

Monitoring International Trends

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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 put financial or other pressures on the Australian sector.

Some recent matters of interest appear on pages 4 to 21. Highlights are listed below:

Products and Treatments

- Bluebird bio announced the publication of positive interim data for its gene therapy to eliminate or reduce chronic blood transfusions in patients with transfusion-dependent β -thalassaemia
- CRISPR gene editing has been used to introduce beneficial natural mutations into blood cells to boost their production of foetal haemoglobin, known to be beneficial to people with beta thalassaemia and sickle cell anaemia.
- Doctors at the University of Illinois at Chicago have been treating sickle cell disease using stem cells from donors previously thought to be incompatible.
- CSL Behring announced the first patient enrolment in the AEGIS-II clinical trial to evaluate the efficacy and safety of plasma-derived CSL112 for the reduction of early recurrent cardiovascular events following an acute myocardial infarction.
- Researchers are using 3D printing to expand treatment options for injuries.

Safety and Patient Blood Management

- Researchers have suggested that 23 per cent of donor blood in some African countries (taken together) contains malaria parasites.
- To reduce the risk of bacterial contamination of platelets for transfusion, the FDA in 2016 issued a draft guidance suggesting additional safety measures beyond a primary bacterial culture for platelets—either pathogen reduction or secondary bacterial testing. The transfusion medicine service at Johns Hopkins introduced a secondary bacterial culture and has reported on its experience.
- Baylor St. Luke's Medical Center in Houston became the first centre in the continental US to enrol patients in Cerus' Phase III study to evaluate the safety and efficacy of INTERCEPT Blood Systems for red blood cells compared with conventional red blood cells in regions impacted by the Zika virus.
- Two studies presented at The International Liver Congress 2018 in Paris took issue with the notions that hepatitis E infections are benign and self-limiting, and that blood-borne transmission is a rare event.
- A University of British Columbia bioengineer has developed a potential strategy for endowing platelets with extra powers.
- A recent study has highlighted the need for better definitions to diagnose transfusion-associated circulatory overload in children.
- An international study found that women with anaemia are twice as likely to die during or shortly after pregnancy compared with those without the condition.
- Researchers reported they can reverse anaemia in mice by injecting a T-cell that has been genetically engineered to secrete erythropoietin (EPO).

- Researchers report that a clinical trial has demonstrated the effectiveness of aspirin in preventing blood clots after major orthopaedic surgeries.
- Researchers have found that the blood-thinning drug, dabigatran, reduces the risk of death, heart attack, stroke, and other heart or blood-vessel complications in patients who have a heart injury following major, non-cardiac surgery.
- AndexXa (andexanet alfa, Portola Pharmaceuticals) has been shown to reverse anti-Factor Xa activity quickly and to sustain it when administered as a bolus followed by a 120-minute infusion.

Regulatory matters

- The European Medicines Agency awarded orphan drug status to Sancilio Pharmaceuticals' Altermia for the treatment of sickle cell disease in paediatric patients.
- In the first approval of a reversal agent of a novel oral anticoagulant, the US Food and Drug Administration (FDA) approved idarucizumab (Praxbind from Boehringer Ingelheim) for the reversal of the anticoagulant dabigatran etexilate mesylate (Pradaxa from Boehringer Ingelheim) in patients requiring emergency surgery or urgent procedures, and in patients diagnosed with uncontrolled/ life-threatening bleeding.
- Shire's Vonvendi [von Willebrand factor (recombinant)] was first approved in the US in December 2015 for the on-demand treatment and control of bleeding episodes in adults with von Willebrand disease. Now the product has US approval for perioperative management of bleeding in these patients.
- The FDA granted breakthrough therapy designation (accelerated review) to Roche's Hemlibra to be used by patients who have not yet developed inhibitors to other treatment. Hemlibra is already approved in the US for people with inhibitors. It was also approved in Japan for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with congenital factor VIII deficiency (haemophilia A) with factor VIII inhibitors.

Company news

- Shire's Board recommended the fifth takeover proposal from Takeda to its shareholders.
- Lonza opened the world's largest dedicated cell and gene therapy facility in Texas. It will serve as a centre of process development from concept through pre-clinical, clinical and commercialization, all the way to the patient.
- CSL Behring has begun adding 1.8 million square feet to its manufacturing facilities in Kankakee, Illinois.
- Canadian company Therapure Biopharma has launched its plasma products and technology division as Evolve Biologics
- Novo Nordisk has acquired an exclusive worldwide license to EpiDestiny's sickle cell disease and thalassemia drug EP101.

Country news

- Members of the American College of Medical Toxicology (ACMT) have been working with public health officials to investigate an outbreak of major bleeding complications associated with synthetic cannabinoid use.
- Gem-Standard, one of Russia's largest producers of drugs derived from blood plasma, is reported to have invested more than \$US 100 million in the building of a new plant in St Petersburg.

Infectious diseases

- A test said to detect antibodies against Zika virus (in samples of blood serum) with high specificity is expected to be available in Brazil before the end of 2018.
- Researchers at the US Centers for Disease Control and Prevention (CDC) have found that Zika virus RNA can be shed for more than 6 months in semen.

- WHO advisers have said the Sanofi's Dengvaxia should be administered only after a test confirms recipients have had a prior infection. A rapid point-of-care diagnostic test is not yet available.
- Residents and visitors in Australia's "Top End" were urged to cover up against mosquitoes following a case of Murray Valley encephalitis acquired in a remote Arnhem Land community.
- BiondVax is preparing for a two-year Phase III trial of its universal flu vaccine candidate
- A human trial in the UK suggested that FLU-v, developed by Imutex, would need to be given only every five to ten years.
- Two new clinical trials testing an experimental vaccine against H7N9 infection have been enrolling volunteers across the US.
- Microbiologists have created a genetic screening tool to identify two key factors that permit the influenza virus to infect human lung cells.
- Georgia State University has signed a licensing deal with Pinnacle Bio to market a point-of-care influenza diagnostic that can detect influenza viruses in 15 minutes.
- Researchers have developed a small molecule that they believe could weaken or even stop H3N2 flu strain in its tracks.
- As at 1 April there had been in Saudi Arabia a total of 1821 confirmed cases of MERS-CoV infection, including 735 reported fatalities.
- The Coalition for Epidemic Preparedness Innovations has provided a grant to assist Themis develop vaccines against Lassa fever and MERS. The public-private vaccine initiative will also fund Inovio's Phase II development of INO-4500, its Lassa fever vaccine, and INO-4700, its MERS candidate
- A newly identified coronavirus in China emerged from horseshoe bats near the origin of the severe acute respiratory syndrome coronavirus (SARS-CoV), which emerged in 2002 in the same bat species.
- Scientists have reported that an Ebola vaccine from Merck appears to provide protection two years after injection. It is currently being deployed in a new outbreak of Ebola in the Democratic Republic of Congo.
- Researchers announced that an open letter had been sent to the World Health Organization (WHO) to increase awareness about the global spread of the retrovirus HTLV-1 (human T-cell leukemia virus) and its deadly nature. They advocate increased screening of blood transfusions and organ transplants, and increased funding for research. As well as potentially leading to leukemia and lymphoma, the virus weakens the patient's immune system and allows bacterial infections, such as pneumonia and bronchiectasis. There can also be neurological conditions associated with the virus. HTLV-1 spreads through unprotected sexual intercourse, sharing of needles, breastfeeding by infected mothers, transfusion of infected blood and transplantation of infected organs. In Australia, the prevalence in Alice Springs has been estimated to be around 40 per cent of the adult population. Since infected people can remain asymptomatic for about 40 years or more, they can unknowingly spread the disease.
- The incidence of severe tissue-destroying Buruli ulcers in Australia has been on the rise and scientists are puzzled as to why Victoria has been particularly affected. Some government research funding has been provided to assist in investigating transmission.
- With bat numbers rising in Northern NSW health authorities have warned residents to avoid contact as they can carry bacteria and viruses including the potentially fatal lyssavirus.
- An outbreak of hepatitis A in a number of Australian states and territories has been linked to imported frozen pomegranates.
- The most recent annual surveillance report from the Kirby Institute says gonorrhoea and syphilis are on the rise in Australia but HIV rates are stable.
- In Nigeria, an outbreak of Lassa fever claimed 119 lives between 1 January and 18 March.

- Researchers at the University of Massachusetts are launching a Phase I trial to determine the safety of a potential DNA vaccine for HIV.

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1. Products and treatments

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

Treating haemophilia

- A study has found, perhaps not surprisingly, that haemophilia A patients who do not need to refrigerate their drug therapy are more satisfied with it and report fewer restrictions on their daily activities¹.

¹ [Tischer B](#), Marino R, Napolitano M, “[Patient preferences in the treatment of hemophilia A: impact of storage conditions on product choice](#),” appeared in the journal *Patient Preference and Adherence*, 26 March 2018 [Volume 2018:12](#) Pages 431—441 DOI <https://doi.org/10.2147/PPA.S151812>

- Catalyst Biosciences announced that the South Korean Ministry of Food and Drug Safety (MFDS) approved the addition of a sixth cohort to the Phase I/II trial of CB 2679d in patients with severe haemophilia B following positive data from the multi-dose Cohort 5².

