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:

- The submission of biological licence applications to the US Food and Drug Administration (FDA) for:
  1. Bayer’s BAY 81-8973 for haemophilia A in adults and children
  2. CSL Behring’s long-acting fusion protein linking recombinant factor IX with albumin
  3. Baxter’s extended half-life recombinant factor VIII, BAX 855, and its treatment for von Willebrand disease BAX 111
- Approval by the FDA of Cerus Corporation’s Intercept Blood System for platelets and its Intercept Blood System for plasma
- Publication in the January issue of Anesthesiology of studies of the two most significant causes of post-transfusion mortality in the US.
- The curing of haemophilia in mice models using a new genome editing method
- The US review of platelet transfusions which suggested that they were associated with increased odds of dying in the hospital, fivefold for patients with heparin-induced thrombocytopenia and double for patients with thrombotic thrombocytopenic purpura.
1. Products

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

**Haemophilia treatments**

a) Alnylam says it is advancing ALN-AT3, an investigational RNAi therapeutic in development for haemophilia and rare bleeding disorders, after positive initial Phase 1 data were recently reported.

b) LFB announced in late December the achievement of patient enrollment target for PERSEPT 1, a multinational Phase III clinical trial of LR769, a novel recombinant form of human Factor VIIa, in adolescent and adult congenital haemophilia A or B patients with inhibitors. This Phase III trial study is being sponsored by LFB’s US subsidiary. Initial results, expected in the first quarter of 2015, will provide the basis for a second Phase III study, PERSEPT 2, which will assess the pharmacokinetics, safety and efficacy of LR769 for the treatment of bleeding episodes in paediatric haemophilia patients with inhibitors. A third study, PERSEPT 3, will evaluate the safety and efficacy of LR769 for prevention of bleeding in patients undergoing surgery. Both these studies are expected to begin in mid-2015.

**Sickle Cell Disease (SCD)**

c) At the 56th Annual Meeting of the American Society of Haematology (ASH) in San Francisco, one poster session examined patient and caregiver perspectives on adherence to iron chelation therapy (ICT), which is used to manage iron overload in patients who have repeat transfusions. A second study provided evidence that blood transfusion improves health-related quality of life for children with SCD.

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1 PERSEPT 1 is an open-label, multicenter study designed to evaluate the efficacy, safety and pharmacokinetics of LR769 in 25 adolescent and adult patients with hemophilia A and B with inhibitors. The study will evaluate two different doses and dosing regimens for the treatment of bleeding episodes. All patients enrolled into the trial will be treated and evaluated for at least 6 months. More details can be found at [https://clinicaltrials.gov/ct2/show/NCT02020369](https://clinicaltrials.gov/ct2/show/NCT02020369).

2 Reasons for adherence included positive effects of ICT on health, support from caregivers and clinicians, and an established routine. Reasons for nonadherence included the taste or texture of the therapy, gastrointestinal symptoms, and mealtime restrictions. Adherence by children tended to improve as they grew older. See Bal V, Cote I, Lasch K, Huang V., *Patient and caregivers*
d) The ASH meeting also saw a poster presentation on an innovative biochip, which evaluates the biophysical properties of red blood cells in sickle cell patients, and has the potential to become a standard test for monitoring the disease because of its widespread applicability and its use of only small volumes of blood.

e) Global Blood Therapeutics announced mid-January that the first cohort of eight subjects had been dosed in its Phase I/II clinical trial of GBT440, for the treatment of sickle cell disease. GBT440 is an oral, once daily dosing, direct-acting sickle haemoglobin modifier for the chronic, prophylactic treatment of SCD. The drug works by increasing haemoglobin's affinity for oxygen. Oxygenated haemoglobin does not polymerize, so sickling of red blood cells is blocked.

f) A tiny microfluidic device to help predict vaso-occlusive crises in SCD has been developed by Ming Dao (Massachusetts Institute of Technology) and colleagues.

Other

g) At the ASH meeting, Alexion presented findings for its drug Soliris (eculizumab) in the treatment of atypical haemolytic uremic syndrome (aHUS), as well as new data regarding medical care for patients with aHUS and paroxysmal nocturnal haemoglobinuria (PNH). Dr. Spero R. Cataland of Ohio State University Medical Center presented the results of two post-hoc sub-analyses from two trials investigating Soliris’ safety and efficacy in children and adult patients with aHUS with or without identified genetic mutations at baseline. Results show that platelet count normalization was achieved by 100 per cent in both paediatric and adult patients with an identified mutation. Platelet count normalization was met by 91 per cent of paediatric and 95 per cent of adult patients without an identified mutation. “Given the life-threatening nature of aHUS and the well-established clinical efficacy of Soliris, these data provide additional evidence for initiating treatment with Soliris immediately upon clinical diagnosis of aHUS. This is particularly important since genetic testing can take several months to complete and, to date, genetic complement mutations can only be identified in 50 per cent to 70 per cent of patients with aHUS,” said Dr. Cataland. Leonard Bell, Chairman and CEO of Alexion, said: “We are pleased that the data presented at ASH continue to expand our understanding of aHUS and PNH... Importantly, significant improvements in haematologic and renal outcomes were observed in paediatric and adult patients with aHUS, both with and without identified genetic mutations, supporting the early initiation of Soliris treatment regardless of mutation status.”

h) Kamada reported that preliminary results from a Phase I/II clinical study of its human Alpha-1 Antitrypsin (AAT) indicated that continuous administration of AAT as therapy for steroid resistant gut graft-versus-host-disease, or GvHD, is feasible. The Fred

other references:

- Abstract #4053 by Jane Little and colleagues from University Hospitals (UH) Case Medical Center and Case Western Reserve University School of Medicine
- Soliris is a terminal complement inhibitor indicated for the treatment of the very rare blood disorder PNH. It is approved in nearly 40 countries to treat the very rare genetic disease aHUS. At the end of 2014 it received the backing of the UK’s National Institute for Health and Care Excellence (NICE) Highly Specialized Technologies Evaluation Committee (EC) as treatment for aHUS for patients in England. The drug was recently granted orphan status in Japan for the treatment of neurological disorder neuromyelitis optica.
- Alexion included findings from its OPTIMA trial, which investigated high sensitivity flow cytometry in the detection of PNH cells in various patient populations.
Hutchinson Cancer Research Center in Seattle, Washington has been conducting the study in cooperation with Baxter and Kamada. The study is an open label, dose escalation, safety and efficacy study evaluating 24 GvHD patients who suffer from inadequate response to steroid treatment. The primary outcome of the study is to evaluate the efficacy of AAT in ameliorating the severe intestinal inflammation associated with GvHD.

