Monitoring International Trends

**posted April 2015**

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:

* Kedrion Biopharma announced that Koate Double Viral Inactivation (DVI) Antihemophilic Factor (human), used in the treatment of haemophilia A, is now being manufactured using a process that involves applying a polyethylene glycol (PEG) depth filtration step during purification of the plasma used. (Section 1)
* Srinivasa R. Raghavan and [Remedium Technologies](http://remediumtechnologies.com/) developed a foam (composed of a polymer derived from crustacean shells) that the US Food and Drug Administration (FDA) is currently evaluating for use on noncompressible injuries. (Section 1)
* [CSL Behring](http://www.cslbehring.com/) announced that the European Medicines Agency (EMA) had begun reviewing the company's Marketing Authorization Application (MAA) for its long-acting fusion protein linking recombinant coagulation factor IX with recombinant albumin (rIX-FP). The FDA in February 2015 accepted for review CSL Behring's Biologics License Application for rIX-FP. Data for rIX-FP will be presented to the International Society on Thrombosis and Haemostasis (ISTH) Congress in Toronto in June 2015. (Section 2)
* The FDA has issued a Boxed Warning for the anaemia treatment, ferumoxytol (Feraheme), to notify users of the potentially fatal allergic reactions that may occur with the drug. (Section 2)
* Janssen acquired XO1 Limited, a firm focused on developing the anti-thrombin antibody ichorcumab. This mimics the activity of a human antibody which appears to produce an anticoagulated state without predisposition to bleeding. (Section 3)
* Novo Nordisk announced it would launch Novoeight (Antihemophilic Factor [Recombinant]) in the US mid-April. Novoeight can be stored at up to 86 degrees Fahrenheit for 12 months. It can be kept at that temperature for up to 4 hours after reconstitution. (Section 3)
* A case study from Canada shows that blood products from a donor with allergies can produce the same reaction in children who receive the donation. (Section 5)
* A UK trial funded by the National Institute for Health Research has evaluated liberal versus restrictive transfusion approaches for cardiac surgery patients. No significant differences between groups were observed with respect to serious complications. No differences were observed for length of ICU stay and health care costs. There was, however, an increase in mortality of borderline statistical significance at three months in patients assigned to the restrictive group. This finding was supported by sensitivity analyses. Further clinical trials are therefore required on the safety of liberal versus restrictive transfusion approaches for cardiac surgery patients. (Section 5)
* Canadian Blood Services is examining whether the age and sex of the donor affects the health of the recipient. (Section 5)
* Data presented at the American Academy of Orthopaedic Surgeons Annual Meeting showed that among patients who underwent total knee or total hip replacement, intraoperative use of tranexamic acid significantly reduced the need for transfusion. (Section 5)
* Researchers from King's College London and the London School of Hygiene and Tropical Medicine report that pregnant women with a severe form of sickle cell disease (SCD) are six times more likely to die during or following pregnancy, and have an increased risk for stillbirth, high blood pressure, and preterm delivery, compared with pregnant women without SCD. (Section 6)
* A coroner in Western Australia recommended that the Australian Dental Association consider advising its members to provide patients who undergo extractions, especially those on warfarin, with written post-operative instructions. (Section 7)
* The Seventeenth International Congress on Infectious Diseases is scheduled to take place in Hyderabad, India, from 2 to 5 March 2016. The program will focus on **Infectious Diseases in South Asia, Tuberculosis and Respiratory Infections, HIV and Viral Hepatitis, Clinical Infectious Diseases, Implementing Global Health Priorities, and Science and Diagnosis of Infectious Diseases. (Section 8)**
* Researchers from the US National Institute of Allergy and Infectious Diseases (NIAID) found the genetics of red blood cells affects whether people are susceptible to, or resilient against, malaria. One of many findings was that children carrying the sickle cell gene may have a lower risk of contracting malaria. (Section 8)
* The US Department of Agriculture's Animal & Plant Health Inspection Service (APHIS) has been monitoring various highly-pathogenic avian influenza (HPAI) virus strains in wild and domestic bird populations in the US's Pacific and Mississippi flyways. With the highly pathogenic avian flu (HPAI) strains H5N2 and H5N8 threatening US poultry flocks, the US Department of Agriculture (USDA) is developing a vaccine as a backup tool to protect them, in case their standard containment measures fail. (Section 8)
* On 3 April, the Chinese veterinary authority reported on a new outbreak of avian flu to the World Organisation for Animal Health (OIE). The outbreak of highly pathogenic H5N6 started on 27 March in Jiangsu at a goose farm with 22,669 birds. Of these, 260 showed symptoms and 93 died; the remaining 22,576 were destroyed. (Section 8)
* At 6 April, the estimated count of human A(H7N9) cases in mainland China since the inception of human infection stood at 619. There had been 27 deaths in 2015.
* The fourth human case of avian influenza A(H5N1) reported from China in 2015 attended hospital in Yunnan province on 20 March. (Section 8)
* WHO’s statistics for Ebola up to 5 April 2015 showed a global total of 14,794 confirmed cases; 2,580 probable cases; and 8,141 suspected cases. Total number of cases was thus thought to be 25,515 (with 10,572 deaths). A total of 30 confirmed cases were reported in the week to 5 April 2015. This was the lowest weekly total since the third week of May 2014. (Section 8)
* Inovio Pharmaceuticals was selected to receive a $US 45 million grant from the US Defense Advanced Research Projects Agency (DARPA) to lead a collaborative team to develop multiple treatment and prevention approaches against Ebola. (Section 8)
* Researchers reported that HIV may begin replicating within a patient’s brain and central nervous system (CNS) as early as four months after infection. (Section 8)
* Healthcare workers fighting polio are facing the challenge of circulating vaccine-derived polioviruses originating from one of the two vaccines used against the illness. They threaten to overtake wild poliovirus as the foremost source of the disease. (Section 8)
* Researchers have now identified blood-based biomarkers in patients with active tuberculosis that could lead to new blood-based diagnostics and tools for monitoring treatment response and cure. (Section 8)

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# 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.*

* 1. Kedrion Biopharma announced from Fort Lee, New Jersey, that Koate Double Viral Inactivation (DVI) Antihaemophilic Factor (human), used in the treatment of haemophilia A, is now being manufactured using a process that further enhances the safety and purity of that product. The process now used with Koate-DVI involves applying a polyethylene glycol (PEG) depth filtration step during purification of the plasma used. The company says the new process shows an enhanced ability to remove or inactivate six of seven viruses tested and says it also has the ability to remove low levels of a transmissible agent similar to that which causes Creutzfeldt-Jakob disease (CJD). Kedrion says assays in clotting tests indicated that Factor VIII activity and antigen, von Willebrand factor potency and antigen, overall protein content, and content of albumin, fibrinogen and IgG remain unchanged. Koate-DVI manufactured using the new process is currently available in 500IU and 1000IU vials, and will be introduced with 250IU vials in mid-2015.
	2. Emmaus Life Sciences of California presented data from the company’s Phase III clinical trial of its pharmaceutical grade L-glutamine (PGLG) treatment (for sickle cell anemia and sickle beta-0 thalassemia) during the 9th Annual Sickle Cell Disease Research and Educational Symposium and 38th National Sickle Cell Disease Scientific Meeting, held April 10-13, 2015 in Hollywood, Florida. The prospective, randomized, double-blind, placebo-controlled, parallel-group, multi-centre clinical trial enrolled 230 adult and paediatric patients from five years of age, across 31 US sites. Clinical benefits of the PGLG treatment were reported[[1]](#footnote-1) to include a reduction in the median frequency of sickle cell crisis, a lower median frequency of hospitalizations, a reduction in median cumulative hospital days, and fewer cases of acute chest syndrome, with a well-tolerated safety profile.
	3. First responders to soldiers wounded in battle have no way to effectively dam blood flows from noncompressible injuries (severe wounds near major organs) explained Srinivasa R. Raghavan of the University of Maryland during a presentation at the American Chemical Society national meeting in Denver. Raghavan announced that he and [Remedium Technologies](http://remediumtechnologies.com/), a start-up company led by one of his former students, have developed a foam, composed of a polymer derived from crustacean shells that the US Food and Drug Administration (FDA) is currently evaluating for use on noncompressible injuries. He said hydrophobic components of the modified chitosan dock in blood cell membranes to help stop bleeding. The researchers dispersed the modified chitosan in an aqueous solution to create a fluid they could spray directly onto noncompressible wounds. As the solution sprays from an aerosol can, it traps bubbles of a biocompatible hydrocarbon propellant gas and begins to foam. The foam expands to cover the injury and block blood flow. The speaker said that coupled with the modified chitosan’s coagulating effect, the foam can reduce blood loss by up to 90 per cent, and this had been demonstrated during tests performed on pig livers. Raghavan stressed that the foam combats blood loss, rather than repairing injured tissue—but that it could help patients survive until a surgeon can deal with the damage. “We really believe we have a material here that can find its way into emergency vehicles and even soldiers’ backpacks,” he said.