Treating beta thalassemia and sickle cell disease

- Bluebird bio announced the publication of positive interim data for its gene therapy to eliminate or reduce chronic blood transfusions in patients with transfusion-dependent β -thalassemia³.
- An international team led by Professor Merlin Crossley of the University of New South Wales has used CRISPR gene editing to introduce beneficial natural mutations into blood cells to boost their production of foetal haemoglobin⁴. These mutations – which are naturally carried by a small percentage of the population—are known to be beneficial to people with beta thalassaemia and sickle cell anaemia.

Other products

- On 23 March CSL Behring announced the first patient enrolment in the AEGIS-II⁵ clinical trial. This will enrol over 17,000 patients from around 1,000 medical centres globally. It will evaluate the efficacy and safety of plasma-derived CSL112 for the reduction of early recurrent cardiovascular events following an acute myocardial infarction. CSL112 is a novel apolipoprotein A-I infusion therapy that has been

² Cohort 6 will enrol up to five patients. Each will receive a single intravenous loading dose of 75 IU/kg, followed by nine daily subcutaneous doses of 150 IU/kg. The loading dose will be administered 30 minutes before the first subcutaneous dose. The study will be completed in coordination with ISU Abxis. “The addition of this sixth cohort will allow us to build on the progressive increase in Factor IX activity levels, from severe to mild hemophilia, that we observed after six daily subcutaneous doses in Cohort 5 of this Phase I/II trial,” said Nassim Usman, CEO of Catalyst. “The Cohort 6 design will also allow us to evaluate the benefits of a single IV loading dose of CB 2679d. Interim results from this sixth cohort are expected in Q3 2018 with additional data in Q4 2018. Data from this cohort will inform the design of future trials, including the upcoming Phase IIb trial, planned to begin in Q3 2018.” CB 2679d was awarded orphan drug designations by the European Commission in June 2017 and by the U.S. Food and Drug Administration (FDA) in September 2017.

³ Alexis A. Thompson, Mark C. Walters, Janet Kwiatkowski, John E.J. Rasko, Jean-Antoine Ribeil, Suradej Hongeng, Elisa Magrin, Gary J. Schiller, Emmanuel Payen, Michaela Semeraro, Despina Moshous, Francois Lefrere, Hervé Puy, Philippe Bourget, Alessandra Magnani, Laure Caccavelli, Jean-Sébastien Diana, Felipe Suarez, Fabrice Monpoux, Valentine Brousse, Catherine Poirot, Chantal Brouzes, Jean-François Meritet, Corinne Pondarré, Yves Beuzard, Stany Chrétien, Thibaud Lefebvre, David T. Teachey, Usanarat Anurathapan, P. Joy Ho, Christof von Kalle, Morris Kletzel, Elliott Vichinsky, Sandeep Soni, Gabor Veres, Olivier Negre, Robert W. Ross, David Davidson, Alexandria Petrusich, Laura Sandler, Mohammed Asmal, Olivier Hermine, Mariane De Montalembert, Salima Hacein-Bey-Abina, Stéphane Blanche, Philippe Leboulch, and Marina Cavazzana, et al., “Gene Therapy in Patients with Transfusion-Dependent β -Thalassemia”, *New England Journal of Medicine*, 2018; 378:1479-1493, [April 19, 2018](#) DOI: 10.1056/NEJMoa1705342

⁴ [Gabiella E. Martyn](#), [Beeke Wienert](#), [Lu Yang](#), [Manan Shah](#), [Laura J. Norton](#), [Jon Burdach](#), [Ryo Kurita](#), [Yukio Nakamura](#), [Richard C. M. Pearson](#), [Alister P. W. Funnell](#), [Kate G. R. Quinlan](#) and [Merlin Crossley](#) “Natural regulatory mutations elevate the fetal globin gene via disruption of BCL11A or ZBTB7A binding”, published 2 April, 2018, *Nature Genetics* volume 50, pages498–503 (2018) doi:10.1038/s41588-018-0085-0

⁵ ApoA-I Event reducinG in Ischemic Syndromes II. Before AEGIS-II, results from the Phase IIb AEGIS-I study were presented at the American Heart Association Scientific Sessions 2016 and published in *Circulation*. An additional Phase II trial demonstrated renal safety of CSL112 in patients with moderate renal impairment who experienced a heart attack. These data were presented at the American College of Cardiology's 67th Annual Scientific Session and published in the *Journal of the American College of Cardiology*.

shown to have an immediate and significant impact on the ability to remove cholesterol from arteries. C. Michael Gibson, Professor of Medicine at Harvard Medical School and Chairman of the study, said: "The AEGIS-II study will tell us if a rapid enhancement of the body's ability to remove cholesterol from the arteries can reduce the rate of early recurrent CV events in heart attack survivors."

- A clinical trial ([NCT01785056](#)) of Privigen⁶ in 14 scleroderma patients was completed in January 2018. The trial aimed to assess the safety and efficacy of IVIG, compared with a placebo, over six months of treatment. Results have not yet been announced.
- Researchers from the University of Nebraska-Lincoln, MIT and Massachusetts General Hospital are using 3D printing to expand treatment options for injuries. They use plasma filled with platelets, which release growth factors to repair injuries, in bio-ink, a 3D-printed mixture of cells and gel⁷.
- The EXTEND trial — an open-label extension study of four trials investigating eltrombopag for the treatment of immune thrombocytopenia — has evaluated long-term safety and efficacy. The results are reported to show that adults with chronic or persistent immune thrombocytopenia maintained increased platelet counts and decreased bleeding rate after treatment.
- Scientists at MIT have developed a portable device that can measure white blood cell levels in chemotherapy patients without having to take a blood sample⁸.

2. Safety and patient blood management

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

Appropriate Transfusion

- Researchers have suggested that 23 per cent of donor blood in some African countries (taken together⁹) contains malaria parasites. Dr. Philippe Guerin, director of the Worldwide Antimalarial Resistance Network and professor of medicine at Oxford University's Centre for Tropical Medicine and Global Health, presented the findings at the [seventh Multilateral Initiative on Malaria Pan African Malaria Conference](#) in Dakar, Senegal.
- To reduce the risk of bacterial contamination of platelets for transfusion, the FDA in 2016 issued a draft guidance suggesting additional safety measures beyond a primary bacterial culture for platelets—either pathogen reduction or secondary bacterial testing. The transfusion medicine service at Johns Hopkins introduced a secondary bacterial culture. Thirteen months after implementation it reported 93.5 per cent of platelet products (23,044/24,653) had undergone testing, with eight

⁶ An intravenous immunoglobulin developed by CSL Behring

⁷ Negar Faramarzi, Iman K. Yazdi, Mahboubeh Nabavinia, Andrea Gemma, Adele Fanelli, Andrea Caizzone, Leon M. Ptaszek, Indranil Sinha, Ali Khademhosseini, Jeremy N. Ruskin, Ali Tamayol, "Patient-Specific Bioinks for 3D Bioprinting of Tissue Engineering Scaffolds", [Advanced Healthcare Materials](#), <https://doi.org/10.1002/adhm.201701347>

⁸ Aurélien Bourquard, Alberto Pablo-Trinidad, Ian Butterworth, Álvaro Sánchez-Ferro, Carolina Cerrato, Karem Humala, Marta Fabra Urdiola, Candice Del Rio, Betsy Valles, Jason M. Tucker-Schwartz, Elizabeth S. Lee, Benjamin J. Vakoc, Timothy P. Padera, María J. Ledesma-Carbayo, Yi-Bin Chen, Ephraim P. Hochberg, Martha L. Gray and Carlos Castro-González, "Non-invasive detection of severe neutropenia in chemotherapy patients by optical imaging of nailfold microcirculation", *Scientific Reports* volume 8, Article number: 5301 (2018) doi:10.1038/s41598-018-23591-0 [Non-invasive detection of severe neutropenia in chemotherapy patients by optical imaging of nailfold microcirculation...](#)

⁹ Percentages varied across the nine countries included, ranging from zero to as much as 74 per cent.

positive cultures identified, five of them probably being true positives (confirmed by repeat testing). During the period, no septic transfusion reactions were recorded¹⁰.

- Baylor St. Luke's Medical Center in Houston became the first centre in the continental US to enrol patients in Cerus' RedeS study. This is a Phase III study to evaluate the safety and efficacy of INTERCEPT Blood Systems for red blood cells compared with conventional red blood cells in regions impacted by the Zika virus.
- Two studies presented at The International Liver Congress 2018 in Paris took issue with the notions that hepatitis E infections are benign and self-limiting, and that blood-borne transmission is a rare event. Scientists from Hamburg and Hanover demonstrated that hepatitis E (HEV) can be fatal, especially in immunocompromised patients. They also showed that blood products are an important source of infection in those who are immunosuppressed¹¹.
- [Masimo](#) announced findings at the 2018 Annual Meeting of the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA). Scientists had investigated the utility of Masimo non-invasive and continuous haemoglobin (SpHb) in supporting and enhancing red blood cell transfusion best practices as part of post-operative patient blood management¹².
- A University of British Columbia bioengineer has developed a potential strategy for endowing platelets with extra powers¹³. Christian Kastrup, an Associate Professor in the Department of Biochemistry and Molecular Biology says: "Coagulation, which depends on a series of complex biochemical reactions, works great for scrapes and paper cuts. But trauma often overwhelms this intricate, delicate process. We wanted to make it more resilient."
- A recent study¹⁴ has highlighted the need for better definitions to diagnose transfusion-associated circulatory overload (TACO) in children.