i) Kamada expects to report results in the first half of 2015 from its US Phase II/III clinical trial its anti-rabies immunoglobulin as a post-exposure prophylaxis. It hopes to file a biologics license application with the FDA before the end of 2015. Kamada has a strategic agreement with Kedrion for the clinical development and marketing of the product in the US.

j) One in four Jews is a carrier of one or more of the nineteen known preventable Jewish genetic diseases, according to the Center for Jewish Genetics. Although Sephardic Jews and non-Jews can carry these diseases, they appear twice as often for Ashkenazi Jews as they do for the rest of the population. JScreen, launched through the Emory University School of Medicine’s Department of Human Genetics, is an at-home, carrier-screening program.

k) Pharming Group and Salix Pharmaceuticals announced in January that the first patient had been treated in their Phase II clinical study of Ruconest, (C1 Esterase Inhibitor [Recombinant]) 50 IU/kg, for prophylaxis in patients with hereditary angioedema (HAE). Patients being enrolled are deficient in C1 inhibitor and have a history of at least four attacks per month. The trial is a randomized, double-blind study, in which 30 patients will receive Ruconest either once or twice weekly, or placebo in each of three treatment periods. With the crossover design, all patients will receive each of the dosing regimens. The study is being conducted at sites in Canada, Europe, Israel, and the US.

l) Cerus announced in December that that its Phase II study on red blood cells when treated with the INTERCEPT blood system has met its primary endpoint. The randomized, single-blind, controlled, multi-center was conducted in 26 healthy subjects. Each subject was given two transfusions of the subject's own red blood cells: one INTERCEPT-treated and the other a control not treated for pathogen inactivation. Preliminary analysis showed that more than 75 per cent of treated red blood cells continued to circulate 24 hours following transfusion, thereby meeting the primary endpoint of the study. The INTERCEPT treated red blood cells had a recovery of 83 per cent compared with 85 per cent for control red blood cells. Both INTERCEPT-treated and control red blood cells met the criteria for red blood cell recovery as recommended by the FDA. Cerus will move the INTERCEPT red blood cell program into Phase III in the U.S. Cerus has already completed a Phase III study on the INTERCEPT red blood cell system in Europe in patients with acute anaemia and is filing for CE mark approval.

m) Researchers at Héma-Québec produced eye drops using a concentrate of plasminogen to save the sight of a young patient with ligneous conjunctivitis, a rare disorder that occurs in patients with plasminogen deficiency.

Market size

n) Allied Market Research forecasts the Global Erythropoietin (EPO) market will reach $US 11.9 billion annually by 2020. Europe led the global EPO drug market in 2013 closely followed by North America. Darbepoetin alfa is the fastest growing drug class because of its high potency and minimal side-effects. The market is seeing

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8 “Global Erythropoietin (EPO) Drugs Market (Type, Application and Geography) - Size, Share, Global Trends, Company Profiles, Demand, Insights, Analysis, Research, Report, Opportunities, Segmentation and Forecast, 2013-2020”
biosimilars for the 'off-patent' drug erythropoietin alfa⁹. Rising incidences of cancer, end stage renal disease and HIV are largely responsible for the growing demand for EPO drugs. The kidney therapeutic segment is expected to be the largest by 2020. Companies are investing in research and development to expand product use to newer disorders such as neural diseases and in wound healing.

The global plasma fractionation market is estimated at $US 16,573.4 million for 2014 and growing at a compound annual growth rate of 8.9 per cent during the period of 2014 to 2019¹⁰. The market is driven by aging population, increasing numbers of haemophilia patients, improved diagnosis, increasing emphasis on prophylaxis, increasing off-label use of albumin and increasing use of immunoglobulin in chronic diseases.

2. 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
a) In mid-December Bayer filed with the FDA a biologics licence application for BAY 81-8973, a compound for the treatment of haemophilia A in adults and children. BAY 81-8973 is a full-length recombinant factor VIII (rFVIII) which has demonstrated efficacy when used in standard dosage for prophylaxis two times or three times per week. This application follows Bayer’s recent submission to the European Medicines Agency (EMA) for approval of the same indication in the European Union.

b) CSL Behring submitted a biologics license application to the FDA for its long-acting fusion protein linking recombinant coagulation factor IX with recombinant albumin (rIX-FP). If approved by the FDA, rIX-FP will provide patients with haemophilia B a long-acting treatment option with dosing intervals up to 14 days.

c) Baxter and development partner Nektar Therapeutics announced early in January that a biologics license application for an investigational, extended half-life recombinant factor VIII treatment for haemophilia A had been submitted to the FDA. This submission for BAX 855 was based on positive results of a Phase III study. In the trial, 137 previously treated patients aged 12 years or more either experienced a twice weekly prophylaxis or an on demand treatment. In the twice weekly prophylaxis group, patients experienced a 95 per cent reduction in median annualized bleed rate compared with the on demand treatment group, 1.9 vs. 41.5, respectively. BAX 855 also treated bleeding episodes, with 96 per cent controlled with 1 or 2 infusions. The researchers reported no inhibitor development in patients after treatment and no serious adverse events such as hypersensitivity. The most common adverse reaction was headache. The trial is ongoing. The drug will also be trialled in paediatric patients with severe haemophilia.

d) The FDA approved Octapharma’s manufacturing facility in Vienna for the production of Octagam 10% [Immune Globulin Intravenous (Human) 10% (100 mg/mL) Liquid Preparation], which became available in the US during October 2014. Octagam 10% for the US market can now be manufactured at FDA-licensed facilities in Stockholm, Sweden and Vienna.

