

Monitoring International Trends

posted March 2016

The NBA monitors international developments that may influence the management of blood and blood products in Australia. Our focus is on:

- Potential new product developments and applications;
- Global regulatory and blood practice trends;
- Events that may have an impact on global supply, demand and pricing, such as changes in company structure, capacity, organisation and ownership; and
- Other emerging risks that could potentially put financial or other pressures on the Australian sector.

A selection of recent matters of interest appears below. Highlights include:

- OPKO Health dosed the first patient in a Phase IIa study evaluating the safety of its long-acting factor VIIa in haemophilia patients. (Section 1)
- Baxter dosed the first patient in a Phase I clinical trial to evaluate safety and pharmacokinetics of BAX 826 for haemophilia A. BAX 826 is Baxalta's second longer half-life treatment based on Advate. (Section 1)
- BioMarin Pharmaceutical has enrolled the first patient in a Phase I/II trial for BMN 270, an investigational gene therapy for haemophilia A. (Section 1)
- In preclinical studies Pluristem's PLX-R18 has shown a 100 per cent recovery rate in animals exposed to radiation. (Section 1)
- Baxter has filed its haemophilia A therapy Adynovi with regulators in Europe. Adynovi is its extended circulating half-life recombinant Factor VIII. The trade name under which it sought US approval was Adynovate. (Section 2)
- Swedish Orphan Biovitrum (SOBI) and Biogen received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommending that marketing authorisation be granted for Alprolix® (rFIXFc), a longer-acting recombinant factor IX Fc fusion protein therapy. (Section 2)
- The US Food and Drug Administration (FDA) approved CSL Behring's Idelvion (coagulation Factor IX [recombinant], albumin fusion protein; albutrepenonacog alfa). The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended approval of albutrepenonacog alfa in February. (Section 2)
- CSL Behring announced an increase in the global supply of Privigen as the first export was shipped from its new manufacturing facility in Broadmeadows. (Section 3)
- Grifols announced plans to invest another €77m in its biologics plant at Grange Castle in County Dublin. It is bringing forward plans for the construction of a purification plant for albumin to meet rising demand. (Section 3)
- Potentially tainted heparin from China has again been found, this time in France. (Section 4)
- The European Parliament's agriculture and rural development committee has backed proposed measures to prevent and stop outbreaks of animal diseases, including avian flu and African swine fever. (Section 4)
- A Canadian study suggested that transfusion with fresh red blood cells prepared by whole blood filtration increased risk for in-hospital mortality. The researchers suggested that further study was needed of the potential effect of whole blood processing methods on patient outcomes. (Section 5)
- Research has suggested that in cases of bleeding of the upper gastrointestinal tract blood transfusions should be considered with caution. (Section 5)

- Experience in Afghanistan with the “Cold Storage Platelets” program suggests it may help immensely when treating patients suffering from severe trauma with extensive blood loss. (Section 5)
- A new study claims that concentrations of iron similar to those delivered in standard treatments such as tablets and infusions may trigger DNA damage within ten minutes. (Section 5)
- Research has found significant differences between the blood clot structure in adults and newborns, helping researchers better understand the challenges in addressing post-operative bleeding in neonatal patients. (Section 5)
- Viagra is being trialled to see if it can reduce the number of emergency caesareans, reduce stillbirths and prevent babies suffering oxygen starvation. (Section 5)
- Biomimetic calcium phosphate apatites to improve the freeze-drying and rehydration of red blood cells. (Section 6)
- Researchers reported that there is drop-to-drop variation in blood component measures from finger prick blood that is greater than variation in drops of venous blood. (Section 6)
- In a world first medical trial, children with cerebral palsy will be infused with umbilical cord blood to test whether the stem cells can repair brain injury. (Section 6)
- In the US, an International Trade Commission judge has ruled that Novo Nordisk infringed a Baxter International patent that is part of a larger investigation into whether Baxter can block allegedly infringing imports of the Danish company's haemophilia drug into the US. (Section 7)
- The World Health Organization (WHO) announced in early March that local transmission of Zika had been reported in 31 countries across Latin America and the Caribbean. It said sexual transmission of the Zika virus was more common than previously thought. WHO estimates at least 15 companies and academic groups are researching vaccines against Zika. (Section 7)
- Advisers to WHO recommended changing two of the three strains for the trivalent flu vaccines for the Northern Hemisphere's 2016-17 season. After consideration of the latest circulating zoonotic flu viruses, the advisers also recommended that two new candidate vaccine viruses be prepared: one against H5N6 avian flu and one against variant A(H1N1). (Section 7)
- By 10 March, 708 human cases of avian influenza A(H7N9) had been reported by the Chinese mainland health authorities since 2013, with 752 globally. (Section 7)
- By 15 March Saudi Arabia had recorded 1347 laboratory confirmed cases of MERS-CoV infection, including 571 deaths. (Section 7)
- Researchers from the US National Institutes of Health reported they had successfully tested, in rabbits, a human monoclonal antibody as prophylaxis against MERS.
- A new treatment for Ebola has protected macaques from the virus several days after the animals were infected. (Section 7)
- Researchers have found that the bacterium that causes Lyme disease protects itself from antibiotics by forming a slime-like layer (biofilm). (Section 7)

Table of Contents

1. Products	3
Haemophilia	3
Other	4
2. Regulatory	6
3. Market structure and company news	7

4. Country-specific events	8
5. Safety and patient blood management	9
Appropriate Transfusion	10
Treating anaemia	11
Other	12
6. Research	13
7. Legal matters	16
8. Infectious diseases	17
Zika Virus	17
Other mosquito-borne diseases	18
Influenza: strains, spread, prevention and treatment	18
MERS-CoV (Middle East Respiratory Syndrome-Coronavirus)	19
Ebola virus disease	19
Other diseases: occurrence, prevention and treatment	20

1. Products

Here the NBA follows the progress in research and clinical trials that may within a reasonable timeframe make new products available, or may lead to new uses or changes in use for existing products.

Haemophilia

- a) OPKO Health dosed the first patient in a phase IIa study evaluating the safety of its long-acting factor VIIa in haemophilia patients. The phase IIa study is a dose escalation study to determine safety and explore efficacy endpoints in patients with OPKO's long-acting version of coagulation factor VIIa (Factor VIIa-CTP¹) for the treatment of bleeding episodes in haemophilia A or B patients with inhibitors to factor VIII or factor IX. The study is enrolling 24 patients in the US. Phillip Frost, chairman and chief executive officer of OPKO said: "Later this year, we expect to initiate a second phase IIa trial for Factor VIIa-CTP in a subcutaneous formulation that, if successful, could provide prophylactic therapy to prevent bleeding episodes and thereby change the treatment paradigm for patients with haemophilia."² Factor VIIa-CTP has orphan drug designation³ in both the US and Europe.

¹ Factor VIIa-CTP is a novel, long-acting recombinant Factor VIIa utilizing OPKO's proprietary technology to extend its circulatory half-life without the use of polymers, encapsulation techniques, or nanoparticles. The technology is based on a naturally occurring peptide, the C-terminal peptide (CTP) of the beta chain of human chorionic gonadotropin. The CTP technology is also used in OPKO's hGH-CTP, its long-acting recombinant human growth hormone product which is being evaluated in phase III clinical trials for adults and phase II trials for children with growth hormone deficiencies. OPKO recently announced a global agreement with Pfizer for the development and commercialisation of hGH-CTP.

² Currently, Factor VIIa therapy is available only as an intravenous (IV) formulation which, due to Factor VIIa's short half-life, requires multiple infusions to treat a bleeding episode in haemophilia A or

- b) Baxter dosed the first patient in a Phase 1 clinical trial to evaluate safety and pharmacokinetics of BAX 826 for haemophilia A. Using proprietary polysialic acid (PSA) technology to extend circulating half-life, BAX 826 is under investigation as Baxalta's second ⁴ longer half-life treatment based on Advate [Antihemophilic Factor (Recombinant)]. The open-label, dose-finding study looks to enrol 30 patients in three dosing cohorts. Baxalta expects to complete enrolment by the end of 2016. John Orloff, head of Research and Development and chief scientific officer, said. "Baxalta is dedicated to advancing innovative research on the principle of direct factor replacement, a proven treatment model, to support as many patients as possible." The company is also interested in gene therapy.
- c) BioMarin Pharmaceutical has enrolled the first patient in a Phase I/II trial for BMN 270, an investigational gene therapy for the treatment of patients with haemophilia A⁵. BMN 270 is designed to restore factor VIII plasma concentrations. The gene therapy program was originally licensed from University College London and St. Jude Children's Research Hospital in February 2013 and has since been developed at BioMarin's facilities. The FDA has awarded the gene therapy orphan drug status.

