Monitoring International Trends

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

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

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

- BioMarin Pharmaceutical released preliminary data on its investigational gene therapy treatment for haemophilia A. (Section 1)
- Data on Bluebird bio's gene therapy in severe sickle cell disease and transfusion-dependent β-thalassemia was discussed at the American Society of Gene & Cell Therapy Annual Meeting. (Section 1)
- Europe's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending an extension to the marketing authorisation for Baxalta's subcutaneous immunoglobulin, HyQvia. (Section 2)
- NovoNordisk submitted to the US Food and Drug Administration (FDA) a Biologics License Application for its long-acting factor IX. (Section 2)
- The European Commission approved Swedish Orphan Biovitrum and Biogen's recombinant factor IX Fc Fusion protein therapy. (Section 2)
- The FDA granted seven years of marketing exclusivity for CSL Behring's Coagulation Factor IX (Recombinant), Albumin Fusion Protein, with an extended dosing interval]. (Section 2)
- In Australia, the Therapeutic Goods Administration (TGA) approved a monoclonal antibody that reverses the anticoagulant effect of dabigatran in patients who require emergency surgery or have life-threatening bleeding. (Section 2)
- Baxalta delivered strong sales and earnings for the first quarter of 2016. (Section 3)
- To mark its centenary, CSL Behring announced a $25 million R&D Fellowship program. (Section 3)
- Biogen will spin off its haemophilia interests as a public company. (Section 3)
- GlobalData estimates the market for recombinant haemophilia products will reach $US 6.25 billion annually by 2024. (Section 3)
- Technavio forecasts a compound annual growth rate of over 35 per cent for alpha-1 antitrypsin drugs globally to the end of 2020. (Section 3)
- In India, Novo Nordisk launched NovoEight, reportedly at half its international price. (Section 4)
- In the US, the FDA (with support from AABB) called for strategies to reduce the risk of transfusion-transmitted Babesia microti (a tick-borne disease) by advocating for additional screenings in states with the highest prevalence. (Section 4)
- A recent study concluded that "antiplatelet therapy appears to increase intraoperative blood loss in lumbar surgery, even when the medication is discontinued at least 7 days preoperatively". (Section 5)
- Researchers are exploring whether rejuvenating the red blood cells in stored blood can extend the time between transfusions for sickle cell patients. (Section 5)

- A new randomized trial suggests that giving platelet transfusions to patients presenting with an intracerebral haemorrhage who are taking antiplatelet agents is associated with worse outcomes. (Section 5)
- A retrospective study has suggested that in men undergoing radical prostatectomy perioperative blood transfusion was associated with increased 30-day morbidity, readmission, pulmonary complications, and surgical site infections. (Section 5)
- Researchers report that intravenous or oral iron with or without an erythropoiesis-stimulating agent may help prevent post-operative anaemia and reduce blood transfusions without significantly raising the risk of adverse events. (Section 5)
- New Health Sciences (of Bethesda, Maryland) has received a grant from the US National Heart Lung and Blood Institute to develop and test anaerobic storage technology for donated blood. (Section 6)
- Chugai Pharmaceutical revealed that a lawsuit was filed against the company at the Tokyo District Court by Baxalta, reportedly claiming that a new drug under development by Chugai (which is majority owned by Swiss company Roche) for the treatment of haemophilia A (ACE910) is infringing its patent. (Section 7)
- Dr. Amir Attaran of the University of Ottawa has warned that holding the Olympics in the middle of a Zika outbreak could cause a "full-blown global health disaster." The International Olympic Committee claims that there is "no justification for cancelling, delaying, postponing or moving the Rio Games.'' The World Health Organization (WHO) issued a set of recommendations for athletes and tourists but took no official position on delaying or moving the Olympics. (Section 8)
- Brazilian health officials have said that their biggest worry for the Olympics is not the Zika virus but swine flu. (Section 4)
- Researchers found that human cells were more likely to be infected with Zika virus in vitro if they contained antibodies to dengue virus. (Section 8)
- With concern rising that an outbreak of yellow fever in Angola will spread, WHO urged travellers to Angola to ensure they are vaccinated. However, the manufacturer of yellow fever vaccine, Sanofi Pasteur, says it continues in short supply and ordering restrictions are in place. (Section 8)
- Human cases of H7N9 are continuing to occur in China. (Section 8)
- The first human infection involving H5N6 avian flu was reported by China in 2014. China has reported 12 cases in total, nine since last December. (Section 8)
- As at noon on 15 May Saudi Arabia had experienced 1383 laboratory confirmed cases of MERS-CoV infection, including 592 deaths. (Section 8)
- NewLink and Merck plan to submit their Ebola vaccine for regulatory approval in 2017. (Section 8)

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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.

Manufactured blood

a) Jo Mountford (from the Institute of Cardiovascular and Medical Sciences at the University of Glasgow) and her team produced ten billion red blood cells in 2014. The team – funded by the Wellcome Trust and incorporating universities and organisations from around the UK – is now able to produce the cells in around 30 days. "We can choose what blood group we make," says Mountford. The key to growing red blood cells is manufacturing stem cells. A bioreactor system has been created, which can produce ten litres of blood at a time.

Haemophilia treatment

b) BioMarin Pharmaceutical released preliminary data from an ongoing Phase I/II clinical trial with BMN 270, an investigational gene therapy treatment for haemophilia A. Eight patients with severe haemophilia A received a single dose of BMN 270, six

of them at the highest dose, with follow-up ranges from five to 16 weeks. All high dose patients improved from severe to moderate, mild or normal range in terms of factor levels based on World Federation of Haemophilia criteria.

c) Dimension Therapeutics announced positive preclinical results from its partnered haemophilia A program with Bayer[1].

Sickle Cell Disease, Thalassemia

d) At the American Society of Gene & Cell Therapy (ASGCT) 19th Annual Meeting[2], an oral presentation given by one of Bluebird bio's academic collaborators highlighted previously presented data from an ongoing gene therapy clinical trial. Marina Cavazzana, of Hospital Necker, University Paris Descartes, presented interim data from the HGB-205 study of LentiGlobin in severe sickle cell disease and transfusion-dependent β-thalassemia[3]. b

e) Global Blood Therapeutics will be giving a presentation mid June with data from an ongoing phase I/II study of GBT 440, whose primary target indication is sickle cell anaemia (SCA).

Other

f) Erythropoietin, the anaemia drug known as EPO, has been shown to prevent damage and help the brain heal in some babies born with hypoxic-ischaemic encephalopathy[4].

g) Protalex[5] announced that after an interim data review by its independent Safety Monitoring Committee it was continuing enrolment and increasing the dose for the patients in its European Phase Ib trial of PRTX-100 in adults with chronic immune thrombocytopaenia (ITP).

h) Humacyte is launching a Phase III study of its lab-grown blood vessel Humacyl in 350 patients with end-stage renal disease who are on haemodialysis and don't qualify for a standard surgical treatment. Humacyte will conduct the Humanity trial at 35 sites in the US, Europe and Israel. Results from a Phase II trial were published in *The Lancet*.

