Monitoring International Trends

posted May 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:

Section 1- Products

a. Botest presented results demonstrating safe and effective switch from high dose intravenous hepatitis B immunoglobulin to subcutaneous Zutectra,
b. Researchers are trialling a patient's own platelet rich plasma as a gel to dress burns.
c. Scientists synthesized clot-promoting nanoparticles with a corticosteroid to stop inflammation; injected these into rats after traumatic injury. The nanoparticles increased oxygen levels and reduced internal bleeding and cell damage.
d. Prolong Pharmaceuticals, presented data on its product Sanguinate, reporting its novel ability to rapidly reverse sickling of human red blood cells in an *in vitro* model.
e. To combat hypovolemia and haemorrhage in trauma, researchers are considering a hydroxocobalamin (Cyanokit), a treatment for cyanide poisoning.
f. Cerus presented at an AAAB Symposium on Implementation of Pathogen-Reduced Blood Components.
g. A combination of an antiviral drug and an anticancer drug eliminates the hepatitis B virus in mouse models**.**
h. Scientists have found a cell receptor that, when chemically stimulated and with the help of glucocorticoids, significantly increases red blood cell production.

Section 2 - Regulatory

a. The FDA has approved Emergent Biosolutions' intravenous recombinant factor IX (Ixinity).
b. Kamada has received Orphan Drug Designation from the European Medicines Agency's (EMA) Committee for Orphan Medicinal Products (COMP) for its human intravenous Alpha-1 Antitrypsin (AAT) to treat graft-versus-host disease (GvHD).
c. The FDA has granted orphan drug designation to Prolong Pharmaceuticals' sickle cell disease treatment, Sanguinate,
d. GlaxoSmithKline and its Italian partners have applied to the EMA to market an investigational gene therapy to treat an ultra-rare white blood cell deficiency.
e. The FDA granted Boehringer Ingelheim Priority Review for its Biologics License Application for idarucizumab to reverse the anticoagulant effect of dabigatran, the active ingredient in Pradaxa
f. The FDA granted Orphan Drug Designation to Dilaforette's proprietary polysaccharide drug sevuparin for the treatment of patients with sickle cell disease.

Section 3 – Market Structure and Company News

a. The intravenous immunoglobulin (IVIg) market has been forecast to grow at a compound annual growth rate of 6.8 per cent between 2015 and 2021.

b. Bayer broke ground for its $US 100 million product testing facility in California for new haemophilia A treatments.
c. Denmark's Novo Nordisk will invest $US 225 million in a new haemophilia treatment manufacturing facility in Kalundborg, Denmark.
d. Green Cross has selected Montreal for its new plasma fractionation plant.
e. In South Korea, SK Plasma held a ground-breaking ceremony for a plasma fractionation plant in Andong.

Section 4 – Country Specific Events

a. US health officials recommended ending the lifetime ban on blood donations from gay and bisexual men, substituting a policy barring donations from men who have had sex with other men in the previous year.

Section 5 – Safety and Patient Blood Management

a. Research suggests that paediatric patients undergoing heart surgery do better when given fresh whole blood from single donors instead of blood components from multiple donors.
b. A study has found that obese patients taking warfarin may be more prone to bleeding problems.

Section 6 - Research

a. Bioengineers think they have made progress towards making all blood universal
b. Researchers have described[1] how the respiratory cycle involves three gases not two.

Section 7 – Legal Actions and Enquiries

a. In Singapore a blood donor who made a false declaration was jailed and fined.
b. CSL Plasma is facing a lawsuit from a woman who claims the company discriminated against her by turning her away because she's transgender.

Section 8 – Infectious Diseases

a. Australia has had its worst Ross River virus outbreak for twenty years.
b. Zika virus has been reported in Vanuatu for the first time.
c. A major outbreak of avian flu in commercial poultry in the US Midwest has led to the culling of millions of birds across fifteen states. Prices for eggs and turkey meat have been rising.
d. In mainland China, the total number of reported human cases of influenza A (H7N9) since people began falling ill reached 640 by 10 May. Researchers reported that the potential pandemic risk may be greater for H7N9 avian flu than for H5N1.
e. WHO confirmed that in the first three months of 2015 Egypt recorded 119 confirmed human cases of H5N1, including 30 deaths.
f. By 1 May, WHO had been notified of 1111 laboratory-confirmed cases or Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) globally, including 422 deaths.
g. Twelve cases of MERS-CoV in Saudi Arabia were reported between 9 May and 11 May. These brought the national cumulative total to 996 cases.
h. In Saudi Arabia, 29 per cent of live camels have been found to be carrying MERS-CoV in their noses, and 62 per cent of dead camels have the virus in their lungs.
i. Doctors are recognizing "post-Ebola Syndrome" as a serious condition.
j. GlaxoSmithKline and the University of North Carolina at Chapel Hill are together launching a research centre to focus on finding a cure for HIV/AIDS.
k. Scientists at Iowa State University and the US Department of Agriculture have used retina tests to detect animals infected with BSE.

[1] in the *Proceedings of the National Academy of Sciences*

Table of Contents

1. Products

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

Plasma and recombinant products

a. LFB announced, through its rEVO Biologics subsidiary, that after the interim analysis of the PERSEPT 1 safety and efficacy data by the independent Data Monitoring Committee, the study would proceed. PERSEPT 1 (Program for the Evaluation of Recombinant Factor Seven Efficacy by Prospective Clinical Trials) is a Phase III clinical trial of a next generation recombinant Factor VIIa (LR769) in adult and adolescent congenital haemophilia A or B with inhibitors to Factor VIII or Factor IX.
b. Kamada on 19 May hosted a panel discussion[2] titled "New Treatment Prospects for AATD[3] Patients: Results from a Phase II/III Inhaled AAT Trial" at the American Thoracic Society 2015 International Conference in Denver, Colorado. Pnina Strauss, Vice President-Clinical Development and Intellectual Property at Kamada, began the session by presenting the full data set from the Phase II/III clinical study of inhaled AAT for the treatment of AATD, including analyses of lung function and quality-of-life data[4]. Referring before the event to the European study, the CEO of Kamada David Tsur said: "The recently reported final results from the study showed clinically and statistically significant improvements in spirometric measures of lung function, particularly in bronchial airflow measurements…..These favourable results were even more evident when analyzing the overall treatment effect throughout the full year…..We believe the combination of lung functions, which are the gold standard measurements for pulmonary diseases, and symptom improvements, along with the safety profile of the product, give us confidence that these data support our decision to submit a Marketing Authorization Application with the European Medicines Agency for Conditional Approval of our inhaled AAT therapy to treat AATD patients."
c. The 2015 Scientific Symposium of the Hemostasis and Thrombosis Research Society in New Orleans was presented with additional data from a Phase III trial evaluating Baxter's recombinant von Willebrand Factor (rVWF), BAX 111, for the treatment of patients with von Willebrand disease (vWD). The trial met its primary efficacy endpoint of the number of patients who achieved treatment success for control of bleeding episodes. Baxter submitted its regulatory application to the FDA in late 2014. Bax 111 is designated an Orphan Drug by both the FDA and EMA for the treatment of vWD.
d. Also at the Hemostasis and Thrombosis Research Society annual meeting in New Orleans, Bio Products Laboratory announced the results from a phase III study examining the pharmacokinetics, efficacy, and safety of its factor X coagulation drug in patients with hereditary factor X deficiency[5]. Dr. Steve Austin, of St. George's