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⁹ Amgen’s Epogen (erythropoietin alfa), experienced patent expiry in 2014. Biosimilars have been launched by Biocon, Ranbaxy, and Emcure Pharmaceuticals. Amgen currently owns the patent Aranesp for darbepoetin alfa; this will expire by 2016. Other companies in the EPO drug market are Johnson & Johnson, Roche, LG Life Sciences Ltd., Intas Pharmaceuticals, Teva Pharmaceutical Industries Ltd., and Celltrion, Inc.

e) Baxter has filed a biologics license application with the FDA for BAX 111, an investigational drug for the treatment of patients with von Willebrand disease (VWD), the most common type of inherited bleeding disorder\(^{11}\). If approved, BAX 111 will be the first recombinant treatment in clinical development for VWD. The filing was based on results of a Phase III, multi-center clinical trial assessing the safety, efficacy and pharmacokinetics of BAX 111. Trial sites were located in the US, Europe, Australia, Japan, Russia and India. BAX 111 was granted an orphan-drug designation by the FDA and the European Commission in November 2010.

Blood donation, processing, storage and use; blood substitutes

f) In a letter dated 16 December 2014, the FDA approved Cerus’ Intercept Blood System for plasma. This system is used by blood establishments in the preparation of plasma in order to reduce the risk of transfusion-transmitted infections (TTI), including HIV, hepatitis B and C and West Nile Virus. The photochemical process involves a controlled exposure to ultraviolet light and amotosalen, a chemical that facilitates the inactivation process. The plasma is then purified to remove the chemical and its byproducts. Some viruses (e.g. human parvovirus B19) and spores formed by certain bacteria are resistant to the Intercept process.

g) In a letter dated 18 December 2014, the FDA approved Cerus’ Intercept Blood System for platelets. It noted that “this device is intended to be used for ex vivo preparation of apheresis platelet components in order to reduce the risk of transfusion-transmitted infection (TTI) including sepsis, and to potentially reduce the risk of transfusion-associated graft versus host disease (TA-GVHD).”

h) The FDA approved Roche’s cobas TaqScreen MPX Test, v2.0, to detect and identify HIV 1, HIV 2, and hepatitis B and C in the plasma of donated blood, organs, and tissues.

i) At the end of December, the FDA issued draft guidance for industry on Bacterial Detection Testing by Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion. Comment was invited.

Other

j) The FDA has approved a test to screen for Severe Combined Immunodeficiency (SCID) in newborns. It has recommended all States screen newborns for SCID along with other disorders.

k) In early January, Cohera Medical of Pittsburgh received a letter from the FDA saying its premarket approval application for TissuGlu Surgical Adhesive is approvable (the company then works with the FDA to achieve final approval). TissuGlu is a strong, biocompatible, and easy-to-use surgical adhesive. It is indicated for the approximation of tissue layers where subcutaneous dead space exists between tissue planes in abdominoplasty. It is an alternative to the use of closed suction drains, reducing the number of post-operative invasive treatments and improving the patient recovery process. TissuGlu has been CE approved and for sale in Germany through a Cohera direct sales force since 2012 and has been used in over 2,000 surgical procedures since that time.

l) Hospira submitted a biologics license application to the FDA for its anaemia drug Retacrit, a biosimilar. Retacrit received approval in Europe in 2008.

m) The FDA approved Daichi-Sankyo’s Savaysa (edoxaban tablets) to reduce the risk of stroke and dangerous blood clots (systemic embolism) in patients with atrial fibrillation that is not caused by a heart valve problem. The anticoagulant edoxaban inhibits factor Xa. It was approved in Japan in 2011 for the prevention of venous

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\(^{11}\) A bleeding disorder may also be acquired. Baxter’s drug Obizur was approved by the FDA in October 2014 for treating bleeding episodes in adults with acquired Hemophilia A.
thromboembolism in patients undergoing total knee replacement surgery, total hip replacement surgery and hip fracture surgery.

n) The UK’s National Institute for Health and Care Excellence (NICE) recommended Boehringer Ingelheim’s dabigatran, or Pradaxa, for National Health Service patients in England and Wales, for the treatment and prevention of deep vein thrombosis and pulmonary embolism.

o) GSK announced the submission of a supplemental new drug application to the FDA for eltrombopag (Promacta12), seeking an additional indication in paediatric patients six years and older with chronic immune (idiopathic) thrombocytopenia (ITP)13 who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy.

3. Market structure and company news

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

a) Novo Nordisk is seeking a new CEO, to replace Lars Rebien Soerensen who has led the company for 14 years but is not expected to remain until his contract runs out in 2019.

b) Baxter’s spin-off of its pharmaceutical business as Baxalta is on track for mid-2015 and the company says it will enhance shareholder value.

c) Baxter’s recombinant factor eight, Advate, has in the short term been retaining market share better than some analysts expected in the face of competition from the first of the long-acting products coming on the market.

d) Baxter agreed to sell its proprietary Vero cell technology and related assets, including its production facility in Bohumil, Czech Republic, to Nanotherapeutics. The Vero cell platform is a cell-based technology for vaccines production. The agreement includes related vaccines for H5N1, H1N1 and seasonal influenza and investigational vaccine programs for Ross River virus, chikungunya and West Nile virus. Baxter had previously sold its commercial vaccines business and related traditional manufacturing facilities to Pfizer. President of Baxter BioScience, Ludwig Hantson, said "The divestiture of the vaccines franchise will allow Baxter BioScience to enhance focus in core therapeutic areas of hematology, oncology and immunology, as it prepares to become an independent biopharmaceutical company. In addition, these transactions provide flexibility to direct resources toward strategic priorities that will drive future growth."

e) CSL employs 120 staff in China, across five major cities. In 2013-14, CSL earned $US 300 million through albumin sales in China, a 29 per cent increase on the previous year.

f) CSL Behring has significant manufacturing capacity in Switzerland, and its market capitalisation fell in December when the Swiss government lifted its cap on the Swiss franc.

g) ProMetic Life Sciences has contracted with Generium Pharmaceuticals for various plasma-derived biopharmaceuticals to be manufactured and commercialized in Russia and the Commonwealth of Independent States (CIS). The agreement