Other

- d) The European Medicines Agency (EMA) granted orphan drug designation to True North Therapeutics' TNT009 for the treatment of autoimmune haemolytic anaemia including Cold Agglutinin Disease, in which autoantibodies target and destroy red blood cells, causing anaemia, fatigue and potentially fatal thrombosis. Nancy Stagliano, CEO of True North, said: "We recently initiated a phase Ib clinical study evaluating TNT009 in patients with Cold Agglutinin Disease and look forward to reporting top-line data later this year."
- e) A Phase III study has demonstrated that Aranesp (darbepoetin alfa) reduces red blood cell transfusions in patients with myelodysplastic syndrome.
- f) Arch Therapeutics has begun patient enrolment in its first clinical trial in Europe evaluating its AC5 Surgical Haemostatic Device for the control of bleeding. The randomized single-blind study will evaluate the safety and efficacy of AC5 in up to 45 patients undergoing a dermatological procedure. Ten of the patients will be on antiplatelet therapy at the time. Each patient will have two skin lesions surgically removed. One of the wounds will be treated with AC5 and the other with the control. The primary endpoint is time till bleeding has stopped. The company says the product stops bleeding in as little as ten seconds. It is transparent, conforms to

B patients with inhibitors. Also, frequent infusions are onerous when used as prophylactic therapy, especially for children.

³ Orphan drug designation in the EU is awarded to potential treatments for life-threatening or chronically debilitating rare diseases affecting fewer than five in 10,000 individuals in the Union. Products receiving orphan drug designation are eligible to receive market exclusivity for a period of up to ten years, as well as development incentives such as regulatory and protocol assistance and scientific advice.

⁴ Adynovate [Antihemophilic Factor (Recombinant), PEGylated] was approved in the US for on demand and prophylaxis treatment in adolescent and adult patients (12 years and older) with haemophilia A and is under regulatory review in Japan, Canada and Switzerland.

⁵ This dose escalation study will evaluate the safety and efficacy of BMN 270 gene therapy in up to 12 patients with severe haemophilia A. The primary endpoints are to assess the safety of a single intravenous administration of a recombinant AAV, human-coagulation factor VIII vector and to determine the change from baseline of factor VIII expression level at 16 weeks after infusion. The kinetics, duration and magnitude of AAV-mediated Factor VIII activity in individuals with haemophilia A will be determined and correlated to an appropriate BMN 270 dose. Secondary endpoints include assessing the impact of BMN 270 on the frequency of Factor VIII replacement therapy, the number of bleeding episodes requiring treatment and any potential immune responses. Patients will be monitored for safety for five years.

irregular wound geometry and is not sticky or glue-like, making it ideal for laparoscopic procedures.

- g) Rigel Pharmaceuticals initiated a Phase II clinical trial to evaluate fostamatinib, its oral spleen tyrosine kinase (SYK) inhibitor, as a potential treatment for autoimmune haemolytic anaemia (AIHA). In this blood disorder the immune system produces antibodies that result in the destruction of the body's own red blood cells. Symptoms can include fatigue, shortness of breath, rapid heartbeat, jaundice or enlarged spleen. Doctors currently treat acute and chronic cases with corticosteroids, other immuno-suppressants, or splenectomy.
- h) In preclinical studies Pluristem's PLX-R18 has shown a 100 per cent recovery rate in animals exposed to radiation. Within 48 hours of injecting PLX-R18, bone marrow blood cell production returned to normal. "We saw that injecting the placenta cells enabled nearly 100 per cent of the population to recover, compared to 30 per cent of the group that did not receive the injections," stated Yaky Yanay, President and COO of Pluristem Therapeutics in a recent *Jerusalem Post* article. The US National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) is initiating studies in large animals to determine the proper dosage for PLX-R18. Once the dose is established, NIAID will move into the pivotal and final trial for full FDA approval of PLX-R18 for use in humans. US approval could come quickly for PLX-R18, with no need for Phase I, II, or III trials in humans. This is because the US Food and Drug Administration (FDA) can't require that humans be exposed to harmful levels of radiation for the purpose of a clinical trial. Cases like this fall under the FDA's established Animal Rule, whereby the treatment is tested in large animals. These studies are being paid for by the NIH, not Pluristem. Stockpiling PLX-R18 would be the most likely move by the US government following FDA approval. Pluristem's ability to deliver doses from its factory in Israel positions PLX-R18 to compete with Amgen's cancer drug Neupogen⁶. The FDA has already cleared PLX-R18 to be used in humans for a different indication. Pluristem is about to enter a Phase I trial for PLX-R18 in humans for the treatment of hematopoietic recovery following bone marrow transplants, an indication to treat the side effects of radiation and chemotherapy.
- i) Achillion Pharmaceuticals, has started a phase I study on its first orally administered small molecule complement factor D inhibitor, ACH-4471⁷. The company says that ACH-4471 has the potential to be developed as the first orally-bio-available, highly differentiated treatment of paroxysmal nocturnal haemoglobinuria and other ultra-rare diseases.
- j) NuvOx Pharma of Tucson will conduct a trial of its investigational new drug, NVX-508 for vaso-occlusive crisis and acute chest syndrome in sickle cell disease, after receiving approval from the FDA to do so. NuvOx also has received an "orphan drug" designation from the FDA for its NVX-508 for the sickle-cell complications. Orphan-drug status, which applies to drugs to treat relatively rare diseases, provides sponsors with special development and commercial incentives and a seven-year period of market exclusivity after marketing approval.

⁶ First approved in 1991, Neupogen boosts white blood cell production to fight infections in cancer patients going through chemo and radiation therapy. It has since been approved for other cancer-related indications. Similar to Pluristem's FDA approval track, Neupogen was tested for Acute Radiation Syndrome in large animals, was approved under the Animal Rule, and was developed in collaboration with NIAID.

⁷ The randomized, placebo-controlled, single-ascending dose study is being conducted in healthy volunteers to evaluate single ascending doses of ACH-4471 in order to assess its safety, tolerability, pharmacokinetics and pharmacodynamics. Additionally, a second phase I study evaluating multiple-ascending doses of ACH-4471 in healthy volunteers is expected to commence in the second quarter of 2016. Interim data should be out in the third quarter of 2016.

2. Regulatory

The NBA monitors overseas regulatory decisions on products, processes or procedures which are or may be of relevance to its responsibilities.

- a) Baxalta submitted a supplemental Biologics License Applications to the US Food and Drug Administration (FDA) seeking approval for the use of Adynovate [Antihemophilic Factor (Recombinant), PEGylated] to treat children under the age of 12 with haemophilia A⁸ and for use in surgical settings⁹. Adynovate is an extended circulating half-life recombinant Factor VIII (rFVIII) treatment for haemophilia A based on Advate [Antihemophilic Factor (Recombinant)]¹⁰. Adynovate was approved by the FDA in November 2015 for use in adolescent and adult haemophilia A patients (12 years and older) for prophylaxis to reduce the frequency of bleeding episodes and for on-demand treatment and control of bleeding. Adynovate has a twice-weekly dosing schedule.”
- b) Baxter has filed its haemophilia A therapy Adynovi (known as Adynovate in the US) with regulators in Europe for approval for paediatric, adolescent and adult patients for treatment, prophylaxis and use during surgery.
- c) Swedish Orphan Biovitrum (SOBI) and Biogen received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommending that marketing authorisation be granted for Alprolix® (rFIXFc), a recombinant factor IX Fc fusion protein therapy for the treatment of hemophilia B. Alprolix offers prolonged protection against bleeding episodes with prophylactic dosing intervals.
- d) The FDA approved CSL Behring’s Idelvion (coagulation Factor IX [recombinant], albumin fusion protein; albutrepenonacog alfa), for use in children and adults with haemophilia B¹¹. Idelvion is the first coagulation factor-albumin fusion protein product to be approved by the FDA, and the second Factor IX fusion protein product

⁸ The submission of Adynovate to treat children under the age of 12 was based on results of a phase III trial assessing the efficacy and safety including immunogenicity of Adynovate, which was initially reported in December 2015. Results from the study showed Adynovate met its primary endpoint and no patients developed inhibitors to Adynovate. Also, no treatment-related serious adverse events were reported. 72.7 per cent of patients had no joint bleeds while on treatment with Adynovate (n=66) and 37.9 percent experienced zero bleeds. The median overall annualized bleeding rate (ABR) among patient participants treated with Adynovate was 2.0 (range 0-49.8; mean ABR 3.0), which was comparable to the rates seen in the adult study.

