemia: An insidious presentation of sickle cell beta+ thalassemia, a rare sickle cell variant

Sickle cell disease variants can commonly present with life-threatening complications, however, the authors suggest that clinicians should also look for milder findings like asymptomatic chronic anaemia mimicking iron deficiency. In this report, they present a 75-year-old African American female, who was referred to the haematology clinic with chronic anaemia. Despite having no history of vaso occlusive crisis, she was subsequently diagnosed with sickle cell beta plus thalassemia.

2.6 Thalassemia

Extramedullary haematopoiesis in patients with transfusion dependent β-thalassaemia

Beta-thalassaemia occurs due to a deficient production of the beta-globin chain of haemoglobin, with one of the complications being extramedullary haematopoiesis (EMH), or the production of blood cells outside the marrow. Researchers reviewed case reports and studies related to EMH to determine its prevalence and found that although cases were more common in non-transfusion dependent thalassaemia, reported cases suggested a higher prevalence of EMH in transfusion dependent beta-thalassemia than previously thought.

Differences in longitudinal growth patterns of children and adolescents with transfusion-dependent haemoglobin E/β-thalassemia and those achieving successful haematopoietic stem-cell transplantation

Short stature is very common among children with transfusion-dependent thalassemia. This study aimed to identify and compare the growth patterns of children with transfusion-dependent haemoglobin E (Hb E)/β-thalassemia against those of children successfully undergoing Haematopoietic stem-cell transplantation (HSCT). The mean weight and height of transfusion-dependent patients decreased gradually and were lowest at age 13, while post-HSCT subjects saw significant improvement in their mean weight and height after receiving treatment.

A randomised double-blind placebo-controlled clinical trial of oral hydroxyurea for transfusion-dependent β-thalassaemia

This study examines the effect of a repurposed drug, hydroxyurea, on patients with transfusion dependent β-thalassaemia. Hydroxyurea is currently used for sickle cell patients, allowing them to produce the foetal form of haemoglobin. β-thalassaemia patients have low levels of normal haemoglobin so require regular transfusion. This study found that 44% of patients responded to hydroxyurea treatment, increasing the amount of foetal haemoglobin in their red blood cells and lowering the transfusion volume required to treat anaemia.

Use of Deferasirox film-coated tablets in paediatric patients with transfusion dependent Thalassemia

Patients with severe forms Thalassemia require regular blood transfusions, as well as treatment to improve the level of iron in the blood (chelation). Deferasirox is a film-coated tablet designed as an iron chelation therapy. The study aimed to assess the efficacy and safety of Deferasirox in pediatric patients. The study confirmed that treatment was safe for older children but resulted in adverse events in younger patients. Deferasirox maintained a stable iron load but required use of relatively higher doses to affect chelation.

Long-term efficacy and safety of the oral pyruvate kinase activator mitapivat in adults with non—transfusion-dependent alpha- or beta-thalassemia

Thalassemia is caused by the imbalanced production and precipitation of haemoglobin in red blood cells. This leads to a deficit in cellular energy stores. Mitapivat, a drug currently undergoing trials may help red blood cells produce more energy and improve longevity. Researchers noted that a favorable efficacy-safety profile was observed with long-term use of Mitapivat in trial participants with thalassemia. They also noted that Mitapivat, through its unique mechanism of action, may represent a novel therapeutic approach for this condition.

Comparison of the effects of calcium channel blockers plus iron chelation therapy versus chelation therapy only on iron overload in children and young adults with transfusion-dependent thalassemia

Myocardial iron deposition is a significant cause of morbidity and mortality in patients with transfusion-dependent thalassemia (TDT). This study investigated the whether the channel blocker Amlodipine combined with regular chelation therapy may reduce myocardial iron overload. It found that Amlodipine is safe, and when combined with chelation therapy appears to be more effective in reducing cardiac iron overload than chelation only in children and young adults with TDT.

Iron overload status in patients with non-transfusion-dependent thalassemia in China

This study, aimed at investigating the prevalence and severity of iron overload in Chinese non-transfusion dependent thalassemia patients, looked at 178 patients who attended the Guangxi Medical University in China from January 2017 to May 2019. Researchers found that the most critical risk factor for iron overload was patient age, with data showing a trend toward a significant increasing prevalence of iron overload in older age categories.

2.7 CAR-T therapy

Carvykti cell therapy approved by FDA for multiple myeloma

The US FDA has approved a new blood cancer treatment for use in multiple myeloma. The drug ‘Carvykti’ (ciltacabtagene autoleucel) is a CAR-T therapy built from patients' immune cells. The therapy is currently undergoing review by the Medical Services Advisory Committee in Australia.

Immunocore claims first-ever FDA approval for TCR cancer therapy

The FDA has provided the first cancer therapeutic based on T cell receptor technology. The approved therapy Kimmtrak has been approved for the treatment for the treatment of unresectable or metastatic uveal melanoma.

FDA grants orphan drug designation to CAR T-cell therapy for advanced ALL

The FDA has granted orphan drug designation to CNCT19, a chimeric antigen receptor T-cell therapy for the treatment of relapsed or refractory acute lymphoblastic leukemia. CNCT19 is an autologous, gene-edited CAR T-cell therapy that targets the CD19 protein on the surface of cancer cells.

FDA grants orphan drug designation to CAR T-cell therapy for gastric cancer

The FDA has granted orphan drug designation to CTB001, an investigational chimeric antigen receptor T-cell therapy for treatment of gastric cancers. CTB001 is an autologous, gene-edited CAR T-cell therapy that targets the claudin18.2 protein on the surface of cancer cells.

2.8 Immune system and immunotherapy

Intravenous immunoglobulin nonresponse in paediatric patients treated for Kawasaki disease at a US hospital

Kawasaki disease most often affects children under five and is typically treated by intravenous immunoglobulin and aspirin. This study investigated why certain children admitted to a US academic hospital between 2010-2019, did not respond to treatment with intravenous immunoglobulin. They found that patients who received ibuprofen were more likely to be non-responsive while aspirin dosing varied but was not predictive of non-response.