# Regulatory

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

### Plasma and recombinant products

* 1. [CSL Behring](http://www.cslbehring.com/) announced on 30 March that the European Medicines Agency (EMA) had started the Centralized Procedure for reviewing the company's Marketing Authorization Application (MAA) for its long-acting fusion protein linking recombinant coagulation factor IX with recombinant albumin (rIX-FP)[[2]](#footnote-2). If European Commission approval is forthcoming, rIX-FP will provide haemophilia B patients in the European Union (EU), as well as the European Economic Area (EEA) countries, with a long-acting treatment option with dosing intervals up to 14 days. In [February 2015](http://www.cslbehring.com/newsroom/FDA-accepts-for-review-BLA-for-rIX-FP-for-hemophilia-b), the FDA accepted for review CSL Behring's Biologics License Application for rIX-FP. Pivotal data for rIX-FP will be presented during the International Society on Thrombosis and Haemostasis (ISTH) Congress in Toronto in June 2015.CSL Behring's MAA is based on data from the PROLONG-9FP clinical development program, covering patients from the age of 1 to 61 years[[3]](#footnote-3).
	2. Kamadareceived recognition from the Canadian Intellectual Property Office (CIPO) for Patent Application No. 2,538,998 entitled, “Large Scale Preparation of Alpha-1 Proteinase Inhibitor and Use Thereof.” The Chief Executive Officer of Kamada, David Tsur said: “Securing global protection for our novel plasma-derived products production technologies, including methods of use and manufacturing processes, is critically important as we develop highly-purified AAT in both intravenous and inhaled methods of administration to address major unmet needs in a variety of important disease states including pulmonary diseases, type-1 diabetes and Graft-versus-Host disease…….Baxter Healthcare Corporation was granted distribution rights in Canada for our intravenous AAT product, Glassia, but has not commenced selling in this territory to date. In addition, two of the sites from the Phase II/III clinical trial of our inhaled AAT therapeutic to treat AATD were in Canada”.

### Other

* 1. Johnson & Johnson's [Ethicon](http://go.questexweb.com/dc/rs2MVsy89GkWyRZEc6BcuAVZlzgAhgZnF2rQs1xWJlJKd1HvWfQ7-UWcVsBCRsPUCxjc6WnUM-m4uohiYuiVQNum38y8mOKYm7vRQRyFJL5e2U9ZVAcGBcxXhyI5FDb7tcVGzng-s6-vm6lhgaLjybkCl6le_3fE56YlwfPmHF3mYutHlI6sCKic5Mm-URYR4rvz9MAEAGDfmo5UBofyT6f5jk_3-nyqPMC25i8bj8MKpJ30W4tCN7vpcB2kx6xK/L941FQ00l0Ys0Mtmj0Q0e0u) division received clearance from the FDA for an expanded indication of its Evarrest patch, which can now be used to help control bleeding during adult liver surgery. The patch is bio-absorbable, and uses human thrombin and fibrinogen proteins that aid clotting. It was originally approved by the FDA in 2012 for use in stopping unexpected and uncontrollable bleeding during non-cardiac surgery.
	2. Novartis announced that the FDA had granted an accelerated approval to an oral suspension formulation of deferasirox (Jadenu) for the treatment of patients aged two or more with chronic iron overload due to multiple blood transfusions. The drug was approved with a Boxed Warning regarding renal failure, hepatic failure, and gastrointestinal haemorrhage. In 2005 deferasirox became the first FDA approved oral therapy for chronic iron overload, but that formulation-Exjade-had to be dissolved in liquid. As well as being indicated for transfusion related iron overload, the oral suspension formulation is indicated for patients 10 years or more with non-transfusion-dependent thalassemia.
	3. Protalex of New Jersey announced that the FDA had reviewed its Investigational New Drug Application (IND) and concluded that clinical studies with PRTX-100 in patients with Immune Thrombocytopenia (ITP)[[4]](#footnote-4) may begin. PRTX-100 is a highly purified form of Staphylococcal Protein A[[5]](#footnote-5). The Company will begin enrolment in a Phase I/II open-label, dose-escalating study of PRTX-100 in adults with persistent/chronic ITP in the second quarter of 2015. Protalex believes that its drug is superior to the two most recently approved drugs used to treat ITP, Nplate (romiplostin) and Promacta (eltrombopag). Both of those drugs escalate platelet production but according to Protalex do not appear to affect the underlying platelet destruction process. In contrast, its own pre-clinical data indicate that PRTX-100 may have the potential to reduce the immune-mediated destruction of the platelets. PRTX-100 has already established an acceptable safety profile based on data from patients treated in five clinical studies including patients with rheumatoid arthritis, also an autoimmune disease.
	4. The FDA has issued a Boxed Warning for the anaemia treatment, ferumoxytol (Feraheme), to warn patients and health care workers about the potentially fatal allergic reactions that may occur with the drug’s use[[6]](#footnote-6). It also recommends that patients immediately alert their health care professional or seek emergency care if they develop breathing problems, low blood pressure, light headedness, dizziness, swelling, a rash, or itching during or after Feraheme administration; it requests patients who have experienced adverse reactions to the product to report them to the FDA’s MedWatch Adverse Event Reporting program.

# 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.*

* 1. Novo Nordisk announced it would launch Novoeight® (Antihaemophilic Factor [Recombinant]) in the US mid-April. The FDA approved Novoeightfor use in adults and children with haemophilia A for the control and prevention of bleeding, perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes. Novoeight can be stored at up to 86 degrees Fahrenheit for 12 months. It can be kept at that temperature for up to 4 hours after reconstitution.
	2. Biogen Idec is now known as Biogen, with a new logo.
	3. At the US National Kidney Foundation spring meeting **Hospira** presented data from two studies on a proposed biosimilar, Retacrit. The drug is a proposed biosimilar to Amgen’s Epogen (epoetin alfa) and Janssen's Procrit (epoetin alfa). In February the FDA accepted Hospira’s Biologics License Application (BLA), seeking approval for Retacrit in the US. Hospira is set to be acquired by Pfizer. The deal is expected to close in the second half of 2015. The transaction is valued at approximately $US 17 billion.
	4. Belgium-based Janssen Pharmaceuticals (a Johnson & Johnson company) has acquired XO1 Limited, a firm focused on developing the anti-thrombin antibody ichorcumab. This mimics the activity of a human antibody which appears to produce an anticoagulated state without predisposition to bleeding. Initially, ichorcumab was developed by Cambridge University Hospitals and Cambridge University with support from the university's commercialization arm Cambridge Enterprise. The product was licensed to XO1 in order to take its development towards the clinic.

# 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.*

* 1. In East Baltimore, Maryland, [Johns Hopkins Hospital](file:///C%3A%5Ctopic%5Chealth%5Chealthcare%5Cjohns-hopkins-hospital-PLCUL000168-topic.html) has almost completed a unit designed to care for patients with Ebola and other dangerous infections. It joins a very small group of US hospitals with such facilities. The unit includes three patient rooms, each with rooms on either side of it for donning and removing protective equipment. It has a dedicated laboratory for testing patient specimens. Its separate waste management system can treat linens, protective equipment and bodily fluids on-site. It is equipped to perform ultrasounds and X-rays without transferring patients beyond containment. The unit is designed to contain airborne pathogens, using specialized air handling systems and negative air pressure. It has systems to sterilize complete rooms using a vaporized hydrogen peroxide solution. This biocontainment unit gives Hopkins facilities such as those at the National Institutes of Health (NIH) Clinical Center in Bethesda, Emory University Hospital in Atlanta and Nebraska Medical Center in Omaha, all of which have cared for Ebola patients. There is a fourth US biocontainment unit at Rocky Mountain Laboratories, an NIH facility in Hamilton, Montana.
	2. AABB (formerly the American Association of Blood Banks) held a symposium on Implementation of Pathogen‐Reduced Blood Components on 27-28 April 2015 in Bethesda, Maryland. It said the recent FDA approval of pathogen‐reduced platelet and plasma systems made it necessary to examine the legal implications of licensure for blood collectors and transfusion services. Representatives from US and international blood centres outlined their plans and implementation experiences respectively. Available haemovigilance data were reviewed. Hospital perspectives on the clinical utility of treated platelets were discussed.