[2] The panel included Professor Kenneth R. Chapman, Director, Canadian Registry for Alpha-1 Antitrypsin Deficiency Asthma and Airway Centre, Toronto Western Hospital, University of Toronto; Professor Gerry McElvaney, Beaumont Hospital, Dublin; Professor Robert A Stockley, Lung Investigation Unit, Queen Elizabeth Hospital, Birmingham University; and Dr Jan Stolk, Department of Pulmonology, Leiden University Medical Center, The Netherlands and acting Chairman of the Alpha 1 International Registry. The session was chaired by Professor Robert A. Sandhaus, Founder and Director of the Alpha1-Antitrypsin Deficiency Program at National Jewish Health Hospital in Denver, Colorado, and the Clinical Director of the Alpha-1 Foundation.

[3] Alpha-1 Antitrypsin Deficiency

[4] The event including slides was made available in the Investor Relations section of the Company's website at www.kamada.com

[5] The data were generated from an open-label, multicenter, prospective study of sixteen patients with severe or moderate hereditary factor X deficiency. Subjects received on-demand treatment for spontaneous or traumatic bleeding episodes, or received specific short-term preventative therapy.

Hemophilia Centre in London, and an investigator in the study, said: “The data show that the BPL factor X product helped restore haemostasis and reduced bleeding in factor X deficient subjects suffering from various bleeds.” The data have been submitted to the US Food and Drug Administration (FDA) for review[6].

e. Children living with haemophilia can find it hard to talk about their condition or describe its implications for them. Sobi has now, with the support of Consultant Nurse Dr Kate Khair and her team at the Great Ormond Street Hospital for Children, developed the *Magic Movie Maker*, which is being introduced in the UK. It is a free iPad app which helps children to communicate with others about their haemophilia.
f. Biotest on April 23 presented the efficacy and safety results from the Zutectra-Early-Use-Study (ZEUS) at the 50th International Liver Congress 2015 in Vienna. They demonstrated safe and effective switching from high dose intravenous hepatitis B immunoglobulin (HBIG) to subcutaneous HBIG, Zutectra, at the earliest one week after liver transplantation. There was no Hepatitis B virus reinfection after six months of Zutectra prophylaxis with excellent safety and tolerability data.The Zutectra dossier has been submitted to EMA for EU-Approval**.**[7]
g. US researchers are testing using a patient’s own platelet rich plasma as a gel for dressing burns[8]. They hope this might deal with a common problem with burns, which is that they can continue to worsen for hours or days after the original incident. Earlier experience suggested that the high concentration of growth factors in the platelet-rich plasma might stimulate growth of new blood vessels and skin tissue.

Sickle cell disease

h. Mast Therapeutics reported that patient enrolment in its EPIC study of its lead candidate, vepoloxamer (MST-188), in sickle cell disease has passed the halfway point. The company expects to report top-line results in the first quarter of 2016.
i. Prolong Pharmaceuticals, presented data [9]on its product Sanguinate, reporting its novel ability to rapidly reverse sickling of human red blood cells (RBCs) in an in vitro model and thus returning the RBCs to a more normal, morphologic shape. The company reported that Sanguinate was able to reproducibly transfer therapeutic gases to RBCs of sickle cell patients; that both the carbon monoxide and oxygen forms of Sanguinate were capable of "unsickling" the abnormal RBC; that the "unsickling" event was rapid; and that there was a significant decrease in cytokine RNA and protein markers of inflammation following treatment with Sanguinate of whole blood samples from patients. Sanguinate is now in a Phase II study for the reduction or prevention of delayed cerebral ischemia following subarachnoid

---

The primary efficacy endpoints included recovery rate and half-life, while secondary measures included the patient’s overall assessment of efficacy and the number of infusions needed to treat a bleed. The success criteria were met. Two subjects reported six adverse events which may have been related to the medication: There were no serious drug-related adverse events, and no patients withdrew due to adverse events.

[6]There is not at present any specific factor X product approved by the FDA for the treatment of patients with hereditary factor X deficiency. There are estimated to be between 400 to 600 patients in the US known to suffer from the deficiency.

[7] The international clinical phase III study was performed in 17 transplant centres in four of the Big-Five EU-Markets, Italy, Spain, France and United Kingdom.47 adult patients suffering from life-threatening terminal liver disease due to long-lasting chronic hepatitis B or HCC (hepatocellular carcinoma) completed the study. The earliest conversion to subcutaneous administration contributes to a more time efficient, less costly patient care and better convenience for the patient.
Biotest submitted the dossier for "Zutectra-early-use" after liver transplantation to the EMA for EU-approval. The approval process is expected to be finalized in Q4 2015.

[8] The study is being conducted at the University of Utah and other burns centres.

[9] "Anti-inflammatory activity and rapid reversal of sickle cell morphology by SANGUINATE mediated gas transfer in vitro" was presented at the 9th Annual Sickle Cell Disease Research & Educational Symposium and 38th National Sickle Cell Disease Scientific Meeting in Hollywood, Florida.

haemorrhage. Phase II trials are also planned for vaso-occlusive crisis and leg ulcers secondary to sickle cell disease as well as for preventing delayed graft function following kidney transplantation. The product is being evaluated in international trials for the treatment of beta-thalassemia.

Other

j. Researchers from Virginia Tech University and Case Western Reserve University in Cleveland synthesized clot-promoting nanoparticles with a corticosteroid to stop inflammation; injected these haemostatic dexamethasone nanoparticles into rats immediately after the animals sustained traumatic injuries; and found that the nanoparticles increased oxygen levels and reduced internal bleeding and cell damage[10]. With explosions responsible for most combat-related injuries, the researchers said development of the compounds for emergency trauma care could reduce mortality from haemorrhage.

k. To combat hypovolemia and haemorrhage in trauma, researchers from the San Antonio Military Medical Center are considering a possible use for hydroxocobalamin (Cyanokit) approved in 2007 for use in the US as a treatment for cyanide poisoning. A member of the vitamin B12 family, hydroxocobalamin scavenges for nitric oxide in the bloodstream, leading to an increase in blood pressure and systemic vascular resistance[11].