Prediction of fetal blood group antigens from maternal plasma using Ion AmpliSeq HD technology

Fetal blood group and platelet antigens may trigger maternal immunisation, causing a fetal disease. Noninvasive prenatal diagnostics (NIPT) predicts fetal genotype, identifying pregnancies with no risk. All current techniques detect fetal antigen alleles with unspecific background and without estimation of fetal fraction, thus new protocols for detection of fetal BG/HPA alleles with ultrahigh sensitivity still need to be tested to improve NIPT.

Breast milk contains red cell isohaemagglutinins: An observational study of 176 mothers

Maternal antibodies are transferred to child through breast milk. These antibodies help developing the immune response in children. This study of 176 mothers found that Anti-A, anti-B and allo-antibodies to red cell antigens are consistently present in breast milk, supporting previous findings on a larger scale.

The safety and efficacy of intravenous immunoglobulin in autoimmune encephalitis

This single-arm, open-label study assessed the efficacy and safety of 10% intravenous IVIG treatment in newly diagnosed patients with possible autoimmune encephalitis. Researchers performed a prospective clinical trial of IVIG for functional recovery in autoimmune encephalitis. They found that IVIG improved neurological functional outcomes evident by day eight of the trial while adverse effects were tolerable.

3 Transfusion

This section includes published research and industry publications on transfusion procedures to improve patient outcomes and reduced wastage of blood products.

3.1 Paediatrics

Effect of washed versus unwashed red blood cells on transfusion-related immune responses in preterm newborns

This trial compared the effect of transfusion with washed compared and unwashed packed red blood cells on pro-inflammatory cytokines and endothelial activation in preterm newborns born before 29 weeks' gestation. Researchers found that the post-transfusion increase in cytokines did not change between the first and third transfusions in the newborns receiving unwashed packed red blood cells but decreased in newborns receiving washed packed red blood cells. Researchers concluded that the pro-inflammatory immune response to transfusion in preterm infants can be modified when packed red blood cells are washed prior to transfusion.

Red blood cell transfusions can increase mortality rates of newborns on ECMO, study finds

Researchers have suggested that newborns in respiratory failure who require extracorporeal membrane oxygenation (ECMO) and transfusion of red blood cells are at risk when higher volumes of red blood cells are administered. A study has indicated that the higher volume of red blood cells the newborns receive, the higher their mortality rate. This study expands on previous research findings released in Transfusion in February 2020.

Relationship between allergic transfusion reactions and allergic predisposition among paediatric patients with haematological/oncological disease

This study looked at the occurrence of allergic transfusion reactions (ATR) in 363 paediatric patients to investigate any correlation to a patient's allergic predisposition. Researchers found that the allergic constitution of patients, as determined by IgE levels, may predict the onset of ATRs.

3.2 Administration

Transfusion of non-red blood cell blood products does not reduce survival following cardiac surgery

This study built on previous research that showed cardiac surgery patients who receive perioperative packed red blood cell transfusions had increased associated mortality. The authors investigated if there was an association between non-packed red blood cell blood product transfusions and increased mortality. The authors found that cardiac surgery patients requiring blood products alone, without packed red blood cell transfusion, had similar postoperative and long-term survival compared to patients not requiring blood products.

The international experience of bacterial screen testing of platelet components with automated microbial detection systems: An update

Bacterial contamination of platelet components represents one of the highest risks for transfusion-transmitted bacterial infection, which may cause septic transfusion reactions in patients. The study reviewed automated culture protocols employed by national blood services in the United Kingdom, Australia, Canada and large blood collection organisations and hospital transfusion services in the United States. The authors found that despite every effort, bacterial contamination and risk of septic transfusion reactions remains. Although significant risk reduction was achieved in most cases, the authors surmise that zero-risk transfusion is unattainable with current technologies.

Impact of platelet transfusion on outcomes in trauma patients

Trauma-induced coagulopathy includes thrombocytopenia and platelet dysfunction that impacts patient outcomes. This observational study was carried out on a multicentre prospective trauma registry. Platelet count at admission, although mainly in normal range, was associated with trauma severity and coagulopathy and was predictive of bleeding intensity and outcome. Early platelet transfusion within 6 hours was associated with a decrease in mortality in patients with severe haemorrhage.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy: Impact of platelet transfusion on pulmonary function of haematology oncology patients

Intravenous immunoglobulins are an established treatment for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Biomarkers for disease activity are lacking, making the need for ongoing treatment difficult to assess, leading to potential overtreatment, and high health care costs. Researchers aimed to determine whether withdrawing intravenous immunoglobulin treatment would result in worse outcomes, to determine how often patients are overtreated. Results were inconclusive, but researchers suggested that a considerable proportion of patients could stop treatment and almost all patients who relapsed in the trial were re-stabilised quickly.

Reported transfusion-related acute lung injury associated with solvent/detergent plasma

Antibody-mediated transfusion-related acute lung injury (TRALI) is caused by donor leukocyte antibodies or human neutrophil antigens in plasma-containing products. In the Netherlands 55,000 units of solvent/detergent plasma (SDP), a pooled plasma product, are transfused yearly. It is produced by combining plasma from hundreds of donors, a product which the authors of this report suggest has led to some practitioners considering the product to be safe from TRALI exposure. The authors refute this and provide evidence that TRALI can occur with the use of SDP.

Transfusion double whammy? Adrenaline-takotsubo-anaphylaxis-Kounis (ATAK) complex post transfusion?

Researchers in New Zealand investigated three cases of adrenaline-takotsubo-anaphylaxis-Kounis (ATAK) complex, a recently described complex where that has symptoms of both takotsubo cardiomyopathy and Kounis syndrome. Three cases were reported to the New Zealand Blood Service haemovigilance programme that appeared to have features in common suggestive of the ATAK complex. All three patients had a blood component transfused, an initial severe allergic reaction, treatment with adrenaline and heart failure or circulatory overload. The researchers suggest that transfusion-related severe allergic reactions may quickly develop into transfusion-associated circulatory overload in some patients.