# Appropriate transfusion

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

* 1. A case study from Canada[[7]](#footnote-7) shows that blood products from a donor with allergies can produce the same reaction in children who receive the donation. An 8 year old boy who had received a blood transfusion had an anaphylactic reaction within 10 minutes of eating salmon although he had previously eaten salmon without allergic reaction. The boy later experienced an allergic reaction to peanut butter although he had eaten peanut products before. After about four months. The boy’s allergic reactions subsided after about four months. Canadian Blood Services found on investigation that one donor of blood products to the boy had a severe allergy to peanuts, tree nuts, shellfish, and all fish, including salmon. That donor was excluded from future donations.
	2. A UK trial funded by the National Institute for Health Research has evaluated liberal versus restrictive transfusion approaches for cardiac surgery patients. 2003 patients from [[8]](#footnote-8)seventeen hospitals were included. One thousand patients were randomly assigned to receive restrictive transfusions, only when their haemoglobin level dropped below 7.5 grams per decilitre. Those in the liberal-threshold group received transfusions when haemoglobin levels dropped below 9 grams per decilitre. The rates of transfusion were almost twice as high in the liberal group as in the restrictive group. No significant differences between groups were observed with respect to serious complications such as heart attack, stroke, acute kidney injury, bowel infarction, or infections. No differences were observed for most other outcomes such as length of ICU stay and health care costs. There was, however, an increase in mortality of borderline statistical significance at three months in patients assigned to the restrictive group. This finding was supported by sensitivity analyses. Further clinical trials are therefore required on the safety of liberal versus restrictive transfusion approaches for cardiac surgery patients.
	3. Canadian Blood Services, through its Network Centre for Applied Development (netCAD) is examining whether the age and sex of the donor affects the health of the recipient. Jason Acker, senior development scientist for Canadian Blood Services and a professor at the University of Alberta, says: “We’re really at the cusp of a change in how we think about blood products. “The future could be a lot more customized collection and distribution based on what those patients need.” His lab is looking at the differences in blood characteristics between younger and older women and comparing them with samples from men of the same ages. He asks: “What kind of properties does the blood from young, female donors have? We’re finding that those young red blood cells are more pliable—they have a better chance of squishing through the capillary vessels—and have higher concentrations of haemoglobin than the red cells that we get from an older donor.” His results will mesh with findings from researchers at McMaster University in Hamilton and Ottawa Hospital Research Institute who are trawling patient information collected on 800,000 transfusions in Ontario between 2006 and 2014, matching the age and sex of the donor with information about the patient’s health, including how long they stayed in hospital and whether the stay ended in death. Nancy Heddle, who leads McMaster’s transfusion research program, says it is also examining whether how blood components are manufactured affects the patient.
	4. Data presented at the American Academy of Orthopaedic Surgeons Annual Meeting[[9]](#footnote-9).showed that among patients who underwent total knee or total hip replacement, intraoperative use of tranexamic acid significantly reduced the need for transfusion. The retrospective study considered 883 patients. 330 were not treated with TXA intraoperatively, because their surgery took place before the introduction of a comprehensive preoperative blood management (PBM) protocol. 553 patients underwent surgery after the introduction of a PBM protocol which included intraoperative treatment with TXA. The researchers examined patient demographics, comorbidities, preoperative haemoglobin levels, protocol compliance, treatment, operative times and postoperative transfusion. The effects of PBM protocol, treatment and TXA administration on patient outcomes were examined using multiple logistic and linear regression models. In patients who had preoperative haemoglobin levels between 10 g/dL and 13 g/dL, preoperative intervention for anemia was implemented. However, use of intraoperative TXA was found to have the greatest effect on reducing patients’ odds of needing transfusion. Additionally, patients who had higher hemoglobin levels preoperatively had decreased odds of transfusion. Patients who were anaemic prior to the operation required fewer units of blood when treated with TXA.

# 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.*

* 1. Children with common allergic diseases such as atopic dermatitis, allergic rhinitis, urticaria, and allergic conjunctivitis showed a greater risk for developing primary immune thrombocytopenia (ITP), according to a recent US study[[10]](#footnote-10). The population-based, case-control study from the National Health Insurance Research Database considered 1,203 children aged younger than 18 years who were diagnosed with [ITP](http://www.healio.com/search?q=primary%20immune%20thrombocytopenia) between 1998 and 2008, along with 4,812 controls. Children with asthma did not show an increased risk for ITP, while the risk was greater for children with an increasing number of concurrent allergic diseases. Because it was a cross-sectional study, causality between the allergies and ITP could not be determined. The researchers wrote: “However, this study clearly demonstrates an association between allergic diseases and increased risk of ITP in a high number of patients. Further investigations on the environmental and genetic factors and common immunological aberrancies related to allergies and ITP are warranted.”
	2. According to a Singapore-led study[[11]](#footnote-11), Hepatitis B virus exposure *in utero* boosted immune system maturation among a cohort of neonates born to HBV-positive mothers. Michelle Hong, research fellow at Duke-NUS Graduate Medical School, Singapore, said: “Despite causing diseases later in life, HBV might actually be beneficial to humans early in life.”[[12]](#footnote-12)
	3. Research published in the *Proceedings of the National Academy of Sciences* has led to hopes that a blood test using sound to detect cancer could make biopsies a thing of the past. The device uses acoustic waves to separate circulating blood-borne tumour cells from white blood cells.
	4. Scientists at Imperial College London and the Houston Methodist Research Institute have developed biodegradable, silicon "nanoneedles" to deliver genetic material to stimulate the growth of blood vessels[[13]](#footnote-13).
	5. An experimental nanoparticle therapy developed by researchers at Albert Einstein College of Medicine of Yeshiva University (and tested in mice) halved the time it takes to heal wounds compared with no treatment at all. Details were published online in the Journal of Investigative Dermatology. David J. Sharp (professor of physiology & biophysics at Einstein) and his colleagues had earlier discovered that an enzyme called fidgetin-like 2 (FL2) slows down skin cells as they move towards wounds to heal them. They developed a drug that inactivates the gene that makes FL2 and then put the drug in tiny gel capsules and applied these nanoparticles to wounds on mice. They healed much faster than untreated wounds.
	6. Acquired thrombotic thrombocytopenic purpura, or TTP, is an autoimmune disorder which produces blood clots in small arterioles throughout the body, particularly in the brain, heart, pancreas and kidneys. The most effective treatment so far has been daily plasma exchange, with replacement of all or one and a half times the body’s entire blood volume. Such treatment may need to be continued for weeks or, in some patients, months. Long Zheng of the University of Alabama at Birmingham[[14]](#footnote-14), and colleagues[[15]](#footnote-15) have developed a potential new way to treat acquired TTP[[16]](#footnote-16). Their approach could reduce the amount of plasma transfusion needed for TTP patients, and also could perhaps become a new emergency therapy for strokes, heart attacks, and pre-eclampsia. All these are associated with relative deficiency of plasma ADAMTS13 activity. Their work has reached proof-of-concept stage in a mouse TTP model. People with TTP produce an autoantibody that inactivates the enzyme ADAMTS13. It is the loss of ADAMTS13 activity which allows formation of the destructive microvascular clots in important organ tissues. The researchers aimed to hide the enzyme within platelets where the antibody could not “see” it. The research group developed transgenic mice that expressed functional recombinant human ADAMTS13 (rADAMTS13) in mouse platelets. Their findings “suggest that platelets may be ideal carriers for antithrombic ADAMTS13, allowing its release at high concentrations at the site of thrombus formation without being inactivated by the potential circulating anti-ADAMTS13 inhibitors.” Zheng says a next step may be to learn how to pack ADAMTS13 inside human platelets while bags of donated blood are tested for multiple infectious disease markers. These would then need to be tested to determine how many ADAMTS13-loaded platelets need to be transfused to get anti-blood clot and anti-TTP effects in patients.
	7. Scientists at The Scripps Research Institute have found that a particular enzyme in hematopoietic stem cells (HSCs) is the key to keeping stem cells functional. Their work[[17]](#footnote-17) demonstrated that animal models without this enzyme experience dangerous HSC activation and are overcome by lethal anaemia.
	8. The condition where mothers and [foetuses](http://medicalxpress.com/tags/fetuses/) have different antigens is called foetal and neonatal alloimmune thrombocytopenia, or FNAIT. It affects about one in 1,000 live births. In ten to twenty per cent of those cases, foetuses experience bleeding in the brain. Platelets are amongst the cell types that often have different antigens. Foetal platelets can be targeted by the mother's immune system and low platelet counts have been considered the cause of foetal and neonatal brain bleeds. A new study[[18]](#footnote-18) suggests instead, said Dr Heyu Ni[[19]](#footnote-19) “that the [immune system](http://medicalxpress.com/tags/immune%2Bsystem/)'s attack on the new [blood vessel cells](http://medicalxpress.com/tags/blood%2Bvessel%2Bcells/) in the brain is more likely responsible. An antigen, called beta 3 integrin, is found both on platelets and on the cells responsible for developing blood vessels in foetuses.……What we've discovered means that platelet transfusions are necessary to control bleeding after birth but may not be an effective therapy for brain bleeds in foetuses since platelets may be not essential to stop foetal bleeding," said Dr. Ni. "We should consider different therapies to prevent brain bleeds and ensure blood vessels in the brain are developed properly before birth." The different therapy which Dr. Ni's research team considered was intravenous immunoglobulin transfusions. He said while this may be an effective therapy more research is needed to confirm this.
	9. Researchers from King's College London and the London School of Hygiene and Tropical Medicine report that pregnant women with a severe form of sickle cell disease (SCD) are six times more likely to die during or following pregnancy, and have an increased risk for stillbirth, high blood pressure, and preterm delivery, compared with pregnant women without SCD[[20]](#footnote-20). The research team examined published observational studies which included 26,349 [pregnant women](http://medicalxpress.com/tags/pregnant%2Bwomen/) with SCD and 26,151,746 pregnant women who shared attributes with the SCD population, such as ethnicity or location, but were otherwise healthy. Thirteen of the studies originated from high-income countries. They found that even in developed countries with advanced care, there continues to be a much higher maternal mortality rate in women with sickle cell disease compared with the general population.