l. Cerus presented at an AAAB Symposium in Bethesda, Maryland, on "Implementation of Pathogen-Reduced Blood Components", outlining how its INTERCEPT Blood System could improve transfusion services. It said the current label on INTERCEPT, approved by the FDA, refers to decreasing the risk of transfusion-transmitted infections in apheresis platelet components as well as whole blood derived plasma components. Cerus said INTERCEPT also reduces component waste in early platelet release and platelet availability. The company plans to expand its claims to include a seven-day platelet shelf-life extension; to develop a triple set storage INTERCEPT kit to improve the efficiency of collecting platelets; and to continue developing red blood cell systems after completing US Phase II and European Phase III trials.

m. A combination of an antiviral drug and an anticancer drug eliminates the hepatitis B virus in preclinical mouse models. It is being developed by researchers (Dr Marc Pellegrini, Dr Greg Ebert and colleagues) at the Walter and Eliza Hall Institute in Melbourne[12]. A human trial started in December 2014 in Melbourne, Perth and Adelaide. It is at present in Phase I/IIa.

n. Diamond Blackfan anaemia is rare, causing a very serious deficiency in producing red blood cells. The only treatment, other than blood transfusions, is glucocorticoids which have a number of undesirable side effects. Now researchers have identified a cell receptor that, when stimulated by a currently approved cholesterol-lowering drug, and used in combination with low amounts of glucocorticoids, causes a three-to five-

[10] W. Brad Hubbard, Margaret M. Lashof-Sullivan, Erin B. Lavik, and Pamela J. VandeVord, 'Steroid-Loaded Hemostatic Nanoparticles Combat Lung Injury after Blast Trauma', *ACS Macro Lett.*, 2015, *4* (4), pp 387–391 DOI: 0.1021/acsmacrolett.5b00061

[11] Bebarta VS, Garrett N, Boudreau S, et al. "A prospective, randomized trial of intravenous hydroxocobalamin versus whole blood transfusion compared to no treatment for class III hemorrhagic shock resuscitation in a prehospital swine model". Acad Emerg Med. 2015;22(3):321–330.

[12] Gregor Ebert et al,"Cellular inhibitor of apoptosis proteins prevent clearance of hepatitis B virus", *Proceedings of the National Academy of Sciences,* vol.112, no-18, 5797-5802, doi:10.1073/pnas.1502390112; and Gregor Ebert et al,"Eliminating hepatitis B by antagonizing cellular inhibitors of apoptosis", *Proceedings of the National Academy of Sciences,* vol.112, no-18, 5803-5808, doi:10.1073/pnas.1502400112

fold increase in red blood cell production[13]. The research will be the basis for a clinical trial.

o. Scientists from the University of California at Berkeley reported on a pilot study in Cameroon showing a smartphone-run video microscope could measure within minutes certain worms wriggling in a finger-prick of blood, rapidly identifying who is a candidate for medication.

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. The FDA has approved Emergent Biosolutions' intravenous recombinant factor IX (Ixinity) to control and prevent bleeding episodes, and for perioperative management, in both adults and children with haemophilia B. Approval followed a Phase I/III, open-label, uncontrolled, multicentre, global study evaluating safety, efficacy and pharmacokinetics in previously treated adults and children aged 12 years or older with severe to moderately severe (factor IX level <2%) haemophilia B, which showed a mean incremental recovery of 0.98 IU/dL and a mean terminal half-life of 24 hours. Ixinity is a third-generation treatment with no factor IX inhibitors developed in clinical trials. Ixinity contains recombinant coagulation factor IX (trenonacog alfa), a purified single-chain glycoprotein derived from Chinese hamster ovary cells.

b. The FDA approved The Medicines Co's dry powder blood-clotting agent for use in hospitals, a month after the treatment received approval in Europe. Raplixa combines two human plasma-derived blood-clotting proteins-fibrinogen and thrombin. Raplixa is used to control surgical bleeding, in combination with an absorbable gelatine sponge. The Medicines Co expects Raplixa to be complementary to its other haemostatic product Recothrom (recombinant topical thrombin).

c. Swedish Orphan Biovitrum (Sobi) secured Orphan Drug Designation in Switzerland for its long-acting haemophilia drug candidate Elocta (rFVIIIFc) to treat haemophilia A[14]. A marketing authorisation application for Elocta was already under review by the EMA.

d. Baxter submitted a new drug application to Japan's Ministry of Health, Labour and Welfare for the approval of BAX 855, an investigational, extended half-life recombinant factor VIII (rFVIII) treatment based on Advate for patients over 12 years of age with haemophilia A. The submission follows the filing to the FDA in late 2014 and is based on results from a prospective, global, Phase III study of 137 previously treated patients. The results, presented during the European Association for Haemophilia and Allied Disorders (EAHAD) meeting in February 2015, showed that BAX 855 met its primary endpoint in the control and prevention of bleeding episodes and routine prophylaxis for patients who were 12 years or older.

e. Kamada has received Orphan Drug Designation from the EMA Committee for Orphan Medicinal Products (COMP) for its human intravenous Alpha-1 Antitrypsin (AAT) to treat graft-versus-host disease (GvHD). The therapy is in a Phase I/II clinical trial evaluating 24 GvHD patients with inadequate response to steroid treatment following allogeneic bone-marrow stem cell transplant. The trial is being conducted by the Fred Hutchinson Cancer Research Center in Seattle. Preliminary results

[13] "PPARα and glucocorticoid receptor synergize to promote erythroid progenitor self-renewal" *Nature*, online May 11, 2015. nature.com/articles/doi:10.1038/nature14326

[14] Elocta is the European trade name for rFVIIIFc, which is also called as Eloctate in the US, Canada, Australia and Japan, where it is approved to treat haemophilia A.

suggest that continuous administration of AAT as therapy for steroid-resistant gut GvHD is feasible[15]. A Phase III trial is planned to begin in 2016.

Other

f) An FDA staff report recommended The Medicines Co's intravenous anti-clotting drug Kengreal for approval for patients undergoing procedures to open blocked arteries. A final decision from the FDA is expected in June.

g) The European Commission has approved changes to the EU label for the therapeutic indication of Alexion's Soliris (eculizumab) in the treatment of paroxysmal nocturnal haemoglobinuria (PNH). It now includes patients without a history of transfusion. The revised Summary of Product Characteristics now imply evidence of clinical benefit in patients with high disease activity as defined by elevated haemolysis[16] and the presence of associated clinical symptoms such as fatigue, haemoglobinuria[17], abdominal pain, shortness of breath, anaemia, major adverse vascular event, or dysphagia[18]. An update to the atypical haemolytic uraemic syndrome section of the EU label includes new efficacy data emphasising that longer-term treatment with Soliris was associated with a greater proportion of patients achieving clinically significant benefits. New information was provided on the risks of discontinuing treatment.