Changes in the incidence of transfusion reactions in haematological patients over the past 30 years

Patients with haematological diseases are often immunocompromised and susceptible to transfusion reactions. This study aimed to document the incidence of transfusion reaction in adult haematological patients over a 26-year period in a large academic hospital in Croatia to assess the effects of changes in the production of blood components and transfusion practice.

The incidence, degree, and timing of hypocalcemia from massive transfusion

This study aimed to quantify the incidence, degree, and timing of hypocalcemia during the first 24 hours after initiation of a massive transfusion. Researchers hypothesised that hypocalcemia is prevalent during acute resuscitation (first six hours) despite efforts of the treatment team to replete calcium during active resuscitation. Data from 52 massive transfusions were analyzed with 97% of patients found to be hypocalcemic during the first six hours of resuscitation.

Personalised surgical transfusion risk prediction using machine learning to guide preoperative type and screen orders

This study suggested that a machine learning model incorporating both surgery- and patient-specific variables could outperform the traditional approach that uses only procedure-specific information, allowing for more efficient allocation of preoperative type and screen orders. Researchers used patient records to train four machine learning models to predict the likelihood of red cell transfusion using surgery-specific and patient-specific variables and compared these models to a baseline model using procedure-specific information.

Plasma isoagglutinin depletion for blood group independent plasma transfusion

The anti-A and anti-B antibodies contained in plasma limit the use of plasma in emergency situations, as ABO blood group matching is needed. Researchers have report that they have developed a method for anti-A and anti-B depletion by adsorbing plasma isoagglutinins using red blood cells. The authors state that this process may allow for blood group independent plasma transfusion.

A review of electronic medical records and safe transfusion practice for guideline development

This narrative review looks at current clinical guidance, benefits and risks of electronic systems for clinical transfusion practice, combining this with feedback from experienced transfusion practitioners in Australia and New Zealand. It suggests that there is an opportunity to improve the safety, quality and efficiency of transfusion practice by incorporating transfusion practice into electronic medical records. The study did note that poorly designed processes within the electronic systems and the critically important electronic–human process interfaces may increase risk of data leakage.

Donor-recipient sex is associated with transfusion-related outcomes in critically ill patients

This study investigated the association between the sex of donors and recipients and post-transfusion mortality and morbidity in critically ill patients who received red blood cell transfusions from either male only donors or female only donors. The authors found that transfusion of female red blood cells to male recipients increases the risk of intensive care unit mortality compared to female blood to female recipients. They also found that receiving red blood cells from female donors was associated with a trend towards acute respiratory distress syndrome.

Allogeneic blood transfusions and infection risk in lumbar spine surgery: An American College of Surgeons National Surgery Quality Improvement Program Study

Researchers investigated whether perioperative transfusions were associated with postoperative infections and any other adverse events following common elective lumbar spinal surgery procedures. They determined there was an association between transfusion and infection in lumbar spine surgery with sepsis being the most likely infection type. The researchers note that minimising perioperative transfusions, may lead to reduced infections following lumbar spine surgery.

Transfusion avoidance in severely anaemic total hip and total knee arthroplasty patients

Researchers evaluated the influence of restricting transfusions in adults with osteoarthritis undergoing total hip or knee arthroplasty with severe postoperative anaemia to determine the effect of transfusion related complications. They found that restricting transfusions in younger, healthier anaemic patients was not associated with increased adverse outcomes in the cohort of 1,087 total joint arthroplasty patients. It was suggested that younger, healthier patients may not need to undergo transfusion if the indication is based solely on low haemoglobin levels.

3.3 Management

CMV screening of group-specific orders—good stewardship of the blood supply

This United States study evaluated the number of blood units sent from a distribution centre that were out of group to fulfill cytomegalovirus-seronegative requests. Approximately 36% cytomegalovirus-seronegative antigen orders requested were for B-positive patients, but more than half of these orders were filled with O red blood cells. To decrease group O usage for nongroup O patients, there was an increase cytomegalovirus testing for group B donors, as a result there was a 17.37% decrease group O usage for group B patients.

Comparison of the programmed freezer method and deep freezer method in the manufacturing of frozen red blood cell products

Researchers looked at the impact of freezing methods on frozen-thawed red blood cells with the aim of determining which method reduces the occurrence of haemolysis after thawing due to the freeze/thaw process. Red blood cells were frozen using either a programmed freezer method or a deep freezer method. After 4–8 weeks, the frozen red blood cells were thawed and washed so that in vitro characteristics could be compared. The researchers found that the programmed freezer method was more suitable for red blood cell freezing than the deep freezer method in terms of haemoglobin recovery, with a 4%–5%, improvement in the haemoglobin recovery rate.

Tangential flow filtration facilitated washing of human red blood cells: A proof-of-concept study

In this study the researchers examined a novel method of washing stored single red blood cell units to remove accumulated cellular waste using tangential flow filtration driven by a centrifugal pump. Researchers found that compared with traditional cell washing procedures, tangential flow filtration was able to remove extracellular haemoglobin more efficiently but resulted in longer wash times.

Doctors warn against unnecessary blood transfusions in Australian hospitals as donations decline

The work of the National Blood Authority has been highlighted by the ABC. The article, published in ABC Science, discusses how blood products are being used in Australian medical practice with a focus on the impact of the NBA's patient management guidelines on blood usage.

Modelling haemoglobin incremental loss on chronic red blood cell transfusions

This article discusses a model to help clinicians optimise chronic transfusion intervals to minimise transfusion frequency and improve patient outcomes.

The use of low volume RBC units for transfusion

A case study from a trauma centre in the United States looked at ways to improve the administration of O-type blood to limit the risk of group O unit availability. The researchers found that by transfusing low volume red blood cells, they were able to enhance their group O inventory and make available these low volume RBCs to patients in need of emergency transfusions.