# Legal actions and enquiries

*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.*

* 1. A coroner in Western Australia found that the death of a patient, after the extraction of two teeth, had been preventable. Her dentist had not followed industry guidelines[[21]](#footnote-21) for pre- and post-operative care for patients on warfarin, and he had provided her with verbal post-operative instructions when written instructions may have served better. The patient herself had declined to go to hospital after her daughter had found her unwell. A post-mortem revealed the cause of death was acute gastrointestinal haemorrhage secondary to bilateral dental extraction. The coroner recommended that the Australian Dental Association consider advising its members to provide patients who undergo extractions, especially those on warfarin, with written post-operative instructions. He referred the case to the Dental Board of Australia.

# 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).*

### The International Congress on Infectious Diseases

* 1. The Seventeenth International Congress on Infectious Diseases is scheduled to take place in Hyderabad, India, from 2 to 5 March 2016. The program will focus on **Infectious Diseases in South Asia[[22]](#footnote-22), Tuberculosis and Respiratory Infections[[23]](#footnote-23), HIV and Viral Hepatitis[[24]](#footnote-24), Clinical Infectious Diseases[[25]](#footnote-25), Implementing Global Health Priorities[[26]](#footnote-26), and Science and Diagnosis of Infectious Diseases[[27]](#footnote-27) .**
	2. For conference details see <http://www.isid.org./icid/index.shtml>

### Mosquito-borne diseases

* 1. The Pan American Health Organization (PAHO) announced in its weekly update on 3 April that the number of chikungunya cases had increased by 13,239 in the previous week, with the largest increase being in Colombia, which reported 11,671 new cases. The regional total for the previous week had been a 32,504-case increase.
	2. Brazilian researchers reported that a 1,000-plus-case chikungunya outbreak in Feira de Santana last autumn was caused by the East/Central/South African genotype rather than the Asian type responsible for almost all other cases throughout the Americas. The investigators reported in Emerging Infectious Diseases about half the city’s patients lived in the same neighbourhood as the index patient, who had arrived from Angola.
	3. Researchers from the US National Institute of Allergy and Infectious Diseases (NIAID) found[[28]](#footnote-28) the genetics of red blood cells affects whether people are susceptible to, or resilient against, malaria. The investigation studied 1,586 Malian children aged 6 months to 17years from 1 May, 2008, to 29 December, 2011 through 4,091 malaria outcomes. One of many findings was that children carrying the sickle cell gene may have a lower risk of contracting malaria.

### Influenza: strains, spread, prevention and treatment

* 1. The US Department of Agriculture's Animal & Plant Health Inspection Service (APHIS) has been monitoring two highly-pathogenic avian influenza (HPAI) virus strains in wild and domestic bird populations in the US's Pacific and Mississippi flyways. H5N2 already caused significant economic loss and mortality of commercial poultry in British Columbia, in late 2014. H5N8 has been found in both Europe and Asia over the past year and has resulted in the euthanasia of well over 1 million birds. In the US there have been confirmed infections in Washington, Oregon, California, Idaho, Minnesota, Missouri, Kansas and Arkansas in both non-commercial and commercial poultry flocks. The wild bird populations carrying H5N2 and H5N8 are the likely causes of spreading to commercial flocks.
	2. In a new study published at the end of March[[29]](#footnote-29), scientists from the US Geological Survey and US Fish and Wildlife Service identified low pathogenic avian influenza viruses in Alaska that are nearly identical to viruses found in China and South Korea. “Our past research in western Alaska has shown that 70 percent of avian influenza viruses isolated in this area were found to contain genetic material from Eurasia, providing evidence for high levels of intercontinental viral exchange,” said Andy Ramey, a scientist with the USGS Alaska Science Center and lead author of the study. “This is because Asian and North American migratory flyways overlap in western Alaska.” The new study found low pathogenic H9N2 viruses in an Emperor Goose and a Northern Pintail. Both of the H9N2 viruses were nearly identical genetically to viruses found in wild bird samples from Lake Dongting, China and Cheon-su Bay, South Korea.H9N2 viruses are so far not known to infect humans. The USGS recently released a report[[30]](#footnote-30) about the detection of a novel highly pathogenic H5N8 virus in the US that is very similar to the Eurasian H5N8 viruses. “The frequency of inter-hemispheric dispersal events of avian influenza viruses by migratory birds may be higher than previously recognized,” said Ramey.
	3. On 3 April, the Chinese veterinary authority reported on a new outbreak of avian flu to the World Organisation for Animal Health (OIE). The outbreak of highly pathogenic H5N6 started on 27 March in Jiangsu at a goose farm with 22,669 birds. Of these, 260 showed symptoms and 93 died; the remaining 22,576 were destroyed.
	4. University of Guelph researchers have devised a real-time way to analyse farm birds for [avian flu](http://phys.org/tags/avian%2Bflu/). Their nano-biosensor uses a small blood sample and a chemical colour change indicates the presence of avian flu and what [viral strain](http://phys.org/tags/viral%2Bstrain/) is involved. The device uses microscopic gold particles and glowing quantum dots[[31]](#footnote-31).
	5. With the highly pathogenic avian flu (HPAI) strains H5N2 and H5N8 threatening US poultry flocks, the US Department of Agriculture (USDA) is developing a vaccine as a backup tool to protect them, in case their standard containment measures fail. David E. Swayne, director of the USDA Agricultural Research Service's Southeast Poultry Research Laboratory in Athens, Georgia, said he and his colleagues are working on a virus seed strain for a vaccine to combat the two viruses.
	6. A global flu report on 23 March said influenza activity had remained elevated in the northern hemisphere with influenza A(H3N2) viruses predominating. In northern Africa and the Middle East, influenza A(H1N1)pdm09 viruses had been predominating, except in Egypt, where there was co-circulation with A(H3N2) and influenza B viruses. In the temperate countries of eastern Asia, A(H3N2) was predominant, with very little A(H1N1)pdm09 virus activity, while in western Asia, A(H1N1)pdm09 and influenza B were predominant. In tropical countries of the Americas, influenza activity remained low with mainly A(H3N2) viruses detected. In tropical Asia, influenza activity patterns varied, with A(H1N1)pdm09 predominant in Bhutan and India, A(H3N2) predominant in the Hong Kong Special Administrative Region, and influenza B predominant in south China. In the southern hemisphere, influenza activity was at inter-seasonal levels.
	7. At 6 April, the estimated count of human A(H7N9)[[32]](#footnote-32) cases in mainland China since the inception of human infection stood at 619. There had been 27 deaths in 2015. Imported cases elsewhere stood at Hong Kong-13, Taiwan-4, Canada-2 and Malaysia-1.
	8. The fourth human case of avian influenza A(H5N1) reported from China in 2015 attended hospital in Yunnan province on 20 March.
	9. In Egypt WHO said that by 17 March there had been 116 human cases of H5N1 in 2015, with 36 deaths. In Indonesia, a father and young son died of H5N1after visiting a poultry farm. This raised Indonesia's total to 199 cases and its number of deaths to 167. According to the WHO's 3 March global flu count, Egypt had the most H5N1 infections—292—but Indonesia had the highest number of deaths from the disease: 165, compared with 99 in Egypt.