⁹ The submission for use in surgical settings was supported by the positive results of a phase III study evaluating the efficacy and safety of Adynovate for the perioperative control of haemostasis among 15 patients with severe haemophilia A undergoing surgical procedures, which was reported in December 2015. The study data demonstrated that Adynovate achieved haemostasis control in the perioperative period (from start of the procedure until discharge or day 14) for patients with severe haemophilia A.

¹⁰ Adynovate is built on the full-length Advate molecule, in clinical use for over 12 years. Through collaboration with Nektar Therapeutics, Adynovate leverages proprietary PEGylation technology designed to extend the amount of fVIII available for use in the body. This maintains the integrity of the parent molecule (Advate) and extends circulating half-life.

¹¹ The safety and efficacy of Idelvion were evaluated in two multicentre trials, which included a total of 90 adult and paediatric patients with haemophilia B between one and 61 years of age. Idelvion proved itself effective in controlling bleeding episodes and in managing perioperative bleeding. Idelvion used prophylactically significantly decreased the number of spontaneous bleeding episodes annually despite less frequent infusions of Idelvion. The most common side effect observed for Idelvion was headache.

approved in the USA that has an extended life¹². The first was eptinenonacog alfa (Alprolix from Sobi/ Biogen)¹³.

- e) Green Cross Biotherapeutics announced that Health Canada had approved its application to proceed with a multi-centre Phase III clinical trial for Immune Globulin Intravenous (Human) 10% GC5107 (IVIG 10%) intended for the treatment of individuals with primary humoral immunodeficiency (PID).

3. Market structure and company news

The NBA's business intelligence follows company profitability, business forecasts, capital raisings or returns, mergers and takeovers, arrangements for joint research and/or development, contracts for supply of manufacturing inputs, and marketing agreements. Companies considered include suppliers, potential suppliers and developers of products which may be of interest.

- a) CSL Behring announced an increase in the global supply of Privigen as the first export has been shipped from its new manufacturing facility in Broadmeadows. The Turner Privigen Facility¹⁴ has substantially increased CSL Behring's total immunoglobulin (Ig) therapy production capabilities.
- b) CSL says it will more than double the number of its scientists at the University of Melbourne to create a global research hub in Australia.
- c) Swedish Orphan Biovitrum (Sobi) announced its results for the fourth quarter and full year 2015. Revenues for the full year increased 24 per cent compared with the previous year. Revenues for the fourth quarter were 15 per cent higher year-on-year and the product revenues grew 21 per cent¹⁵.
- d) Cerus and the American Red Cross have signed a multiyear purchase agreement for the Intercept Blood System for platelets and plasma, which inactivates a broad spectrum of viruses, gram-positive and gram-negative bacteria, spirochetes, parasites and leukocytes and is intended to reduce the risk of transfusion-transmitted infection in platelet and plasma components. The American Red Cross is the largest supplier of blood products in the US.
- e) Blood Centers of America has selected Cerus as its supply partner for pathogen reduction technology.
- f) Cerus has entered into an agreement with Puerto Rico's Banco de Sangre de Servicios regarding the Intercept Blood System for platelets and plasma to help protect the local blood supply during the Zika outbreak.
- g) The Octapharma Group published its 2015 annual results reporting a revenue increase of over 18 per cent compared with the 2014 figure. Chairman and Chief Executive of the Octapharma Group, Wolfgang Marguerre, said: "The year 2015 has been another record-breaking year for Octapharma in which we reached sales in excess of €1.5 billion with a pre-tax profit of €363 million. Being profitable means we can better serve patients globally by investing in the things that make a real difference; making our factories bigger, expanding our fleet of plasma centres, developing new products and exploring novel recombinant technologies." Octapharma owns production facilities in Austria, France, Germany, Mexico and Sweden.

¹² With Idelvion a 14-day dosing interval was achieved while maintaining high levels of factor activity, above 5 percent over 14 days at 75 IU/kg. This reduces the monthly number of units needed for prophylaxis therapy.

¹³ which fuses factor IX to the Fc portion of IgG subclass I.

¹⁴ named after Peter Turner, former President of CSL Behring and former Chief Operating Officer of the CSL group

¹⁵ Sobi's report for the fourth quarter and full year 2015 can be found on <http://www.sobi.com/Investors--Media/Reports/>.

- h) Grifols has announced plans to invest another €77m in its biologics plant at Grange Castle in County Dublin. It is bringing forward plans for the construction of a purification plant for albumin to meet rising demand. Construction will begin towards the end of this year, with the plant expected to be ready by early 2020.
- i) For the fourth quarter of 2015, Baxalta reported that in its haemophilia business, which represents nearly 60 per cent of overall sales, revenue slipped 2.4 per cent from a year earlier. The company attributed the decline to adverse exchange rates, which dented international sales. Adjusted for currencies, haematology revenue rose 6 per cent, Baxalta said.
- j) Baxter is continuing to unload its shares in Baxalta.
- k) Dilaforette AB, a Karolinska Development portfolio company focused on innovative treatments for patients with sickle-cell disease, and Arabian Gulf University, based in Bahrain, have signed a clinical collaboration agreement for the Phase II proof of concept trial of Dilaforette's sevuparin in patients with sickle cell disease experiencing acute vaso-occlusive crisis. Sevuparin is a proprietary polysaccharide drug, which has the potential to restore blood flow and prevent further microvascular obstructions caused by abnormal blood cells. With its anti-adhesive properties, sevuparin could thereby offer treatment of the underlying cause of vaso-occlusive crisis, with earlier pain relief, shorter hospital stay, reduced need of opioids and improved quality of life.
- l) RNAi biotech Alnylam Pharmaceuticals is planning to spend \$US 200 million on a manufacturing plant it expects to open by 2018.
- m) Arsia Therapeutics announced collaboration with Biogen to focus on providing meaningful treatment administration improvements for haemophilia patients by enabling subcutaneous versions of treatments that are currently administered via intravenous infusion.
- n) Kedrion Biopharma Inc. announced it has gained exclusive rights to commercialize another immunoglobulin (IG) brand—BIVIGAM, a 10 per cent liquid licensed by Biotest. Kedrion Biopharma Inc. is the US subsidiary of Kedrion Biopharma, headquartered in Italy. This brings the total number of immunoglobulin therapies in the Kedrion Biopharma portfolio to four.

4. Country-specific events

The NBA is interested in relevant safety issues which arise in particular countries, and also instances of good practice. We monitor health issues in countries from which Australia's visitors and immigrants come.

- a) Potentially tainted heparin from China has again been found, this time in France. According to a recent report filed by the EMA, an inspection of Dongying Tiandong Pharmaceutical in Dongying City, Shandong Province, by French regulators uncovered data suggesting the drug maker has manipulated tests of crude heparin supplies that had showed the presence of ruminant DNA. It said that there was no evidence that the samples used to do retesting came from the same batches that showed the ruminant. The company was issued a statement of noncompliance by France, which also recommended that its EU GMP certificate be revoked and that EU members consider a recall of all of its products in their countries¹⁶
- b) The EMA launched on 7 March the PRiority MEdicines (PRIME) scheme, designed to strengthen the agency's support of drugs that may offer new treatments or advantages over existing treatments. It offers enhanced early support to drug

¹⁶ When "ruminant" animals like cattle are used, there is a chance the raw material could be contaminated with bovine spongiform encephalopathy (BSE) or oversulphated chondroitin sulphate (OSCS), a cheap filler product that saves money but can be deadly to patients. In 2008, heparin contaminated with OSCS was tied to the deaths of 80 patients in the US.

developers to strengthen clinical trial designs to generate high-quality data for market authorization applications.