Administration of blood products in the prehospital setting can decrease trauma patient mortality

This study consisted of two randomised controlled trials to determine if providing up to two units of plasma in the prehospital setting resulted in better patient outcomes. They found a significant reduction in 30-day mortality for those who received plasma transfusion compared to those who did not. The strongest evidence indicated a benefit for plasma transfusion among severely injured patients with a transport time greater than 20 minutes.

How we manage blood product support and coagulation in the adult patient requiring extracorporeal membrane oxygenation

Researchers looked at the management protocols for transfusion support and anticoagulation in adult patients requiring extracorporeal membrane oxygenation (ECMO, or life support) in the United States. They found a lack of robust evidence to guide optimal anticoagulation and transfusion strategies in the critically ill patient population but suggest that emerging evidence may support more restrictive transfusion protocols, noting that more rigorous studies were needed.

Survey of blood centre readiness regarding removal of DEHP from blood bag sets

European regulations state that the chemical Di(2-ethylhexyl) phthalate (DEHP) must be removed from blood bag sets in Europe by 27 May 2025. Researchers surveyed Blood centres in Europe, Asia and North America and found that there were concerns with meeting the sunset date for DEHP, considering that limited non-DEHP blood bag and RBC storage solutions are currently available.

Analysis of the variable factors affecting changes in the blood concentration of cyclosporine before and after transfusion of red blood cell concentrate

The blood concentration of cyclosporine is often elevated following the transfusion of red blood cell concentrate to patients after allogeneic haematopoietic stem cell transplantation. The aim of this study was to identify the factors affecting changes in the blood concentration of cyclosporine before and after transfusion.

The timing of gamma irradiation and its effect on cell-free and microvesicle-bound haemoglobin

Gamma irradiation of red cell concentrates is used to prevent transfusion-associated graft-versus-host disease in at-risk patients. This study looked at four separate pools of seven leukoreduced red cell concentrates. Units from each set were subject to irradiation at six different points during storage, with one unit serving as a nonirradiated control. All testing was performed immediately following unit expiry on day 43. The study found that the earlier in storage cycle that units were irradiated, the higher the haemolysis and the lower the proportion of microvesicle-bound haemoglobin.

Unusual non-platelet predominant clumping in a haematopoietic progenitor cell apheresis collection bag

A case of clumping has been reported in a blood collection after the collection process, but before the blood was able to be stored. Collection was performed on a 61-year-old man with multiple myeloma using the Spectra Optia system with peripheral intravenous access. The authors state that no platelet clumping or alarms occurred during the collection, which lasted for 329 minutes at room temperature. At procedure completion, the return pressure alarm sounded and after reinfusion, large aggregates suddenly accumulated in the product bag.

Residual risks of bacterial contamination for pathogen-reduced platelet components

This review looked at the residual risks of transfusion-transmitted bacterial infections by platelet transfusion after pathogen inactivation. The relationship between bacterial load in the platelet component and the timing and capacity of reduction of various pathogen inactivation technologies was analysed, as well as the risks from spore-forming microorganisms and the possible introduction of microorganisms after inactivation.

3.4 Research

Antibodies against biotin-labeled red blood cells can shorten post-transfusion survival

The study investigates the causes and consequences of biotin-labeled red blood cell immunisation. Researchers re-exposed three previously immunised adults to biotin-labeled red blood cells which caused an anamnestic increase of plasma biotin-labeled red blood cell antibodies at 5–7 days. Researchers concluded that re-exposure of immunised subjects to biotin-labeled red blood cells can induce anamnestic antibody response that can cause an underestimation of red cell survival.

International Society of Blood Transfusion survey of experiences of blood banks and transfusion services during the COVID-19 pandemic

A survey was distributed to International Society of Blood Transfusion members in 95 countries to determine the impacts of COVID-19 on the blood supply, collection and use, transfusion demands and operational challenges. Decreases in blood donations occurred in 70.6% of collecting facilities and operational challenges included loss of staff, increased workloads and delays in reagent supplies with almost half of the respondents' agencies modifying their disaster plans during the pandemic.

Development and validation of a safe transfusion training assessment tool

Researchers developed a safe transfusion assessment tool (STAT) at the University of California. A total of 20 core competencies in transfusion medicine were identified and learning objectives and assessment items pertinent to each competency were created. The tool was administered to 100 participants of varying training levels and specialty which demonstrated the ability of the STAT to assess essential knowledge in transfusion medicine relevant to trainees and clinicians in multiple programs and practice settings.

Efficacy of packed red blood cell transfusions based on weight versus formula in thalassemic children: An open-label randomised control trial

This Indian study aimed to compare the efficacy of packed red blood cells transfusions of different volumes calculated either by weight or by a formula using weight, pretransfusion haemoglobin of patient and proportion of packed red blood cells. Sixty patients aged 3–9 years were enrolled and randomly allocated to two groups. Researchers found the number of donor exposures and annual pure red cell requirement was significantly lower in the formula-based group.

The importance of intravenous immunoglobulin treatment in critically ill patients with necrotising soft tissue infection: a retrospective cohort study

Necrotising soft-tissue infections can often prove fatal and the use of immunoglobulins within a combination therapy including broad-spectrum antibiotics has been debated. The study assessed the potential benefits of immunoglobulins in treatment for infections but no clear evidence for a benefit of immunoglobulins with consistent antibiotic use was found. Patients receiving immunoglobulins appeared more severely ill. The authors suggest that immunoglobulins should be administered on a case-to-case basis, while more evidence from larger randomised controlled trials is obtained.

Increased prevalence of transfusion-transmitted diseases among people with tattoos: A systematic review and meta-analysis

This Korean study sought to identify the prevalence and risk of transfusion-transmitted diseases in people with tattoos compared with the non-tattooed population. Researchers found that tattoos were associated with an increased prevalence of transfusion-transmitted diseases.