2. Regulatory

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

a) Europe's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending an extension to the marketing authorisation for Baxalta's subcutaneous immunoglobulin, HyQvia[6].

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[1] Preclinical data were highlighted in a poster, titled "Optimized AAV-Mediated Human Factor VIII Gene Therapy in Hemophilia A Mice and Cynomolgus Macaques" (Abstract No. 760), presented at the 19th American Society of Gene and Cell Therapy (ASGCT) Annual Meeting, in Washington, DC, May 4-7, 2016.

[2] May 4-7, 2016 in Washington, D.C. The abstracts are available online on the ASGCT Annual Meeting website.

[3] "Clinical Outcomes of Gene Therapy with BB305 Lentiviral Vector for Sickle Cell Disease and β-Thalassemia", Abstract Number**:** 279. *Note: Data previously presented at the 2015 American Society of Hematology Annual Meeting*.

[4] HIE causes a drop in oxygen and blood flow to the brain and other organs, causing disability such as cerebral palsy, or death, in around 40 per cent of newborns affected. Researchers from the University of California at San Francisco reported in the journal *Pediatrics.*

[5] of New Jersey

[6] The CHMP adopted an extension to the existing indication as follows: "Replacement therapy in adults, children and adolescents (0-18 years) in: primary immunodeficiency syndromes with impaired antibody production; hypogammaglobulinaemia and recurrent bacterial infections in patients with

b) The European Commission granted Takeda Pharmaceutical Company Limited of Osaka an expanded indication for surgical patch TachoSil (human thrombin/human fibrogen) for use in adults for supportive sealing of the dura mater[7] to prevent postoperative cerebrospinal leakage following neurological surgery[8].
c) NovoNordisk submitted a Biologics License Application for the approval of its long-acting factor IX, nonacog beta pegol to the US Food and Drug Administration (FDA)[9]. Nonacog beta pegol is a glycopegylated recombinant factor IX with an improved pharmacokinetic profile[10], developed for patients with haemophilia B. Novo Nordisk filed for approval of the product in Europe earlier this year.
d) The European Commission approved Swedish Orphan Biovitrum and Biogen's Alprolix (recombinant factor IX Fc Fusion protein therapy, or rFIXFc)[11]. This is an extended half-life therapy, for the treatment of haemophilia B. Alprolix is indicated for both on-demand and prophylaxis treatment of people of all ages. The approval covers all 28 European Union member states and maintains the drug's orphan designation. Because Alprolix offers prolonged protection against bleeding episodes, patients have fewer prophylactic injections. It can be administered with an initial dose every seven to ten days with the ability to adjust the dosing interval based on individual response.
e) The FDA granted seven years of marketing exclusivity[12] for CSL Behring's Idelvion [Coagulation Factor IX (Recombinant), Albumin Fusion Protein, with an extended

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chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contra-indicated; hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients; and hypogammaglobulinaemia in patients pre- and post-allogeneic hematopoietic stem cell transplantation (HSCT)." If a decision to change the marketing authorisation is granted by the European Commission, detailed recommendations for the use of this product will be described in the updated summary of product characteristics (SmPC).

[7] Dura mater is the outermost and most fibrous of the three membranes covering the brain and spinal cord.

[8] TachoSil first received Marketing Authorization in the European Union in June 2004. With the new expanded indication, TachoSil becomes the first and only dual action surgical patch approved in adults for: improvement of haemostasis, or the arrest of bleeding; tissue sealing; suture support in vascular surgery; and supportive sealing to prevent postoperative cerebrospinal leakage following neurological surgery.

[9] The filing of nonacog beta pegol is based on the results from a clinical trial which involved 115 patients with severe or moderately severe haemophilia B. Nonacog beta pegol was found to be efficacious in routine prophylaxis, treatment of bleeding episodes and surgery for adults, adolescents and children. The drug appeared to be well-tolerated and no safety concerns were identified. In the phase III trials, once-weekly administration of 40 IU/kg nonacog beta pegol maintained factor IX activity levels above 15 per cent, reduced the median annualised bleeding rate (ABR) to 1.0 and showed a potential to prevent bleeds in target joints. Furthermore, these patients reported a significant improvement in quality of life during the trial.

[10] Compared with the standard factor IX product, nonacog beta pegol has a five times longer half-life. Patients in the paradigm study achieved a higher level of factor IX in the circulation despite less frequent dosing of nonacog beta pegol.

[11] The Commission's approval of Alprolix was based on results from two global Phase III clinical trials that demonstrated the efficacy, safety and pharmacokinetics of Alprolix for haemophilia B: the B-LONG study for previously treated adults and adolescents, and the Kids B-LONG study for previously treated children under age 12.

[12] Under the Orphan Drug Act, the FDA Office of Orphan Products Development may grant orphan drug designation to drugs or biologics intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the US, or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug. The first orphan designated product receiving FDA approval for the orphan indication is eligible to receive a seven-year marketing exclusivity period for the orphan indication. CSL Behring received orphan drug designation for Idelvion in 2012. Idelvion will be the only recombinant factor IX albumin fusion protein for treating haemophilia B that the FDA will approve for seven years. Other

dosing interval]. In clinical trials, Idelvion maintained factor IX activity levels above 5 per cent over 14 days, resulting in a median annualized spontaneous bleeding rate (AsBR) of 0.00. Idelvion was approved by the FDA in March 2016[13] for use in children and adults with haemophilia B, for on-demand control and prevention of bleeding episodes, perioperative management of bleeding and routine prophylaxis to prevent or reduce the frequency of bleeding episodes. The European Commission has also approved Idelvion as an orphan medicinal product with ten years of market exclusivity in the European Union. The drug has approval from Health Canada. Regulatory agencies in Australia, Switzerland and Japan have also been asked to review CSL Behring's marketing applications for Idelvion.

f) In Australia, the Therapeutic Goods Administration (TGA) approved Idarucizumab (Praxbind), a monoclonal antibody that reverses the anticoagulant effect of dabigatran (Pradaxa) in patients who require emergency surgery or have life-threatening bleeding. Approval follows the publication of Phase III trial results in *The New England Journal of Medicine* in 2015. The REVERSE-AD study, which included patients from eight sites in Australia, found that idarucizumab rapidly reversed the anticoagulant effect of dabigatran in 88-98 per cent of patients who had serious bleeding or required urgent surgery. Boehringer Ingelheim says trials of its drug have shown no pro-thrombotic effect, and that treatment with dabigatran can be resumed as early as 24 hours after administration of the reversal agent.
g) Health Canada announced approval of Praxbind "with conditions". Those conditions, include providing Health Canada with additional clinical data from an ongoing clinical trial for Praxbind.

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.