- c) The European Parliament's agriculture and rural development committee has backed proposed measures to prevent and stop outbreaks of animal diseases, including avian flu and African swine fever. "The draft EU law, on diseases that are transmissible among animals and potentially to humans too, will put more emphasis on prevention and help keep pace with scientific progress," noted a parliament communiqué.
- d) Venezuela has settled debts with at least three global drug companies by giving them bonds that trade at a heavy discount, a further sign of the OPEC nation's worsening financial crisis¹⁷. There are reports the country is not able to supply immunoglobulin for a significant number of patients with Guillaume-Barre syndrome, said to be following infections with the Zika virus.
- e) Researchers from Beijing Normal University have published *the Blue Book of Thalassemia in China*. The project was initiated by Beijing AngelMon Charity Foundation, a Chinese charity that offers financial help to thalassemia patients, along with the China Thalassemia Union and China Siyuan Foundation for Poverty Alleviation. China has an estimated 300,000 people with mild or severe thalassemia.
- f) Canada's Health Minister said she believes pay-for-plasma blood clinics, similar to a new clinic in Saskatoon, will ultimately help the country's health system fill the gap between supply and demand for plasma products. "Plasma products are necessary for a number of conditions, often severe and life threatening conditions," said Health Minister Jane Philpott in the House of Commons. "Unfortunately the supply does not meet the demand for these plasma products. So this is one facility that has opened up in Saskatchewan recently that actually compensates donors for their time." The Minister was responding after NDP health critic Don Davies called on Health Canada to shut down Canadian Plasma Resources in Saskatoon. The clinic opened its doors offering \$C 25 gift cards for every plasma donation.
- g) New Zealand doctors were reported by *New Zealand Radio News* to be angry with Bayer for withdrawing new-age anticoagulant Xarelto from the market after failing to secure a positive reimbursement decision from the government agency Pharmac. With three months' warning, it pulled the drug from 1,500 patients in December; Bayer had been providing the drug for free during more than three years of negotiations, a practice it said was unsustainable. "Imminent might have been the wrong word to use but when we set the programme up we certainly believed that funding was only a matter of a fairly short amount of time," Jan Twomey, Bayer's medical director for Australia and New Zealand, told the news service.
- h) The Hong Kong Red Cross Blood Transfusion Service (BTS) is said to have collected 261,000 units of blood during 2015, an increase of 2.8 per cent compared with the previous year. However, the number of first-time donors has continued to decline over the past three years.

5. Safety and patient blood management

We follow current issues in patient safety and achieving favourable patient outcomes.

¹⁷ Novartis AG , Bayer AG and Sanofi SA acquired dollar-denominated bonds from state-owned oil company PDVSA that they were reported to have resold for as little as a third of their face value. This contributed to some \$500 million in foreign exchange losses that the three companies suffered in Venezuela in 2015.

Appropriate Transfusion

- a) A retrospective registry cohort study conducted in Canada¹⁸ suggested that transfusion with fresh red blood cells prepared by whole blood filtration increased risk for in-hospital mortality. The researchers suggested that further study was needed of the potential effect of whole blood processing methods on patient outcomes. “The potential for harm with the transfusion of stored red blood cells has been an area of controversy for over 15 years,” wrote Nancy M. Heddle, professor of medicine and haematology at McMaster University in Hamilton, Ontario, and colleagues. “More than 50 observational studies have been reported, and several large randomized controlled trials on the effect of red blood cell storage on morbidity and mortality in transfused patients have been completed or are ongoing.” Heddle and colleagues evaluated 91,065 transfusions performed in 23,634 patients between 2008 and 2014¹⁹. They looked for an association between in-hospital mortality and duration of storage or red blood cell processing method (whole blood filtration vs. red cell filtration²⁰). Heddle and colleagues acknowledged study limitations, including the potential for confounding factors inherent in retrospective analyses, and recommended a controlled trial be considered: “To our knowledge, this is the first study to link product quality and demographic, clinical and outcome data from recipients in a large cohort of transfused adults, and to show an association between fresh whole blood filtered red cells and increased in-hospital mortality,” Heddle and colleagues wrote. “The feasibility of undertaking a randomized controlled trial to address this issue needs further discussion; nevertheless, the potential effect of whole blood processing methods on patient outcomes is worthy of further investigation, since adverse outcomes could be reduced by minor changes to blood processing methods and inventory management policies.”
- b) John Olynyk, one of the authors of a three-year study and Fiona Stanley Hospital’s head of gastroenterology, said bleeding of the upper gastrointestinal tract is one of the most common reasons for attending a hospital emergency department, accounting for about 1100 presentations in Western Australia each year. The research suggested blood transfusions should be considered with caution. They found patients with a haemoglobin level exceeding 90 grams per litre on admission were 10 times more likely to experience further bleeding if they received an early transfusion of red blood cells. They also found the more cells such patients received, the greater their risk of further bleeding and associated complications, including death. Professor Olynyk said: “Unless a patient has major UGIT bleeding, red blood cells, platelets and plasma should not be given as a matter of course,” he said.
- c) Maisie Jackson, of the University of Pennsylvania, and colleagues sought to investigate if institutions within the Pennsylvania and New Jersey region have a protocol in place to encourage appropriate adherence to restrictive transfusion guidelines. They surveyed blood bank supervisors at 83 hospitals. The researchers received responses from 48 hospitals: 93 per cent of respondents had an institutional policy encouraging transfusion at the restrictive threshold. Dr Jackson noted: “two hospitals had no policy whatsoever. It’s a low number, but nonetheless alarming.” Of those institutions with a transfusion policy, nearly all indicated institutional use of at least one behavioural intervention, although the methods of intervention varied

¹⁸ Heddle, N M et al., “Fresh Red Blood Cells May Be Associated with Mortality Depending on How They Are Processed Before Transfusion”, *Lancet Haematology* 2016; online March 4, 2016

¹⁹ They used data from three hospitals in Hamilton, Ontario, and used data from Canadian Blood Services to link information on each red blood cell unit to recipient data.

²⁰ “In the red cell filtration method ... after collection of a whole blood donation, the whole blood unit is stored for 20 hours at room temperature and then processed into a red blood cell unit, a unit of plasma, and a buffy coat platelet concentrate,” Heddle and colleagues wrote. “The red blood cell is then filtered at room temperature to remove white blood cells ... Conversely, the whole blood filtration method does not yield a platelet concentrate.”

greatly. At almost two-thirds of institutions, ordering physicians were required to include a rationale for the transfusion at the time it was ordered, while others had an internal transfusion review panel to discuss appropriate use of a blood product or employed routine phone calls to clinicians when orders did not fit criteria. "There was an incredible amount of variability in behaviour interventions," Dr Jackson explained during a poster presentation at the New York State Society of Anesthesiologists 69th Post Graduate Assembly. "It has generally been agreed that behavioural interventions work, and we've found that they do, but we do not yet know which ones work better than others." Although only 56 per cent of institutions used two or more behavioural approaches, it is widely assumed that the use of multimodal approaches will prove most effective.

- d) A change in clinical procedures developed in Afghanistan is suggested to assist patients suffering from trauma. The "Cold Storage Platelets" program, which involves extracting the platelets from a donor's blood and storing it in a refrigerator for up to three days until it's needed, is a cutting-edge new process that medical officials say will help immensely when treating patients suffering from severe trauma with extensive blood loss, reported Capt. Jacquelyn Messenger, commander, 153rd Blood Support Detachment, a unit under the 3rd Multifunctional Medical Battalion. "This will be especially beneficial for battlefield injuries, because a lot of what we see today is acute trauma," said Messenger, who is also the Area Joint Blood Program officer for Afghanistan. "This process alters the structure of the platelets, causing activation which allows them to form the clot faster preventing additional blood loss."