### Ebola

* 1. WHO’s statistics for Ebola up to 5 April 2015 showed a global total of 14,794 confirmed cases; 2,580 probable cases; and 8,141 suspected cases. Total number of cases was thus thought to be 25,515 (with 10,572 deaths). A total of 30 confirmed cases were reported in the week to 5 April 2015. This was the lowest weekly total since the third week of May 2014. Case incidence in Guinea decreased to 21, compared with 57 confirmed cases the previous week. Liberia reported no confirmed cases. Sierra Leone reported a fifth consecutive weekly decrease from 25 confirmed cases in the week to 29 March 2015 to 9 in the week to 5 April 2015. By 5 April treatment capacity exceeded demand in Liberia and Sierra Leone. National authorities in both countries had begun to decommission surplus facilities. Each will retain a core capacity with additional rapid-response capacity held in reserve.
	2. The Liberian government has recommended that Ebola survivors practise safe sex indefinitely, until it is known how long the virus might remain present in body fluids including semen. Previously, the active virus had been detected for up to 82 days, but a recently acquired infection suggests this was an underestimate.
	3. Inovio Pharmaceuticals was selected to receive a $US 45 million grant from the US Defense Advanced Research Projects Agency (DARPA) to lead a collaborative team[[33]](#footnote-33) to develop multiple treatment and prevention approaches against Ebola. These include a therapeutic DNA-based monoclonal antibody product dMAb[[34]](#footnote-34); a highly potent conventional protein-based therapeutic monoclonal antibody (mAb)[[35]](#footnote-35); and Inovio's DNA-based vaccine against Ebola, with the first patient expected to be dosed in the second quarter of 2015[[36]](#footnote-36).
	4. Canadian company Tekmira Pharmaceuticals is restarting its study of an experimental Ebola treatment[[37]](#footnote-37). The FDA is allowing it to administer TKM-Ebola, to a small number of healthy people once a day for a one-week safety trial. Some patients in the trial will receive the drug and the rest a placebo. TKM-Ebola works by blocking genes that help the virus reproduce.
	5. A report in *Nature* showed that a candidate vaccine developed by Baltimore biotech [**Profectus Biosciences**](file:///C%3A%5Corganization%5Cprofectus-biosciences%5C)[[38]](#footnote-38) could protect monkeys against the “Makona” strain of the Ebola virus that caused the recent outbreak in West Africa. Profectus makes a vaccine “platform”, **VesiculoVax**, designed to protect against three filovirus diseases: Ebola Zaire, Ebola Sudan and Angola strain of Marburg. The Makona strain is about “97 percent identical” to Ebola Zaire, said Profectus Bioscience’s Chief Scientific Officer John Eldridge. The recent Ebola outbreak brought funding and interest from the US **National Institutes of Health (NIH), US Department of Defense** and the US Biomedical Advanced Research and Development Authority (BARDA). They formed a consortium to fund the development of Profectus vaccines with $US 55 million. The Profectus vaccine is attenuated[[39]](#footnote-39) and does not contain Ebola[[40]](#footnote-40). Profectus hopes human trials may be able to begin mid-year.
	6. The results of several global phase 1 trials of the rVSV-ZEBOV vaccine were published in *The New England Journal of Medicine*. [[41]](#footnote-41) “The prompt, dose-dependent production of high levels of antibodies following a single injection and the overall favorable safety profile[[42]](#footnote-42) of this vaccine make rVSV-ZEBOV a promising candidate that might be particularly useful in outbreak interventions,” said lead trial investigator Richard T. Davey, M.D., of the US National Institute of Allergy and Infectious Diseases (NIAID). The rVSV-ZEBOV vaccine was originally developed at Canada’s Public Health Agency, then licensed to NewLink Genetics Corp., which sold the rights to Merck & Co. rVSV-ZEBOV is derived from the cattle virus rVSV, which scientists engineered to produce a Zaire strain of the Ebola virus (ZEBOV). rVSV-ZEBOV is one of two experimental vaccines tested in a recent phase 2 [Liberian clinical trial](http://www.nih.gov/news/health/mar2015/niaid-26a.htm). The other vaccine whose safety and efficacy were tested was the chimpanzee-derived cold virus cAd3-EBOZ vaccine (developed by GlaxoSmithKline). Scientists reported both of the vaccines appeared to be safe.
	7. With funding from NIH, BioCryst (of Durham, North Carolina) is currently conducting Phase 1 safety studies of BCX4430 for safety in healthy volunteers. Now the US Department of Health and Human Services’ Office of the Assistant Secretary for Preparedness and Response (ASPR) granted $US 12 million to BioCryst Pharmaceuticals, for the advanced development of its experimental drug for Ebola, including preparing for large-scale manufacturing of the drug and conducting related studies. BCX4430 is a small molecule that prevents the Ebola virus from reproducing in the body. In non-human primate studies, the drug was effective against Ebola virus and Marburg virus (another filovirus), suggesting that BCX4430 could prove to be a broad spectrum antiviral drug. The initial work will be supported by ASPR’s Biomedical Advanced Research and Development Authority (BARDA)[[43]](#footnote-43). There is provision for the contract to be extended up to August 2017 and to a total of $US 35 million.
	8. Emergent BioSolutions, based in Gaithersburg, Maryland, announced on 16 March that it had signed an agreement to produce an experimental Ebola vaccine that contains a modified virus as a booster. A phase I trial to test the safety of the vaccine will be conducted by the Jenner Institute of Oxford, UK. The new vaccine is a version of the modified chimpanzee adenovirus (ChAd3) vaccine developed by GlaxoSmithKline (GSK) and the National Institute of Allergy and Infectious Diseases (NIAID). It will contain Emergent’s modified vaccinia Ankara (MVA) vector (MVA EBOZ) to boost antibody levels and T-cell responses. MVA EBOZ is made in an avian cell line, which removes the need for eggs in the manufacturing process, adds consistency to vaccine lots, and has the potential to increase the number of doses delivered, according to the company. Two other Ebola vaccine trials are in progress for candidates that use MVA, one involving ChAd3 with a booster vaccine from Bavarian Nordic called MVA-Filo, and a prime-boost regimen from Johnson & Johnson and Bavarian Nordic.
	9. A study reported in the journal *Vaccine[[44]](#footnote-44)* demonstrated the durability of a 'disseminating' cytomegalovirus (CMV)-based Ebola virus (Zaire ebolavirus; EBOV) vaccine strategy that could perhaps reduce ebola virus infection in wild African apes, not only stabilizing their numbers but also reducing the incidence of future human ebola outbreaks[[45]](#footnote-45). In a 2011 study the team showed the ability of a CMV-based vaccine to provide short-term protection against the ebola virus in a mouse challenge model. The new study showed that ebola-specific immune responses were being maintained for more than 14 months (equivalent to half the life span of a mouse) following only a single dose of the vaccine. The next step, is to trial the vaccine using CMV in the macaque EBOV challenge model. The multi-institutional study was led by Dr Michael Jarvis of Plymouth University. The project has been incorporated as a component of an international research program, which includes organisations such as the World Wildlife Fund and US National Institutes of Health.
	10. At the Seventh International Symposium on Filoviruses, Kineta Inc. of Seattle presented pre-clinical animal and in vitro data from molecules which inhibit viral pathogens including Ebola, influenza A & B, dengue, West Nile, Lassa fever, respiratory syncytial virus and human coronaviruses. The results showed molecules function by triggering host innate antiviral immunity rather than focusing on a specific viral target[[46]](#footnote-46). Dr. Shawn Iadonato, Chief Scientific Officer at Kineta, said: “Current direct acting antivirals that typically have selective action against a single virus have a high risk of eliciting drug resistance. These novel and potent host-directed innate immune molecules offer broad spectrum protection without development of drug resistance, and we believe our approach to developing a therapy for Ebola is the first of its kind.”