Mergers. takeovers and spinoffs

a) Shire announced that, conditional upon the completion of its acquisition of Baxalta, it is appointing Baxalta board members Gail Fosler and Albert Stroucken as Shire non-executive directors. Baxalta Chairman Wayne Hockmeyer had withdrawn himself from consideration for appointment to the Shire board, citing "personal and family reasons".
b) Biogen has announced it will spin off its haemophilia business as a publicly traded company, and focus on its neurodegenerative portfolio.
c) The University of Leicester's spin-out firm Haemostatix[14] is developing a pipeline of topical products for surgical bleeding. Its two lead products are PeproStat, a liquid

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therapies for haemophilia B, using alternative technologies or pursuing different indications, may still receive FDA approval.

[13] FDA approval of Idelvion was based on results from the PROLONG-9FP clinical development programme, which included a global phase II/III pivotal clinical study. Data from this study were recently published in the journal *Blood.* PROLONG-9FP included phase I through phase III open-label, multicentre studies evaluating the safety and efficacy of Idelvion in children and adults (ages 1 to 61 years) with haemophilia B (factor IX levels =2 per cent).The data from PROLONG-9FP showed median annualized spontaneous bleeding rates (AsBR) of 0.00 and factor IX activity levels above 5 percent in patients using Idelvion prophylactically. This result was achieved for both 14-day dosing and 7-day dosing. The data for on-demand therapy showed that 94 per cent of bleeds were controlled with one infusion, while 99 per cent were controlled with one or two infusions.

[14] Based at BioCity, Nottingham

applied to wounds for controlling bleeding during surgery, and ReadyFlow (currently at the late pre-clinical stage) which is a blood-free transparent gel that can be applied to irregular bleeds. A phase II trial of Peprostat is expected to begin in 2017 and a Phase I study of ReadyFlow in 2018. Now drug development services provider Ergomed[15] has announced the proposed acquisition of Haemostatix for about £28m, including milestone and sales-based payments.

Company results

d) On 30 April, shares in Shire rose five per cent in the first trading hour, in response to first quarter 2016 earnings results, which exceeded analysts' expectations. Strong revenue came from sales of Firazyr and Cinryze—Shire's two main drugs that treat the potentially fatal swelling disease, hereditary angioedema. Sales for the quarter rose by 39 per cent to $128 million and 11 per cent to $164 million, respectively.

e) Baxalta exceeded its guidance and delivered strong sales and earnings for the first quarter of 2016. In that quarter, on a GAAP[16] basis, Baxalta's global revenues of $US 1.5 billion increased 14 per cent from the prior-year period. Excluding the impact of foreign currency, sales increased 18 per cent. Global haematology revenues of $US 843 million increased 8 per cent (excluding the impact of foreign currency). Growth was driven by the introduction in the US of Adynovate[17], as well as heightened demand for Advate[18] and FEIBA[19]. Also contributing to performance was growth in sales of Rixubis[20], and Obizur[21] Immunology sales of $US 653 million advanced 13 per cent on a pro forma basis (excluding the impact of foreign currency). The company has a differentiated portfolio of immunoglobulin therapies, including HyQvia[22].

f) Swedish Orphan Biovitrum announced its results for the first quarter 2016. Revenue for the quarter totalled 1.27 billion Swedish kronor ($US 156.6 million), an increase of 48 per cent at constant exchange rates compared with first quarter 2015. Revenues included a one-time credit from Biogen of 322 million kronor triggered by the first commercial sales of haemophilia treatment Elocta (efmoroctocog alfa). Operating profit came in at 410 million kronor versus 102 million kronor a year ago. Gross margin was 74 per cent (60 per cent a year ago). Earnings before interest and taxes (EBITA) were 502 million kronor, beating consensus expectations of 463 million kronor ,compared with 172 million kronor a year ago, while earnings per share were 1.13 kronor (versus 0.28 kronor).

g) Bayer's first quarter earnings beat estimates.

h) Grifols quarte one net profit was 125.2 million euros ($US 143.8 million) versus 128.5 million euros year ago; its quarter one sales were 958.9 million euros versus 908.4 million euros a year ago.

i) Kamada, of Ness Ziona, Israel**,** announced financial results for the three months ended 31 March, 2016. Highlights included: total revenues of $US 14.8 million compared with $US 8.9 million in the 2015 first quarter; gross profit of $US 4.8 million compared with $US 0.4 million in the 2015 first quarter; and adjusted net loss of $US 1.9 million compared with an adjusted net loss of $ US4.8 million in the 2015 first

[15] Ergomed provides clinical development, trial management and pharmacovigilance services to over 80 clients of varying size.
[16] Generally accepted accounting principles
[17] [Antihaemophilic Factor (Recombinant), PEGylated], an extended circulating half-life recombinant Factor VIII (rFVIII) treatment for haemophilia A
[18] [Antihaemophilic Factor (Recombinant)], again for haemophilia A
[19] [Anti-Inhibitor Coagulant Complex], an inhibitor treatment.
[20] [Coagulation Factor IX (Recombinant)], a treatment for haemophilia B
[21] [Antih emophilic Factor (Recombinant), Porcine Sequence], for the treatment of acquired haemophilia A.
[22] [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase]

quarter[23]. For the year ending December 31, 2016, Kamada expects total revenues to be between $US75 million and $US 80 million.

Agreements

j) Swedish Orphan Biovitrum (Sobi) announced that it has extended the existing manufacturing agreement with Pfizer for the drug substance for ReFacto AF/Xyntha. The agreement has been extended until 31 December 31, 2023, and the drug substance will continue to be manufactured in Sobi's Good Manufacturing Practice (GMP) biologics facility in Stockholm, Sweden.

k) Orchard Therapeutics, with funding of $US 30 million from venture backers F-Prime Capital, announced formal partnerships with University College London (UCL), Great Ormond Street Hospital for Children NHS Foundation Trust (GOSH), the University of Manchester, the University of California Los Angeles and Boston Children's Hospital. The aim is to develop transformative gene therapies for serious and life-threatening orphan diseases. The company's development programs exploit the potential of *ex-vivo* autologous hematopoietic stem cell gene therapy to restore normal gene function in primary immune deficiencies, metabolic diseases and haematological disorders. Orchard's lead candidate is *ex-vivo* autologous lentiviral stem cell gene therapy for severe combined immunodeficiency caused by adenosine deaminase deficiency. Interim clinical data show significant immune reconstitution and 100 per cent survival in 32 patients treated at GOSH and UCLA.

Market forecasts

l) GlobalData estimates the market for drugs for recombinant haemophilia A and B will reach $US 6.25 billion annually by 2024, with a compound annual growth rate of 1.52 per cent from 2014. Growth is seen to be driven by increased use of routine prophylaxis and further replacement of plasma-derived therapy with recombinant therapy.

m) Technavio's analysts have forecast a compound annual growth rate of more than 35 per cent for alpha-1 antitrypsin drugs globally to the end of 2020. Amongst their reasons are increasing diagnosis of alpha-1 antitrypsin deficiency (AATD) and novel product opportunities.

n) Persistence Market Research reported the global IVIg market is growing strongly because of aging populations.