Treating anaemia

- e) Anaemia is common in patients with chronic kidney disease and almost universal in patients who receive maintenance dialysis. Erythropoiesis-stimulating agents (ESAs) that boost blood cell production are often used to correct anaemia, but when some clinical trials revealed that routine use of ESAs could increase the risks of stroke, myocardial infarction (heart attack) and venous thromboembolic disease (blood clots), use of these medications in the US declined in conjunction with changes in the drugs' labelling to meet FDA requirements. The drug's use in the US also declined in response to changes in 2011 concerning how US Medicare pays for components of dialysis. As a result, levels of haemoglobin in patients receiving dialysis have decreased and the use of blood transfusions, which ESAs were intended to reduce, have increased. A new US study examines whether these recent changes in the use of anaemia drugs for patients on dialysis have contributed to changes in rates of death or cardiovascular events. The findings, which appear in the *Journal of the American Society of Nephrology (JASN)*²¹, indicate that these risks appear to be decreasing for patients on dialysis as well as for older adults who are not on dialysis.²²

²¹ Glenn Chertow et al., "Epoetin Alfa and Outcomes in Dialysis amid Regulatory and Payment Reform," appeared online at <http://jasn.asnjournals.org/> on February 25, 2016. doi: 10.1681/ASN.2015111232

²² Glenn Chertow (Stanford University School of Medicine) and his colleagues conducted a study of US patients who were on dialysis during the period 1 January, 2005 to 31 December, 2012. The analysis included approximately 250,000 patients receiving maintenance dialysis in each calendar year between 2005 and 2012. The researchers found that there were marked declines in ESA use and resulting haemoglobin concentrations, and a consequent increase in transfusions in patients starting in 2010 and continuing through 2012. They also observed decreasing death rates and rates of major cardiovascular events, starting at least in 2005. "While rates of death and cardiovascular events remain very high in the dialysis population, these rates have been declining over the past several years. Interestingly, we also saw favorable trends for most cardiovascular events in the much larger population of Medicare beneficiaries—mostly persons over 65—who were not on dialysis," said Dr. Chertow. "These secular trends make it difficult to know for sure whether the lower than expected

- f) A new study claims that concentrations of iron similar to those delivered in standard treatments such as tablets and infusions may trigger DNA damage within ten minutes²³. Researchers from Imperial College, London used human endothelial cells, which line blood vessels, and added a placebo or an iron solution of 10 micromolar (a similar concentration to that seen in the blood after taking an iron tablet). They found that within ten minutes, cells treated with the iron solution had activated DNA repair systems. These were still activated six hours later. Claire Shovlin from Imperial College said: "At the moment, each standard iron tablet contains almost 10 times the amount of iron men are recommended to eat each day and these dosages have not changed for more than 50 years. This research suggests we may need to think more carefully about how much iron we give to people, and try and tailor the dose to the patient," she added.
- g) FibroGen announced the publication²⁴ of Phase II data showing roxadustat, an investigational oral agent for the treatment of anaemia in patients with chronic kidney disease, maintained haemoglobin levels among patients on haemodialysis previously treated with and switched from epoetin alfa—regardless of baseline iron repletion status, degree of inflammation (measured by C-reactive protein level), or prior iron regimen—over two time periods of six and 19 weeks. The global Phase III program for Roxadustat is currently under way.
- h) Kultigin Turkmen, associate professor of nephrology at Necmettin Erbakan University in Turkey, and colleagues reported²⁵ that the platelet/lymphocyte ratio, a marker of inflammation, may predict which end-stage renal disease (ESRD) patients with anaemia will be resistant to treatment with erythropoiesis-stimulating agents (ESAs).

Other

- i) A new study²⁶ finds significant differences between the blood clot structure in adults and newborns, helping researchers better understand the challenges in addressing post-operative bleeding in neonatal patients²⁷. The researchers also found that the current standard of care for treating post-operative bleeding may pose an increased risk of thrombosis in newborns compared with adults²⁸.

rates of stroke and heart failure that we observed in the dialysis population in 2012 were due to decreasing use of ESAs, other health-related factors, or to improvements in clinical practice."

²³ The findings were published in the journal *PLOS ONE*.

²⁴ "Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis: A Phase 2, Randomized, 6-to 19-Week, Open-Label, Active-Comparator, Dose-Ranging, Safety and Exploratory Efficacy Study", in the *American Journal of Kidney Disease*.

²⁵ in *Therapeutic Apheresis and Dialysis*

²⁶ Ashley C. Brown, et al, "Fibrin Network Changes in Neonates after Cardiopulmonary Bypass", *Anesthesiology*, February 2016, doi:10.1097/ALN.0000000000001058 by researchers at North Carolina State University, the University of North Carolina at Chapel Hill, Emory University, Children's Healthcare of Atlanta and the Georgia Institute of Technology.

²⁷ They hypothesised that fibrinogen from neonates would form clots that are different from those formed by adult fibrinogen, and found that to be correct. They were, however, surprised to find that fibrinogen from adults did not integrate well with the fibrinogen in neonates, so the two types wouldn't stick to each other and form a clot. "We knew that neonates-infants less than one month old-are more likely than adults to suffer from severe bleeding after heart surgery, which poses a variety of health risks," says Ashley Brown, first author of the paper. "The current standard of care is to give neonatal patients blood products-such as a protein called fibrinogen-derived from adult blood.....But neonatal blood and adult blood aren't the same; many of the components involved in clotting in newborns have differing levels of activity, or effectiveness, compared to the same components in adults. Our goal was to better understand how clotting in neonates differs from that in adults, so that we can move closer to developing more effective treatment strategies for these infants."

²⁸ The study found that neonate fibrinogen formed less dense, more fragile clots than adult fibrinogen; and that a mixture of adult and neonate fibrinogen formed clots that were also fragile and less dense. Clots of neonate fibrinogen dissolve about twice as quickly as clots formed from adult fibrinogen, and

- j) A trial at the University of Queensland will test whether Viagra can reduce the number of emergency caesareans, reduce stillbirths and prevent babies suffering oxygen starvation, which can cause brain damage, epilepsy and other problems. Women in labour will be given up to three doses of the drug—one every eight hours—in an attempt to boost the supply of oxygen-rich blood to the womb²⁹.
- k) The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) has again expressed an opinion on DEHP³⁰ exposure from medical equipment. SCENIHR reviewed medical DEHP exposure in 2008 and again in 2014. New studies on DEHP activity and alternative plasticisers have now become available. Patients facing haemodialysis, massive blood transfusion, intravenous feeding, heart transplantation or coronary artery bypasses, are likely to have the highest exposures from DEHP in PVC, used for tubing and blood bags. These exposures may “significantly exceed” the tolerable daily intake (TDI), says the committee. People who undergo regular exposures, such as haemodialysis, will be at greater risk than those who undergo one-off operations. DEHP exposures for intensive care patients, well in excess of tolerable levels, have been noted by previous Belgian and US studies. The opinion says DEHP risks may be greatest for children and newborns because of their low body weights. Premature neonates in intensive care units and infants having heart/lung bypass operations are identified as a high-risk population group. The opinion makes the point that the benefit of medical devices must also be considered, and “the survival of premature infants often depends on the availability of the same medical devices that result in a relatively high DEHP exposure”. Whenever possible, it adds, material with low release potential should be used. “The potential for replacement of DEHP in these products should be considered against their efficiency in the treatment, as well as the toxicological profile and leaching properties of the alternative materials,” it says. “There is a strong need to develop and collect data on exposure of alternative materials in the actual conditions of use.” SCENIHR notes that the most recent studies suggest DEHP exposure levels of the general population are declining. Food is the largest source.

6. Research

A wide range of scientific research has some potential to affect the use of blood and blood products. However, research projects have time horizons which vary from “useful tomorrow” to “at least ten years away”. Likelihood of success of particular projects varies, and even research which achieves its desired scientific outcomes may not lead to scaled-up production, clinical trials, regulatory approval and market development.

- a) A project involving The University of Cambridge and the research and consultancy division of the Biopharma group (amongst others) has used biomimetic calcium phosphate apatites to improve the freeze-drying and rehydration of red blood cells.

that clots formed from an adult and neonate fibrinogen mixture in any proportion dissolved at approximately the same rate as adult-only clots. “This suggests that using adult fibrinogen in neonatal patients may pose an increased risk of embolism or other adverse thrombotic events,” says Nina Guzzetta, MD, corresponding author on the study. Brown said: We are investigating possible alternatives to help neonates form a better clot after major surgery without having to use adult fibrinogen. For example, we are investigating the use of synthetic platelet-like particles developed by our team to augment haemostasis—the biological process that stops bleeding—in blood samples collected from these patients.”

²⁹ Reported in the *Journal of Translational Medicine*, scientists behind the study said: ‘Viagra improves blood supply and potentially could reduce the risk of hypoxia (oxygen starvation).’