### Other diseases: occurrence, prevention and treatment

* 1. Saudi Arabia announced two new MERS cases in the first six days of April, compared with 53 in the whole of March and 75 in February. The Health Ministry’s confirmed count of MERS cases was by then 976, with 424 deaths.
	2. Researchers reported[[47]](#footnote-47) that HIV may begin replicating within a patient’s brain and central nervous system (CNS) as early as four months after infection. “Independent viral replication within the CNS has two important implications,” they wrote. “First, HIV-1 replication can lead to CNS dysfunction and injury. Second, independent CNS replication may also provide a reservoir distinct from that found in CD4+ T cells in the blood and lymphoid tissue.” The researchers also suggested four separate stages of early infection characterized by the relationship between HIV in the blood and in the CNS. This model, the researchers wrote, implies distinct interaction mechanisms between the virus and the host. Dianne Rausch**,** director of the Division of AIDS Research within the US National Institute of Mental Health, said in a press release: “These results underscore the importance of early diagnosis and treatment with antiretroviral therapy. Any delay runs the risk that the virus could find refuge and cause damage in the brain, where some medications are less effective—potentially enabling it to re-emerge, even after it is suppressed in the periphery.”
	3. Healthcare workers fighting polio are facing the challenge of circulating vaccine-derived polioviruses originating from one of the two vaccines used against the illness. They threaten to overtake wild poliovirus as the most prominent source of the disease. They look genetically like the vaccine, but behave in nature like their wild counterparts. These vaccine-derived viruses start in the intestines of a tiny fraction of people who receive the oral polio vaccine. The oral vaccine uses live, but attenuated, strains of poliovirus. In about one in a million people, though, the attenuated poliovirus mutates and regains its potency. Even if these mutated viruses don’t sicken the person in whom they originate, they may escape into the environment in the individuals’ faeces and start infecting people: in areas with poor sanitation systems, untreated sewage spreads the new viruses to others, who can become ill.[[48]](#footnote-48)
	4. Researchers have been exploring the suspected causal link between enterovirus D68 and the sudden development of paralysis in children in California and Colorado between 2012 and 2014. They found the genetic signature of a specific type of enterovirus D68, B1, in half the children who developed acute flaccid myelitis (sudden muscle weakness and paralysis).The B1 strain does not always lead to these complications. "This suggests that it's not only the virus, but also patients' individual biology that determines what disease they may present with," said Dr. Charles Chiu, associate professor of laboratory medicine and director of the University of California, San Francisco-Abbott Viral Diagnostics and Discovery Center. “Given that none of the children have fully recovered, we urgently need to continue investigating this new strain ... and its potential to cause acute flaccid myelitis".[[49]](#footnote-49)
	5. Globally, in 2013, there were an estimated nine million cases of active tuberculosis, and 1.5 million people died. In addition, WHO estimates that two billion people are asymptomatically infected with and are considered to have latent infection which can activate when their immune systems are weakened. Researchers have now identified blood-based biomarkers in patients with active tuberculosis that could lead to new blood-based diagnostics and tools for monitoring treatment response and cure. The study was led by immunologist Jyothi Rengarajan, assistant professor of medicine (infectious diseases), Emory University School of Medicine and Emory Vaccine Center, and Susan Ray, Emory professor of medicine (infectious diseases) and Hospital Epidemiologist at Atlanta's Grady Memorial Hospital. The study report was published online on 30 March in the Journal of Clinical Investigation.
1. in an abstract submitted to *the Journal of Sickle Cell Disease and Hemoglobinopathies* [↑](#footnote-ref-1)
2. CSL says of its rIX-FP**:** *CSL Behring engineered rIX-FP to extend the half-life of recombinant factor IX through genetic fusion with recombinant albumin. CSL Behring selected recombinant albumin as its recombinant genetic fusion partner for its coagulation factor proteins due to its long physiological half-life. In addition, recombinant albumin has been shown to have a good tolerability profile, low potential for immunogenic reactions and a well-known mechanism of clearance. The cleavable linker connecting recombinant factor IX and recombinant albumin has been specifically designed to preserve the native function of the coagulation factor in the fusion protein, while benefiting from recombinant albumin's long physiological half-life.* [↑](#footnote-ref-2)
3. The program included open-label, multicenter, safety and efficacy studies of rIX-FP in previously treated patients with hemophilia B (FIX </= 2%). The Phase II/III pivotal study (patients ages 12 to 61 years) compared the change in frequency of spontaneous bleeding events between on-demand treatment and a weekly prophylaxis regimen in patients previously receiving only on-demand treatment; and the number of patients developing inhibitors against factor IX as primary outcome measures. The study evaluated multiple prophylaxis regimens, including 7-day and 14-day intervals. A sub-study evaluated the prevention and control of bleeding in patients with hemophilia B undergoing a surgical procedure. The primary outcome measures of the Phase III paediatric study (patients ages 1 to 11 years) are pharmacokinetics parameters of rIX-FP and the number of subjects developing inhibitors against factor IX. All patients received a weekly prophylaxis regimen.Study design details for rIX-FP (CSL654) are available at [clinicaltrials.gov](https://www.clinicaltrials.gov/ct2/show/NCT01496274?term=CSL654&rank=4). [↑](#footnote-ref-3)
4. ITP is an autoimmune condition marked by bruising and increased bleeding as a result of immune-mediated accelerated destruction of platelets and impaired production of platelets. ITP is acknowledged by the FDA as an orphan disease (a condition that affects fewer than 200,000 people nationally). [↑](#footnote-ref-4)
5. The drug is the subject of ongoing clinical development in rheumatoid arthritis (RA) under a separate IND submitted earlier to the FDA. [↑](#footnote-ref-5)
6. The Boxed Warning includes:

	* *Administer intravenous (IV) iron products only to patients who require IV iron therapy.*
	* *Do not administer Feraheme to patients with a history of allergic reaction to Feraheme or other IV iron products.*
	* *Administer diluted Feraheme anly as an IV infusion and only over a minimum of 15 minutes. Feraheme should not be given as an undiluted IV injection.*
	* *Closely monitor patients for signs and symptoms of serious allergic reactions, including monitoring blood pressure and pulse during Feraheme administration and for at least 30 minutes following each infusion.*
	* *Carefully consider the potential risks and benefits of Feraheme administration in elderly patients with multiple or serious medical conditions, as these patients may experience more severe reactions.*
	* *Carefully consider the potential risks and benefits of Feraheme administration in patients with a history of multiple drug allergies. Patients with multiple drug allergies may also be at higher risk.* [↑](#footnote-ref-6)
7. Published in the Journal of the Canadian Medical Association. Co-author Dr. Julia Upton, a lecturer in the department of pediatrics at the University of Toronto. [↑](#footnote-ref-7)
8. [Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, Reeves BC, “Liberal or restrictive transfusion after cardiac surgery”. *N Engl J Med* 2015;372: 997-1008.](http://www.ncbi.nlm.nih.gov/pubmed/25760354) Also [Spertus J. “TITRe”ing the approach to transfusions after cardiac surgery”. *N Engl J Med* 2015;372: 1069-70.](http://www.ncbi.nlm.nih.gov/pubmed/?term=%22TITRe%22ing+the+approach+to+transfusions+after+cardiac+surgery) [↑](#footnote-ref-8)
9. Styron JF, et al. Paper #591. Presented at: American Academy of Orthopaedic Surgeons Annual Meeting. March 24-28, 2015; Las Vegas. [↑](#footnote-ref-9)
10. [Chiang M-R, et al., *Pediatr Res*. 2015;doi:10.1038/pr.2015.6.](http://www.nature.com/pr/journal/v77/n4/abs/pr20156a.html) [↑](#footnote-ref-10)
11. [Michelle Hong](http://www.nature.com/ncomms/2015/150325/ncomms7588/abs/ncomms7588.html#auth-1), [Elena Sandalova](http://www.nature.com/ncomms/2015/150325/ncomms7588/abs/ncomms7588.html#auth-2),[Diana Low](http://www.nature.com/ncomms/2015/150325/ncomms7588/abs/ncomms7588.html#auth-3),[Adam J. Gehring](http://www.nature.com/ncomms/2015/150325/ncomms7588/abs/ncomms7588.html#auth-4),[Stefania Fieni](http://www.nature.com/ncomms/2015/150325/ncomms7588/abs/ncomms7588.html#auth-5), [Barbara Amadei](http://www.nature.com/ncomms/2015/150325/ncomms7588/abs/ncomms7588.html#auth-6),[Simonetta Urbani](http://www.nature.com/ncomms/2015/150325/ncomms7588/abs/ncomms7588.html#auth-7), [Yap-Seng Chong](http://www.nature.com/ncomms/2015/150325/ncomms7588/abs/ncomms7588.html#auth-8), [Ernesto Guccione](http://www.nature.com/ncomms/2015/150325/ncomms7588/abs/ncomms7588.html#auth-9) and [Antonio Bertoletti](http://www.nature.com/ncomms/2015/150325/ncomms7588/abs/ncomms7588.html#auth-10), ‘Trained immunity in newborn infants of HBV-infected mothers’, *Nature Communications* 2015 ;doi:10.1038/ncomms7588. [↑](#footnote-ref-11)
12. Hong and colleagues analyzed immune cells in umbilical cord blood of 20 infants born to Asian mothers who were positive for Hepatitis B and compared the result with cord blood of seven infant controls born from mothers negative for Hepatitis B, to determine the impact exposure has on the newborn immune system. A second cohort of Caucasian mothers and babies was also studied [↑](#footnote-ref-12)
13. #  [C. Chiappini](http://www.nature.com/nmat/journal/vaop/ncurrent/full/nmat4249.html#auth-1), [E. De Rosa](http://www.nature.com/nmat/journal/vaop/ncurrent/full/nmat4249.html#auth-2), [J. O. Martinez](http://www.nature.com/nmat/journal/vaop/ncurrent/full/nmat4249.html#auth-3), , [X. Liu](http://www.nature.com/nmat/journal/vaop/ncurrent/full/nmat4249.html#auth-4), , [J. Steele](http://www.nature.com/nmat/journal/vaop/ncurrent/full/nmat4249.html#auth-5), [M. M. Stevens](http://www.nature.com/nmat/journal/vaop/ncurrent/full/nmat4249.html#auth-6), [E. Tasciotti](http://www.nature.com/nmat/journal/vaop/ncurrent/full/nmat4249.html#auth-7) , “Biodegradable ​silicon nanoneedles delivering nucleic acids intracellularly induce localized *in vivo* neovascularization”, *Nature Materials* (2015), published online March 2015 DOI:DOI:10.1038/nmat4249

 [↑](#footnote-ref-13)
14. As professor and division director of [Laboratory Medicine](http://www.uab.edu/medicine/pathology/divisions-a-sections/laboratory-medicine) in the [Department of Pathology](http://www.uab.edu/medicine/pathology/) [↑](#footnote-ref-14)
15. Brandy Pickens, Yingying Mao, Dengju Li, Don Siegel and Douglas Cines from the departments of Pathology and Laboratory Medicine, University of Pennsylvania; and Mortimer Poncz from the Division of Hematology, Children’s Hospital of Philadelphia. [↑](#footnote-ref-15)
16. Their paper,“[Platelet-delivered ADAMTS13 inhibits arterial thrombosis and prevents murine models of thrombotic thrombocytopenic purpura](http://www.bloodjournal.org/content/early/2015/03/23/blood-2014-07-587139)”, was published in the journal *Blood.* [↑](#footnote-ref-16)
17. published in the journal *Blood*, senior author Karsten Sauer [↑](#footnote-ref-17)
18. Published in the *Journal of Clinical Investigation* [↑](#footnote-ref-18)
19. A Canadian Blood Services scientist, working in the Keenan Research Centre for Biomedical Science of St. Michael's Hospital [↑](#footnote-ref-19)
20. The research was published in *Blood,* the Journal of the American Society of Hematology (ASH), senior study author Eugene Oteng-Ntim, of the Guy's and St. Thomas' NHS Foundation Trust and Honorary Senior Lecturer at King's College London. [↑](#footnote-ref-20)
21. The Australian Dental Association therapeutic guidelines involved obtaining a blood test for INR 24 hours before surgery and providing tranexamic acid mouthwash, which delays the natural breakdown of blood clots pre- and post-surgery. (The INR or international normalized ratio is a measure of blood clotting.) [↑](#footnote-ref-21)
22. Including Malaria: The Spread of Artemisin Resistance, Acute Encephalitis Syndrome, Dengue and Chikungunya, The Neglected Six: Leishmaniasis, Rabies, Leptospirosis, Melioidosis, Typhoid, and Leprosy [↑](#footnote-ref-22)
23. Including New Tools for the Control of Multi Drug Resistant Tuberculosis, New Drugs and Access to New Drugs, Implications of HIV Co-Infection, Advances in Diagnosis of Latent and Active Disease, Role of New Biomarkers and Adjunct Host-Directed Therapies, Childhood and Adult Pneumonia, Update on Influenza [↑](#footnote-ref-23)
24. Including HIV: The Quest for a Cure Continues, The Debate Over HIV Pre-Exposure Prophylaxis, Combating the Silent Epidemic of Viral Hepatitis, A World Without HCV-Is it Reality? HIV/HCV/HBV Treatment Update [↑](#footnote-ref-24)
25. Including Enteric Infections: Management, Vaccines and Research Highlights, Infections in the Era Of Cancer Treatments, Transplants and New Biologics, Healthcare Associated Infections (Surgical Infections, Prosthetic and Device Associated Infections), Fungal Infections Around the World, Appropriate Use of Antimicrobials, Vaccines (Current Practices and Controversies) [↑](#footnote-ref-25)
26. Including Use It and You Will Lose It (The Global Overuse of Antibiotics),The Bugs are Always Ahead of Us (Highly Resistant Pathogens Around the Globe), Infectious Disease Surveillance in Global Hotspots and Outbreak Preparedness in an Interconnected World, The One Health Concept and Emerging Infectious Diseases (Where People, Animals and the Environment Meet) [↑](#footnote-ref-26)
27. Including The Human Microbiome and its Relationship to Health and Disease

Host and Pathogen Genomics (Applicability and use in under resourced countries, Personalized medicine and infectious diseases, Update on Genetic Sequencing Techniques), Advances in Molecular Diagnosis and Point-Of-Care Tests, Drug Development and Antibiotic Pipeline, Next Generation Vaccines to Combat Global Health Threats [↑](#footnote-ref-27)
28. Tatiana M Lopera-Mesa, x

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# Rick M Fairhurst, “Effect of red blood cell variants on childhood malaria in Mali: a prospective cohort study”, *The Lancet Haematology,* x

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# Volume 2, number 4.April 2015 DOI: [http://dx.doi.org/10.1016/S2352-3026(15)00043-5](http://dx.doi.org/10.1016/S2352-3026%2815%2900043-5)