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12 Revolade in the EU and the rest of the world.
13 ITP is characterised by a low platelet count. Some children with acute ITP do not require treatment and/or their disease resolves, but up to 30 per cent of patients experience persistent disease at 12 months and are diagnosed with chronic ITP and are at risk of severe bleeding.
includes the co-development and global commercialization of two plasma-derived coagulation factors. The Generium plasma purification facility will be able to process up to 600,000 litres of plasma annually. The design will be based on ProMetic's Laval facility. Construction has begun and is expected to be completed by 2017. Of the US $17 million fees to be paid by Generium, US $6 million is to be paid up front, with US $11 million of staged payments at defined milestones.

h) Isis and Alnylam, leaders in RNA-targeted therapeutics, have entered into a new agreement, extending their existing strategic partnership (formed in 2004) to lead the development and commercialization of RNA therapeutics. The new agreement includes a cross-license of intellectual property (IP) on four disease targets, with each company having exclusive RNA therapeutic licence rights for two programs. There is also a non-exclusive technology IP cross-license, providing each company rights to some of each other's technology advances for RNA therapeutics through to April 2019. Alnylam is currently developing an investigational RNAi therapeutic targeting antithrombin (AT) for the treatment of haemophilia and rare bleeding disorders. ALN-AT3 is in a Phase 1 clinical trial enrolling haemophilia patients.

i) ADMA Biologics received a $US 5 million tranche from Hercules Technology Growth Capital, Inc. The $5 million was based upon ADMA achieving clinical endpoints of a Phase III clinical study of RI-002 as a treatment for Primary Immunodeficiency Disease (PIDD), under its existing loan and security agreement.

j) Sangamo BioSciences president and CEO Edward Lanphier presented an update on the company's clinical and preclinical ZFP Therapeutic programs and an overview of business strategy at the J.P. Morgan Healthcare Conference in San Francisco. He mentioned

i) the initiation in the first half of 2015 of a Phase I clinical trial of the zinc finger nuclease (ZFN)-modified hematopoietic stem cell approach for the possible cure of beta-thalassemia. The company also expects to file an investigational new drug application for this approach in sickle cell disease by the end of the year. Both programs are partnered with Biogen Idec.

ii) the initiation In the first half of 2015 of a Phase I clinical trial of the company's ZFP Therapeutic, SB-728, in stem cells, which is designed to enable functional control of HIV. All subjects have been accrued in an ongoing Phase II trial (SB-728-1401) of this approach in T-cells, and initial data are expected from this study by the end of 2015.

iii) continued attempts to expand delivery capabilities and potential therapeutic applications of Sangamo's ZFP technology, including the recently announced initiative to develop in vivo RNA delivery of ZFNs to address in vivo gene knockout targets in the liver. The potential to dose patients with ZFNs in several treatments provides the opportunity to "dose to effect" or to administer the ZFNs until a sufficient level of permanent modification is obtained to provide a life-long therapeutic outcome.

iv) Sangamo Biosciences has in-licensed nanoparticle technology to enable systemic messenger RNA (mRNA) delivery of Sangamo's proprietary zinc finger nucleases (ZFNs). mRNA delivery of ZFNs is being used in the development of the next generation of Sangamo's ZFP Therapeutics. Edward Lanphier, Sangamo's president and CEO, said "Specifically, this strategy opens up an entirely new set of therapeutic genome-editing targets; mRNA delivery could enable progressive and permanent knock out of a gene at the DNA level versus repressing its expression using continued and chronic administration of antisense or RNAi therapeutics."

k) Cerus Corporation announced the pricing of an underwritten public offering of 12,727,273 shares of its common stock offered at a price to the public of $US 5.50 per share for expected gross proceeds of $70.0 million. Cerus said it would use the net proceeds from the offering for continued development activities related to the Intercept Blood System, to fund commercialization efforts for the INTERCEPT Blood
System in the US and elsewhere and for other general corporate purposes including regulatory activity, selling, general and administrative expenses, and working capital.

l) Cohera Medical signed an exclusive sales and marketing distribution agreement with B. Braun for its TissuGlu Surgical Adhesive in Germany, Spain and Portugal. B. Braun Surgical, S.A. will exclusively market and sell TissuGlu in the territories of Germany, Spain and Portugal through its existing Closure Technologies commercial teams.

4. Country-specific events

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

a) Towards the end of December the US National Institutes Health (NIH) allowed five studies involving a mouse model for MERS-CoV and two influenza studies to continue after a 2-month moratorium on such “gain of function” studies.

b) FDA Commissioner Margaret Hamburg announced in December 2014 that “the agency will take the necessary steps to recommend a change to the blood donor deferral period for men who have sex with men from indefinite deferral to one year since the last sexual contact…….Additionally, in collaboration with the NIH’s National Heart Lung and Blood Institute (NHLBI), the FDA has already taken steps to implement a national blood surveillance system that will help the agency monitor the effect of a policy change and further help to ensure the continued safety of the blood supply……The FDA intends to issue a draft guidance recommending this proposed change in policy in 2015, which will also include an opportunity for public comment”.

c) The Solomon Islands Red Cross suspended its blood collection program. The National Referral Hospital was appealing for blood donations.

d) In Ireland in 2010, the health service agreed with Alexion on funding for ten patients to receive Soliris (eculizumab), which controls the breakdown of red blood cells. This was a pilot “Access with Evidence” program, and the program is full. Not surprisingly, a patient with paroxysmal nocturnal haemoglobinuria (PNH) who cannot access the program is angry. The drug costs €437,000 per patient per year.

e) South Australian pharmacists will be able to vaccinate adults who are not already eligible for a free flu shot as part of the National Immunisation Program.

5. Safety and patient blood management

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

Appropriate transfusion

a) A recent meta-analysis\(^\text{14}\) has concluded that the use of tranexamic acid in patients undergoing spinal surgery appears to be effective in reducing the amount of blood loss, the volume of blood transfusion, the transfusion rate, and the postoperative partial thromboplastic time. The authors found data too limited for any conclusions regarding safety. They said more high-quality randomized controlled trials are required before a recommendation can be made concerning the administration of tranexamic acid during surgery.