Tangential flow filtration (TFF) facilitated washing of human red blood cells: A proof-of-concept study

This study investigated the proof-of-concept use of TFF for washing single RBC units with an emphasis on the removal of cell-free haemoglobin from the unit. Compared with traditional cell washing procedures, the designed system was able to remove extracellular haemoglobin more efficiently but resulted in longer wash times.

Ex vivo enzymatic treatment converts blood type A donor lungs into universal blood type lungs

A major challenge in lung transplantation is the need for ABO blood group matching. Researchers used two enzymes, FpGalNAc deacetylase and FpGalactosaminidase, to convert blood group A lungs to blood group O lungs during an ex vivo lung perfusion. Researchers demonstrated that they could successfully remove blood group A antigen with no overt changes in lung health. In an ex vivo simulation of transplantation, the authors showed reduced antibody and complement deposition, suggesting that this technique may reduce antibody-mediated injury.

4 Gene therapies

This section includes industry updates and research on the progress of gene therapies though regulatory bodies as well as gene therapy safety.

4.1 Blood related gene therapies

Haemophilia A patients in Roctavian trial largely bleed-free at two years

Researchers are reporting that more than 80% of the men with severe haemophilia A treated with the investigational gene therapy Roctavian (valoctocogene roxaparvovec) in a Phase 3 GENEr8-1 trial remained bleed-free two years later.

Haemophilia B Patients Given EtranaDez Gene Therapy in Trial Stop Prophylaxis

Researchers have reported that nearly all men with moderate-to-severe haemophilia B given the experimental gene therapy EtranaDez (etranacogene dezaparvovec) in a HOPE-B trial have stopped using prophylactic therapies.

EtranaDez, potential haemophilia B gene therapy, under EMA review

The European Medicines Agency (EMA) has agreed to review a request by CSL Behring to approve its gene therapy EtranaDez for people with haemophilia B. CSL Behring lodged a request for marketing authorisation application which will be reviewed under as an accelerated assessment.

4.2 Regulatory and industry developments

Novartis and Voyager Therapeutics agree on gene therapy deal worth $1.7bn

Novartis has confirmed a license option agreement with Voyager Therapeutics. Voyager will receive an initial $54m to license its new class of adeno-associated virus (AAV) capsids to Novartis for use on three central nervous system targets, along with an option to include two more targets.

5 COVID-19

This section contains news articles, peer reviewed papers and industry publications on the changing COVID-19 pandemic and management of the virus across the world including effects on blood and related services.

5.1 COVID-19 effect on blood, blood diseases and related services

Once viewed as a promising COVID-19 treatment, convalescent plasma falls out of favor

This report from the Journal of the American Medical Association looks at the current state of convalescent plasma treatment for COVID-19 infection. The report highlights the importance of the guidance provided to the medical community from the World Health Organization (WHO), the US FDA and the Infectious Diseases Society of America (IDSA) that suggested limiting the use of convalescent plasma and the subsequent reduction in demand for the treatment.

Passive transfer of COVID-19 antibodies with platelet transfusions

Researchers evaluated platelet units and platelet recipients for COVID-19 antibodies with the aim of identifying the presence of COVID-19 spike protein immunoglobulin G antibodies in transfusion recipient's blood after platelet transfusion. Twenty-three patients received platelets with COVID-19 spike protein immunoglobulin G antibodies; 13 of which had of COVID-19 antibodies detected post transfusion while 10 recipients did not. The study demonstrated a significant rate of passive transfer of COVID-19 spike protein immunoglobulin G antibodies through platelet transfusions.

Real world, single centre experience of COVID-19 vaccination in immune thrombocytopaenia

This study reviewed the COVID-19 vaccination status of 211 patients who were under active follow-up for or treatment of immune thrombocytopaenia (ITP) at a single centre in the United Kingdom from 1 January 2021 to 31 August 2021. The study found that 17 of the 211 patients had an incidence of immune thrombocytopenia relapse following COVID-19 vaccination.

5.2 COVID-19 news

The Omicron subvariant BA.2 is now the dominant variant of COVID-19 worldwide, the distribution of antibody drugs designed to treat the primary Omicron variant has been curtailed in the United States as the effectiveness is limited. The Australian Technical Advisory Group on Immunisation (ATAGI) has advised that three doses of a COVID-19 vaccine are required to be 'up to date' and have recommended fourth vaccination doses for older people and people that are immunocompromised. The Therapeutic Goods Administration has provisionally approved the Moderna COVID-19 vaccine for children 6 years and older.

- WHO: BA.2 subvariant is dominant Omicron variant around the world
- Mandating booster vaccination for disability support workers
- Household Impacts of COVID-19 Survey, February 2022
- TGA approval of Moderna's COVID-19 vaccine for people 6 years and older
- Changes to fully vaccinated definition flagged

5.3 COVID-19 policies, and industry

Australia's biosecurity emergency pandemic measures to end

The Australian government has announced that following medical advice, the Biosecurity Emergency Determination relating to COVID-19 for Australia will not be renewed when it lapses on 17 April 2022. The determination gave the Australian government emergency powers to enact policies to deal with the COVID-19 pandemic.

TGA advice for consumers on purchasing COVID-19 rapid antigen tests

The Therapeutic Goods Administration (TGA) is urging Australians to only purchase COVID-19 rapid antigen tests (RATs) that are approved for use in Australia to avoid the risk of poor test performance that could arise from using unapproved, repackaged, or repurposed RATs.

FDA postpones advisory committee meeting to discuss request for authorisation of Pfizer-BioNTech COVID-19 vaccine for children 6 months through 4 years of age

The US FDA delayed approval of COVID-19 vaccinations for children under five. The FDA said that based on a preliminary assessment, they needed to allow more time to evaluate additional data and information regarding whether the potential for a third dose should be considered as part of the decision-making process.