³⁰ Diethylhexyl phthalate

- b) Researchers reported in the *American Journal of Clinical Pathology*³¹ that there is drop-to-drop variation in blood component measures from finger prick blood that is greater than variation in drops of venous blood. "These data suggest caution when using measurements from a single drop of finger prick blood," they concluded.
- c) Researchers in the UK³² have questioned the effectiveness of platelet rich plasma injections in treating musculoskeletal soft tissue injuries³³. They noted that autologous platelet-rich plasma (PRP) is increasingly used to treat musculoskeletal soft tissue injuries, either on its own or as an adjunct to surgery, but did not recommend routine use as there is insufficient evidence of clinical efficacy. Instead, they said its use should be restricted to research settings; that patients receiving PRP should be made aware of the limited evidence of efficacy, so that they can make an informed decision about their care; and that clinicians should be aware of the concentration of PRP, and yield of bioactive proteins, produced by their selected preparation device.
- d) Scientists at Case Western Reserve University School of Medicine have identified a novel mechanism that could be used to protect the brain from damage due to stroke and a variety of neurodegenerative conditions, including sporadic Creutzfeldt-Jakob disease, Alzheimer's disease, and Parkinson's disease. They studied a by-product of haemoglobin called haemin that is released from red blood cells during stroke and is toxic to neurons, interested in how neurons may be protected from this haemin-induced toxicity³⁴.
- e) Also at Case Western Reserve University, researchers have developed a microfluidic platform integrated with a cell dimensioning algorithm for quantitative assessment of dynamic deformability and adhesion of red blood cells in controlled microphysiological flow. Accurate measurement of deformability and adhesion, which are key biophysical factors of vaso-occlusion in sickle cell disease, holds potential for evaluation of disease progression, offering insight into disease pathophysiology, and development of novel therapeutics³⁵.
- f) Melbourne researchers have pioneered a new approach to killing bacteria that has become resistant to antibiotics. Scientists at Monash University, the University of Melbourne and the Walter and Eliza Institute have used a locally developed experimental cancer drug to prevent antibiotic-resistant infections from spreading in the body³⁶.

³¹ Bond MM, Richards-Kortum RR. "Drop-to-Drop Variation in the Cellular Components of Fingerprick Blood: Implications for Point-of-Care Diagnostic Development". *Am J Clin Pathol*. 2016. doi:10.1309/AJCP1L7DKMPCHPEH.

³² David J Keene and Keith Willett from the Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, at the University of Oxford, and Joseph Alsousou from the Department of Molecular and Clinical Cancer Medicine, at the University of Liverpool

³³ BMJ 2016; 352 doi: <http://dx.doi.org/10.1136/bmj.i517> (Published 17 February 2016) Cited as: BMJ 2016;352:i517

³⁴ Ajai K. Tripathi, Neena Singh, " Prion Protein-Hemin Interaction Upregulates Hemoglobin Synthesis: Implications for Cerebral Hemorrhage and Sporadic Creutzfeldt-Jakob Disease", *The Journal of Alzheimer's Disease*, Volume 51, Number 1, Pages 107-121

³⁵ A report was published in *Technology*. Principal investigator Umut Gurkan.

³⁶ The drug effectively causes the body's immune cells or macrophages to commit suicide, and take out the infection before it has a chance to multiply. Usually macrophages consume and kill infectious bacteria (phagocytosis). Some bacteria like legionella, which is naturally resistant to some antibiotics, have evolved to take over the macrophage, and use it as a host where they breed. The bacteria then kills the immune cell, takes over other macrophages and the cycle continues until the body is fully infected. Lead researcher Dr Thomas Naderer, from the Monash University Biomedicine Discovery Institute, said that because the bacteria are difficult to kill with drugs once they have been consumed by the immune cell, "we decided to focus on the host cell, the macrophage, and see if there was a way to program it to commit suicide." Dr Naderer found that during the invasion, the legionella bacteria killed off a vital protein called MCL-1. This left a second protein, BCL-XL, keeping the host cell alive and enabling bacterial growth. When an experimental drug blocked this survival protein, it caused the macrophage and the bacteria to die. Dr Naderer said that anti-cancer drugs that induce

- g) TGV-Laboratories of New York said lab tests showed that its MV-4 drug candidate can break down the protective barriers of both enveloped and non-enveloped viruses, and can be developed into targeted synthetic antiviral drugs to treat the diseases³⁷. Victor and George Tetz said they were able to kill influenza viruses, HIV, herpes viruses, polio and adenoviruses in laboratory tests, and that they “are eager” to test their discovery against Zika, Ebola and avian flu.
- h) In a world first medical trial at the Royal Children's Hospital in Melbourne, children with cerebral palsy will be infused with umbilical cord blood. The hope is that stem cells from cord blood can repair brain injury that leads to cerebral palsy. The trial, led by the Murdoch Childrens Research Institute, has begun recruiting children with cerebral palsy whose families have chosen to store a sibling's cord blood at private banks. The two-year study will investigate any changes in motor skills in these children.
- i) Cleveland Clinic researchers have demonstrated³⁸ that gut microbes alter platelet function and risk of blood clot-related illnesses like heart attack and stroke³⁹.
- j) Canadian scientists have developed a formula to predict the refractive index of blood at different concentrations, temperatures and wavelengths. The formula, which they created, based on tests of a blood-mimicking phantom⁴⁰, paves the way for clinical tests of blood properties using a simple refractometer⁴¹.
- k) Scientists from the Universities of Sheffield and Warwick have found that using a block copolymer hydrogel, which forms a soft 3D network of nanometer-sized worms in water, prevents damage to red blood cells that have been frozen at low temperatures for long periods of time. The worm gel not only facilitates cryoprotection of red blood cells, but may also serve as a suitable matrix for tissue engineering⁴².
- l) Pune-based Serum Institute of India and US-based Mass Biologics of the University of Massachusetts Medical School have developed a fast-acting anti-rabies drug in a laboratory set-up. It is a first-of-its-kind human monoclonal antibody—identical to

cancer-cell suicide could be used to prevent bacterial infections, as they induce death only of infected cells, but leave uninfected immune cells alive. The team's research paper "Eliminating Legionella by inhibiting BCL-XL to induce macrophage apoptosis" was published in *Nature Microbiology*.

³⁷The company says MV-4 possesses a unique broad-spectrum antiviral mechanism of action that can break down the protective phospholipids and glycoproteins of enveloped viruses and outer capsid proteins of nonenveloped viruses—an important characteristic because, in general, nonenveloped viruses are more stable and less sensitive to existing medications and survive much longer in the environment

³⁸ See *Cell's* March 10, 2016 online edition and March 24 print edition. Lead author Lerner Research Institute and section head of Preventive Cardiology & Rehabilitation in the Miller Family Heart & Vascular Institute at Cleveland Clinic.

³⁹ When choline (found in animal products like meat and egg yolk) is ingested, gut microbes play a role in breaking it down and producing the compound Trimethylamine *N*-oxide (TMAO). High blood levels of TMAO are said to be associated with heightened risk of heart attacks and strokes in humans, even after adjusting for traditional cardiac risk factors, renal function, markers of inflammation, medication use, and cardiovascular disease status. The researchers found that TMAO directly alters platelet function, increasing thrombosis potential.

⁴⁰ Mohammed Yahya and Ziad Saghir, of Ryerson University in Toronto, have attempted to make refractive index a viable metric for diagnosis with their new, phantom-derived formula. The phantom consisted of dry human haemoglobin dissolved in a saline solution. Using a refractometer, the researchers measured the phantom's refractivity at different concentrations, temperatures and wavelengths, before using the data to construct an empirical model of the refractive index. “Empirical modelling to predict the refractive index of human blood”, *Phys Med Biol*. 2016 Feb 21;61(4):1405-15. doi: 10.1088/0031-9155/61/4/1405. Epub 2016 Jan 25.

⁴¹ A relatively high refractive index – that is, a strong ability to bend transmitted light – indicates a good concentration of haemoglobin, whereas a low refractive index indicates a deficiency – anaemia.

⁴² Mitchell, D E, et al., “Combining Biomimetic Block Copolymer Worms with an Ice-Inhibiting Polymer for the Solvent-Free Cryopreservation of Red Blood Cells”, *Angewandte Chemie*, Volume 55, Issue 8. February 18, 2016 .Pages 2801–2804 DOI: 10.1002/anie.201511454

human immune cells. The drug, called Rabishield, is designed to provide immediate protection by instantly deactivating the rabies virus. The current line of treatment for rabies includes immediate vaccination and administration of the human rabies immunoglobulin.