Significant share trading by company directors

o) Pfizer CEO Ian C. Read sold 275,000 shares of the stock on Monday, 9 May. The shares were sold at an average price of $US 33.80, for total transaction proceeds of $US 9,295,000.00. Following the completion of the sale, the chief executive officer owned 1,446,738 shares of the company's stock, valued at $US 48,899,744.40. The transaction was disclosed in a filing with the Securities and Exchange Commission (SEC). Pfizer reported a profit for first-quarter 2016 that increased 27 percent from the previous year. Revenue for the quarter was $US 13.01 billion, against a comparable year-ago figure of $US 10.86 billion.

p) A 4 May report said that Bo Jesper Hansen, outgoing chairman of Swedish Orphan Biovitrum (Sobi), had sold 8 million shares, leaving him with 893,846.

[23] Since the beginning of 2016, Kamada has reported additional positive interim results from a Phase I/II clinical trial of its alpha-1 antitrypsin (AAT) to treat steroid-refractory Graft Versus Host Disease (GvHD), which is being conducted in collaboration with Baxalta and the Fred Hutchinson Cancer Research Center; submitted a Marketing Authorization Application (MAA) with the European Medicines Agency (EMA) for its proprietary inhaled AAT therapy as a treatment for AAT deficiency (AATD); and initiated a Phase II clinical trial with its proprietary AAT for the prevention of lung transplant rejection, which is being conducted in collaboration with Baxalta.

Other

p) To mark its centenary, CSL Behring announced a $25 million R&D Fellowship program for early stage and translational research.
q) Therapure Biopharma of Mississauga, Ontario, hosted a political delegation including Canada's Federal Minister of Finance and Federal Minister of Innovation, Science and Economic Development. Nick Green, President and CEO of Therapure, said: "It was a great opportunity to demonstrate how the contribution under the Advanced Manufacturing Fund (AMF) is being used to develop our PlasmaCap technology and scale-up to clinical manufacture of plasma proteins." The company says PlasmaCap expanded bed absorption (EBA) technology yields more protein from the same amount of plasma, and separates the proteins faster, and at lower cost than existing processes in use globally.
r) Cerus announced in the US that the Walter Reed National Military Medical Center has begun routine use of the INTERCEPT Blood System for apheresis platelets.
s) Green Cross Corporation of Korea plans to issue bonds worth $US 86 million to finance expansion in the advanced pharmaceutical markets of North America and to increase production of vaccines and plasma-derivative products.

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) In India, Novo Nordisk reportedly launched NovoEight at half its international price, and Baxalta is expected to introduce Advate in the second half of 2016. The World Federation of Haemophilia says almost half the global haemophilia population lives in India.
b) A task force in India considering the development of manufacturing capabilities in the pharmaceutical industry has recommended to the government that it prepare a vision document with short term and long term plans for the plasma industry.
c) In India, a health ministry committee recently rejected a request from Sanofi for a trial waiver for its dengue vaccine, Dengvaxia. According to the Indian panel, the evidence for the dengue vaccine so far is insufficient to waive a clinical trial.
d) Brazilian health officials have said that their biggest worry for the Olympics is not the Zika virus but swine flu. Daniel Soranz, the municipal secretary of health for the city of Rio de Janeiro, told a group of journalists that the H1N1 virus is the biggest threat to public health during the winter months in Rio. He is urging visitors to be vaccinated against the flu before arrival, and also against measles, rubella and mumps. He says while yellow fever is not a problem in Rio those visiting other areas of Brazil should seek vaccination before leaving home.
e) The first human infection involving H5N6 avian flu was reported by China in 2014. China has reported 12 cases in total, nine since last December.
f) Lebanon reported its first highly pathogenic H5N1 outbreak in poultry, while Ghana and Mexico reported further outbreaks. Nigeria has been hit hard by H5N1.
g) Southern Mexico reported six more highly pathogenic H7N3 outbreaks, nearly all at commercial poultry farms.
h) Iraq reported its first outbreaks of bird flu in a decade.
i) The bird flu outbreak in the south west of France led to a three-month ban on the production of *foie gras*.
j) Australia's Senate inquiry "Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients" decided to produce an interim report before its work was disrupted by the federal election.

k) In the US, the FDA (with support from AABB) called for strategies to reduce the risk of transfusion-transmitted *Babesia microti* (a tick-borne disease) by advocating for additional screenings in states with the highest prevalence, like Minnesota, Wisconsin and New York.
l) In the US, platelet rich plasma therapy is being advertised to treat hair loss, with each session costing $US 400, bring your own plasma. .
m) The Irish Blood Transfusion Service said it "wishes to reconsider its position on blood donation from men who have sex with men". It hosted a two day conference in Dublin on the matter.
n) Singapore's Health Sciences Authority (HSA) is fast-tracking its evaluation[24] of a dengue vaccine, hoping to issue a decision within six months. Sanofi submitted an application to register the vaccine in March.

5. Safety and patient blood management

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

Appropriate Transfusion

a) In the US, a retrospective review of a population-based registry found that fewer perioperative blood transfusions have occurred for oncologic abdominal surgery over the last nine years[25]. The review was conducted by Giorgos C. Karakousis, assistant professor of surgery at the Hospital at the University of Pennsylvania and chair of the cancer committee at the Abramson Cancer Center in the Perelman School of Medicine, and colleagues. They reported: "The relative risks and benefits of allogeneic blood transfusion are particularly complex for the oncological surgery patient……Transfusion-related immunomodulation has been recognized for more than 30 years, when it was observed that renal allograft survival was improved with preoperative blood transfusion. Whether the immunosuppressive effects of allogeneic transfusion are associated with an increased risk of cancer recurrence has not been definitely established, although associations in a variety of abdominal malignant tumors have been observed."
b) A recent study[26] concluded that "antiplatelet therapy appears to increase intraoperative blood loss in lumbar surgery, even when the medication is discontinued at least 7 days preoperatively".
c) In people with sickle cell disease, red cells stiffen and adopt a sickled appearance. They can stick to each other and to blood vessel walls, causing blockages that interfere with oxygen delivery and lead to painful and dangerous crises. To improve blood flow many sickle cell patients receive monthly blood transfusions. Ian Welsby[27] and Jay Raval[28] are exploring whether an FDA-approved method for rejuvenating the red blood cells in stored blood can extend the time between transfusions for patients with sickle cell disease. The FDA-approved product is the solution Rejuvesol, used to extend the life of donated red blood cells of rare blood types. Rejuvenated blood