h) The FDA has granted orphan drug designation[19] to Prolong Pharmaceuticals' sickle cell disease (SCD) treatment, Sanguinate, which the company says is the only biologic currently under clinical development for SCD's co-morbidities, which include sickle cell crisis, acute chest syndrome, leg ulcers, and both paediatric and adult stroke. The drug has anti-vasoconstrictive properties that facilitate the transfer of oxygen to oxygen-deprived cells and tissues and reduces blood vessel inflammation. Sanguinate is the subject of multiple clinical trials to establish its safety and efficacy in SCD and other diseases caused by ischemia[20], hypoxia[21] and/or haemolysis. Currently, the drug is undergoing a phase II study in reducing or preventing delayed cerebral ischemia following subarachnoid haemorrhage, with more phase II trials planned for vaso-occlusive crisis and leg ulcers secondary to SCD, as well as for preventing delayed graft function following kidney transplantation.

i) GlaxoSmithKline and its Italian partners Fondazione Telethon and Ospedale San Raffaele have applied to the EMA to market an investigational gene therapy (GSK2696273) for the treatment of an ultra-rare white blood cell deficiency condition popularly known as 'bubble boy disease'. They are seeking approval for use in patients with adenosine deaminase severe combined immunodeficiency syndrome (ADA-SCID), for whom no suitable human stem cell donor is available. The syndrome occurs where a faulty gene inherited from both parents stops production of ADA, a protein essential for the formation of lymphocytes and a functioning immune system. The data backing the submission concerns 18 children treated with GSK2696273, the first of whom was treated over thirteen years ago. All patients are

[15] AAT has been found to have anti-inflammatory, tissue-protective, immune-modulatory and anti-apoptotic properties in direct or indirect consequence of its underlying anti-protease capabilities.
[16] Haemolysis is the rupturing of red blood cells and the release of their contents into surrounding fluid.).
[17] Haemoglobinuria is a condition in which the protein haemoglobin is found in abnormally high concentrations in the urine.
[18] Difficulty in swallowing
[19] Amongst the benefits of orphan drug designation is a period of market exclusivity following approval of the drug.
[20] Ischaemia is a restriction of blood supply to the tissues, hence a shortage of oxygen and glucose needed to keep the tissues alive.
[21] Hypoxia is a reduction of oxygen supply to the tissues below physiological levels, although the tissues are adequately perfused by blood.

still alive, although three required either follow-up enzyme replacement therapy or a bone marrow transplant. The company said there were no significant tolerability events related to the therapy.

j) The World Health Organization (WHO) view has been that "the registration of all interventional trials is a scientific, ethical, and moral responsibility" but estimates suggest that up to half of industry and academic clinical trials are not reported. Now WHO has established guidelines and called for "ethics committees, regulatory authorities, professional bodies, sponsors, investigators, and funding agencies to act in their jurisdictions to ensure results from all interventional clinical trials are reported and publicly disclosed."[22]

k) The FDA granted Boehringer Ingelheim Priority Review for its Biologics License Application (BLA) for idarucizumab, which is being investigated specifically to reverse the anticoagulant effect of dabigatran, the active ingredient in Pradaxa (dabigatran etexilate mesylate) in patients needing emergency intervention or experiencing an uncontrolled or life-threatening bleeding event. The idarucizumab BLA will be reviewed under Accelerated Approval and is the first US review for a reversal agent in the novel oral anticoagulant (NOAC) class.

l) The FDA granted Orphan Drug Designation[23] to Dilaforette's proprietary polysaccharide drug sevuparin[24] for the treatment of patients with sickle cell disease. The company plans to begin recruiting patients during the first half of 2015 for a Phase II study.

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.

Market forecasts

a. Research and Markets have forecast[25] the intravenous immunoglobulin (IVIg) market will grow at a compound annual growth rate of 6.8 per cent between 2015 and 2021[26]. In 2014, three classes of medical conditions together accounted for 53 per cent of global IVIG market revenue; hypogammaglobulinemia, chronic inflammatory demyelinating polyneuropathy (CIDP), and immunodeficiency. Myasthenia gravis is however expected to be the fastest growing segment with a double digit growth during the next few years, due to the increasing adoption of IVIg as first line treatment. Congenital AIDS is also projected to be a fast-growing application. The

[22] In *PLOS Medicine*, WHO official Vasee Moorthy's team noted that WHO demands all researchers report main findings of trial results to their nations' primary clinical trial registries within a year of finishing their their studies, and that they publish results in peer-reviewed journals within two years of finishing their studies.

[23] The FDA's Office of Orphan Products Development grants orphan drug designation to novel drugs and biologics that are intended for the safe and effective treatment, diagnosis or prevention of rare diseases or disorders that affect fewer than 200,000 people in the United States.

[24] Sevuparin (DF02) may restore blood flow and prevent further microvascular obstructions caused by abnormal blood cells in patients with sickle cell disease. Athe company says the anti-adhesive properties of the drug could treat underlying causes of vaso-occlusive crisis, leading to earlier pain relief, shorter hospital stay, reduced need of opioids and improved quality of life.

[25] "Global Intravenous Immunoglobulin Market (By Application, Types and Geography)-Size, Share, Global Trends, Company Profiles, Demand, Insights, Analysis, Research, Report, Opportunities, Segmentation and Forecast, 2014-2021" http://www.researchandmarkets.com/research/j56vff/global

[26] Allied Market Research estimates that about 130 tons of IVIG was issued in 2014.

report suggests that the concept of hyper-immune globulin is likely to increase the efficacy of IVIg treatments. While the high cost of IVIg infusions is seen to restrict market growth, the report suggests improved production and purification techniques and improved plasma yield could counter cost constraints. It refers to “anticipated approval” for Alzheimer's disease and multiple sclerosis.

Company results

b. Swedish Orphan Biovitrum (Sobi) posted first-quarter core profit well above market expectations. The company has a market capitalisation of around $US 4.3 billion. Sobi announced it has received a takeover offer, which some analysts believe to have been from Pfizer[27].

c. Biotest’s 2014 sales of 582 million euros represented a 16.2 per cent increase on the previous year. Full year profit after tax of 19.2 million euros was less than a year earlier.

d. Following Bluebird Bio’s earnings report[28] on May 6th and the Deutsche Bank 40th Annual Health Care Conference on May 7th, its stock price increased by 15 per cent. The company confirmed speculations that investors should anticipate Phase I/II clinical trial data (from the HGB-205 study in patients with sickle cell disease) at the European Haematology Association in June. Bluebird released abstracts from the trial on May 21.

e. Cerus Corporation reported an operating loss of $US 14.4 million in the first quarter of 2015, compared with $US 9.2 million in the same period last year. Cerus’ President and CEO, William Greenman, nevertheless expressed optimism: "We are encouraged by the recent advocacy for pathogen reduction in the US market, including a *New England Journal of Medicine* editorial urging an FDA mandate for the technology[29], and a two-day symposium on pathogen reduction sponsored by the AABB[30]. Also of significance is the recent contract with the (US) National Institutes of Health[31], an organization that leads standards of practice across many areas of medicine.....We look forward to the transfusion medicine community's further engagement on the topic of improved bacterial contamination measures for platelet components.” The company had enrolled the first patient in the TRUE Study with the American Red Cross to address chikungunya and dengue blood safety risks with pathogen reduced platelets.