ATAGI statement on defining 'up-to-date' status for COVID-19 vaccination

The Australian Technical Advisory Group on Immunisation (ATAGI) has advised that three doses of a COVID-19 vaccine are required to be up to date to provide protection against both infection and severe disease. ATAGI emphasised the importance of being up to date with immunisation particularly for people at higher risk of severe disease, such as older people and/or those with underlying special risk medical conditions, and those who work in settings where limiting disease transmission is critical.

Red Cross introduces COVID vaccination policy

The Australian Red Cross introduced a mandatory vaccination policy for all staff members and volunteers. The organisation, which runs Lifeblood, requires all of employees and volunteers to have two doses vaccine doses by 31 March 2022.

ATAGI recommendations for use of Pfizer COVID-19 vaccine as a booster dose in adolescents aged 16-17 years

The Australian Technical Advisory Group on Immunisation (ATAGI) has recommended booster vaccination with the Pfizer COVID-19 vaccine, for all adolescents aged 16-17 years who have previously received any TGA approved or recognised vaccines. ATAGI recommends that the booster be administered 3 months after receiving the last primary dose.

5.4 COVID-19 research and treatment

Effect of sotrovimab on hospitalisation or death among high-risk patients with mild to moderate COVID-19: A randomised clinical trial

Researchers conducted a randomised trial to determine whether the neutralising antibody sotrovimab administered to patients with mild to moderate COVD-19 symptoms prevents the progression to severe symptoms. Among non-hospitalised patients with mild to moderate COVID-19 and at risk of disease progression, a single intravenous dose of sotrovimab, compared with placebo, significantly reduced the risk of a composite end point of all-cause hospitalisation or death.

The COVID Heart—One year after COVID-19 infection, patients have an array of increased cardiovascular risks

A comprehensive analysis of the cardiovascular outcomes among patients in the US Veterans Health Administration (VHA) system has been published in *Nature Medicine*. The study found that patients who had contracted COVID-19 were at increased risk of a broad range of cardiovascular disorders including cerebrovascular disorders, dysrhythmias, ischemic and non–ischemic heart disease, pericarditis, myocarditis, heart failure, and thromboembolic disease.

Secondary attack rates for Omicron and Delta variants of COVID-19 in Norwegian households

This study used individual-level registry data from the Norwegian emergency preparedness register to determine the secondary infection rate amongst Norwegian households from 1 December 2021 to 8 January 2022. The study found that the secondary attack rate of COVID-19 in Norwegian households was moderately higher when cases were identified as the Omicron variant rather than the Delta variant.

COVID-19 and dengue virus co-infection: Epidemiology, pathogenesis, diagnosis, treatment, and management

A concerning occurrence in areas where dengue is endemic has been the co-infection of COVID-19 and dengue. COVID-19 cases have been on the rise in dengue-endemic regions posing a threat of a co-epidemic. This study investigated the risk of comorbidity in co-infection cases finding that it is greater than that of a single viral infection. The researchers noted that although the pathophysiologies of the two infections are different, the viruses have comparable effects within the body, resulting in identical clinical symptoms in the case of co-infection, which adds to the complexity and makes detection more difficult.

The usefulness of peripheral blood cell counts to distinguish COVID-19 from dengue during acute infection

This study aimed to identify differences between COVID-19 and dengue during the acute phase of infection, based on inexpensive blood count cell data. Researchers found that neutrophil, platelet, and leucocyte ratios were higher in patients with COVID-19 than in dengue patients and could differentiate between COVID-19 and dengue with reasonable accuracy.

Placental tissue destruction and insufficiency from COVID-19 causes stillbirth and neonatal death from Hypoxic-Ischemic injury

This study was designed to evaluate the role of the placenta in causing stillbirth and neonatal death following maternal infection with COVID-19 and confirmed placental positivity for COVID-19. Researchers found that the pathology abnormalities composing COVID-19 placentitis caused widespread and severe placental destruction resulting in placental blood loss and insufficiency.

Association of COVID-19 vaccination with symptomatic COVID-19 infection by time since vaccination and Delta variant predominance

This study found that among adults, the chance of symptomatic COVID-19 infection after COVID-19 vaccination (as an estimate of vaccine effectiveness) was higher during Delta variant predominance, suggesting lower protection.

Waning 2-Dose and 3-Dose effectiveness of mRNA vaccines against COVID-19 associated emergency department and urgent care encounters and hospitalisations among adults during periods of Delta and Omicron variant predominance

This study found that vaccine effectiveness against COVID-19–associated emergency department/urgent care (ED/UC) visits and hospitalisations was higher after the third dose than after the second dose, but waned with time since vaccination. For example, during the Omicron-predominant period, vaccine effectiveness against COVID-19 associated ED/UC visits and hospitalisations was up to 91% during the two months after a third dose and decreased to 78% by the fourth month after a third dose.

Durability of anti-spike antibodies in infants after maternal COVID-19 vaccination or natural infection

COVID-19 vaccination in pregnancy generates functional anti-spike (anti-S) IgG antibodies in maternal circulation that are detectable in umbilical cord blood at birth and can protect the newborn and infant from COVID-19. This study found that the majority of infants born to COVID-vaccinated mothers had persistent anti-S antibodies at 6 months, compared with children born to mothers that had a natural COVID-19 infection.

Long-term immune and inflammatory responses in individuals recovering from COVID-19 with and without post-acute symptoms

This study looked at patients recovering from COVID-19 to determine which factors most affect long-term health outcomes. They found that those requiring hospitalisation or intensive care during acute infection had higher levels of memory T helper cell responses during recovery. Whereas the higher percentage of COVID-19 specific T helper cell responses initially observed in hospitalised patients matched those in participants who were not hospitalised approximately 4 months following acute infection, T helper cell responses remained elevated in those who had required ICU level care. The study also found higher virus-specific cytotoxic T cell responses in the subset of participants with pre-existing lung diseases.