¹⁰ [Bloch EM, Marshall CE, Boyd JS, Shifflett L, Tobian AAR, Gehrie EA, and PM Ness. Implementation of secondary bacterial culture testing of platelets to mitigate residual risk of septic transfusion reactions. *Transfusion* 2018 <https://doi.org/10.1111/trf.14618>](#)

¹¹ In a large observational study two infected but immune-competent individuals who had preexisting liver disease died after developing acute-on-chronic liver failure. Eight immunosuppressed patients died within 5 years of being diagnosed with HEV infection, with three of these deaths considered to be related to the HEV infection. Dr Sven Pischke from the University Hospital Hamburg-Eppendorf in Germany said: "We have shown in this study that HEV infection can be associated with significant morbidity and mortality, and that a severe disease course is not limited to those who are immunocompromised. Based on these findings, we urge all hepatologists to consider HEV". The second study was a retrospective analysis of 37 immunosuppressed patients with HEV infection. Eleven of these patients developed chronic HEV infection and, in four of these, the source of infection was traced to an HEV-positive blood donation. Dr Dirk Westhölter from the University Hospital Hamburg-Eppendorf said: "The number of notified transfusion-transmitted HEV infections has so far been relatively low, probably due to under-reporting and under-recognition. This study confirms that blood products are an important source of HEV infection for immunosuppressed individuals and it has led us to recommend HEV RNA screening of all blood products destined for transplant or immunosuppressed patients".

¹² Baricchi R, Marraccini C, Merolle L, Berni P, Bonini A, Mazzi A, Pertinhez T.A., and Di Bartolomeo E. "Patient blood management: transfusion appropriateness in the postoperative period". *Proceedings from the 2018 NATA Annual Meeting*, Lisbon, Portugal. #P30.

¹³ [V. Chan, M. Sarkari, R. Sunderland, A. E. St. John, N. J. White, C. J. Kastrup](#), "Platelets loaded with liposome-encapsulated thrombin have increased coagulability", *Journal of Thrombosis and Haemostasis*, published: 20 April 2018 <https://doi.org/10.1111/jth.14006>

¹⁴ [Reference: De Cloedt L, Emeriaud G, Lefebvre E, Kleiber N, Robitaille N, Jarlot C, Lacroix J, and F Gauvin. "Transfusion-associated circulatory overload in a pediatric intensive care unit: different incidences with different diagnostic criteria". *Transfusion*, <https://doi.org/10.1111/trf.14504>](#)

Recognising and treating anaemia

- An international study led by Queen Mary University of London of over 300,000 women across 29 countries found that women with anaemia are twice as likely to die during or shortly after pregnancy compared with those without the condition¹⁵.
- Researchers reported they can reverse [anaemia](#) in mice by injecting a type of white blood cell known as a T-cell that has been genetically engineered to secrete erythropoietin (EPO), which stimulates production of red blood cells. They also found that human T-cells grown in the laboratory can be genetically modified to secrete EPO¹⁶.
- Keryx Biopharmaceuticals announced the publication¹⁷ of a post-hoc analysis of Auryxia Phase III trial data for iron deficiency anaemia in adult patients with chronic kidney disease but not on dialysis.
- A recent report suggests that intravenous iron repletion with sodium ferric gluconate complex does not reduce platelet counts in patients with chronic kidney disease and iron deficiency anaemia¹⁸.
- Daxor Corporation announced the publication of new research¹⁹ using the BVA-100 blood volume analyzer to indicate significant, often unrecognized blood loss in cardiac surgery. The company said the paper demonstrated that the BVA-100 could show the intravascular fluid derangements that standard tests miss, quantifying whole blood and red blood cell volume with 98 per cent accuracy, alerting doctors to possible anaemia due to blood loss.

Other

- Janssen and Bristol-Myers Squibb [announced a collaboration](#) to address the development and commercialization of Factor X1a inhibitors for the prevention and treatment of thrombotic conditions. Anticoagulant compound BMS-986177 will be advanced into Phase II clinical trials for broad therapeutic indications.
- Researchers report²⁰ that a clinical trial has demonstrated the effectiveness of aspirin in preventing blood clots after major orthopaedic surgeries. David Zukor, chief of

¹⁵ Jahnavi Daru, Javier Zamora, Borja M. Fernández-Félix, Joshua Vogel, Olufemi T. Oladapo, Naho Morisaki, Ozge Tunçalp, Maria Regina Torloni, Suneeta Mittal, Kapila Jayaratne, Pisake Lumbiganon, Ganchimeg Togoobaatar, Shakila Thangaratinam, and Khalid S Khan, “The risk of maternal mortality in women with severe anaemia in pregnancy and the postpartum: a multilevel analysis”, *The Lancet Global Health*. DOI: [10.1016/S2214-109X\(18\)30078-0](https://doi.org/10.1016/S2214-109X(18)30078-0)

¹⁶ Richard T. O’Neil et al. “Transposon-modified antigen-specific T lymphocytes for sustained therapeutic protein delivery in vivo”, *Nature Communications* (2018). DOI: [10.1038/s41467-018-03787-8](https://doi.org/10.1038/s41467-018-03787-8)

¹⁷ [Pablo E. Pergola](#), [Steven Fishbane](#), [Robin D. LeWinter](#), [John F. Neylan](#), [Katrin Uhlig](#), [Geoffrey A. Block](#), [Glenn M. Chertow](#). “Hemoglobin response to ferric citrate in patients with nondialysis-dependent chronic kidney disease and iron deficiency anemia”, First published: 25 March 2018, online issue of the *American Journal of Hematology*. <https://doi.org/10.1002/ajh.25088>

¹⁸ Watkins M, Pal S, Shirsat P, et al. “Effect of intravenous iron repletion on platelet counts in patients with chronic kidney disease and iron deficiency anemia”. Data presented at the National Kidney Foundation’s 2018 Spring Clinical Meetings in Austin, Texas, April 10-14. Poster 153.

¹⁹ [Mark Nelson](#), [Jeffrey Green](#), [Bruce Spiess](#), [Vigneshwar Kasirajan](#), [Patricia Nicolato](#), [Hangcheng Liu](#), [Ryan S. Meshkin](#), “Measurement of Blood Loss in Cardiac Surgery: Still Too Much” *The Annals of Thoracic Surgery*. April 2018 Volume 105, Issue 4, Pages 1176–1181
DOI: <https://doi.org/10.1016/j.athoracsur.2017.11.023>

²⁰ David R. Anderson, Michael Dunbar, John Murnaghan, Susan R. Kahn, Peter Gross, Michael Forsythe, Stephane Pelet, William Fisher, Etienne Belzile, Sean Dolan, Mark Crowther, Eric Bohm, Steven J. MacDonald, Wade Gofton, Paul Kim, David Zukor, Susan Pleasance, Pantelis Andreou, Steve Doucette, Chris Theriault, Abongnwen Abianui, Marc Carrier, Michael J. Kovacs, Marc A. Rodger, Doug Coyle, Philip S. Wells, and Pascal-Andre Vendittoli, et al., “Aspirin or Rivaroxaban for

orthopaedics at the Jewish General Hospital, Montreal, and one of many researchers involved, says development of blood clots in patients following major orthopaedic surgery is the leading cause of preventable in-hospital death. For five days after surgery, the 3,424 participants in the trial took the anticoagulation medication rivaroxaban before being randomly selected to continue with that or receive aspirin. Of the 1,707 patients treated with aspirin eleven experienced postoperative venous thromboembolism, compared with 12 of the 1,717 patients who continued with rivaroxaban. Researchers recommended that further clinical trials should involve a randomized group of patients prescribed only aspirin to enable measurement of its effectiveness against rivaroxaban. Dr Zukor said: "Rivaroxaban is known to be effective, but the great advantage of aspirin is that it is far less expensive, easily available, and has an excellent safety profile."

- Researchers have found that the blood-thinning drug, dabigatran, reduces the risk of death, heart attack, stroke, and other heart or blood-vessel complications in patients who have a heart injury following major, non-cardiac surgery. In the first randomized controlled trial to evaluate a treatment for myocardial injury after non-cardiac surgery (MINS), Dr. P.J. Devereaux, scientific lead for perioperative research at the Population Health Research Institute of Hamilton Health Sciences and McMaster University, Canada, was principal investigator. This MANAGE trial found that patients who had MINS and received dabigatran twice daily were 28 per cent less likely to suffer a major vascular complication during an average of 16 months of follow-up. The results of the MANAGE trial were presented at the American College of Cardiology's 67th Annual Scientific Session.
- Also presented at the American College of Cardiology's meeting were results showing that AndexXa (andexanet alfa, Portola Pharmaceuticals) quickly reversed anti-Factor Xa activity when administered as a bolus, and sustained this reversal when followed by a 120-minute infusion.