\(^{14}\) Fan Zhang, Kun Wang, Feng-Ning Li, Xuan Huang, Quan Li, Zhi Chen, Yi-Bo Tang, Hong-Xing Shen, Qing-Xin Song, “Effectiveness of tranexamic acid in reducing blood loss in spinal surgery: a meta-analysis”, *BMC Musculoskeletal Disorders* 2014, 15:448 doi:10.1186/1471-2474-15-448. The electronic version of this article can be found online at: [http://www.biomedcentral.com/1471-2474/15/448](http://www.biomedcentral.com/1471-2474/15/448)
b) In a recent meta-analysis\(^\text{15}\), a trend toward reduced 90-day mortality was observed in severe sepsis patients resuscitated with albumin compared with crystalloid and saline. Furthermore, the 90-day mortality of patients with septic shock decreased significantly.

c) Dr Nancy Dunbar, at the Dartmouth-Hitchcock Medical Center\(^\text{16}\) in Lebanon, New Hampshire has described how she and others had "figured out how to harness the power of the electronic medical record to embed evidence-based transfusion criteria into the computerized physician order entry process through the best practices alert functionality." She said pathologists are provided with "real-time" education and reminders with each order. The proportion of two-unit transfusions decreased after the implementation of the electronic best practices alert — from 47 per cent to 15 per cent.

d) Research led by Jonathan H. Chen, from the Stanford University Medical Center in California\(^\text{17}\) has found a range of reasons clinicians ignore best practice alerts for blood product transfusions. Acute bleeding was the most common reason, followed by protocolized behaviours on specialty services. Some transfusions occurred in anticipation of surgical intervention and some occurred almost immediately prior to hospital discharge.

e) Results of a randomized controlled trial suggest that a liberal blood transfusion strategy did not affect mortality compared with a restrictive transfusion strategy among high-risk elderly patients with a history of, or risk factors for, cardiovascular disease. Jeffrey L. Carson, professor of medicine and chief of the division of general internal medicine at Rutgers Robert Wood Johnson Medical School, and colleagues conducted the FOCUS trial in 2,016 patients recruited from 47 hospitals in the US and Canada between July 2004 and February 2009. Patients were at least 50 years old with a history of risk factors for cardiovascular disease. Patients had postoperative haemoglobin concentrations lower than 100 g/L within 3 days of surgery to repair a hip fracture.

f) A Johns Hopkins-led study\(^\text{18}\) was the first US-wide review of nearly 100,000 combined hospital admissions for three rare blood cell disorders: thrombotic thrombocytopenic purpura (TTP), heparin-induced thrombocytopenia (HIT) and immune thrombocytopenic purpura (ITP). It found that one in every 13 hospitalized patients with heparin-induced thrombocytopenia and one in every 10 hospitalized patients with thrombotic thrombocytopenic purpura received a platelet transfusion. Platelet transfusions were associated with increased odds of dying in the hospital, fivefold for patients with heparin-induced thrombocytopenia and double for patients with thrombotic thrombocytopenic purpura. The most serious complications were arterial blood clots. Aaron Tobian of the Johns Hopkins University School of Medicine commented: “There was some suggestion that transfusion may be harmful in these conditions, but it really was not known until now. Our study is the first one to show that platelet transfusions are frequently administered to patients with ITP, HIT and TTP, and that they're associated with higher odds of arterial blood clots and mortality in TTP and HIT.”

\(^{15}\) Jing-Yuan Xu, Qi-Hong Chen, Jian-Feng Xie, Chun Pan, Song-Qiao Liu, Li-Wei Huang, Cong-Shan Yang, Ling Liu, Ying-Zi Huang, Feng-Mei Guo, Yi Yang, and Hai-Bo Qiu, “Comparison of the effects of albumin and crystalloid on mortality in adult patients with severe sepsis and septic shock: a meta-analysis of randomized clinical trials”, Crit Care. 2014; 18(6): 702. Published online 2014 Dec 15. doi: 10.1186/s13054-014-0702-y

\(^{16}\) Cancer care is co-ordinated by the Norris Cotton Cancer Center

\(^{17}\) published in the January issue of the Journal of Hospital Medicine.

\(^{18}\) Published 14 January 2015 in Blood, the journal of the American Society of Haematology.
g) Various transfusion ratio concepts of packed red blood cells (pRBCs), fresh frozen plasma (FFP) and platelets (PLTs) have been used in trauma care. A recent study\textsuperscript{19} assessed the haemostatic potential of two predefined ratios using an \textit{in vitro} thrombelastometric approach. It concluded the coagulation functionality of the 1:1:1 ratio predominated over the 3:1:1 ratio.

h) The January issue of \textit{Anesthesiology} reported on studies of the two most significant causes of post-transfusion mortality in the US: transfusion related acute lung injury (TRALI) and transfusion associated circulatory overload (TACO). Senior author for both papers was an associate professor of anaesthesiology at the Mayo Clinic, Rochester, Minnesota. The studies emphasised that both conditions were under-recognised and under-reported.

Other.

i) A study in the Netherlands\textsuperscript{21} claims to have found a way to improve the prognosis for patients with the most severe and disabling strokes. If doctors can directly remove large clots blocking blood vessels in the brain, they can save brain tissue from dying, so patients can return to an independent life. The researchers used a new type of snare to grab the clots. It is a stent (in this case a small wire cage), on the end of a catheter that is inserted in the groin and passed through an artery to the brain. When it arrives at the clot, the stent is opened and pushed into the clot, which it snags.

j) A study\textsuperscript{22} based on Danish health care system registries has found that people with atrial fibrillation who take nonsteroidal anti-inflammatory drugs while on an antithrombotic therapeutic regimen may be at risk for serious bleeding or thromboembolisms.

k) A poster session on Health Services and Outcomes Research during the 56th Annual Meeting of the American Society of Hematology (ASH) in San Francisco estimated payers in the US would see a reduction in overall medical costs if patients switched to newer, novel oral anticoagulants. The study considered ten clinical trials involving dabigatran, rivaroxaban, and apixaban. The study's lead author, Alpesh N. Amin, consults for Bristol-Myers Squibb and for Pfizer, joint makers of apixaban.

l) Portola Pharmaceuticals announced that its experimental drug andexanet alfa met the main goal (of reversing the effect of Johnson and Johnson and Bayer’s anticoagulant drug Xarelto) in a late-stage study in healthy volunteers aged 50-75 years. Further data is expected in mid-2015. Portola announced last October that the drug reversed the effect of Eliquis, an anti-clotting drug by Bristol-Myers Squibb Co and Pfizer Inc.

m) A study report\textsuperscript{23} at the ASH annual meeting said patients who suffered unprovoked pulmonary embolism had a significant reduction in the composite risk for recurrent venous thromboembolism and major bleeding when they received anticoagulation for an additional 18 months, but that the benefits associated with extended anticoagulation did not persist after treatment ceased.

n) Germany’s Pieris began a Phase I clinical trial of its anaemia drug PRS-080, which sequesters hepcidin, usually regarded as the master negative regulator of iron metabolism. Pieris CEO Stephen Yoder said: "Underpinned by a six million Euro grant...