[24] The evaluation includes reviewing whether the vaccine is safe, of good quality and "effective for use" in the local population. It will also match it gainst the prevalent strains of dengue in Singapore, and review the vaccine's potential risks and side effects.
[25] Brett L. Ecker et al," Blood Transfusion in Major Abdominal Surgery for Malignant Tumors Trend Analysis Using the National Surgical Quality Improvement Program ONLINE FIRST**"**, *JAMA Surg*. Published online January 13, 2016. .doi:10.1001/jamasurg.2015.5094
[26] Peter T. McCunniff, et al., "Chronic Antiplatelet Use Associated With Increased Blood Loss in Lumbar Spinal Surgery Despite Adherence to Protocols", *Orthopedics,* posted April 27, 2016. DOI: 10.3928/01477447-20160419-04
[27] a cardiac anesthesiologist and intensivist at Duke University
[28] a pathologist and transfusion medicine expert at the University of North Carolina

can be frozen. Before the blood is issued for transfusion, the rejuvenation solution is washed out

d) A new randomized trial suggests that giving platelet transfusions to patients presenting with an intracerebral haemorrhage (ICH) who are taking antiplatelet agents is associated with worse outcomes. The Platelet Transfusion in Cerebral Haemorrhage (PATCH) trial[29] was discussed[30] in Barcelona at the European Stroke Organisation Conference (ESOC) 2016 by Yvo B. Roos, Academic Medical Centre, Amsterdam. The trial was simultaneously published online 10 May in *The Lancet*. "Our results show that when you see a patient with ICH who is on antiplatelet therapy you should not treat with platelet transfusions," Dr Roos told *Medscape Medical News*. "We have very clear results showing a worse outcome if they are given platelets compared with no treatment." Serious adverse events during the hospital stay occurred in 42 per cent of patients who received platelet transfusions and 29 per cent of those who received standard care. In-hospital mortality was 24 per cent in participants assigned to platelet transfusion and 17 per cent in those assigned to standard care. Dr Roos noted that the results of the PATCH trial were counterintuitive, but it was important to pay attention to randomized data. He said the practice of giving platelets to patients with ICH and taking antiplatelets was "quite common, particularly in the US." On the mechanism behind the harmful effect, Dr Roos said this was unknown, but he pointed out that transfusion experts have acknowledged that patients receiving platelet transfusions represent the smallest group of transfusion patients but have the largest amount of problems. "It might not be just about clotting. They can have pro-inflammatory effects as well. We need to study this further."

e) In the *Lancet* paper mentioned in the previous paragraph, the authors concluded: "Given the widespread use of platelet transfusion for other acute bleeding disorders despite a shortage of randomized evidence, our findings should lead to further trials so that this potentially hazardous and costly intervention is only used for prophylactic or therapeutic indications when supported by evidence from randomized controlled trials." In an accompanying editorial, Calin I. Prodan, University of Oklahoma Health Sciences Center, said that the study has several limitations, such as relatively small sample size, a potential for chance imbalances in several prognostic variables, and an inability to analyze the relationship between the intervention and several subtypes of severe adverse events. He said: "However, these data, generated from what is an important, pragmatic real-life trial done in emergency settings, provide strong support against the use of routine platelet transfusion as a treatment option for acute intracerebral haemorrhage after antiplatelet therapy". Dr Prodan concluded that: "Although another trial awaiting completion might support or challenge the findings of PATCH, for now, more is not better (and it may well be worse) for platelets in intracerebral haemorrhage."

f) At the American Urological Association annual meeting in San Diego, first author Justin T. Matulay, of Columbia University Medical Center, New York, presented findings from a retrospective analysis of 30-day postoperative outcomes in men undergoing radical prostatectomy from 2005 to 2013, using the National Surgical Quality Improvement (NSQIP) database. The primary outcome was 30-day postoperative morbidity, and secondary outcomes were 30-day mortality, readmission, length of stay, infectious complications, and pulmonary complications. The authors found that of the 21,293 radical prostatectomies performed during the period covered, 810 patients (3.9 per cent) received a perioperative blood

[29] The PATCH trial was a multicentre, open-label, masked-endpoint, randomized trial at 60 hospitals in the Netherlands, United Kingdom, and France. Most (71 of the 97) patients receiving antiplatelet agents were taking aspirin. The dose of platelets used was 1 unit of platelet concentrate; patients on clopidogrel received 2 units.

[30] 10 May, 2016

transfusion. They reported that perioperative blood transfusion was associated with increased 30-day morbidity, readmission, pulmonary complications, and surgical site infections[31].

Treating anaemia

g) Rockwell Medical announced that the US Food and Drug Administration (FDA) had approved its New Drug Application for Triferic Powder Packet for commercial sale as an iron replacement product to maintain haemoglobin in adult patients with haemodialysis dependent chronic kidney disease[32].

h) .A study published in *Annals of Pharmacotherapy* reports that the use of intravenous (IV) or oral iron with or without an erythropoiesis-stimulating agent may help prevent post-operative anaemia and reduce blood transfusions without significantly raising the risk of adverse events. Taylor D. Steuber, from Butler University College of Pharmacy and Health Sciences, Indianapolis, and colleagues studied patients undergoing elective orthopaedic surgery[33]. They found that pre-operative administration of oral iron, IV iron, ESA alone or in combination resulted in significantly reduced transfusion rates. Rates of transfusion were generally less with combination therapy of ESA with oral or IV iron. However. the short-term peri-operative or post-operative administration of oral or IV iron showed conflicting results where some studies demonstrated a statistically significant reduction in blood transfusions and others demonstrated none. The researchers concluded the drugs may be an option at the lowest effective dose when given before the planned procedure.

Other

i) Octapharma USA initiated a voluntary market withdrawal of Octagam 5% [Immune Globulin Intravenous (human)] 5% Liquid Preparation] labelled with lot number K551A8441. Octapharma said there had been no reports of serious injury at that time, but there had been several reports of allergic type skin reactions. The product is administered intravenously to treat primary humoral immunodeficiencies, such as congenital agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome and other severe combined immunodeficiencies. The recalled product was produced in Vienna.

j) Medical technology developer New Health Sciences (of Bethesda, Maryland)**,** has received a three-year, $US 3 million grant from the US National Heart Lung and Blood Institute (part of the National Institutes of Health). The grant is to develop and test anaerobic storage technology for donated blood. The company says it aims to commercialize the gas-optimized *Hemanext* storage system, designed to help preserve the quality of red blood cells during prolonged storage.

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[31] Transfusion in the perioperative period has been associated with worse overall survival for several other malignancies besides prostate cancer. It may be that the allogeneic blood stimulates an inflammatory response that may promote tumor growth.

[32] Robert L Chioini, Founder, Chairman and Chief Executive Officer of Rockwell, said: “The Triferic powder packet is similar to the size of a packet of sugar. It is much smaller and lighter than the current Triferic liquid ampule and it enables us to place three-times greater the number of units in an even smaller carton. This reduces storage space to maintain inventory.” Triferic is added to the bicarbonate concentrate on-site at the dialysis clinic. Once in dialysate, Triferic crosses the dialyzer membrane and enters the blood where it immediately binds to transferrin and is transported to the erythroid precursor cells to be incorporated into haemoglobin. The company says Triferic delivers sufficient iron to the bone marrow and maintains haemoglobin without increasing iron stores (ferritin).