New capacity

g) Bayer broke ground in Berkeley, California, for its $US 100 million product testing facility for new haemophilia A treatments. The company expects to complete the 80,000-square-foot structure in 2017. Kogenate FS[32] is already manufactured and tested on the Berkeley site. Bayer in December 2014 filed for FDA approval of Kovaltry, a long-acting recombinant factor VIII treatment that could allow haemophilia A patients to dose once a week, rather than twice. The Berkeley site has made batches of Kovaltry and has also made the experimental drug BAY94-9027[33] for clinical trials.

---

[27] Pfizer has been suggested by others as a potential buyer of GlaxoSmithKline (GSK).
[28] The earnings report showed that Bluebird had no debt and $US 469 million cash. The company reported that they had enough cash to support clinical trials until 2017.
[29] Snyder EL et al, *N Engl J Med* 2015 Apr 22, Epub ahead of print
[30] AABB Symposium on Implementation of Pathogen-Reduced Blood Components (April 27-28, Bethesda, Maryland).
[31] An INTERCEPT platelet and plasma supply agreement
[32] Sales of Kogenate FS in 2014 amounted to $US 1.1 billion. It is a recombinant factor VIII.
[33] Generically known as damoctocog alfa pegol, this has been designed to extend the circulating half-life of rFVIII through site specific attachment of a polyethylene glycol (PEG) polymer to the light chain of the rFVIII molecule, while preserving its full biologic activity.

h) Denmark's Novo Nordisk will invest $US 225 million in a new haemophilia treatment manufacturing facility in Kalundborg, Denmark. It is expected to be fully operational in 2020. The plant will produce active ingredients for NovoSeven[34] and future products for treating haemophilia[35]. Novo Nordisk already employs more than 2,800 people in Kalundborg.
i) Recently Novo Nordisk's top executive candidate and then company president Kåre Schultz abruptly stepped down after 26 years with the company. He was being groomed to replace Lars Rebien Soerensen, the current CEO, but the company announced Soerensen will remain CEO until "he approaches the end of his contract," which expires in 2019.
j) Biopharmaceutical company Green Cross (Yongin, South Korea) has selected Montreal, Quebec, for its new, $C 315 million plasma fractionation plant, the only plant in Canada to produce IVIg and albumin.
k) In South Korea, SK Plasma (a subsidiary of SK Chemicals) held a ground-breaking ceremony for a plasma fractionation plant in Andong. Its annual capacity will be 600,000 litres of blood products. The plant is scheduled to be completed in 2016 and begin commercial operation from June 2018.

Other

l) CSL will launch its global flu vaccine business early in 2016, combining the former Novartis flu vaccine business, which it purchased for $A 354.5 million, with its own flu vaccine subsidiary, bioCSL, to create the world's second biggest influenza vaccine supplier. CSL has appointed its chief finance officer Gordon Naylor to head the new business.
m) Scientists in the Center for Cell and Gene Therapy at Baylor College of Medicine, Houston Methodist and the Texas Children's Hospital have expanded the use of virus-specific cell therapy in cord blood transplant patients to prevent three post-transplant viruses affecting this group: cytomegalovirus (CMV), Epstein-Barr virus (EBV), and adenovirus[36].
n) ProMetic Life Sciences says it has selected C1-INH as its next plasma-derived drug candidate to be developed. This protein is used for the treatment of hereditary angioedema (HAE), a rare genetic disorder in which C1-INH is lacking. The world market grew at an average rate of 44 per cent in the last three years and reached $US1.1 billion in 2014.
o) Companies active in the blood screening market include Grifols (Spain), Roche Diagnostics (Switzerland), Abbott Laboratories (US), Bio-Rad Laboratories (US), Siemens Healthcare (Germany), bioMérieux (France), Ortho Clinical Diagnostics, Inc. (US), Thermo Fisher Scientific, Inc. (US), Beckman Coulter (US), and Becton, Dickinson and Company (US). Grifols led the global blood screening market for NAT testing in 2014, helped by its acquisition in November 2013 of a blood transfusion diagnostic unit from Novartis for $US 1.675 billion. Grifols is a market leader in analyzers, reagents and instrumentation.
p) Isis Pharmaceuticals has licensed Bayer HealthCare to develop and commercialize ISIS-FXIRx for the prevention of thrombosis[37]. "This first-in-class FXI inhibitor

[34] NovoSeven controls bleeding in haemophilia patients by bypassing clotting inhibitors.
[35] In March Novo Nordisk announced it would launch NovoEight in the US where it is approved for 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.
[36] The results of a clinical trial evaluating safety and efficacy when the approach was translated from the bench to the bedside were published in: Patrick Hanley et al.,"CMV-specific T cells generated from naïve T cells recognize atypical epitopes and may be protective in vivo", *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/… scitranslmed.aaa2546. Original bench results appeared in *Blood* in 2009.
[37] ISIS-FXIRx targets Factor XI, a clotting factor produced in the liver that is an important component of the coagulation pathway. High levels of Factor XI increase the risk of thrombosis.

perfectly complements our in-house thrombosis pipeline and is an innovative development candidate for a variety of anti-coagulation needs," said Dr. Joerg Moeller, Member of the Bayer HealthCare Executive Committee and Head of Global Development. "We believe the novel mechanism of Factor XI inhibition may offer an additional pathway for treating patients for whom there are currently no suitable therapeutic options available."

q) CSL Behring announced five recipients[38] of the 2015 *CSL Behring Professor Heimburger Award* for coagulation research. The global awards program provides start-up grants to young, emerging researchers. The total value of the five grants this year is 100,000 euros.

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.

United States

a. The US Centers for Disease Control and Prevention (CDC) has examined drug use rates and hepatitis C infection reports in Kentucky, West Virginia, Virginia and Tennessee. From 2006 to 2012, the region saw a 364 percent increase in reports of acute hepatitis C infection among people aged 12 to 29, with the rural rate more than twice the urban rate.[39] Three quarters of them admitted they had used intravenous drugs, mainly heroin or prescription opioids. The number of young people admitted for drug treatment who said they had injected any kind of opioid during the six year period rose by 12.6 per cent. The study noted reports of similar findings in Wisconsin, Massachusetts and upstate New York, so this is not isolated to Appalachia. While there is an effective new drug for hepatitis C, Sovaldi, it costs $US 84,000 for a 12 week course. There are an estimated 3.2 million people in the US with hepatitis C.

b. At the 13th annual National Blood Foundation Leadership Forum, AABB's director of Research, and of the Center for Patient Safety, presented preliminary data from the AABB Blood Collection, Utilization and Patient Blood Management Survey[40]. The results showed a downward trend in collections of whole blood and red blood cells in the US between 2008 and 2013, with allogeneic collections down 12 per cent and autologous collections down 53 per cent. AABB member hospitals reported an increase in patient blood management interventions (particularly postoperative interventions) between 2011 and 2013.