\textsuperscript{23} By Francis Couturaud, Abstract #LBA-3, \textit{ASH Annual Meeting and Exposition}; Dec. 6-9, 2014; San Francisco.
from the European Commission, this Phase I clinical trial will bring PRS-080 one step closer to patients not adequately responding to current anaemia therapy.

6. Research

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

a) A study commissioned by the British government reported recently that drug-resistant bacteria could cause 10 million deaths a year and cost world governments billions of dollars. The World Health Organization (WHO) reports there were some 450,000 cases of multi-drug-resistant TB alone in 2012. Now University of Pittsburgh researchers have designed a synthetic compound they hope will fight “superbugs.” The University’s Center for Vaccine Research co-director Ron Montelaro says it will work in a completely different way from traditional antibiotics. “Antibiotics are drugs that typically poison the bacterial cell by blocking some metabolic process. These peptides work more by a physical action, by actually punching a hole in the bacterial membrane”. Some of the testing was done on a blood-borne infection in mice. While two traditional antibiotics slowed or stopped about 50 percent of the bacteria tested, the man-made drug stopped about 90 percent. The findings were published in the journal *Antimicrobial Agents and Chemotherapy*. The work was funded by the US National Institutes of Health (NIH).

b) There is nothing novel about antibiotics from soil. Penicillin came from *Penicillium*, a fungus found in soil, and vancomycin came from a bacterium found in dirt. Most recently, researchers from Northeastern University and NovoBiotic Pharmaceuticals and others have identified a new gram-positive bacteria-targeting antibiotic in a soil sample from the state of Maine. It can kill methicillin-resistant *Staphylococcus aureus* (MRSA) and *Mycobacterium tuberculosis*. So far they have not found any bacteria currently resistant to the antibiotic, which they call teixobactin24.

c) Opko Health, and Immuno Technologies, announced that the NIH has awarded a US $3 million grant to develop a rapid diagnostic test for Lyme disease.

d) Stanford University School of Medicine researchers cured haemophilia in mice models using a new genome editing method25.

e) In a paper published online in the *Journal of Biological Chemistry*26, senior co-author Daniel Kim-Shapiro, professor of physics at Wake Forest, and others have shown that deoxygenated hemoglobin is responsible for triggering the conversion of nitrite to nitric oxide, a process that affects blood flow and clotting. Kim-Shapiro said: “We have shown that conversion of nitrite to nitric oxide by deoxygenated hemoglobin in red blood cells reduces platelet activation….. This action has implications in treatments to reduce clotting in pathological conditions including sickle cell disease and stroke.”

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26 Chen Liu, Daniel Kim-Shapiro et al., “Mechanisms of Human Erythrocytic Bioactivation of Nitrite”, *Journal of Biological Chemistry*, 12/14 DOI: 10.1074/jbc.M114.609222
7. 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.

a) Three men who contracted hepatitis C from contaminated imported blood have begun a legal case in the UK to challenge the compensation scheme. They say it discriminates against them because they have hepatitis C, rather than HIV.

b) British MP Andrew Burt in mid-January led his colleagues in calling for a further review into the circumstances surrounding how haemophilia and other patients were infected by blood products during the 1970s and 1980s. MPs heard an estimated 1,800 deaths had been linked to the incident, with blood products continuing to be imported into the UK during that period and used on patients despite warnings. MPs were told a Scottish public inquiry (the Penrose inquiry) into the issue is expected to report back before the general election on 7 May.

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

Mosquito-borne diseases: dengue, chikungunya and malaria

a) By 20 January an outbreak of dengue fever in Cairns had spread to a third suburb. A ninth case was confirmed in Mooroobool.

b) The first results from the Eliminate Dengue project in Townsville show a trial to infect mosquitoes with a dengue-resistant bacteria is working. Australian researchers, in Mumbai to participate in the Australia Business Week, offered this as a possible solution to Mumbai’s growing dengue problem. They discussed how infecting mosquitoes with the bacteria reduces their life-span to half, eliminating the possibility of the mosquitoes being dengue-virus carriers.

c) Chikungunya continues to rage in South America, the Caribbean and French Polynesia.

d) Scientists at the International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi have developed a synthetic molecule that prevents malaria and tuberculosis microbes from invading human cells. The molecule, code-named M5, targets a set of proteins in the human body that both the malaria parasite and the tuberculosis bacilli exploit to enter human blood cells27.

e) A study of the way malaria parasites behave when they live in human red blood cells has revealed that they can rapidly change the proteins on the surface of their host cells during the course of a single infection in order to hide from the immune system28.

f) University of Massachusetts Amherst microbiologist Stephen Rich and his team report in the Proceedings of the National Academy of Sciences on a new malaria

27 A paper describing their experiments appeared on 14 January in Nature Communication.


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intervention. The new treatment is based on a use of the whole plant *Artemisia annua*, from which the current drug artemisinin is extracted. The team tested a special cultivar developed by Pamela Weathers, professor of biology and biotechnology at Worcester Polytechnic Institute. They found that the whole plant treatment withstands the evolution of resistance and remains effective for up to three times longer than the pure drug.