3. Regulatory

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

- The [European Medicines Agency](#) awarded orphan drug status²¹ to [Sancilio Pharmaceuticals' Altemia](#) for the treatment of [sickle cell disease \(SCD\)](#) in paediatric patients. The drug is a formulation of lipids, encapsulated in a soft gelatin capsule taken once daily. Topline data from a Phase II trial²² in SCD patients aged 5 to 17 was released in [November 2017](#) showing that Altemia achieved goals set. The trial measured the change in the concentration of fatty acids in the red blood cell membrane of patients treated with Altemia or a placebo. Three doses of Altemia were tested. Top-line results also showed a clinically meaningful reduction of vaso-occlusive episodes.
- In the first approval of a reversal agent of a novel oral anticoagulant (NOAC), the US Food and Drug Administration (FDA) approved idarucizumab (Praxbind from Boehringer Ingelheim) for the reversal of the anticoagulant dabigatran etexilate mesylate (Pradaxa from Boehringer Ingelheim) in patients requiring emergency

VTE Prophylaxis after Hip or Knee Arthroplasty," [The New England Journal of Medicine](#), February 22, 2018, N Engl J Med 2018; 378:699-707, DOI: 10.1056/NEJMoa1712746

²¹ Orphan drug designations are granted in Europe for treatments for rare diseases. Orphan drugs may be granted up to 10 years of market exclusivity. The US Food and Drug Administration (FDA) awarded Altemia [rare pediatric drug designation](#) in September 2017 and orphan drug designation in 2015.

²² [NCT02973360](#)

surgery or urgent procedures, and in patients diagnosed with uncontrolled/ life-threatening bleeding.

- Israeli company Kamada Ltd. received feedback from the FDA with respect to its proposed Phase III protocol for its Inhaled Alpha-1 Antitrypsin (AAT) therapy for treatment of Alpha-1 Antitrypsin Deficiency²³. Kamada intends to provide the requested information and data, as well as implement the proposed changes in the study protocol, during the third quarter of 2018. Kamada is also hoping to present its planned Phase III protocol in a Scientific Advice meeting with the European Medicines Agency in the third quarter of 2018.
- Shire's Vonvendi [von Willebrand factor (recombinant)] was first approved in the US in December 2015 for the on-demand treatment and control of bleeding episodes in adults with von Willebrand disease (VWD). Now the product has US approval for perioperative management of bleeding in these patients.
- The FDA granted breakthrough therapy designation (accelerated review) to Roche's Hemlibra to be used by patients who have not yet developed inhibitors to other treatment. Hemlibra is already approved in the US for people with inhibitors. In March it was also approved in Japan for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with congenital factor VIII deficiency (haemophilia A) with factor VIII inhibitors.
- The FDA approved the use of [Leukine](#)²⁴ (sargramostim; [Sanofi Genzyme](#)) to increase survival in children and adults exposed to myelosuppressive doses of radiation²⁵. Leukine is the third FDA-approved countermeasure intended to increase survival in patients with acute radiation syndrome. The other two approved countermeasures are [Neupogen](#) (filgrastim; [Amgen](#)) and [Neulasta](#) (pegfilgrastim; [Amgen](#)).

4. 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.

²³ In July 2017, Kamada had submitted a proposed Phase III study protocol for Inhaled AAT for treatment of AATD to the FDA. In August 2017, the FDA responded with a letter expressing the agency's continued concerns and questions regarding the safety and efficacy of Inhaled AAT for the treatment of AATD and the risk/benefit balance to patients. In March 2018, following further discussions and based on additional feedback received from the FDA, Kamada submitted a revised pivotal Phase III protocol to the FDA, as well as additional information related to the FDA questions and concerns. In response to the revised study protocol and the information provided by Kamada, in April 2018, the FDA issued a response letter providing further guidance regarding the proposed pivotal Phase III protocol, as well as additional questions focused on the Inhaled AAT product characteristics. This correspondence indicated that, while several issues had been addressed, the FDA has continued concerns and questions related to the safety profile of Inhaled AAT.

²⁴ Leukine is a granulocyte-macrophage colony stimulating factor (recombinant). It was approved in 1991 to reduce time to [neutrophil recovery](#) and to reduce the incidence of severe and life-threatening infections after induction chemotherapy in adults aged ≥55 years with acute myeloid leukemia. It now has other indications: to mobilize hematopoietic progenitor cells into peripheral blood for collection by leukapheresis; to speed myeloid recovery in non-Hodgkin's lymphoma, acute lymphoblastic leukemia and Hodgkin's disease in autologous bone marrow transplantation; to speed myeloid recovery in allogeneic bone marrow transplantation; and for use in patients with bone marrow transplantation failure or delay in engraftment.

²⁵ The FDA approval was based on efficacy studies in animals. With administration up to 48 hours after total body irradiation exposure, there was an increased survival in 50 per cent of subjects with potentially fatal exposure, with minimal supportive care.

- On 28 March Japanese drugmaker Takeda announced it was interested in making a bid for Shire but had not yet approached the Shire Board. Under UK takeover rules, that meant it would need to submit a bid by 25 April or walk away from the proposition. Analysts were interested to see if the Takeda announcement sparked competitive bids. Shire was seen as facing challenges in its haemophilia market, particularly new [competition](#) from Roche's Hemlibra. Tax reform in the US has been seen to give Big Pharma [increased](#) deal making capacity. Two of the biggest beneficiaries of tax changes are said to have been [Pfizer](#) and [AbbVie](#). Pfizer is thought to be interested in buying Bristol-Myers Squibb and/or AstraZeneca, while AbbVie had already agreed in the past to buy Shire, until US Treasury regulations [scuttled](#) its plans²⁶.
 - i) Later Takeda was reported to have spoken with several banks about borrowing tens of billions of dollars to fund the possible acquisition of Shire for \$US 50 billion. Shire was worth around \$US 10 billion more than the Japanese group²⁷.
 - ii) A series of increasing offers followed. On 24 April Shire announced the fifth and most recent proposal from Takeda comprised 0.839 new Takeda shares and US\$30.33 in cash for each Shire ordinary share. Shire shareholders would also be entitled to any dividends announced, declared, made or paid by Shire in the ordinary course prior to completion of the possible transaction. At completion, Shire shareholders would own approximately 50 per cent. of the enlarged Takeda and the new Takeda shares would be listed in Japan and in the US. Shire's board recommended this fifth proposal from Takeda to shareholders. Shire had agreed to an extension of the relevant deadline until 5.00 p.m. (London time) on 8 May 2018 to enable the parties to conclude their ongoing discussions.
 - iii) On 24 May reports said Takeda had invited Japanese and overseas banks to participate in the syndication of the \$US 30.85 billion loan to back its \$US 62 billion purchase of Shire. Takeda had already reached an agreement on the bridge loan with JPMorgan Chase, MUFG Bank and Sumitomo Mitsui Banking Corp. The suggested syndication gives more lenders an opportunity to participate in one of the biggest-ever loans in Asia.
 - iv) Takeda arranged to sell off its China joint venture, a 51.34 per cent stake in Guangdong Techpool Bio-Pharma Co. Ltd. for \$US 280 million in cash to Shanghai Pharmaceutical Holding Co. Ltd. and a fund managed by a subsidiary of Guangzhou Industrial Investment Fund Management Co. Ltd.
 - v) On 16 April, Shire had announced that it had entered into a definitive agreement with Servier to sell its oncology business for \$US 2.4 billion.
- Lonza opened the world's largest dedicated cell and gene therapy facility in Texas. Andreas Weiler, business unit head for Emerging Technologies at Lonza Pharma and Biotech said: "Lonza Houston will serve as a center of excellence for cell and gene therapy process development from concept through pre-clinical, clinical and commercialization, all the way to the patient." The facility is already manufacturing for several customers.
- Amgen said it will build a next-generation biomanufacturing plant at its West Greenwich site, Rhode Island.
- Grifols entered a new collaboration agreement with Irsi Caixa AIDS Research Institute²⁸, providing 7.5 million euros (\$US 1.9 million) over five years to advance the search for new treatments for HIV/ AIDS and associated diseases, and to address other challenges in the biomedical field. Grifols will receive preference to exploit the

²⁶ Shire agreed to be acquire by AbbVie in the days of tax inversion, but stricter US treasury rules led AbbVie to abandon the arrangement in October 2014.

²⁷ Takeda was estimated to be carrying debt of \$US 11 billion, while the estimate for Shire was \$US 19 million.

²⁸ The Institute was founded in 1995 by la Caixa Banking Foundation and the Ministry of Health of the Government of Catalonia. It has undertaken research on HIV/AIDS and associated diseases.

outcomes and any resulting patents, while the private non-profit foundation will retain exclusive ownership.