[33] They searched PubMed and MEDLINE from 1964 through to March 2016 for English-language prospective and retrospective human studies and meta-analyses evaluating oral or IV iron, ESA alone, or in combination, in surgery patients with reported blood transfusion outcomes. Nine prospective and retrospective studies as well as 1 meta-analysis were reviewed.

k) NASA's anti-gravity space suit is the inspiration behind LifeWrap, a pressure suit that can prevent deaths from postpartum bleeding.

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) The US National Science Foundation awarded a $US 500,000 grant[34] for research about how and why diseases such as cancer cause "increased stiffness and stickiness of red blood cells," as well as "whether unhealthy red blood cells can be identified by adhesion affinity and stiffness".
b) Adults with blood cancers and other blood disorders need a near-perfect match from a donor's bone marrow, but stem cells from umbilical cord blood don't need to be a perfect match. Their disadvantage is there are too few of them for adult transplants. Now Kristin Hope of McMaster University's Stem Cell and Cancer Research Institute and colleagues[35] say they have found the key to growing the amount of cord blood cells, the key being a specific protein (Musashi-2) that regulates the development of blood stem cells from umbilical cords[36].
c) Researchers at the Florida arm of The Scripps Research Institute (TSRI) have been awarded a $US 2.5 million grant from the National Institute of General Medical Sciences of the US National Institutes of Health to design precision drug candidates that target disease-associated RNAs. Matthew Disney, who will be the principal investigator, said: "A major goal of genome sequencing efforts is to develop drug targets that could enable the development of patient-specific therapies. In this project, we are developing quick ways to convert this information into lead drugs by using several novel and transformative technologies we developed. The new grant will keep us moving forward and allow us to tackle many new challenges in the area of precision medicine[37]."
d) IBM has revealed[38] a new macromolecule-like "molecular Velcro" to kill viruses like Ebola, herpes, dengue and influenza[39]. A company statement said: "In early testing, scientists have seen no resistance. By targeting both viral proteins and host-virus interactions, the antiviral macromolecule sidesteps the normal mutations that enable viruses to escape vaccines through the onset of resistance." Yi Yan Yang, a scientist at the Institute of Bioengineering and Nanotechnology in Singapore, one of the creators of the new material, said: "We have created an anti-viral macromolecule that can tackle wily viruses by blocking the virus from infecting the cells, regardless of

[34] The team will be led by Umut Gurkan, assistant professor of mechanical and aerospace engineering at Case Western Reserve University.
[35] from the universities of Toronto, Montreal and California at San Diego.
[36] Stefan Rentas, et al., "Musashi-2 attenuates AHR signalling to expand human haematopoietic stem cells"**,** *Nature*, 2016; 532 (7600): 508 DOI: 10.1038/nature17665
[37] The new grant will enable the team to explore further the manipulation of microRNAs, which were discovered in the 1990s. microRNAs are short molecules that work within animal and plant cells, each one functioning as a "dimmer switch" for one or more genes, binding to the transcripts of those genes and keeping them from being translated into proteins.
[38] The IBM research appeared in the journal *Macromolecules.*
[39] The polymer has a triple-action process that inhibits and kills the viral molecules. Initially, the macromolecule's structure attracts viruses through hydrogen bonds with electrostatic interactions, which bond to the proteins on the viral surface. Next, a type of sugar in the macromolecule competes with the viruses for interaction with the human cells. Then, basic amine groups make the pH inside the viral cell neutral ,which will inhibit its replication, even if it does manage to enter a human cell.

mutations. It is not toxic to healthy cells and is safe for use. This promising research advance represents years of hard work and collaboration with a global community of researchers." IBM said antiviral cleaning products and even vaccines could be targets from 2018 to 2023.

e) Acetylon Pharmaceuticals of Boston is developing a series of selective[40] histone deacetylase HDAC1/2 inhibitors for the treatment of sickle cell disease and beta-thalassemia, since elevated levels of normal foetal haemoglobin (HbF) protein can reduce disease severity by replacing missing or defective adult haemoglobin. Preclinical data has now been published[41].

7. Legal matters

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

a) Chugai Pharmaceutical revealed that a lawsuit was filed against the company at the Tokyo District Court by Baxalta. Baxalta reportedly alleged that a new drug under development by Chugai (which is majority owned by Swiss company Roche) for the treatment of haemophilia A, (emicizumab or ACE910) is infringing its patent number 4313531. Baxalta filed for an injunction against manufacture, usage, transfer, exportation, and offer of any transfer regarding emicizumab, and requested cessation. ACE910 is currently in late-stage clinical trials by Roche and Chugai. It is a double-headed (bispecific) antibody which simultaneously binds to both Factor IXa and Factor X and mimics the effect of Factor VII. Baxalta has reportedly articulated in its complaint that the act such as manufacturing and usage of emicizumab for clinical trials in Japan infringes its patent, and that emicizumab has a potential to be manufactured and sold in the future. Chugai on the other hand says it is confident that emicizumab does not infringe Baxalta's patent, and that it will pursue the entire court process.

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

Zika Virus

a) Recent experience with the Zika virus in Brazil has emphasised the *Aedes aegypti* mosquito as the vector. Now, for the first time in the Western Hemisphere[42], the Zika virus has been detected in *Aedes albopictus*, or "Asian tiger" mosquito, which

[40] Selective inhibition of HDAC1/2 is expected to reduce toxic side effects versus non-selective HDAC inhibitors.
[41] Jeffrey R Shearstone et al., "Chemical Inhibition of Histone Deacetylases 1 and 2 Induces Fetal Hemoglobin through Activation of GATA2", published online 13 April, 2016 in *PLoS One.*
[42] The Asian tiger was identified as the primary vector for Zika during a 2007 outbreak in the West African country of Gabon.

significantly increased the geographic area seen as at risk for local transmission of the disease[43]. The two species have different behavioural and breeding patterns[44].

b) *Wolbachia* bacterium, which is known to prevent the spread of the dengue virus, has now been shown to block transmission of Zika. Researchers in Brazil reported[45] that *Aedes aegypti* mosquitoes carrying *Wolbachia* bacteria were highly resistant to Zika virus infection, and were unable to transmit the virus via their saliva.

c) Researchers at Florida Gulf Coast University and their colleagues[46] have found that human cells were more likely to be infected with Zika virus *in vitro* if they contained antibodies to dengue virus. Their findings suggest Zika infection will be more severe in areas where dengue is endemic, and point to a potential unintended effect of dengue vaccination[47].

d) Research[48] led by Tariq Rana (professor of paediatrics and genetics at the University of California, San Diego) found that the birth defects caused by Zika virus appear to result from an immune system response that triggers prenatal brain cell suicide and obstructs foetal brain development[49].

e) Several studies showed that Zika virus in pregnant mice could produce microcephaly in their embryos, including work from the University of Sao Paulo, published in *Nature*[50]*;* research from the Chinese Academy of Sciences published in *Cell Stem Cell*[51]*;* and research from the Washington University School of Medicine in St. Louis, published in *Cell*[52]*.*

f) Dr. Amir Attaran of the University of Ottawa[53] has warned that holding the Olympics in the middle of a Zika outbreak could cause a "full-blown global health disaster." The International Olympic Committee (IOC) claims that there is "no justification for cancelling, delaying, postponing or moving the Rio Games.'' The World Health Organization (WHO) issued a set of recommendations for athletes and tourists but took no official position on delaying or moving the Olympics.