c. Federal health officials recommended ending the lifetime ban on blood donations from gay and bisexual men, substituting a policy barring donations from men who have had sex with other men in the previous year. Gay advocates say that requiring

---

[38] Ashwini Bennett, Haematology Department, Monash Health (Australia) *Neutrophil extracellular traps: Their role in acute venous thromboembolism, sickle cell crisis and myeloproliferative neoplasms*
Jenny Klintman, M.D.Skane University Hospital, Clinical Collaboration Research Unit Lund University (Sweden) *Clinical evaluation and characterization of suspected atypical hemolytic uremic syndrome (aHUS*)
Tesse Leunissen, University Medical Centre Utrecht (Netherlands) *High accuracy platelet function testing to predict perioperative micro embolic signals (MES) during carotid endarterectomy (CEA)*
Michelle Sonneveld, Erasmus University Medical Center (Netherlands) *Complement factor H and the relation with von Willebrand Factor and ADAMTS13*
Bryce Andrew Kerlin, Associate Professor of Pediatrics, The Ohio State University College of Medicine (U.S.) *Thrombin signaling mechanisms in nephrotic syndrome*

[39] The CDC defines "non-urban" to include towns of fewer than 50,000.

[40] The survey of AABB member blood centres and hospitals within and outside the US, related to the period from Jan. 1-Dec. 31, 2013.

a year of abstinence from gay and bisexual men is unrealistic, and not supported by science.

Other

d. In France, the LFB group, Biolog-id and the Blood Transfusion Service (Etablissement Français du Sang/EFS) have announced the introduction of an RFID1 traceability system developed by Biolog-id for LFB. All bags containing plasma for fractionation leaving EFS centres will incorporate RFID[41] chips, which will facilitate their registration at LFB, the only company fractionating this plasma.
e. The European Commission's Executive Agency for Health and Consumers (EAHC) commissioned a report[42] from Creative Ceutical which examines the availability of blood products in the EU and addresses regulatory impacts on their supply. The report includes commentary by stakeholders industry groups, patient organizations and health authorities from the EU and its member states.

5. Safety and patient blood management

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

Appropriate transfusion

a. Recent research suggests that paediatric patients undergoing heart surgery do better when given fresh whole blood from single donors instead of blood components from multiple donors. The study was led by Dr David Jobes, of the Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania in Philadelphia[43].

Patient blood management

b. In the US, a meeting of the Oncology Nursing Society was told that a 34,337-patient study found that decreasing the use of premedication[44] before cancer patients were given blood transfusions was not associated with a change in the rate of adverse events.
c. A new study suggests that halving the rate of postpartum haemorrhage during caesarean delivery may be achieved by cooling the uterus. Dr Janice Mitchell, from the Baylor College of Medicine in Dallas, presented the study results to the American Congress of Obstetricians and Gynaecologists Annual Clinical Meeting 2015[45]. The research was awarded a Donald F. Richardson prize. The study involved 200 women who underwent a scheduled caesarean delivery or caesarean delivery after a trial of labour. Half the women were randomly assigned to uterine cooling and the other half were assigned to a control group. Blood loss during surgery was 29 per cent lower in the cooling group than in the control group. Postpartum haemorrhage was less common in the cooling group (9 per cent vs 21 per cent). Dr Sharon Phelan, from the University of New Mexico in Albuquerque, commented: "Core body temperature is associated with a risk for postpartum endometritis, so a lot of anesthesiologists will do all kinds of things to warm mom postpartum, rather than cool her".

---

[41] Radio Frequency IDentification
[42] *An EU-wide overview of the market of blood, blood components and plasma derivatives focusing on their availability for patients*
[43] David R. Jobes, Deborah Sesok-Pizzini and David Friedman, "Reduced Transfusion Requirement With Use of Fresh Whole Blood in Pediatric Cardiac Surgical Procedures," *Annals of Thoracic Surgery*, May 2015. http://doi.org/10.1016/j.athoracsur.2014.12.070
[44] Such as acetaminophen and diphenhydramine
[45] ACOG, Abstract 31. Presented May 5, 2015

d. A US study[46] showed that patients treated with the antiplatelet ticagrelor as well as standard, low-dose aspirin therapy for three years had a statistically significant reduction in heart disease deaths and complications compared with those on aspirin alone. Researchers compared ticagrelor–60mg or 90mg twice daily–with placebo in 21,000 patients taking low-dose aspirin because of recent heart attacks.
e. A study has found that obese patients taking warfarin may be more prone to bleeding problems[47].

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.

Plasma and recombinant products

a. Bioengineers think they have made more progress towards making all blood universal. Stephen G. Withers of the University of British Columbia and his team have broadened an enzyme's ability to remove antigens on the surface of red blood cells.[48]
b. It has been known for some time that there is an imbalance between the amount of oxygen transported in the blood and the amount that is delivered to tissues-but not why. Now, cardiologist Jonathan Stamler, a professor of medicine at Case Western Reserve University School of Medicine in Cleveland, Ohio, and colleagues have described[49] how the respiratory cycle involves three gases and not just two. Current understanding was that red blood cells picked up inhaled oxygen from the lungs and transported it to cells round the body, returning to the lungs with carbon dioxide-a waste product of metabolism-to be exhaled. These researchers found that the respiratory cycle also involves nitric oxide–which controls the release of oxygen from red blood cells into the tissues. They showed that the haemoglobin in red blood cells that picks up oxygen from the lungs also needs to carry nitric oxide to enable blood vessels to open and supply the oxygen to tissues. Professor Stamler says "blood flow to tissues is actually more important in most circumstances than how much oxygen is carried by hemoglobin. So the respiratory cycle is actually a three-gas system."

---

[46] Marc P. Bonaca, Deepak L. Bhatt, Marc Cohen, Philippe Gabriel Steg, Robert F. Storey, Eva C. Jensen, Giulia Magnani, Sameer Bansilal, M. Polly Fish, Kyungah Im, Olof Bengtsson, Ton Oude Ophuis, Andrzej Budaj, Pierre Theroux, Mikhail Ruda, Christian Hamm, Shinya Goto, Jindrich Spinar, José Carlos Nicolau, Robert G. Kiss, Sabina A. Murphy, Stephen D. Wiviott, Peter Held, Eugene Braunwald, and Marc S. Sabatine, for the PEGASUS-TIMI 54 Steering Committee and Investigators, "Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction",*N Engl J Med* 2015; 372:1791-1800. DOI: 10.1056/NEJMoa1500857

[47] The study was led by Adedotun A. Ogunsua, of the University of Massachusetts Medical School in Worcester, and presented May 8 as an abstract at the Arteriosclerosis, Thrombosis and Vascular Biology | Peripheral Vascular Disease Scientific Sessions 2015 in San Francisco.