- m) Researchers⁴³ reported⁴⁴ that bats have the unique ability to carry, but remain unaffected by, lethal diseases. Despite acting as a natural host for viruses, including Middle Eastern Respiratory Syndrome (MERS), Ebola and Hendra virus, bats do not appear to get sick. Researchers examined the genes and immune system of the Australian black flying fox. Dr Michelle Baker⁴⁵ said: “We focused on the innate immunity of bats, in particular the role of interferons—which are integral for innate immune responses in mammals....We have shown that bats only have three interferons, which is about a quarter of the number of interferons we find in people. This is surprising given bats have this unique ability to control viral infections that are lethal in people, and yet they can do this with a lower number of interferons. The team found that bats express a heightened innate immune response even when they were not infected with any detectable virus. Dr Baker said: “In other mammalian species, having the immune response constantly switched on is dangerous—for example, it’s toxic to tissue and cells.....If we can redirect other species’ immune responses to behave in a similar manner to that of bats, then the high death rate associated with diseases, such as Ebola, could be a thing of the past.”

7. Legal matters

The NBA is interested in the implications for Australia of any proceedings against companies, governments and professional practitioners in relation to blood and blood products; or of relevant public enquiries.

- a) In the US, an International Trade Commission judge has ruled that Novo Nordisk AS infringed a Baxter International Inc. patent that is part of a larger investigation into whether Baxter can block allegedly infringing imports of the Danish company's haemophilia drug into the US.
- b) In the US, a complaint filed on November 23rd, 2015 by a New Jersey resident against Xarelto manufacturers Bayer AG and Janssen Pharmaceuticals alleges adverse events⁴⁶ related to the drug, claiming Bayer and Janssen failed to adequately warn consumers about potentially severe health risks linked to the use of the anticoagulant⁴⁷.

⁴³ from CSIRO, Duke-NUS Medical School and the Burnet Institute.

⁴⁴ Peng Zhou et al., “Contraction of the type I IFN locus and unusual constitutive expression of IFN- α in bats” In *Proceedings of the National Academy of Sciences*, www.pnas.org/cgi/doi/10.1073/pnas.1518240113

⁴⁵ a bat immunologist at CSIRO’s Australian Animal Health Laboratory

⁴⁶ The plaintiff alleges that after only six months of taking Xarelto, he suddenly suffered from what physicians considered a life-threatening gastrointestinal bleed.

⁴⁷ The lawsuit is now listed under case number 2:15-cv-06264 in the US District Court for the Eastern District of Louisiana, where all federally-filed Xarelto lawsuits have been transferred by the US Judicial Panel on Multidistrict Litigation to form MDL No. 2592. More than 2,800 cases are being presided over by Judge Eldon Fallon. These 2,800 Xarelto lawsuits are not the only ones. In Philadelphia, another mass tort group has been formed of more than 550 lawsuits by the Court of Common Pleas. Plaintiffs reportedly claim that manufacturers showed reckless negligence by initially releasing the blood thinner to market for consumer use without any accompanying antidote for emergency bleeding situations.

8. Infectious diseases

The NBA takes an interest in infectious diseases because: the presence of disease in individual donors (e.g. influenza), or potential disease resulting from travel (e.g. malaria) means a donor must be deferred; temporary disease burden within a community (e.g. dengue in North Queensland) may limit blood collection in the community for a time; and some people may not be permitted to donate at all (e.g. people who lived in the UK for a period critical in the history of vCJD). Blood donations are tested for a number of diseases (e.g. HIV and Hepatitis B), but there are also emerging infectious diseases for which it may become necessary to test in the future (e.g. Chagas disease, and the tick-borne babesiosis and Lyme disease).

Zika Virus

- a) The World Health Organization (WHO) announced in early March that local transmission of Zika had been reported in 31 countries across Latin America and the Caribbean. It said sexual transmission of the Zika virus was more common than previously thought.
- b) The US Centers for Disease Control and Prevention (CDC) will hold a one-day summit in April with state and local officials ahead of Zika's expected in the USA as a locally-transmitted disease. The virus is already spreading locally in the US Virgin Islands, American Samoa and Puerto Rico.
- c) While a definitive study of the foetal effects of Zika virus has yet to be completed, the US Centers for Disease Control (CDC) reported⁴⁸ that up to 17 February five of nine pregnancies among US women who were infected abroad with the Zika virus resulted in tragic outcomes. Two women miscarried⁴⁹, two chose an abortion when ultrasounds revealed birth defects, and a fifth woman gave birth to a child with severe microcephaly⁵⁰. All five of these women contracted Zika in the first trimester of their pregnancy⁵¹.
- d) Latin American countries currently affected by Zika have been reporting a rise in cases of Guillain-Barré syndrome. The link is supported by data from French Polynesia in 2013 and 2014, when the number of cases of GBS jumped to around eight times the previous level during a Zika outbreak. An analysis of blood samples from 42 people who were diagnosed with GBS at a hospital in Tahiti found "forty-one people carried a type of antibody that suggested that they were recently infected with Zika," according to Arnaud Fontanet from the Pasteur Institute in Paris⁵².
- e) The CDC announced it had increased production of Zika diagnostics and would have one million polymerase chain reaction test kits available by early March. While PCR is the best test during early onset of symptoms, testing for antibody to the viruses is preferred after about a week of illness. CDC is also shipping antibody test materials to state laboratories.
- f) BioCryst Pharmaceuticals said on Monday a dose of its experimental antiviral drug improved survival rates in mice infected with the Zika virus⁵³. The study was conducted at Utah State University under an ongoing program run by the National Institute of Allergy and Infectious Diseases (NIAID), which is part of the US National Institutes of Health (NIH).

⁴⁸ 26 February, 2016, *Morbidity and Mortality Weekly Report*

⁴⁹ Genetic evidence of the Zika virus was detected in tissue specimens

⁵⁰ a condition in which the brain and skull are significantly underdeveloped.

⁵¹ An article in the *New England Journal of Medicine* reports on cases in Rio de Janeiro DOI: 10.1056/NEJMoa1602412

⁵² *The Lancet*, DOI: [10.1016/S0140-6736\(16\)00562-6](https://doi.org/10.1016/S0140-6736(16)00562-6)

⁵³ Two doses of the drug, BCX443, were tested against a placebo and an oral antiviral called ribavirin for their effect on survival of immune-deficient mice infected with Zika. Seven out of eight mice that received the "standard" dose survived but none of the other mice that received either a low dose, the placebo or ribavirin were alive after 28 days.

- g) WHO estimates at least 15 companies and academic groups are researching vaccines against Zika⁵⁴. On paper, developing a Zika vaccine should be easier than for some diseases, since the genetic code of the virus is more than 95 per cent the same across samples, in contrast to the huge variability seen, for example, in HIV. In the US, NIAID expects to begin phase I clinical studies of a vaccine candidate by the end of summer or early fall, which means scientists would likely be ready to determine by 2017 if that candidate is safe and produces a good response.
- h) In the US, the federal health department will ship blood products to Puerto Rico until researchers develop a blood screening test for Zika.
- i) A number of Zika cases have been identified in Queensland amongst returned travellers, and health authorities have been spraying to control mosquitoes in areas where the cases were located.

Other mosquito-borne diseases

- a) Sanofi Pasteur announced that vaccinations with Dengvaxia have commenced in the Philippines.
- b) Uruguay's Bat Conservation Program proposed the deployment of bats to kill the *Aedes aegypti* mosquito that carries the dengue virus.
- c) The FDA announced that genetically engineered mosquitoes that have been under regulatory review for the past five years have passed one of the last remaining hurdles to gain approval for release in a field trial. The agency's preliminary finding was that Oxitec's OX513A *Aedes aegypti* mosquito would pose no significant threat to the environment or to people in Key Haven, a community in the Florida Keys where the company proposed the trial. A 30-day window for public comments was allowed before the FDA's final decision.