- CSL Behring has begun adding 1.8 million square feet to its manufacturing facilities in Kankakee, immediately south of the existing plant, which stands on 64 acres. The entire expansion on the recently purchased neighbouring 74 acres could take as long as 12 years to complete, said plant manager and senior vice president Tricia Stewart and project manager Chris Abell. CSL entered into a \$US 17-million contract to purchase the property in July 2017 and took possession in January. The expansion will increase production of medications built with albumin. The expansion also allows for increased production of intermediates used in products made locally and at other sites around the world.
- Canadian company Therapure Biopharma has launched its plasma products and technology division as Evolve Biologics. Evolve aims to commercialize plasma-derived therapeutics, using its proprietary Plasma Cap EBA purification technology²⁹. Evolve is in the process of developing a portfolio of product candidates, including intravenous immunoglobulin, which is currently in a Phase III clinical trial, and albumin. The company is headquartered in Mississauga, Ontario.
- Novo Nordisk has acquired an exclusive worldwide license to Epi Destiny's sickle cell disease and thalassemia drug EP101. Epi Destiny will receive \$US 400 million in upfront, development and sales milestone payments, plus royalties on any net sales. Epi Destiny retains the rights to continue the drug's development in oncology.
- [Baxter](#) closed the \$US 153 million acquisition of haemostat and sealant assets from [Mallinckrodt Pharmaceuticals](#).

5. Specific country events

- In Quebec, Novo Nordisk announced the availability of Zonovate (Antihemophilic Factor (Recombinant, B-Domain Truncated)), for use in adults and children with haemophilia A, for treatment and control of bleeding episodes, perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes. Zonovate was approved by Health Canada in December 2014.
- A woman in Edmonton who underwent a stem cell transplant for sickle cell disease is the first adult in Canada to have been cured of the disease by this means. Her donor was her sister.
- In the Canadian provinces of Saskatchewan and New Brunswick donors in private plasma collection centres (operated by Canadian Plasma Resources) are paid up to \$C 50 for each donation. Now national advocacy group [BloodWatch.org](#) has appealed to the Nova Scotia government to ban private, for-profit plasma companies from setting up in the province, saying the model discourages voluntary donations and compromises safety.
- Octapharma USA will sponsor "Making the Connection," a national conference for patients with Type 3 von Willebrand Disease (VWD), the rarest and most severe form of the condition. The conference will be held June 22 – 25 in Palm Beach Gardens, Florida.
- Members of the American College of Medical Toxicology (ACMT) have been working with public health officials to investigate an outbreak of major bleeding complications associated with synthetic cannabinoid use.
- Gem-Standard, one of Russia's largest producers of drugs derived from blood plasma, is reported to have invested more than \$US 100 million in the building of a

²⁹ PlasmaCap EBA is claimed to capture plasma proteins at high yields. The technology uses expanded bed adsorption (EBA) chromatography to capture plasma proteins directly from plasma or fractionated plasma materials without the use of cold ethanol.

new plant located in St Petersburg. The output of the facility will include blood substitutes, blood clotting factors, intravenous immunoglobulins, human-protein-based substances and some other drugs, directed towards replacing imports. The plant will be commissioned in 2019.

- A micro-costing study in the UK suggested administration costs per unit for transfusions to a patient on a regular day-unit ward were \$US 71 for red blood cells, \$US 84 for platelets, \$US 55 for fresh-frozen plasma, and \$72 for cryoprecipitate. Not surprisingly, for each blood component, the administration costs for the first unit transfused exceeded administration costs for subsequent units for the same patient³⁰.
- Victims of the contaminated blood scandal in the UK will receive legal funding to prepare for a public inquiry.
- Giving prisoners infected with hepatitis C unrestricted access to direct-acting antiviral therapy had almost eliminated the virus at an Australian correctional facility less than 2 years after its implementation³¹.
- Indonesia is finding it difficult to meet the country's annual blood needs. The Director-General of healthcare services at the Health Ministry Bambang Wibowo said: "Based on WHO records, Indonesia's blood needs each year reaches 5.1 million bags. Meanwhile, we could only provide around 4.2 million."
- Iran exported 3000 litres of plasma to Octapharma in Europe in 2017, via Mahabad in the southwest of Azarbaijan province.

6. Research not included elsewhere

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.

- Daniel Shriner and Charles N. Rotimi³² say sickle-cell anaemia began in one person in West Africa some 7,300 years ago, who was born with the genetic mutation that altered his haemoglobin.³³ Researchers have pinpointed a protein that can sense blood flow and prompt tiny blood vessels called arterioles to dilate. They consider the protein, known as GPR68, could be a significant target for drug development³⁴.

³⁰ [Stokes EA, Wordsworth S, Staves J, Mundy N, Skelly J, Radford K, and SJ Stanworth. Accurate costs for blood transfusion: a microcosting of administering blood products in the United Kingdom National Health Service. Transfusion 2018](#) Also [Cataife G and MB Pagano. How much does a blood transfusion cost? Transfusion 2018](#)

³¹ [Sofia R Bartlett Penny Fox Harris Cabatingan Anissa Jaros Carla Gorton Rhondda Lewis Eugene Priscott Gregory J Dore Darren B Russell](#) "Demonstration of Near-Elimination of Hepatitis C Virus Among a Prison Population: The Lotus Glen Correctional Centre Hepatitis C Treatment Project", Published: 12 March 2018, *Clinical Infectious Diseases*, ciy210, <https://doi.org/10.1093/cid/ciy210>

³² the director of the Center for Research on Genomics and Global Health in the US

³³ [Daniel Shriner](#) and [Charles N. Rotimi](#), "Whole-Genome-Sequence-Based Haplotypes Reveal Single Origin of the Sickle Allele during the Holocene Wet Phase", *The American Journal of Human Genetics*, Volume 102, Issue 4, p547–556, 5 April 2018. DOI: <https://doi.org/10.1016/j.ajhg.2018.02.003>

³⁴ Jie Xu, Jayanti Mathur, Emilie Vessières, Scott Hammack, Keiko Nonomura, Julie Favre, Linda Grimaud, Matt Petrus, Allain Francisco, Jingyuan Li, Fu-li Xiang, James K. Mainquist, Stuart M. Cahalan, Anthony P. Orth, John R. Walker, Shang Ma, Viktor Lukacs, Laura Bordone, Michael Bandell, Bryan Laffitte, Yan Xu, Shu Chien, Daniel Henrion, Ardem Patapoutian, "GPR68 Senses Flow and Is Essential for Vascular Physiology", *Cell*, <https://doi.org/10.1016/j.cell.2018.03.076>

- Researchers at Fred Hutchinson Cancer Research Center in Seattle suggested after an animal trial that gene-edited stem cells from the bone marrow of patients could be a solution to the problem of HIV reservoirs³⁵.
- Doctors at the University of Illinois at Chicago have been treating sickle cell disease using stem cells from donors previously thought to be incompatible³⁶. With the new protocol, patients with aggressive sickle cell disease can receive stem cells from family members if only half of their human leukocyte antigen (HLA) markers match. Previously, donors had to be a family member with a full set of matching HLA markers³⁷.
- Velia Fowler and her lab at The Scripps Research Institute report that a protein called myosin IIA contracts to give red blood cells their distinctive shape³⁸.
- The Bajau people of Malaysia and the Philippines are renowned for their free-diving abilities. They can stay submerged for extended periods. Scientists from the University of Copenhagen and the University of California-Berkeley studied this capability³⁹ and concluded they have unusually large spleens⁴⁰ as the result of a genetic mutation. This has been described as an example of natural selection.
- A microfluidic device developed by Massachusetts General Hospital investigators may help in diagnosing sepsis, which can be life-threatening⁴¹.

7. 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.

³⁵ Christopher W. Peterson, Jianbin Wang, Claire Deleage, Sowmya Reddy, Jasbir Kaur, Patricia Polacino, Andreas Reik, Meei-Li Huang, Keith R. Jerome, Shiu-Lok Hu, Michael C. Holmes, Jacob D. Estes, Hans-Peter Kiem, "Differential impact of transplantation on peripheral and tissue-associated viral reservoirs: Implications for HIV gene therapy", *PLOS Pathogens*, Published: April 19, 2018 <https://doi.org/10.1371/journal.ppat.1006956>

³⁶ Santosh L. Saraf, Annie L. Oh, Pritesh R. Patel, Karen Sweiss, Matthew Koshy, Sally Campbell-Lee Michel Gowhari, Shivi Jain, David Peace, John G. Quigley, Irum Khan, Robert E. Molokie, Nadim Mahmud, Victor R. Gordeuk, Damiano Rondelli "Haploidentical Peripheral Blood Stem Cell Transplantation Demonstrates Stable Engraftment in Adults with Sickle Cell Disease", *Biology of Blood and Bone Marrow Transplantation*, Published online: April 12, 2018 DOI: <https://doi.org/10.1016/j.bbmt.2018.03.031>

³⁷ HLA markers are proteins on the surface of cells that help to regulate the immune system. The human body uses these proteins to identify which cells belong in the body and which cells do not. Because HLA markers are inherited from parents, family members are the most likely to have matching proteins. In transplants, matching HLA markers between the patient and the donor help to limit the risk that the patient's body will reject the donor cells.