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29. [Andrew M. Ramey](http://www.sciencedirect.com/science/article/pii/S0042682215001646), [Andrew B. Reeves](http://www.sciencedirect.com/science/article/pii/S0042682215001646), [Sarah A. Sonsthagen](http://www.sciencedirect.com/science/article/pii/S0042682215001646), [Joshua L. TeSlaa](http://www.sciencedirect.com/science/article/pii/S0042682215001646), [Sean Nashold](http://www.sciencedirect.com/science/article/pii/S0042682215001646), [Tyrone Donnelly](http://www.sciencedirect.com/science/article/pii/S0042682215001646), [Bruce Casler](http://www.sciencedirect.com/science/article/pii/S0042682215001646), [Jeffrey S. Hall](http://www.sciencedirect.com/science/article/pii/S0042682215001646), “Dispersal of H9N2 influenza A viruses between East Asia and North America by wild birds”, *Virology*, [Volume 482](http://www.sciencedirect.com/science/journal/00426822/482/supp/C), August 2015, Pages 79–83 [doi:10.1016/j.virol.2015.03.028](http://dx.doi.org/10.1016/j.virol.2015.03.028) [↑](#footnote-ref-29)
30. Ip HS, Torchetti MK, Crespo R, Kohrs P, DeBruyn P, Mansfield KG, et al. Novel Eurasian highly pathogenic influenza A H5 viruses in wild birds, Washington, USA, 2014. *Emerg Infect Dis. 2015 May* <http://dx.doi.org/10.3201/eid2105.142020> [↑](#footnote-ref-30)
31. The tool was designed by Prof. Suresh Neethirajan, School of Engineering and post-doctoral researcher Longyan Chen. A study about the device will appear in the journal *Sensors*, published by Molecular Diversity Preservation International (MDPI). [↑](#footnote-ref-31)
32. Avian influenza A (H7N9) is an influenza (flu) virus found in birds that was thought to be not normally infectious to humans. However, in spring of 2013, China began reporting infections in people, most being associated with infected poultry or contaminated poultry markets. During the first wave in spring 2013, live bird markets were closed in several parts of China; these market closures appeared to substantially reduce transmission of the virus to humans. During a second wave in autumn 2013, markets were again closed in some provinces, although interventions in some regions were delayed until after the Chinese New Year (January 31, 2014). Research suggests such interventions are needed for a sufficiently long time to prevent recurrence, with permanent closure the most effective measure. [↑](#footnote-ref-32)
33. Other collaborators are: MedImmune, the biologics research and development arm of AstraZeneca; GeneOne Life Sciences and its manufacturing subsidiary, VGXI, Inc.; and David B. Weiner, Professor of Pathology and Laboratory Medicine at The Perelman School of Medicine at the University of Pennsylvania, Emory University and Vanderbilt University. [↑](#footnote-ref-33)
34. This technology could allow a rapid response to an outbreak , being designed and manufactured quickly on a large scale using fermentation technology, and being heat-stable. [↑](#footnote-ref-34)
35. Pathogen specific mAbs constitute a viable approach for immunoprophylaxis against pathogens where anti-viral drugs or vaccinations are not available. mAbs can be administered either just prior to or just after exposure to the pathogen and serve to counter its immediate effects. Unlike vaccines, immunoprophylaxis by mAbs does not result in long term immune memory, so the proctocol might be to administer a mAb for immediate protection and follow it with a vaccine. [↑](#footnote-ref-35)
36. In preclinical testing, Inovio's DNA-based Ebola vaccine protected 100 per cent of animals from mortality and morbidity following exposurs to an otherwise lethal dose of the Ebola virus. [↑](#footnote-ref-36)
37. Tekmira began giving single doses to healthy people in 2014, but the FDA stopped the study in July because it wanted more information about the safety of higher doses; Tekmira was however allowed to dose patients infected with the Ebola virus. [↑](#footnote-ref-37)
38. Also involving the University of Texas Medical Branch in Galveston [↑](#footnote-ref-38)
39. Where the virus is rendered harmless. [↑](#footnote-ref-39)
40. It is based on vesicular stomatitis virus, a danger to livestock. [↑](#footnote-ref-40)
41. Selidji T. Agnandji, Angela Huttner, Madeleine E. Zinser, Patricia Njuguna, Christine Dahlke, José F. Fernandes, Sabine Yerly, Julie‐Anne Dayer, Verena Kraehling, Rahel Kasonta, Akim A. Adegnika, Marcus Altfeld, Floriane Auderset, Emmanuel B. Bache, Nadine Biedenkopf, Saskia Borregaard, Jessica S. Brosnahan, Rebekah Burrow, Christophe Combescure, Jules Desmeules, Markus Eickmann, Sarah K. Fehling, Axel Finckh, Ana Rita Goncalves, Martin P. Grobusch, Jay Hooper, Alen Jambrecina, Anita L. Kabwende, Gürkan Kaya, Domtila Kimani, Bertrand Lell, Barbara Lemaître, Ansgar W. Lohse, Marguerite Massinga-Loembe, Alain Matthey, Benjamin Mordmüller, Anne Nolting, Caroline Ogwang, Michael Ramharter, Jonas Schmidt-Chanasit, Stefan Schmiedel, Peter Silvera, Felix R. Stahl, Henry M. Staines, Thomas Strecker, Hans C. Stubbe, Benjamin Tsofa, Sherif Zaki, Patricia Fast, Vasee Moorthy, Laurent Kaiser, Sanjeev Krishna, Stephan Becker, Marie-Paule Kieny, Philip Bejon, Peter G. Kremsner, Marylyn M. Addo, and Claire-Anne Siegrist. “Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe — Preliminary Report”. April 1, 2015 DOI: 10.1056/NEJMoa1502924 [↑](#footnote-ref-41)
42. Phase 1 trials of rVSV-ZEBOV were conducted in the US, Africa, and Europe. Some people did experience fever and pain. The Geneva trial was put on hold in 2014 after 11 of the 51 participants developed arthritis. The trial resumed in January. [↑](#footnote-ref-42)
43. BARDA develops and procures medical countermeasures – vaccines, medicines, diagnostics and medical equipment –to address the possible public health and medical consequences of chemical, biological, radiological, and nuclear incidents, pandemic influenza, and emerging infectious diseases. BARDA’s Ebola portfolio also includes development of the monoclonal antibody cocktail ZMapp by Mapp Biopharmaceuticals and potential vaccines from GlaxoSmithKline, BioProtection Services/NewLink Genetics, and Profectus BioSciences. If these drugs or vaccines turn out to be both safe and efficacious BARDA could consider purchasing them under Project BioShield for the US Strategic National Stockpile. [↑](#footnote-ref-43)
44. 25 March 2015. Yoshimi Tsuda, Christopher J. Perkins, Patrizia Caposio, Friedericke Feldmann, Sara Botto, Susan Ball, Ilhem Messaoudi, Luka Cicin-Sain, Heinz Feldmann, and Michael A. Jarvis, "A cytomegalovirus-based vaccine provides long-lasting protection against lethal Ebola virus challenge after a single dose". DOI:0.1016/j.vaccine.2015.03.029 [↑](#footnote-ref-44)
45. Using a CMV-based ebola virus vaccine that can spread through wild ape populations is a means to provide high levels of protective ebola virus-specific immunity without the need for direct vaccination in a remote and inaccessible population. [↑](#footnote-ref-45)
46. The compounds were tested against influenza and dengue viruses in mouse models and were effective and well tolerated with a 2-3 log (100-1,000 fold) reduction in the amount of virus in the plasma and lungs. Data also showed strong suppression of Ebola infection in tissue culture with a greater than 2 log reduction in virus load. Kineta will now test the compounds against or Ebola and Lassa haemorrhagic fever in animal models. [↑](#footnote-ref-46)
47. Christa Buckheit Sturdevant, Sarah B. Joseph, Gretja Schnell, Richard W. Price, Ronald Swanstrom, Serena Spudich , “Compartmentalized Replication of R5 T Cell-Tropic HIV-1 in the Central Nervous System Early in the Course of Infection”, *PloS Pathogens*, published 26 March 2015, DOI: 10.1371/journal.ppat.1004720 [↑](#footnote-ref-47)
48. The US Centers for Disease Control and Prevention reported that in Nigeria during the first nine months of 2014, 21 polio cases were caused by the circulating vaccine-derived viruses, compared with six cases from the wild virus. In the same period, Pakistan had 22 cases from circulating vaccine-derived viruses and 170 from wild viruses, while Afghanistan had no cases from vaccine-derived viruses and nine from wild poliovirus. [↑](#footnote-ref-48)
49. The study was published in the March 30 issue of *The Lancet Infectious Diseases*. [↑](#footnote-ref-49)