[48] David H. Kwan, Iren Constantinescu, Rafi Chapanian, Melanie A. Higgins , Miriam P Kötzler, Eric Samain, Alisdair B. Boraston , Jayachandran N. Kizhakkedathu, and Stephen G. Withers, "Toward Efficient Enzymes for the Generation of Universal Blood through Structure-Guided Directed Evolution"*J. Am. Chem. Soc.*, 2015, *137* (17), pp 5695–5705 *J. Am. Chem. Soc.* 2015, DOI: **10.1021/ja5116088**.

[49] in the *Proceedings of the National Academy of Sciences*

Research grants

d) Scientists at Texas Biomedical Research Institute received a grant of $US 3.4 million from the US National Institutes of Health (NIH) to develop a Papillomavirus-based HIV vaccine that offers simultaneous protection against HIV and HPV.
e) NIH awarded $US 12.6 million to a researcher at the Fred Hutchinson Cancer Research Center to research next-generation stem cell gene therapy for HIV control and eradication.
f) The US National Institute of Allergy & Infectious Diseases awarded the University of California at Irvine up to $US 5 million over five years to further develop a bloodstream infection-detection system that reduces diagnosis times and increases accuracy[50]. Eight other institutions received grants to create tools to identify blood bacteria that cause infections in hospitals and other healthcare settings.
g) Researchers and transplant clinicians from the Ansary Stem Cell Institute at Weill Cornell Medical College and the Center for Cell Engineering at Memorial Sloan Kettering Cancer Center have been awarded a $US15.7 million over four years from the New York State Stem Cell Science Program to translate their approach to expand and manipulate hematopoietic stem cells to cure acquired and inherited blood disorders.

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. In Singapore a man who made a false declaration when donating blood was jailed for 15 weeks and fined heavily. He had declared that he had not "had sex with another male" when he in fact had been having a regular sexual relationship with a male partner since 2010. He also had sex with a male stranger. His donated blood was found to be infected with HIV.
b. In Washington State CSL Plasma is facing a lawsuit from a woman who claims the company discriminated against her by turning her away because she's transgender. CSL is already facing a lawsuit from a transgender person in Minnesota.
c. The European Court of Justice considered a complaint by Frenchman Geoffrey Leger, protesting the ban on his donating blood. The Court said lifetime bans may be justified — but only if a donor presents a high risk of acquiring severe infectious diseases, and there is no other method to protect blood recipients. The Court warned that France's law is "liable to discriminate against male homosexuals on the basis of sexual orientation," which is against EU policy, and said the case raised questions about whether lifetime bans are "consistent with the fundamental rights of the EU."

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

[50] The University has filed a patent application for the technology, and Velox Biosystems in Irvine is expected to commercialize of the work.

become necessary to test in the future (e.g. Chagas disease, and the tick-borne babesiosis and Lyme disease).

Mosquito-borne diseases

Malaria

a. Viagra (sildenafil) has been found to have an effect on red blood cells that reduces transmission of the malaria parasite *Plasmodium* from humans to mosquitoes, interrupting the parasite's life cycle and helping to prevent the disease spreading[51].
b. Researchers at Harvard T. H. Chan School of Public Health and the Broad Institute have identified a protein, CD55, on the surface of human red blood cells that serves as an essential entry point for invasion by the malaria parasite.[52] This offers a new avenue for the development of malaria vaccines and treatment.
c. A malaria vaccine was 67 per cent protective[53] against infection in an early-stage trial involving adult men in Kenya.[54] The vaccine was prepared from two different viruses genetically tailored to form a protein found on the surface of the malaria parasite.[55]

Ross River Virus

d. Queensland has had a prolonged outbreak of Ross River Virus, the worst for twenty years. Nigel Beebe, a vector biologist from the University of Queensland and CSIRO, said saltmarsh mosquitoes, which transmit Ross River virus, had enjoyed perfect breeding conditions this year.
e. An increase in Ross River virus cases in mid-west Western Australia led to warnings from the WA Country Health Service about precautions that the public should take.

Chikungunya

f. Researchers at the US Army Medical Research Institute of Infectious Diseases modified an assay that tests whether or not a sample of mosquitoes harbours the chikungunya virus. This test, done with a chemical dipstick, can give a result within an hour[56].
g. Vienna-based Themis Biosciences has raised funds to progress trials of its chikungunya vaccine, after the candidate showed satisfactory immunogenicity, safety and tolerability in a Phase I trial.

---

[51] Scientists led by Ghania Ramdani from the University of Paris Descartes, reported in the journal Public Library of Science *Pathogens*

[52] Elizabeth S. Egan, Rays H.Y. Jiang, Mischka A. Moechtar, Natasha S. Barteneva, Michael P. Weekes, Luis V. Nobre, Steven P. Gygi, Joao A. Paulo, Charles Frantzreb, Yoshihiko Tani, Junko Takahashi, Seishi Watanabe, Jonathan Goldberg, Aditya S. Paul, Carlo Brugnara, David E. Root, Roger C. Wiegand, John G. Doench, Manoj T. Duraisingh. "A forward genetic screen identifies erythrocyte CD55 as essential for Plasmodium falciparum invasion"*. Science* (May 7, 2015). Lead author Elizabeth Egan is research fellow in the Department of Immunology and Infectious Diseases at Harvard Chan and instructor in paediatrics at Boston Children's Hospital.

[53] The researchers demonstrated vaccine efficacy at eight weeks while the WHO Malaria Vaccine Technology Roadmap targets vaccine efficacy of 75 percent over a period of two years.

[54] Caroline Ogwang, Domtila Kimani , Nick J. Edwards, Rachel Roberts, Jedidah Mwacharo, Georgina Bowyer, Carly Bliss', Susanne H. Hodgson, Patricia Njuguna, Nicola K. Viebig, Alfredo Nicosia, Evelyn Gitau, Sandy Douglas, Joe Illingworth, Kevin Marsh, Alison Lawrie, Egeruan B. Imoukhuede, Katie Ewer, Britta C. Urban*, Adrian V. S. Hill, Philip Bejon, the MVVC group, "Prime-boost vaccination with chimpanzee adenovirus and modified vaccinia Ankara encoding TRAP provides partial protection against *Plasmodium falciparum* infection in Kenyan adults", V *Sci Transl Med* 6 May 2015: Vol. 7, Issue 286, p. 286re5 *Sci. Transl. Med*. DOI: 10.1126/scitranslmed.aaa2373

[55] In this technique, known as a "prime-boost strategy", the first virus "primes" the immune cells by exposing them to the malaria protein while the second virus boosts immunity by "boosting" the immunity by restimulating the immune system.

[56] See *Journal of Medical Entomology.*

h. Researchers of the Paul-Ehrlich-Institut have experimentally recombined segments of the chikungunya virus surface protein E2, thus creating artificial proteins. The domain thus generated conferred a protective effect against chikungunya virus in animal testing.[57]

Other mosquito-borne diseases

i. Zika virus has been reported on Vanuatu for the first time. Zika is a flavivirus related to yellow fever, dengue, West Nile, and Japanese encephalitis.
j. California had thirty-one deaths from the West Nile virus in 2014. 801 Californians tested positive for the virus. The record was 880 cases a decade ago.