**Ebola Virus Disease**

a) On 20 January, WHO reported there had probably been around 21,689 cases of Ebola, with 8626 deaths as of 18 January.

b) Ebola has been described as currently the single greatest threat to the survival of gorillas and chimpanzees, having wiped out one-third of their populations since the 1990s. Mortality rates are up to 95 per cent for gorillas and 77 per cent for chimpanzees.

c) WHO said the two most advanced Ebola vaccines would soon be tested in healthy volunteers in West Africa. It reported that the vaccines (one made by GlaxoSmithKline and the other licensed by Merck and NewLink29) have been shown to have "an acceptable safety profile."

d) Johnson and Johnson announced the formation of consortia with leading global research institutions and non-government organizations to work in conjunction with Janssen Pharmaceutical to accelerate the development of its Ebola vaccine regimen. The Innovative Medicines Initiative (IMI)30 plans to award these consortia grants totalling over €100 million to support the development, manufacturing and patient education for the vaccine regimen.

e) BioCryst Pharmaceuticals said its experimental broad-spectrum antiviral drug showed promise against Ebola when tested in monkeys at the United States Army Medical Research Institute of Infectious Diseases. Ten out of 12 monkeys treated with the drug survived, including all six given the higher of two doses31. None of the animals given the placebo survived. The drug is also being tested in an early-stage trial in healthy volunteers. The US National Institutes of Health (NIH) is funding the development of the intramuscular formulation of the drug, BCX4430.

f) Canada’s Tekmira announced it would supply one of its experimental Ebola treatments for clinical studies to be conducted in West Africa in 2015.

g) Kymab of Cambridge in the UK has received a grant from the Wellcome Trust to develop treatments against Ebola using its human antibody discovery platform,

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29 NewLink Genetics Corporation and Merck announced that the Biomedical Advanced Research and Development Authority (BARDA) of the US Department of Health and Human Services (HHS) has awarded NewLink Genetics’ wholly-owned subsidiary, BioProtection Systems, as the prime contractor in a $US 30 million contract to support the manufacturing and development activities of its investigational rVSV-EBOV (Ebola) vaccine candidate, including clinical development through a new 330-person Phase Ib study. The vaccine candidate was initially developed by the Public Health Agency of Canada (PHAC), and is now being developed under an exclusive licensing and collaboration agreement between NewLink Genetics and Merck. Depending on the results of Phase I trials, the US National Institutes of Health announced plans to initiate, in early 2015, a large randomized, controlled Phase II/III study to evaluate the safety and efficacy of this and another investigational Ebola vaccine candidate.

30 The IMI is a public-private initiative aiming to speed up the development of better and safer medicines for patients. Funding for the IMI Ebola+ programme comes from Horizon 2020, the European Union's research and innovation programme, and from in-kind contributions from the European Federation of Pharmaceutical Industries and Associations (EFPIA) partners in the projects. Involved in the consortia are the London School of Hygiene and Tropical Medicine, INSERM, Oxford University, La Centre Muraz, Bavarian Nordic A/S, Vibalogics, the Grameen Foundation and World Vision of Ireland with Janssen Pharmaceutical Companies.

31 A preliminary analysis also showed a reduction of the viral load in the blood of monkeys receiving the drug.
Kymouse. The grant is for Kymab to lead a consortium which includes the Wellcome Trust, Sanger Institute, the University of Westminster and Public Health England, tasked with discovering and developing antibodies against evolving strains of the Ebola virus.

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

a) H7N9, a subtype of influenza found in birds was first identified in humans in China in 2013\(^{32}\). Human cases continue to be reported there eg by 21 January Zhejiang Province had reported 14 human cases this winter, and Guangdong province reported three cases in the first week of January. The strain can cause severe pneumonia and death\(^{33}\) but is not thought to spread easily from person to person. In its October 2014 assessment of the risk posed by H7N9, WHO found 453 laboratory-confirmed cases of the strain and 175 deaths.

b) At the end of January the Public health Agency of Canada confirmed North America’s first human case of H7N9. Two British Columbia residents returned home from China on 12 January carrying the infection.

c) China’s Guangdong province and Hong Kong in the first week of January culled thousands of chickens after Guangdong’s poultry exports to Hong Kong were found to be infected with H7N9. Hong Kong temporarily banned live poultry imports from China.

d) In a report released mid-January, WHO said preliminary studies suggested no major genetic changes in the H5N1 virus in Egypt to explain that country’s busiest month ever for human cases. Eighteen laboratory-confirmed cases were recorded between 4 December and 6 January.

e) A second case of H5N6 avian flu was reported from China’s Guangdong province in December.

f) H5N8, H5N2 and H5N3 outbreaks were found in birds in Europe, North America and Asia. H5N8 is thought to have the potential to cause human disease but none has yet been reported. In mid-January Hong Kong banned Taiwanese eggs, after discovery of a new H5N2 avian influenza strain and the H5N8 flu virus at goose and duck farms in southern Taiwan. The US Department of Agriculture found the H5N8 virus in wild birds in the west, while there was an H5N2 outbreak in birds in Washington State. Scientists writing in the *Proceedings of the National Academy of Sciences (PNAS)* on 6 January said they found a close association between H5N1 outbreaks and wild bird migrations in Asia. H5N1 was confirmed in flocks of birds in India.

g) In the US, the seasonal flu vaccine this winter has proved less effective than expected, as around two-thirds of the H3N2 viruses tested by the US Centers for Disease Control and Prevention (CDC) have proved to be antigenically or genetically different from the H3N2 vaccine virus. The CDC has recommended doctors step up the use of antivirals against the flu.

h) The FDA approved BioCryst Pharmaceuticals’ Rapivab (peramivir) to treat influenza infection in adults. Rapivab inhibits influenza virus neuraminidase, an enzyme that releases viral particles from infected cells. Rapivab is the first neuraminidase inhibitor

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\(^{32}\) A new study says that H9N2, which helped give rise to the deadly H7N9, evolved to become increasingly infectious in chickens in the years leading up to H7N9’s appearance. H9N2 had been circulating on chicken farms in China since 1994. Then the virus recombined in poultry markets with H7 and N9 viruses that had been passed from wild birds to domestic ducks. The resulting H7N9 flu virus jumped to humans in 2013.

\(^{33}\) Scientists led by Sun Shihui from the Beijing Institute of Microbiology and Epidemiology and Zhao Guangyu from the Academy of Military Medical Science reported in the British journal *Clinical Infectious Diseases* that they found that African green monkeys inoculated with H7N9 and treated intravenously with an antibody experienced reduced acute lung infection (ALI) and reduced systemic inflammation.
approved for intravenous use\textsuperscript{34}. It is administered as a single dose, in adult patients who have acute uncomplicated influenza and have shown flu symptoms for no more than 48 hours.