³⁸ Alyson S. Smith et al, "Myosin IIA interacts with the spectrin-actin membrane skeleton to control red blood cell membrane curvature and deformability", *Proceedings of the National Academy of Sciences* (2018). DOI: [10.1073/pnas.1718285115](https://doi.org/10.1073/pnas.1718285115)

³⁹ Melissa A. Ilardo, Ida Moltke, Thorfinn S. Korneliussen, Jade Cheng, Aaron J. Stern, Fernando Racimo, Peter de Barros Damgaard, Martin Sikora, Andaine Seguin-Orlando, Simon Rasmussen, Inge C.L. van den Munckhof, Rob ter Horst, Leo A.B. Joosten, Mihai G. Netea, Suhartini Salingkat, Rasmus Nielsen, Eske Willerslev. "Physiological and Genetic Adaptations to Diving in Sea Nomads". *Cell*, 2018; 173 (3): 569 DOI: [10.1016/j.cell.2018.03.054](https://doi.org/10.1016/j.cell.2018.03.054)

⁴⁰ The spleen has a role during acute oxygen shortage, for example when people hold their breath for an extended period of time. The heart rate slows down, the blood vessels in the extremities constrict, and the spleen shrinks, releasing oxygenated red blood cells. The larger the spleen, the greater the volume of freshly oxygenated blood released into the bloodstream.

⁴¹ [Felix Ellett](#), [Julianne Jorgensen](#), [Anika L. Marand](#), [Yuk Ming Liu](#), [Myriam M. Martinez](#), [Vicki Sein](#), [Kathryn L. Butler](#), [Jarone Lee](#) and [Daniel Irimia](#), "Diagnosis of sepsis from a drop of blood by measurement of spontaneous neutrophil motility in a microfluidic assay", *Nature Biomedical Engineering*, doi:10.1038/s41551-018-0208-z

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, Zika virus and the tick-borne babesiosis and Lyme disease).

Mosquito-borne diseases

- China is said to be developing a super-sensitive radar that can detect the wing-flapping of a mosquito up to 2 kilometres away. Reports suggest that a prototype of the device is being tested at a defence laboratory at the Beijing Institute of Technology (BIT). One commentator described it as a “precision-guided weapon in our war against the deadliest creature on Earth”.
- Drones are being used to recognize outbreaks of mosquitoes transmitting dengue and zika in Brazil.
- A test said to detect antibodies against Zika virus (in samples of blood serum) with high specificity (a low risk of cross-reaction with related microorganisms such as dengue virus) is expected to be available in Brazil before the end of 2018⁴². Technology firm Inovatech, with support from the São Paulo Research Foundation, developed the test in collaboration with scientists at the University of São Paulo's Biomedical Science Institute and at the Butantan Institute.
- Researchers at the US Centers for Disease Control and Prevention (CDC) have found that Zika virus RNA can shed for more than 6 months in semen⁴³.
- Researchers infected infant [rhesus macaques](#) with Zika virus after they were born, and observed that monkeys have abnormal brain development and display atypical behaviour at six months of age⁴⁴.
- David P. Durham, from Yale University, and colleagues developed a model⁴⁵ to evaluate the impact of vaccine strategies on the incidence of prenatal Zika infections, including prioritization of females aged 9 to 49 years followed by males. They wrote: "A Zika vaccine of moderate-to-high efficacy may virtually eliminate prenatal infections through a combination of direct protection and transmission reduction. Efficiency of

⁴² Danielle Bruna Leal de Oliveira, principal investigator for the project, said: "The specificity of the serological tests currently on the market falls within the 69%-75% range. There's at least a 25% chance of a false positive if the patient was infected by dengue virus in the past. Our test's specificity is 93% for Zika."

⁴³ They conducted a prospective study and collected semen and urine samples from Zika infected men twice a month until viral RNA was not detectable by real-time reverse-transcriptase-PCR. Based on individual data from 184 men, only 7 had detectable Zika RNA in their urine. Zika RNA shedding in semen was detected in 60 of the men over the study period. Viral shedding decreased after the first 90 days of illness; one man, however, continued to shed a low level of virus for over 6 months. The researchers concluded that further research is needed to determine the risk of transmission and define effective prevention strategies. [Mead PS, Duggal NK, Hook SA, et al. Zika Virus Shedding in Semen of Symptomatic Infected Men. The New England Journal of Medicine 2018; 378 \(15\): 1377-1385.](#) Also [Feldmann H. Virus in Semen and the Risk of Sexual Transmission. The New England Journal of Medicine 2018; 378 \(15\): 1440-1441.](#)

⁴⁴ The research was reported (4 April) in *Science Translational Medicine*. M. Mavigner et al., "Postnatal Zika virus infection is associated with persistent abnormalities in brain structure, function, and behavior in infant macaques," *Sci Transl Med*, doi:10.1126/scitranslmed.aao6975, 2018.

⁴⁵ David P. Durham, Meagan C. Fitzpatrick, Martial L. Ndeffo-Mbah, Alyssa S. Parpia, Nelson L. Michael, Alison P. Galvani, "Evaluating Vaccination Strategies for Zika Virus in the Americas", *Ann Intern Med*. 2018;168(9):621-630. DOI:10.7326/M17-0641

age-specific targeting of Zika vaccination depends on the timing of future outbreaks"⁴⁶.

- WHO advisers have said that Sanofi's Dengvaxia should be administered only after a test confirms recipients have had a prior infection. A rapid point-of-care diagnostic test is not yet available.
- Laboratory tests confirmed by mid-April that a man in Bowen, Queensland, was suffering from dengue fever, thought to have been contracted while he was overseas. Health authorities warned that an imported case could be spread by local mosquitoes. Residents were advised to take immediate and continuing action to prevent mosquitos from breeding on their property.
- Residents and visitors in Australia's "Top End" were urged to cover up against mosquitoes following a case of Murray Valley encephalitis acquired in a remote Arnhem Land community. February to July is the main risk period for the potentially fatal disease, with the carrier being the common mosquito, *Culex annulirostris*.
- At the Commonwealth Heads of Government Meeting in London, leaders attended a Malaria Summit co-hosted by Rwanda, Swaziland, and the UK. Donors announced new funding for research and development, and member countries were urged to halve malaria across the Commonwealth by 2023.
- At the 7th Multilateral Initiative on Malaria Pan African Malaria Conference in Dakar, Senegal, experts warned that a rapid rise in malaria cases in countries grappling with conflict and famine could thwart the last 10 years of progress against the disease.
- Bill Gates told a forum on malaria that gene-editing technologies that alter mosquitoes' DNA could prove critical in the fight, and ethical concerns should not block progress.

Influenza: seasonal influenza and avian influenza

Because of the capacity of influenza viruses for re-assortment, the spread of influenza strains in animals and birds is of interest as one or more strain may eventually develop the potential to cause a pandemic in humans. There are also strains which, while primarily infecting and being transmitted by animals or birds, nevertheless can infect humans, and the concern there is that human-to-human transmission might develop.

- BiondVax is preparing for a two-year Phase III trial of its universal flu vaccine candidate⁴⁷. The study will test the vaccine in about 9,600 participants aged 50 or more across four to six countries in Eastern Europe⁴⁸. The company is also beginning a Phase II trial in the US sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID) and involving 120 adults ages 18 to 49 at three trial sites.
- A human trial in the UK suggested that FLU-v, developed by Imutex, is more effective than existing vaccines. It expected to cost between £20 and £50 per patient but would need to be given only every five to ten years.

⁴⁶ They found that for a base-case vaccine efficacy of 75 per cent and vaccination coverage of 90 per cent, immunizing females aged 9 to 49 years would reduce the incidence of prenatal infections by at least 94 per cent, depending on the country-specific Zika attack rate. They pointed out, however, that where an outbreak is not expected for at least a decade, vaccinating women aged 15 to 29 years is more efficient than vaccinating women aged 30 years or older.

⁴⁷ M-001 consists of nine epitopes common to most influenza virus strains including both Type A and B. M-001 has had six successful clinical trials (two Phase I/II and four Phase II). It has been shown to be safe, well-tolerated, and immunogenic to a variety of influenza strains.

⁴⁸ The European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) has accepted BiondVax's Phase III trial plan. The CHMP said that "a single pivotal efficacy trial that provides a robust demonstration of efficacy against laboratory-proven influenza like illness could suffice for an approval."

- The northern hemisphere flu vaccine to be released later this year includes a new H3N2 formulation for the first time since 2015. However, a Rice University study forecasts that it will probably have the same reduced efficacy against the dominant circulating strain of influenza A as the vaccine given in 2016 and 2017 because of viral mutations related to vaccine production in eggs.
- Two new clinical trials testing an experimental vaccine against H7N9 infection have been enrolling volunteers across the US. The trials, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), will test different dosages of the inactivated influenza vaccine candidate known as 2017 H7N9 IIV, as well as different vaccination schedules. The trials will evaluate whether an [adjuvant](#) would be helpful to boost immune responses. The vaccine has been developed by Sanofi Pasteur with support from the Biomedical Advanced Research and Development Authority, part of the US Department of Health and Human Services.
- Microbiologists at the University of Chicago have created a genetic screening tool to identify two key factors that permit the influenza virus to infect human lung cells. With gene editing tools producing a library of modified cells, each minus a different gene, researchers can determine which changes affect their response to flu. The aim is to find potential targets for antiviral drugs⁴⁹.
- Georgia State University has signed a licensing deal with Pinnacle Bio to market a point-of-care influenza diagnostic developed by Suri Iyer, professor in the Department of Chemistry and the Center for Diagnostics & Therapeutics. Iyer and his colleagues say they have designed an accurate test that can detect influenza viruses in 15 minutes. The test requires only a nasal swab and detects a protein on the surface of the virus to identify influenza A and influenza B—the two main flu strains in humans.
- Researchers have [developed](#) a small molecule that they believe could weaken or even stop H3N2 flu strain in its tracks. It works by exploiting a flaw in the mechanism the virus uses to replicate, according to the team, which presented their research at the 255th National Meeting & Exposition of the American Chemical Society (ACS) in New Orleans.
- In the Netherlands, a child less than two years old developed a new reassortant A(H1N2) of seasonal influenza viruses that was detected in the routine sentinel influenza surveillance for influenza-like illness and other acute respiratory infections⁵⁰.