Influenza: strains, spread, prevention and treatment

k. A major outbreak of avian flu (including H5N2)[58] in commercial poultry in the Midwest of the US has led to the culling of millions of birds across fifteen states. Prices for eggs and turkey meat have been rising.
l. In mainland China, the total number of reported human cases of H7N9 since people began falling ill reached 640 by 10 May.
m. Scientists at the University of Georgia have used a virus commonly found in dogs as the foundation for a new vaccine against A(H7N9) influenza[59]. Study co-author Biao He, the Fred C. Davison Distinguished University Chair in Veterinary Medicine in UGA's College of Veterinary Medicine, said: "We have developed a vaccine that protected both mice and guinea pigs against a lethal H7N9 challenge, and we think it may be a very strong candidate for human vaccine tests."
n. An international research team led by the Chinese Centre for Disease Control and Prevention reported[60] that the potential pandemic risk may be greater for H7N9 avian flu than for H5N1 according to a side-by-side analysis of the epidemiology of sporadic cases and clusters caused by the diseases.
o. A serologic study of poultry and wild-bird workers in China found that 63 of 15,689 samples were positive for exposure to the H6 avian flu virus, higher than seen for H5N1 but lower than low-pathogenic H9N2.
p. WHO confirmed that in the first three months of 2015 Egypt recorded 119 confirmed cases of H5N1, including 30 deaths. China had four cases and one death. Indonesia had added two new cases, for a total of 199 since 2003. Egypt's total during that time was 329.

MERS

q) By 1 May, WHO had been notified of 1111 laboratory-confirmed cases of MERS globally, including 422 deaths.
r) Twelve cases of MERS in Saudi Arabia were reported between 9 May and 11 May. These brought the national cumulative total to 996 cases.
s) Researchers have found that 29 per cent of live camels in Saudi Arabia are carrying MERS-CoV in their noses, and 62 per cent of dead camels have the virus in their lungs[61].

---

[57] Weber C, Büchner SM, Schnierle BS (2015) "A Small Antigenic Determinant of the Chikungunya Virus E2 Protein Is Sufficient to Induce Neutralizing Antibodies which Are Partially Protective in Mice". *PLoS Negl Trop Dis* 9(4): e0003684. doi:10.1371/journal.pntd.0003684

[58] H5N8 was found in backyard poultry in Indiana. It has also been seen in the Pacific flyway, in commercial chicken and turkey farms in California and a backyard poultry flock in Oregon, and in captive falcons. It was also found in captive falcons in Idaho and Washington.

[59] The study was reported in the journal *PLOS ONE*

[60] On 4 May, in *Clinical Infectious Diseases*

[61] Khalafalla AI, Lu X, Al-Mubarak AIA, Dalab AHS, Al-Busadah KAS, Erdman DD. "MERS-CoV in upper respiratory tract and lungs of dromedary camels, Saudi Arabia, 2013–2014." *Emerg Infect Dis*. 2015 http://dx.doi.org/10.3201/eid2107.150070

Ebola

t) A doctor who left Emory University Hospital last October after fighting Ebola returned two months later with fading sight and intense pain and rising pressure in his left eye. His blood had been clear of the virus, but it was lurking in his eye[62]. He has also had debilitating joint and muscle pain, deep fatigue and hearing loss. He is not alone, as "post-Ebola Syndrome" has become a reality for many.

u) A healthcare worker in Italy has been diagnosed with Ebola, after returning from volunteering in an Ebola treatment centre in Sierra Leone.

v) A study[63] has shown that the Ebola virus can survive on hospital surfaces for up to a fortnight.

w) The Canadian Association for HIV Research heard on 1 May that a combination of three HIV drugs fights Ebola in the laboratory. Researchers at the University of Toronto [64] tried lamivudine, AZT, and tenofovir in the lab. While each was individually effective against Ebola, the combination of the three worked best, reducing the virus' rate of replication by 88 per cent. The researchers didn't use the actual Ebola virus, but a modified version that won't infect humans. They hope to gain access to a Biosafety Level 4 lab, where work with the actual virus is permitted.

Other diseases: occurrence, prevention and treatment

x. DiaVax Biosciences[65] plans to create two vaccines to protect people with weak immune systems against cytomegalovirus (CMV) infections. Researchers are using targeted immune system cells, called CMV-specific T cells. The treatments have already been tested on recipients of organ and stem-cell transplants. Dr. Don Diamond, chairman of the Department of Experimental Therapeutics at City of Hope and chairman designate of the Scientific Advisory Board of DiaVax, said the vaccines "have the potential to become a model for the treatment of other opportunistic infections as well".

y. GlaxoSmithKline and the University of North Carolina at Chapel Hill are together launching a research centre to focus on finding a cure for HIV/AIDS. Glaxo and UNC will jointly own a new company, Qura Therapeutics, which will manage intellectual property and other business matters.

z. Duke University researchers have been awarded $US20 million from NIH to develop an HIV vaccine.

aa. Scientists at Iowa State University and the US Department of Agriculture have used retina tests to detect animals infected with BSE months before they showed traditional signs of illness.

bb. A micro-needle patch being developed by the Georgia Institute of Technology and the CDC could make measles vaccination easier. It can be administered by minimally trained workers and simplifies storage, distribution, and disposal. The underside of the patch carries 100 solid, conical micro-needles made of polymer, sugar, and vaccine that are a fraction of a millimetre long and dissolve quickly, leaving the patch

---

[62] Jay B. Varkey, Jessica G. Shantha, Ian Crozier, Colleen S. Kraft, G. Marshall Lyon, Aneesh K. Mehta, Gokul Kumar, Justine R. Smith, Markus H. Kainulainen, Shannon Whitmer, Ute Ströher, Timothy M. Uyeki, Bruce S. Ribner, and Steven Yeh, "Persistence of Ebola Virus in Ocular Fluid during Convalescence", *New England Journal of Medicine*, May 7, 2015. DOI: 10.1056/NEJMoa1500306

[63] Reported in the July issue of *Emerging Infectious Diseases*

[64] including Dr Donald Branch, an associate professor in the department of laboratory medicine and pathobiology

[65] a new company created by City of Hope and Fortress Biotech. City of Hope is a private, not-for-profit clinical research center, hospital and graduate medical school in California, best known as a cancer treatment center. It played a role in the development of synthetic human insulin in 1978. The medical centre has performed over12,000 hematopoietic stem cell transplants with patient outcomes that consistently exceed national averages. Fortress Biotech is a company which acquires, develops and commercializes new pharmaceutical and biotechnology products.

to be discarded. The patch has been shown to produce a strong immune response in rhesus macaques. Human clinical trials could begin in 2017.