Myocarditis following a third Pfizer vaccination dose in military recruits in Israel

Researchers in Israel assessed whether a third vaccine dose with the Pfizer BioNTech is associated with the risk of myocarditis (inflammation of the heart muscle). During the booster vaccination rollout, over 120,000 Israeli Defence Force members were vaccinated with eight members, all young men, diagnosed with myocarditis resulting from vaccination. Cases were mild, without arrhythmia or signs of congestive heart failure and all cases remained without residual cardiac injury on hospital discharge.

Effect of antiplatelet therapy on survival and organ support–free days in critically ill patients with COVID

This study investigated the effect of antiplatelet therapy on 1557 critically ill adult patients with COVID-19 from 105 sites in eight different countries. Researchers found that treatment with an antiplatelet agent, compared with no antiplatelet agent, not likely to provide improvement in the number of organ support–free days within 21 days.

6 Other items of interest

This section contains general industry and regulator updates as well as developments in non-blood and non-COVID related diseases that may have flow on affects to the blood industry.

6.1 Government, industry and development news

COVID-19 disrupts health services in over 90% of countries

A survey conducted by the WHO found that disruptions in basic health services such as vaccination programs and treatment of diseases like AIDS were reported in 92% of 129 countries.

6.1.1 Australia

Australian Government Department of Health: Vital health support for flood-affected regions

The Australian Government will provide more than $35.9 million in funding to ensure the continuity of health services in flood affected areas of New South Wales and Queensland.

New malaria treatment gets first approval for use in children

The Therapeutic Good Administration has provided approval for the use of an anti-malaria treatment tafenoquine (Kozenis) in children from the age of two in Australia. Tafenoquine can cure a type of malaria caused by Plasmodium vivax, which is common in Southern Asia.

Stepwise access to safe plasma proteins in resource-constrained countries: Local production and pathways to fractionation

The International Society of Blood Transfusion (ISBT) Working Party for Global Blood Safety workshop in September 2021 has highlighted that patient access to plasma-derived medicinal proteins is still poor or absent in low- and middle-income countries due to the unavailability or unaffordability of the products.

Endometriosis clinics to be set up in every state and territory, pregnancy screening made free of charge

The Australian government has announced a $58 million investment over the next four years to set up specialist endometriosis clinics for treatment of the disorder. The government also announced that genetic testing will be made free for couples planning to have a child, under an $81 million program announced this week.

Landmark PBS listing for Australians with leukaemia

The Australian government has announced that Australians with acute myeloid leukaemia (AML) will have access to a new treatment option through the Pharmaceutical Benefits Scheme (PBS). Mylotarg (gemtuzumab ozogamicin) is being listed for the treatment of patients with previously untreated *de novo* CD33-positve AML, for use in combination with standard intensive chemotherapy.

New treatment for Australians with rare blood disease

Australians with paroxysmal nocturnal haemoglobinuria (PNH) will have access to a new treatment through the Pharmaceutical Benefits Scheme. Ultomiris (ravulizumab) will be listed for the first time for patients with PNH. Ultomiris protects the red blood cells from damage and destruction by blocking the body's inflammatory response.

Soliris (eculizumab) available on PBS from 1 March 2022

The Australian Government has announced that from 1 March 2022, eculizumab (Soliris) will be available under the Section 100 Highly Specialised Drugs (HSD) program of the Pharmaceutical Benefits Scheme. Until now, Soliris has been available under the Life Saving Drugs Program. The change applies to all existing patients with paroxysmal nocturnal haemoglobinuria (PNH).

Support for research to reduce pressure on emergency departments

The Australian Government will invest up to $24 million in research to improve acute care systems and reduce emergency department waiting times.

6.1.2 United States of America

CSL's plasma fight heats up as US customs defends ban

Blood products companies CSL Behring and Grifols are continuing to pursue a case against a ruling by the US Customs and Border Protection that stopped Mexican citizens from crossing the US-Mexico border to donate plasma. The companies lost their initial bid to have the ban overturned in December, but are appealing, with oral arguments scheduled for April 1.

Past asbestos testing on inmates could affect Johnson & Johnson talc lawsuits

Pharmaceutical company Johnson & Johnson are currently in the midst of a legal battle over the payment of liabilities relating to the sale of its talc related products. They have been implicated in a well-known historical medical misconduct case which involved the injection of asbestos fibers into the skin of American prisoners in Philadelphia.

Voluntary lot withdrawals of Immune Globulin Intravenous (IGIV) and Immune Globulin Subcutaneous (IGSC) for increased reports of allergic/hypersensitivity reactions

A voluntary recall has been issued for lots of Intravenous Immunoglobulin and Subcutaneous Immunoglobulin in the United States.

CSL share price surges 6.5pc on results, guidance beat

Pharmaceutical company CSL is almost doubling new plasma donor collection fees in areas of the US and offering free flu vaccines, as it tries to improve collection rates during the COVID-19 pandemic. As a result, plasma donations are up 18 per cent on the same period last year, but the biotech's earnings have been impacted as a result. CSL is also in the middle of a recruitment drive to find more employees for their US plasma facilities as competition for healthcare workers increase.

FDA sets out advice to developers of gene editing medicines

The US FDA has issued draft guidelines for the developers of gene products that incorporate gene editing with a focus on the importance of carefully assessing potential safety risks for animal and human participants in experimental treatments.

U.S. FDA clears Terumo Blood and Cell Technologies' new plasma collection technology

The FDA has approved the use of a new plasma collection system developed by Terumo Blood and Cell Technologies. The new collection system 'Rika' is designed to collect plasma faster and reduce the chance of operator error. CSL will start to use the system in its plasma centres in the United States this year.

6.1.3 The world

Early advice: Ontario Regional Blood Coordinating Network to remove cryoprecipitate from transfusion guidelines

The Ontario Regional Blood Coordinating Network has reported that they will remove the blood product cryoprecipitate from its inventory of components and from its upcoming transfusion handbook, *Bloody Easy 5*. The organisation confirmed that they will cease discussion of cryoprecipitate use as they believe it has been replaced with "safer, more accurately prescribed and purified product" such as Factor VIII, von Willebrand Factor and Fibrinogen Concentrate. The updated guidelines are yet to be published, but will replace the current version, Bloody Easy 4.