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[43] In the US *albopictus* ranges as far north as New England and the lower Great Lakes.

[44] The *aegypti* mosquito thrives in urban areas by laying eggs in discarded containers, while the Asian tiger mosquito lives outdoors, laying its eggs in tree stumps. It can survive colder weather. Its preferred vehicle for international travel is shiploads of used tyres or on ornamental plants.

[45] H. Dutra et al., "*Wolbachia* blocks currently circulating Zika virus isolates in Brazilian *Aedes aegypti* mosquitoes," *Cell Host & Microbe***,** doi:10.1016/j.chom.2016.04.021, 2016.

[46] Lauren M Paul, et al, "Dengue Virus Antibodies Enhance Zika Virus Infection"**,** published on the preprint server bioRxiv on 25 April. doi**:** http://dx.doi.org/10.1101/050112 . Articles available as preprints have not been peer reviewed.

[47] The authors conclude in their abstract: "Our results suggest that pre-existing DENV immunity will enhance ZIKV infection *in vivo* and may increase disease severity. A clear understanding of the interplay between ZIKV and DENV will be critical in informing public health responses in regions where these viruses co-circulate and will be particularly valuable for ZIKV and DENV vaccine design and implementation strategies."

[48] Dang et al., "Zika Virus Depletes Neural Progenitors in Human Cerebral Organoids through Activation of the Innate Immune Receptor TLR3, 2016, Cell Stem Cell 19, 1–8, July 7, 2016 ª 2016 Elsevier Inc. http://dx.doi.org/10.1016/j.stem.2016.04.014

[49] The virus apparently activates an immune receptor,TLR3. This turns off genes that fetal stem cells need to specialize into brain cells, and appears to switch on genes that trigger cell suicide.

[50] F. Cugola et al., "The Brazilian Zika virus strain causes birth defects in experimental models," *Nature,* doi:10.1038/nature18296, 2016.

[51] C. Li et al., "Zika virus disrupts neural progenitor development and leads to microcephaly in mice," *Cell Stem Cell***,** doi:10.1016/j.stem.2016.04.017, 2016.

[52] J. Miner et al., "Zika virus infection during pregnancy in mice causes placental damage and fetal demise," *Cell,* doi:10.1016/j.cell.2016.05.008, 2016.

[53] writing in the *Harvard Public Health Review*

g) Cayman Islands Mosquito Research and Control Unit (MRCU) is planning a multi-phase roll out of Oxitec's solution[54] to help reclaim the island from mosquitoes carrying Zika. In March, WHO recommended pilot deployment of Oxitec's solution to respond to the Zika crisis and the FDA released a preliminary Finding of No Significant Impact (FONSI) on Oxitec's solution for an investigational trial in the Florida Keys. MRCU already performed the world's first suppression trial with Oxitec's OX513A self-limiting mosquito - a genetically engineered non-biting male that mates with disease-transmitting wild *Aedes aegypti* females - which successfully reduced the target mosquito population by 96 per cent.

h) NewLink and Merck plan to submit their Ebola vaccine for regulatory approval in 2017. NewLink has received a $US 26.1 million boost from the US Biomedical Advanced Research and Development Authority (BARDA), bringing the company's total BARDA funding to more than $US 70 million. The candidate is the furthest along in the Ebola vaccine race and is the only one to report Phase III results, albeit from a novel trial structure. Due to the waning Ebola epidemic, the investigators had to devise a "ring" study, identifying Ebola patients' contacts as a "ring" of people at risk for the disease. The vaccine posted 100 per cent efficacy in interim results. In January, Gavi, the global vaccine alliance, signed a $US 5 million pact with Merck to fund the vaccine through late-stage trials, licensure and prequalification by WHO by the end of 2017. If approved, Gavi will stockpile the vaccine for use in future outbreaks. Merck has also filed an application with WHO to allow the use of the vaccine if an outbreak occurs before it is licensed.

i) Johnson & Johnson reported that its Zika candidate prompted an immune response in 100 per cent of participants in a Phase I trial. J&J is working on a "prime-boost" vaccine with Bavarian Nordic, while a number of other companies, including GlaxoSmithKline, Inovio and Maryland-based Profectus and Novavax, are also developing Ebola vaccines.

j) Massachusetts Institute of Technology researchers have led a team in developing a paper-based test that they say can diagnose the Zika virus in just a few hours. It is designed to distinguish Zika from the dengue virus.

k) Quest diagnostics received FDA authorization for a commercial test for the Zika virus for emergency use. The test detects RNA from the Zika virus in human blood serum.

Other mosquito-borne diseases

l) An "aggressive" breed of mosquito has been found to be responsible for the spread of dengue in the Torres Strait. It's the first time *Aedes albopictus*, also known as the "Asian tiger mosquito", has been identified by health officials as having transmitted dengue fever among people in Australia. The disease has hitherto spread from person to person by the *Aedes aegypti* mosquito which is considered endemic only in north Queensland, including Cairns and Townsville.

m) A clinical trial[55] of Sanaria PfSPZ (*Plasmodium falciparum sporozoite)* vaccine showed that it provided protection for at least 14 months in subjects who were exposed to *Plasmodium falciparum* parasites. The findings put the vaccine on track to be the first providing durable protection against *Plasmodium falciparum,* the malaria parasite that causes about 438,000 deaths and 214 million cases annually.

n) With concern rising that an outbreak of yellow fever in Angola will spread, WHO urged travellers to Angola to ensure they are vaccinated. However, the manufacturer of yellow fever vaccine, Sanofi Pasteur, says it continues in short supply and ordering restrictions are in place.