MERS-CoV

- As at 1 April there had been in Saudi Arabia a total of 1821 newly confirmed cases of MERS-CoV infection, including 735 reported fatalities. Seven cases had been reported since 21 March.
- Researchers from Saudi Arabia reported⁵¹ that investigations surrounding MERS-CoV cases detected in hospitals should cast a wide net when testing health workers and other contacts, regardless of contact type or symptom level. Their study was based

⁴⁹ Julianna Han, Jasmine T. Perez, Cindy Chen, Yan Li, Asiel Benitez, Matheswaran Kandasamy, Yoontae Lee, Jorge Andrade, Benjamin tenOever, Balaji Manicassamy, “Genome-wide CRISPR/Cas9 Screen Identifies Host Factors Essential for Influenza Virus Replication”, *Cell Reports*, 23(2), 596–607 DOI: <https://doi.org/10.1016/j.celrep.2018.03.045>

⁵⁰ The reassortant was made up of genes from currently circulating seasonal influenza virus subtypes A(H1N1)pdm09 (the haemagglutinin [HA] and the nonstructural [NS] protein genes) and A(H3N2) (the rest of the genes).

⁵¹ In a study published online 9 April 2018 in the *International Journal of Infectious Diseases*. Hala Amer, Abdulrahman S. Alqahtani, Faisal Alaklobi, Juhaina Altayeb, Ziad A Memish, “Health Care Workers’ Exposure to MERS CoronaVirus (MERS-CoV): Revision of Screening Strategies Urgently Needed” DOI: <https://doi.org/10.1016/j.ijid.2018.04.001>

on experiences with a June 2017 hospital outbreak in Riyadh⁵². In another study⁵³, a case series of seven children with the disease led researchers to affirm that the disease is typically milder in children than in adults⁵⁴.

- Saudi researchers reported⁵⁵ that it was difficult distinguishing pneumonia from volume overload in a patient with renal failure, which delayed a MERS-CoV diagnosis at a Riyadh hospital last year. This resulted in a superspreading event that sickened 44 people at three health facilities.
- The Coalition for Epidemic Preparedness Innovations (CEPI) has provided a grant to assist Themis develop vaccines against Lassa fever and MERS⁵⁶. The public-private vaccine initiative will also fund Inovio's Phase II development of INO-4500, its Lassa fever vaccine, and INO-4700, its MERS candidate⁵⁷.

SADS-CoV

- A newly identified coronavirus⁵⁸ in China emerged from horseshoe bats near the origin of the severe acute respiratory syndrome coronavirus (SARS-CoV), which emerged in 2002 in the same bat species⁵⁹. The new virus is named swine acute

⁵² They focussed on health workers exposed to the virus during an outbreak at King Saud Medical City in Riyadh, which occurred simultaneously with outbreaks at two of the city's other hospitals. Health workers who had unprotected contact with confirmed cases were isolated and tested 24 hours after exposure. They were permitted to return to work after testing negative for the virus twice, 3 days apart, and remaining symptom-free. Further testing was done based on symptoms the workers experienced during 14-days post exposure. Of 1,223 healthcare workers tested, 17 were positive for MERS-CoV infection. Of 15 who received adequate follow-up, 6 were positive on the first sampling, while 8 were positive on the second sampling. Time to negative testing of the 15 patients ranged from 4 to 47 days, with an average of 14.5 days. The first two index patients in the outbreak were super spreaders, with the first linked to nine health worker exposures and the second to six exposures. The third and fourth index patients each passed the virus to two healthcare workers. The range of exposures related to health worker infections included routine nursing care, being co-located in a clinical area, conversing, intubating, and connecting infected patients to breathing support. All healthcare workers who tested positive were asymptomatic or had mild disease. The researchers concluded that evidence supports 2015 WHO guidance that called for liberal testing of all close contacts and the need for repeated testing.

⁵³ Published in *Frontiers of Medicine*. Alfaraj, S.H., Al-Tawfiq, J.A., Altuwaijri, T.A. et al. "Middle East respiratory syndrome coronavirus in pediatrics: a report of seven cases from Saudi Arabia", *Front. Med.* (2018). <https://doi.org/10.1007/s11684-017-0603-y>

⁵⁴ The children were treated for MERS-CoV at Prince Mohamed Bin Abdulaziz Hospital in Riyadh between April 2014 and November 2016, a period during which 295 people with confirmed MERS-CoV infections were treated at the hospital. Two of the children had co-morbidities, one with bronchial asthma and chronic renal disease and the other with sickle cell disease. Four of the children received medical care within 1 to 7 days of symptom onset. The main symptom was fever, with vomiting, diarrhea, cough, and shortness of breath. Three of the children were asymptomatic contacts of confirmed MERS-CoV patients. Overall two children had thrombocytopenia, two had abnormal chest x-rays, one needed a ventilator and two required. All seven children left hospital with no subsequent complications. Researchers wrote that, while MERS infections are typically rare and mild in children, "further studies are needed to better understand pediatric MERS-CoV in terms of clinical presentation, infectivity, and outcome".

⁵⁵ [Hala Amer](#), [Abdulrahman S. Alqahtani](#), [Hind Alzoman](#), [Nawfal Aljerian](#), [Ziad A. Memish](#), "Unusual presentation of Middle East respiratory syndrome coronavirus leading to a large outbreak in Riyadh during 2017", *American Journal of Infection Control*, DOI: <https://doi.org/10.1016/j.ajic.2018.02.023>

⁵⁶ Austrian biotech Themis was awarded \$US 37.5 million to develop its vaccines using its measles vector platform.

⁵⁷ Inovio will receive up to \$US 56 million over five years. It is developing both candidates based on its DNA vaccine platform called ASPIRE.

⁵⁸ that killed nearly 25,000 piglets in 2016-17

⁵⁹ SARS-CoV infected more than 8,000 people and killed 774. No SARS-CoV cases have been identified since 2004.

diarrhea syndrome coronavirus (SADS-CoV). It does not appear to infect people at present⁶⁰.

Ebola

- Scientists have reported⁶¹ that an Ebola vaccine from Merck appears to provide protection two years after injection. An [earlier study](#) showed the vaccine, which is given in a single shot, rapidly generated protection against the virus. But how long that protection would last was not then known. Merck is working toward a [2018 licensure filing](#) with the FDA. The company said: “This publication is the first demonstration of the durability of the antibody responses induced by V920⁶² out to 2 years. We are encouraged by these important results and testing of long-term follow-up samples from additional trials is planned or ongoing to corroborate these findings.”
- This vaccine, rVSV-Zebov⁶³, is amongst a number of Ebola vaccines in development, but is the candidate selected for use in ring vaccination⁶⁴ in a new outbreak of Ebola in the Democratic Republic of Congo. As of 27 May, a total of 54 cases of haemorrhagic fever were reported in the region, including 35 confirmed cases of Ebola, 13 probable and 6 suspected.
- A research team, led by Robert Stahelin of Purdue University, believes it may be possible to stop the replication of Ebola virus by mutating its most important protein⁶⁵.
- A new study found that high doses of the antiviral drug favipiravir extended survival in non-human primates infected with Ebola virus⁶⁶.

HTLV-1

- In a letter published in [The Lancet](#), researchers announced⁶⁷ that an open letter had been sent to the World Health Organization (WHO) to increase awareness about the

⁶⁰ The study investigators identified SADS-CoV on four pig farms in China’s Guangdong Province. Scientists were from EcoHealth Alliance, Duke-NUS Medical School, Wuhan Institute of Virology and other organizations. Work was funded by the US National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health. The research is published in the journal *Nature*. P Zhou, *et al.* “Fatal swine acute diarrhea syndrome caused by an HKU2-related coronavirus of bat origin”. *Nature*. DOI: 10.1038/s41586-018-0010-9 (2018).

⁶¹ [Angela Huttner](#), [Selidji Todagbe Agnandji](#), [Christophe Combescure](#), [José F Fernandes](#), [Emmanuel Bache Bache](#), [Lumeka Kabwende](#), [Francis Maina Ndungu](#), [Jessica Brosnahan](#), [Thomas P Monath](#), [Barbara Lemaître](#), [Stéphane Grillet](#), [Miriam Botto](#), [Olivier Engler](#), [Jasmine Portmann](#), [Denise Siegrist](#), [Philip Bejon](#), [Peter Silvera](#), [Peter Kremsner](#), [Claire-Anne Siegrist](#), “Determinants of antibody persistence across doses and continents after single-dose rVSV-ZEBOV vaccination for Ebola virus disease: an observational cohort study”, *The Lancet Infectious Diseases*, 4 April 2018. DOI: [https://doi.org/10.1016/S1473-3099\(18\)30165-8](https://doi.org/10.1016/S1473-3099(18)30165-8)

⁶² The vaccine’s developmental designation. In scientific trials, the vaccine is identified as rVSV-ZEBOV.