Influenza: strains, spread, prevention and treatment

- a) Advisers to WHO recommended changing two of the three strains for the trivalent flu vaccines for the northern hemisphere's 2016-17 season. The recommendation swaps out the H3N2 A/Switzerland-like virus for influenza A/Hong Kong-like H3N2 and replaces the influenza B/Phuket-like virus with an influenza B/Brisbane-like virus. The influenza switch represents a lineage change, from Yamagata to Victoria. WHO said there are two newly emerging 2009 H1N1 subclades that continue to evolve, but viruses in them aren't antigenically distinguishable from the A/California-like vaccine strain. For quadrivalent vaccines that contain vaccine viruses against both influenza B lineages, the WHO team recommends an influenza B/Phuket-like virus for the Yamagata strain. These new recommendations match the ones WHO made in September for the Southern Hemisphere's 2016 flu season. After consideration of the latest circulating zoonotic flu viruses, the advisers recommended that two new candidate vaccine viruses be prepared: one against H5N6 avian flu and one against variant H1N1 (H1N1v).
- b) On 6 March, Egypt confirmed its first H5N1 human avian flu case for the year. Egypt reported some 160 human cases of H5N1 avian influenza during 2014-2015.
- c) Taiwan detected an H5N8 outbreak in chickens on 23 February, and H5N2 in both chickens and geese the following day. In Nigeria, outbreaks of H5N1 arose in multiple locations.
- d) By 10 March, 708 human cases of avian influenza A(H7N9) had been reported by the Chinese mainland health authorities since 2013, with 752 globally.
- e) Researchers at Vanderbilt University Medical Center have isolated human antibodies against this strain of avian flu that has killed more than 200 people in China and which could eventually pose a global pandemic threat. They reported⁵⁵ that the

⁵⁴ Vaxart, for instance, which develops oral recombinant vaccines that are administered by tablet rather than by injection, has initiated preclinical testing of an oral vaccine for Zika virus.

⁵⁵ Natalie Thornburg, et al., "H7N9 influenza virus neutralizing antibodies that possess few somatic mutations", *The Journal of Clinical Investigation*. 2016 Mar 7. pii: 85317. doi: 10.1172/JCI85317. The

antibodies against H7subtype viruses exhibit "remarkable neutralizing potency," and thus may represent a new way to protect people who have been exposed.

- f) New results from a study⁵⁶ performed at the University of Helsinki suggest that genomic information from circulating influenza viruses can help in producing more efficient seasonal vaccines. The researchers were able to develop a simple approach for reliable real-time tracking and prediction of viral evolution based on whole-genome sequences of influenza viruses.

MERS-CoV (Middle East Respiratory Syndrome-Coronavirus)

- a) As at noon on 19 March Saudi Arabia had recorded 1354 laboratory confirmed cases of MERS-CoV infection, including 575 deaths.
- b) Researchers from the US National Institutes of Health reported⁵⁷ they had successfully tested in rabbits a human monoclonal antibody as prophylaxis against MERS⁵⁸.
- c) A Kenyan study⁵⁹ which included experts from Germany, and Switzerland, reported MERS-CoV antibodies in two people who tended livestock, despite the participants reporting low levels of contact with camels.

Ebola virus disease

- a) GeoVax Labs has signed a Cooperative Research and Development Agreement for Material Transfer with the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) to collaborate on developing a vaccine against haemorrhagic fever viruses. GeoVax and USAMRIID will share materials and related information for *in vitro* and *in vivo* assessment of GeoVax's MVA-VLP tetravalent vaccine against Ebola Zaire, Ebola Sudan, Marburg, and Lassa fever viruses.
- b) London's Royal Free Hospital has again discharged Pauline Cafferkey, the Scots nurse who recovered from Ebola in 2014, was readmitted in October 2015 with meningitis following on from her Ebola, and then was recently admitted a third time suffering from a late complication. Although Cafferkey's case has been described by experts as unusual, WHO says Ebola can persist in parts of the body not covered by the immune system, including inside the eye, the brain, the spinal cord or in semen.
- c) A new treatment for Ebola has protected macaques from the lethal virus several days after the animals were infected. The therapy uses an antibody mAb114 that scientists

research was led by James Crowe Jr., the Ann Scott Carrell Professor and director of the Vanderbilt Vaccine Center.

⁵⁶ Sergei S. Belanov, et al., "Genome-wide analysis of evolutionary markers of human influenza A(H1N1)pdm09 and A(H3N2) viruses may guide selection of vaccine strain candidates". *Genome Biology and Evolution*, 2015; evv240 DOI: [10.1093/gbe/evv240](https://doi.org/10.1093/gbe/evv240)

⁵⁷ In the *Journal of Infectious Diseases*

⁵⁸ The antibody m366 was administered one day before the rabbits were infected with MERS. When it was administered intravenously, rabbits receiving 1 milligram per kilogram (mg/kg) had a 40-fold reduction of MERS-CoV RNA titres 1 day after infection, and those receiving a 10 mg/kg dose had a 65-fold reduction. The researchers recorded a statistically significant reduction of greater than 500-fold 3 days post-infection in both groups. When the monoclonal antibody was administered intranasally, results were even more encouraging. One day post-infection, animals receiving the lower dose of m366 had a more than 1,000-fold reduction in MERS-CoV RNA, while those receiving 10 mg/kg had a greater than 9,000-fold reduction. Then three days after infection, most of the rabbits cleared MERS-CoV RNA completely. The researchers also found almost no viral antigen on immune histochemical evaluation, indicating that m366 prevented infection of the lower respiratory tract. Having established that m366 had promise as a prophylactic, the investigators tested its efficacy as a treatment post-infection. Although they found that the concentrations of serum neutralizing antibodies were similar to those in the prophylactic study, the monoclonal antibody did not reduce viral RNA titres when administered as a treatment. Analysis of lung specimens from the infected rabbits showed severe lung inflammation. than previously reported.

⁵⁹ published in *Emerging Infectious Diseases*

at NIAID collected from the blood of an Ebola patient more than a decade after the person recovered from the disease.

Other diseases: occurrence, prevention and treatment

- a) In 2015 there were a total of 495 patients registered in South Fly [Western Province of Papua New Guinea⁶⁰] with TB, of whom 194 had extra-pulmonary TB and 301 had pulmonary TB. The TB/HIV rate is low, about three per cent of the patients are co-infected⁶¹.
- b) Cases of whooping cough rose in the Hunter, with the region experiencing a shortage of the booster vaccine recommended for people who come into close contact with newborn children. Supplies of the whooping cough booster had dried up in the middle of the Hunter's worst outbreak of the disease in five years.
- c) NSW Health urged anyone who had visited the Town Hall area in the Sydney CBD to see their doctor if they showed symptoms such as fever, chills, a cough and shortness of breath, following an outbreak of legionnaires' disease.
- d) Researchers at the University of Exeter, with academics from the University of Milan, the Defence Science and Technology Laboratory and the London School of Hygiene and Tropical Medicine, have created a vaccine which has the potential to protect humans from the infection melioidosis, also called Whitmore's disease, found in most tropical regions⁶². Melioidosis is caused by the bacterium *Burkholderia pseudomallei*. It is thought to be spread in soil and dust.
- e) University of New Haven researchers found that the bacterium that causes Lyme disease (*Borrelia burgdorferi*) protects itself from antibiotics by forming a slime-like layer called a biofilm⁶³. This may explain why in many cases, Lyme disease returns after a patient has completed antibiotic treatment.

⁶⁰ Daru, located on an island near the mouth of the Fly River, is just north of Torres Strait. The Torres Strait Islands Treaty signed by Australia and PNG allows for free movement of people (without passports or visas) between the Torres Strait Islands and PNG for traditional activities. The Torres Strait Islanders, who are culturally akin to the coastal peoples of PNG, became Australian citizens in 1967 with full access to health and social services and freedom to travel and work in Australia. Of 60 patients living in the Western Province of PNG who sought treatment between 2000 and 2006 in the Torres Strait Islands because of limited access to health care in the Western Province of PNG, 15 were found to have multidrug resistant tuberculosis (MDR-TB).

⁶¹ Immunosuppression, such as in HIV, alters the pathogenesis of TB, greatly increasing the frequency of extrapulmonary involvement. Extrapulmonary (EP) sites include lymph nodes, pleura, bones/joints, kidneys, brain, pericardium, meninges, and abdomen. EPTB occurs in about 10-20% of HIV-negative patients with TB, but in HIV-positive, 40 to 80% of HIV-infected people with TB have EPTB

⁶² See the journal *Vaccine*.

⁶³ see the *European Journal of Microbiology and Immunology*