'Embarrassingly large' stocks of available UK blood products weren't used by Newcastle doctors, Infected Blood Inquiry hears

The United Kingdom Infected Blood Inquiry continues, with a former senior doctor from Newcastle's blood transfusion centre telling the inquiry that there were "embarrassingly large" stocks of NHS blood factor concentrate products to treat haemophiliacs available at the centre but the director preferred to use commercially-made products. Haemophiliacs treated at the centre were given Factor VIII contaminated with lethal viruses like HIV and Hepatitis C.

6.2 Other diseases and developments

6.2.1 Research

Mortality from congenital Zika syndrome — Nationwide cohort study in Brazil

A study into the on-going effects of infection with the Zika virus has found that prenatal exposure to Zika virus causes congenital anomalies, diseases of the nervous system, and infectious diseases. Recorded infant deaths in Brazil were more than 11 times higher among children born with congenital Zika syndrome than those without the syndrome.

Efficacy and safety of intravenous high-dose immunoglobulin in treatment of the severe form of Japanese encephalitis

This study explored the efficacy and safety of intravenous immunoglobulin in the treatment of severe Japanese encephalitis (JE). The study of 124 children diagnosed with the severe or very severe form of JE found that intravenous immunoglobulin showed good efficacy, safety, and tolerance for treatment of the severe form of JE.

Ebola virus can hide in brain, persist even years after treatment

Researchers have demonstrated how Ebola virus, which can persist in certain areas of the body, can re-emerge to cause fatal disease even long after treatment with monoclonal antibodies.

Mosquitoes are seeing red: Why new findings about their vision could help you hide from these disease vectors

Researchers at the University of Washington have found that common mosquito species fly towards specific colours, including red, orange, black and cyan after detecting a gas that humans exhale, while ignoring other colours, such as green, purple, blue and white.

Mosquitoes learn to avoid five common pesticides after a single non-lethal dose, study finds

Researchers have found most female mosquitoes who survived a dose of pesticide learned to avoid that chemical when they later encountered again. The results were consistent across five pesticides commonly used to control mosquitoes across the world.

6.2.2 Zika, Chikungunya and Kunjin

Trials for Zika and Chikunguya vaccines are under way, with positive results so far. Researchers found that children with congenital Zika syndrome were twice as likely to suffer from infectious and parasitic diseases, nervous system diseases, and congenital malformations.

- Congenital Zika syndrome is associated with higher risk of death
- Zika Virus Vaccine Shows Promising Results in Preclinical Studies
- Field-based patient trial for cell-free Zika testing delivers highly accurate results
- Chikungunya vaccine candidate safe and immunogenic in Phase III
- Mosquito-borne disease warning for the Kimberley region

6.2.3 Dengue

Cases of dengue infection continue to fluctuate with some areas reporting a plateau and others reporting a spike. In the Pacific, cases continue to rise particularly in Fiji and the Philippines. The increase in cases led to the US Centers for Disease Control and Prevention issuing an alert for people travelling to the Asia-Pacific region.

- Timor-Leste dengue outbreak tops 3,000 cases
- Sri Lanka sees rise in dengue, COVID-19 cases
- Dengue Alert for Eastern Asia and the Pacific Islands
- Malaysia records 26,365 dengue fever cases last year, lowest in 10 years
- More than 2,000 leptospirosis, dengue fever cases reported in Fiji
- 52 cases of Dengue in Delhi this year Civic body

6.2.4 Avian influenza outbreaks

The spread of avian flu in the world's bird population has resulted in mass culls of domestic livestock. The have outbreaks of the H5N1 variant in Europe, Africa, North America and Asia, with some governments offering compensation to farmers affect by the outbreak.

- Ghana: Govt Releases Gh₵20.1 million for compensation to poultry farmers
- Flu: Nigeria loses over 2m birds in 391 farms
- Cameroon reports outbreak of H5N1 bird flu
- Bird Flu That Can Infect Humans Found for First Time in Namibia
- France announces bird flu support fund for stricken poultry farmers
- 12 European states report avian flu in poultry
- Romania reports bird flu outbreak on farm near Bulgarian border
- Philippines confirms 8 new bird flu outbreaks in Luzon
- Nepal reports bird flu outbreak on poultry farm
- Avian flu alert raised in South Korea
- Avian flu detected in commercial flock in western Nova Scotia
- More avian flu in poultry in 6 states; Ontario farms also hit

6.2.5 Japanese Encephalitis

Japanese Encephalitis been found in 28 Australian piggeries, with 18 human infections recorded in the most recent outbreak. Australian Health authorities are monitoring the outbreak and the Australian government announced a $69 million package to help control spread of the virus. The Australian government has declared Japanese Encephalitis a communicable disease of National significance with cases confirmed in South Australia, New South Wales, Queensland and Victoria. Two deaths have been reported and Victoria has announced plans to vaccinate at risk people against the virus. A public health warning has been issued for an outbreak of Japanese Encephalitis in Eastern Australia. The virus was found in pig farms in Eastern Australia and is one of several mosquito-borne viruses that health authorities are warning may become more prevalent as a result of wet weather influenced by the La Nina pattern.

- $69 million for Japanese encephalitis virus (JEV) response
- Japanese encephalitis virus situation declared a Communicable Disease Incident of National Significance
- Japanese encephalitis: Victoria to vaccinate as outbreak spreads further
- Anti-mosquito measures mobilise to head off Japanese encephalitis threat

6.2.6 Other

- CDC issues travel notice for Nigeria due to Lassa fever outbreak
- Mauritania Crimean-Congo haemorrhagic fever update
- Record number of Lyme disease cases reported in 2021
- Measles outbreak adds to Afghanistan's humanitarian crisis
- Measles outbreak in Congo: 4600 cases, 123 deaths
- Extensively drug resistant Shigella sonnei infections
- Early treatment can decrease the severity and duration of leptospirosis