\textbf{MERS-CoV}\textsuperscript{35}

a) As at January 20, 2015, WHO has reported 955 human cases, including 351 deaths. New cases of MERS continue to occur, eg in Saudi Arabia\textsuperscript{36} and Oman.

b) Researchers from King Faisal University (Saudi Arabia) and the University of Hong Kong said of their small study of interaction between camels and humans “Our findings do not imply that dromedaries are not a source of infection for humans, but are consistent with observations that human disease is not directly proportional to potential exposure to a virus that seems to be common in dromedary camels”.\textsuperscript{37}

c) Greek researchers have concluded that inadequate infection control has contributed to the widespread transmission of MERS\textsuperscript{38}.

d) The Saudi Health Ministry announced on 21 January 2015 the appointment of US experts to halt the spread of infectious diseases, including MERS-CoV. There had been 837 MERS infections and 361 fatalities in the country since September 2012. The experts are from the CDC. The decision includes training and support for Saudi professionals under the Field Epidemiology Training Program (FETP).

e) The Saudi Ministry was reported by \textit{Arab News} to have suspended 38 contracts worth a total SR1 billion ($266 million). The contracts were all related to MERS. The ministry said some of the companies contracted had not performed the work they were signed to do.

f) MERS has been transmitted from one person to another in the US; a University of Iowa scientist has reportedly been sanctioned for working on the virus without appropriate approval and in an inappropriate laboratory setting.

\textbf{Other diseases: occurrence, prevention and treatment}

a) NHS England and Public Health England are spending £11.5 million in an attempt to eliminate tuberculosis from England by 2020. The UK has the second-highest rate of TB in western Europe, five times higher than in the US. Without intervention, England alone would have more TB cases than the whole of the US within two years.

b) US researchers say they have developed a vaccine that counters Chronic Wasting Disease of deer and elk and therefore holds promise of doing the same for Creutzfeldt Jakob disease of humans, Bovine Spongiform Encephalopathy of cattle and scrapie in sheep. Senior study investigator and neurologist Thomas Wisniewski, a professor at New York University, Langone, said: “Now that we have found that preventing prion infection is possible in animals, it’s likely feasible in humans as well.” The team says that if further vaccine experiments prove successful, a relatively small number of animals (as few as 10 per cent) could be inoculated to induce herd immunity for elk and deer in the wild. They are thought at present to be likely to spread CWD prions to cattle. A report on a vaccine developed by researchers at Colorado State University which has proved to be partially successful in combating chronic wasting disease in deer can be found in the journal \textit{Vaccine}.

\textsuperscript{34} Other neuraminidase inhibitors approved by the FDA are oseltamivir(Tamiflu), administered orally, and zanamivir, which is inhaled.

\textsuperscript{35} the Middle East Respiratory Syndrome Coronavirus

\textsuperscript{36} Between 6 and 9 January 2015, the Kingdom of Saudi Arabia notified WHO of 5 additional cases of MERS infection, including 1 death.

\textsuperscript{37} Their paper was published in \textit{Emerging Infectious Diseases}

\textsuperscript{38} Helena C. Maltezou, Sotirios Tsiodras, “Middle East respiratory syndrome coronavirus: Implications for health care facilities”, \textit{American Journal of Infection Control}, December 2014 , Volume 42, Issue 12, Pages 1261–1265 DOI: http://dx.doi.org/10.1016/j.ajic.2014.06.019
c) European researchers say they have linking the infectious agent behind scrapie in sheep with sporadic CJD (sCJD), a fatal human disease. They say they have no proof that consuming lamb infected with scrapie can lead to sCJD in humans, but tests on humanised laboratory mice show that potentially scrapie is capable of infecting humans. The way the infection spreads in the brain is identical to that seen in cases of sCJD. The scientists, led by Dr Olivier Andreoletti, from the National Veterinary School of Toulouse, wrote in the journal *Nature Communications*: "Our data on their own do not unequivocally establish a causative link between natural exposure to sheep scrapie and the subsequent appearance of sCJD in humans. However, our studies clearly point out the need to consider this possibility."

d) Novira Therapeutics’ Hepatitis B antiviral, NVR 3-778 is a small molecule drug that inhibits the Hepatitis B core or capsid protein. The company released Phase Ib trial results, which showed the drug was well-tolerated in the 40 subjects.

e) The Northern Territory recorded its first death for the year from melioidosis. The bacteria, which lives in soils and muddy water in the NT, the Kimberley region of Western Australia and northern Queensland and South-East Asia, comes to the surface after drenching rains. The Territory usually has 35 to 45 cases per wet season, though sometimes the figure is as high as 100. Last wet season there were 66 cases.

f) Researchers at the University of Rochester Medical Center have been testing a new oral vaccine to prevent HIV. The pill is based on a live virus, adenovirus, which is a common cause of respiratory and gastroenteritis infections. It contains a protein that triggers the body to launch an immune response against HIV.

g) Researchers have found that a combination of antibodies from llamas can destroy-or neutralize—a wide range of circulating HIV viruses.

h) Deep fried ice cream from a Chinese restaurant was blamed for a salmonella outbreak in Queensland. Eggs used in the batter were considered to be the source.

i) The CDC and the Kansas Department of Health and Environment are investigating a new virus linked to the death of a Kansas resident during the summer of 2014. The so-called Bourbon virus is thought to be transmitted through the bites of ticks or other insects. Symptoms in the Kansas resident resembled other tick-borne diseases, including fever and fatigue.

j) GSK announced that a Phase III trial to assess the efficacy of HZ/su, an investigational vaccine for the prevention of shingles, had met its primary endpoint. The most common adverse events were local reactions (pain, redness, swelling at the injection site) and systemic symptoms (muscle pain, fatigue and headache).

k) A three year old Victorian child has died and other children have become very ill after consuming unpasteurized milk.

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39 Hervé Cassard et al., “Evidence for zoonotic potential of ovine scrapie prions”, *Nature Communications* Article number:5821 Published 16 December 2014 doi:10.1038/ncomms6821

40 Laura E McCoy et al., “Molecular Evolution of Broadly Neutralizing Llama Antibodies to the CD4-Binding Site of HIV-1”, *PloS Pathogens*, December 18, 2014DOI: 10.1371/journal.ppat.1004552