⁶³ VSV denotes vesicular stomatitis virus, which does not infect humans. Researchers replaced a specific glycoprotein with one from the Zaire strain of Ebolavirus (hence “Zebov”). It is live attenuated vaccine. Only one dose is required to induce immunity.

⁶⁴ The subjects for ring vaccination are front-line health professionals, people who have been in contact with confirmed cases of Ebola, and contacts of these contacts.

⁶⁵ “A cationic, C-terminal patch and structural rearrangements in Ebola virus matrix VP40 protein control its interactions with phosphatidylserine”, [Journal of Biological Chemistry](#), 2 March, 2018, 293, 3335-3349. doi: 10.1074/jbc.M117.816280

⁶⁶ Jérémie Guedj, Géraldine Piorkowski, Frédéric Jacquot, Vincent Madelain, Thi Huyen Tram Nguyen, Anne Rodallec, Stephan Gunther, Caroline Carbonnelle, France Mentré, Hervé Raoul, Xavier de Lamballerie “Antiviral efficacy of favipiravir against Ebola virus: A translational study in cynomolgus macaques”, published 27 Mar 2018 *PLOS Medicine* <https://doi.org/10.1371/journal.pmed.1002535>

global spread of the retrovirus HTLV-1 (human T-cell leukemia virus) and its deadly nature. They advocate increased screening of blood transfusions and organ transplants, as well as increased funding for research⁶⁸.

- Robert Gallo⁶⁹ in an interview⁷⁰ described HTLV-1 as a "cousin" to HIV-1. HTLV-1 was the first retrovirus to be discovered (in 1979-1980), but very shortly research interest transferred to HIV and the intensifying AIDS epidemic. He said: "There are a few labs at the NIH⁷¹ who are working on it, but they are very underfunded." In their letter, the three authors said HTLV-1 is "the most potent carcinogenic oncovirus and potentially the most oncogenic risk factor including chemical carcinogens⁷²." They noted that as well as leading to adult T-cell leukemia, the virus weakens the patient's immune system and allows bacterial infections, such as pneumonia and bronchiectasis. There can also neurological conditions associated with the virus, such as [HTLV-1-associated myelopathy/tropical spastic paraparesis \(HAM/TSP\)](#).
- The Global Virus Network, an international coalition of medical virologists, says that as with HIV, the spread of HTLV-1 is through body fluids and unprotected sexual intercourse. Transfusion of infected blood, transplantation of infected organs, sharing of needles, and breastfeeding by an infected mother can all transmit the virus.
- HTLV-1 does not always occur in communities which are highly visible, or which have ready access to medical care. It is endemic in parts of South America (Brazil), Africa, the Caribbean, and Asia. In Australia, the prevalence in Alice Springs has been estimated at around 40 per cent of the adult population⁷³, an increase from 14 per cent in 1993. Since infected people can remain asymptomatic for about 40 years or more, they can unknowingly spread the disease.

Other diseases: occurrence, diagnosis, prevention and treatment

- In Australia, the incidence of severe tissue-destroying Buruli ulcers has been on the rise and scientists are puzzled as to why Victoria has been particularly affected⁷⁴. Some government research funding has been provided to assist in investigating transmission.
- Sanofi will develop a new vaccine manufacturing facility at Sanofi Pasteur's Canadian headquarters in Toronto, to service increasing demand for five-component acellular pertussis antigens. It will also be able to produce the antigens used in the diphtheria and tetanus vaccines.
- At the beginning of April, health officials warned of a measles outbreak in the southern Brisbane and Logan areas, confirming four cases in the preceding three weeks. The Metro South Hospital and Health Service offered a targeted immunisation campaign with free clinics.

⁶⁷ [Fabiola Martin](#), [Yutaka Tagaya](#), and [Robert Gallo](#), "Time to eradicate HTLV-1: an open letter to WHO", *The Lancet*, [Volume 391, No. 10133](#), p1893–1894, 12 May 2018, DOI: [https://doi.org/10.1016/S0140-6736\(18\)30974-7](https://doi.org/10.1016/S0140-6736(18)30974-7)

⁶⁸ about the nature, prevention (including vaccination), and treatment of the disease.

⁶⁹ co-founder and director of the Institute of Human Virology at the University of Maryland School of Medicine, and also co-founder and scientific director of the Global Virus Network (GVN) and co-chair of the [GVN HTLV-1 Task Force](#)

⁷⁰ With *MedPage Today*

⁷¹ US National Institutes of Health

⁷² Gallo said the closest virus to it in terms of carcinogenicity is hepatitis B.

⁷³ See the preliminary study from the [Baker Institute for Heart and Diabetes](#)

⁷⁴ Daniel P O'Brien, Eugene Athan, Kim Blasdel and Paul De Barro, "Tackling the worsening epidemic of Buruli ulcer in Australia in an information void: time for an urgent scientific response", published online: 16 April 2018 *Med J Aust* 2018; 208 (7): 287-289. || doi: 10.5694/mja17.00879

- With bat numbers rising in Northern NSW health authorities have warned residents to avoid contact as they can carry bacteria and viruses which can be harmful to humans, including the potentially fatal lyssavirus⁷⁵.
- At 13 April, NSW Health was investigating a possible contamination source following confirmation 3 people had developed legionnaires' disease after spending time in the vicinity of Macquarie Fields.
- An outbreak of hepatitis A in a number of Australian states and territories has been linked to imported frozen pomegranates.
- In Nigeria, an outbreak of Lassa fever claimed 119 lives between 1 January and 18 March.
- Researchers at the University of Massachusetts are launching a Phase I trial to determine the safety of a potential DNA vaccine for HIV. The vaccine was developed by Shan Lu, a professor of biochemistry and molecular pharmacology. The trial will be administered by the HIV Vaccine Trial Network (HVTN), which is sponsored by the US National Institutes of Health.
- Scientists have developed an antibody that protects rhesus monkeys from infection by simian HIV (SHIV), a virus similar to HIV that causes an AIDS-like illness in these monkeys. They report⁷⁶ that protection lasts up to 20 weeks, and that regular use of anti-HIV antibodies could provide long-term prevention of HIV infection in humans.
- The most recent annual surveillance report from the Kirby Institute says gonorrhoea and syphilis are on the rise in Australia but HIV rates are stable.
- Research from Northwestern Medicine offers new insights into how cytomegalovirus — a common virus in the herpes family — replicates within human cells⁷⁷, and identifies which proteins could be therapeutically targeted to suppress infection⁷⁸.
- East Asian ticks, sometimes called long horned or bush ticks, have been found in New Jersey. These ticks spread a virus called SFTS, severe fever with thrombocytopenia syndrome. Symptoms include fever, fatigue, chill, headache, nausea, muscle pain, diarrhoea, vomiting, abdominal pain, disease of the lymph nodes, conjunctival congestion and in some cases, death⁷⁹.
- Emergent BioSolutions plans to launch mobile manufacturing units that can produce hyperimmune therapeutics for known and emerging infectious diseases⁸⁰.

⁷⁵ <http://www.health.nsw.gov.au/Infectious/factsheets/Pages/rabies-australian-bat-lyssavirus-infection.aspx>

⁷⁶ [Rajeev Gautam](#), [Yoshiaki Nishimura](#), [Natalie Gaughan](#), [Anna Gazumyan](#), [Till Schoofs](#), [Alicia Buckler-White](#), [Michael S. Seaman](#), [Bruce J. Swihart](#), [Dean A. Follmann](#), [Michel C. Nussenzweig](#) and [Malcolm A. Martin](#), “A single injection of crystallizable fragment domain–modified antibodies elicits durable protection from SHIV infection” *Nature Medicine* (2018) published 16 April, doi:10.1038/s41591-018-0001-2

⁷⁷ Cytomegalovirus can be life-threatening for people with weakened immune systems or babies infected before birth. It is the leading cause of congenital birth defects and can result in hearing loss, small head size, vision impairment and developmental delay.

⁷⁸ [Dean J. Procter](#), [Avik Banerjee](#), [Masatoshi Nukui](#), [Kevin Kruse](#), [Vadim Gaponenko](#), [Eain A. Murphy](#), [Yulia Komarova](#) [Derek Walsh](#), “The HCMV Assembly Compartment Is a Dynamic Golgi-Derived MTOC that Controls Nuclear Rotation and Virus Spread”, *Developmental Cell*, Volume 45, Issue 1, p83–100.e7, 9 April 2018, DOI: <https://doi.org/10.1016/j.devcel.2018.03.010>

⁷⁹ SFTS was first identified in China in 2009, and the number of cases that have been reported in South Korea, China, and Japan has increased sharply in the past nine years.

⁸⁰ Emergent BioSolutions has developed and manufactured plasma-derived hyper immunes, which have large amounts of specific antibodies in the serum. Dr. Laura Saward, Emergent BioSolutions senior vice president and Antibody Therapeutics Business Unit Head said: “On this hyperimmune platform, we have successfully developed and manufactured FDA-licensed products such as treatments for inhalation anthrax and complications from smallpox vaccination”. She explained the process starts with plasma donors who have been stimulated to have an immune response and develop antibodies to fight specific diseases.