[54] Oxitec uses advanced genetics and molecular biology to control The de3ngue- carrying mosquito, *Aedes aegyptgi.*

[55] Reported in *Nature Medicine*

Influenza: strains, spread, prevention and treatment

o) Chinese researchers reported[56] that asymptomatic migratory birds may play a role in dissemination of highly pathogenic H5N8 avian influenza, and that they also may facilitate viral evolution and reassorttment.
p) H5N6 outbreaks in poultry have been reported in a few Asian countries, but so far China is the only one reporting human cases.
q) Human cases of H7N9 are continuing to occur in China[57]. Researchers found the risk of death from H7N9 infection was highest during China's second and third epidemic waves, also shifting to affect younger people and rural residents[58].
r) Lebanese authorities slaughtered thousands of chickens after cases of the H5N1 virus were discovered at a poultry farm in the Bekaa Valley.
s) Iraq reported its first outbreak of bird flu in ten years.
t) Oxford University spin-out company Vaccitech has received funds from Oxford Sciences Innovation to take a universal flu vaccine through clinical trials.
u) UK research (from the University of Birmingham) suggests patients be given their influenza vaccinations in the morning because the injections could offer stronger protection at that time. "We know that there are fluctuations in immune responses throughout the day and wanted to examine whether this would extend to the antibody response to vaccination," said principal study investigator Dr. Anna Phillips. The morning group experienced a significantly larger increase in antibody concentrations at the end of a one-month period following the initial vaccination against two out of three of the flu strains.

MERS-CoV (Middle East Respiratory Syndrome-Coronavirus)

u) As at noon on 15 May Saudi Arabia had experienced 1383 laboratory confirmed cases of MERS-CoV infection, including 592 deaths. There were three currently active cases.

Ebola virus disease

v) An international team of scientists[59] says the Ebola virus can lie dormant in a survivor for over a year, and then re-emerge to infect others, which explains why Ebola is still around in Liberia. "We believe that most, if not all, the clusters of new Ebola cases have come from [persistent infections in survivors, but sometimes it's very hard to determine that with certainty," says Dr Thomas Frieden, who directs the US Centers for Disease Control and Prevention (CDC). Dr Daniel Bausch, an infectious disease expert at Tulane University says "Sexual transmission is our No. 1 concern". It appears that semen can stay infectious for more than a year, much longer than previously thought.
w) Another study[60] reported that the Ebola virus can persist in the semen of survivors of the epidemic for up to nine months after their recovery. The researchers showed the persistence of the virus in semen decreases with time: the virus, present in 28.5 per cent of samples taken between the first and third months, was subsequently detected in only 16 per cent between the fourth and sixth months, in 6.5 per cent between the seventh and ninth months, and zero per cent after 12 months.

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[56] Zhou LC, Liu J, Pei EL, Xue WJ, Lyu JM, Cai YT, et al. "Novel avian influenza A(H5N8) viruses in migratory birds, China, 2013–2014". *Emerg Infect Dis*. 2016 Jun. http://dx.doi.org/10.3201/eid2206.151754
[57] At 11 May, 747 human cases of avian influenza A(H7N9) had been reported since 2013 by the Chinese health authorities.
[58] The study appeared in *Emerging Infectious Diseases*, 12 May
[59] Reporting in the journal *Science Advances*
[60] The findings were published in the *Journal of Infectious Diseases*.

x) A team led by Francesco Piraino of Ecole Polytechnique Federale de Lausanne (EPFL) has made a smartphone-sized medical device that can detect Ebola virus in real time using only a very small amount of blood[61].

y) Geovax Lab's President and CEO, Robert McNally, and Chairman, David Dodd, have updated shareholders on the company's key initiatives, which include expansion of the Company's haemorrhagic fever vaccine program with the goal of a single vaccine to prevent infection from two lethal strains of Ebola virus, plus Marburg and Lassa Fever viruses[62].

Other diseases: occurrence, prevention and treatment

z) Researchers[63] have found a section of protein[64] in thale cress (*Arabidopsis*) that behaves like a prion when it is inserted into yeast.

aa) Outbreaks of *Salmonella* in South Australia and the Northern Territory have been linked to tainted bean sprouts. The US had a *salmonella* outbreak across twelve states from bean sprouts.

bb) More than 100 Australian babies were hospitalised with parechovirus in 2013 and 2014. According to a study by the Australasian Society for Infectious Diseases (ASID), doctors found a year later that many of these babies had developmental problems.

cc) In Sydney, legionnaire's disease was diagnosed in further patients, there was one death, and a number of cooling towers in Sydney CBD tested positive for *legionella*.

dd) By 13 May, South Australia had had eleven patients diagnosed with meningococcal infection, three in the previous week. Ten were of the meningococcal B strain, which is not covered on the national vaccine register.

ee) The Bill & Melinda Gates Foundation has awarded Takeda Pharmaceuticals $US 38 million for development of a low-cost polio vaccine. Takeda will "develop, license, and supply at least 50 million doses per year of so-called Sabin-strain inactivated poliovirus vaccine (sIPV) to more than 70 developing countries".

ff) Researchers reported on treatment of tick-borne diseases[65]: "Evidence is evolving regarding the diagnosis, treatment, and prevention of Lyme disease, HGA[66], and babesiosis. Recent evidence supports treating patients with erythema migrans for no longer than 10 days when doxycycline is used and prescription of a 14-day course of oral doxycycline for early neurologic Lyme disease in ambulatory patients. The duration of antimicrobial therapy for babesiosis in severely immunocompromised patients should be extended to 6 weeks or longer".

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[61] Francesco Piraino et al. "A Digital–Analog Microfluidic Platform for Patient-Centric Multiplexed Biomarker Diagnostics of Ultralow Volume Samples", *ACS Nano*, 2016, *10* (1), pp 1699–1710**.** DOI: 10.1021/acsnano.5b07939

[62] Other initiatives mentioned are the development of a vaccine to prevent Zika virus infection under multiple collaborative arrangements; and preventive HIV vaccine clinical trial initiatives and follow-on development activities with the US National Institutes of Health (NIH) and the HIV Vaccine Trials Network (HVTN).

[63] led by Susan Lindquist, **a** biologist at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts.

[64] The protein, Luminidependens (LD), is normally involved in responding to daylight and regulating flowering time. When a part of the LD gene is inserted into yeast, it produces a protein that does not fold up normally, and which spreads this misfolded state to proteins around it in a domino effect that causes aggregates or clumps. Subsequent generations of yeast cells inherit the effect: their versions of the protein also misfold. The study is reported on April 25 in the *Proceedings of the National Academy of Sciences*.

[65] Edgar Sanchez at al, "Diagnosis, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and BabesiosisA Review", *JAMA.* 2016;315(16):1767-1777. doi:10.1001/jama.2016.2884.

[66] Human Granulocytic Anaplasmosis

gg) Researchers have described[67] a new pathogenic *Borrelia burgdorferi* sensu lato genospecies (candidatus *Borrelia mayonii*) in the upper midwestern USA, which causes Lyme borreliosis with unusually high spirochaetaemia. They recommend clinicians be aware of this new B burgdorferi sensu lato genospecies, its distinct clinical features, and the relevant diagnostic tests.

[67] Bobbi S Pritt et al, "Identification of a novel pathogenic Borrelia species causing Lyme borreliosis with unusually high spirochaetaemia: a descriptive study", *The Lancet Infectious Diseases,* Volume 16, No. 5, p556–564, May 2016 ,DOI: http://dx.doi.org/10.1016/S1473-3099(15)00464-8