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:

- ❖ Bluebird Bio has released early safety and efficacy data based on long-term follow up of the first patient with severe sickle cell disease treated with the company's LentiGlobin BB305. (Section 1)
- ❖ A recent study relevant to patients with Alpha-1 Antitrypsin Deficiency suggested that "treatment with an $Alpha_1$-Proteinase Inhibitor may slow the accelerated loss of lung tissue that is a characteristic of this potentially debilitating disease". (Section 1)
- ❖ During the American Thoracic Society 2015 International Conference in Denver, a panel discussed the updated data from Kamada's European and Canadian Phase II/III clinical study of inhaled alpha-1 antitrypsin to treat alpha-1 antitrypsin deficiency. (Section 1)
- ❖ The European Medicines Agency has released its draft *Guideline on epidemiological data on blood transmissible infection*. (Section 2)
- ❖ Biogen has submitted a Marketing Authorisation Application for Alprolix (recombinant factor IX, long-acting) to the European Medicines Agency. (Section 2)
- ❖ The FDA has accepted for review BPL's amended Biologics License Application for Coagadex for hereditary factor X deficiency. (Section 2)
- ❖ Baxter submitted a Marketing Authorization Application to 17 authorities in Europe seeking approval of its 20 per cent concentration subcutaneous immune globulin treatment for patients with primary immunodeficiencies. (Section 2)
- ❖ Health Canada approved a new, low-volume presentation size for the existing indications of Berinert, a plasma-derived, pasteurized and nanofiltered C1-esterase inhibitor concentrate. (Section 2)
- ❖ CSL Behring announced that the European Medicines Agency Committee for Medicinal Products for Human Use has recommended granting marketing authorisation for Respreeza, a highly purified alpha-1 protein derived from human plasma, indicated to treat patients with severe alpha-1 antitrypsin deficiency. (Section 2)
- ❖ Data from the US national babesiosis surveillance program and annually reported transfusion-transmitted babesiosis (TTB) cases show that the TTB-risk to US blood supply is rising. (Section 2)
- ❖ Verax Biomedical gained FDA clearance to expand the use of its rapid test that screens for bacterial contamination in blood platelets. (Section 2)
- ❖ The FDA granted orphan drug designation for Apitope's pre-clinical drug candidate ATX-F8-117 which is designed to prevent or treat inhibitors in patients with haemophilia A. (Section 2).

- Baxter International announced that its board of directors had approved the planned separation of its biopharmaceuticals operations. Baxalta would begin trading as an independent company on 1 July, 2015 on the New York Stock Exchange. (Section 3)
- Pfizer received a request for additional information from the US Federal Trade Commission with respect to its previously announced proposal to acquire Hospira. (Section 3)
- A state-of-the-art production line for the manufacturing of anti-D immunoglobulin was recently completed at Kedrion's facility in Melville, New York. (Section 3)
- Green Cross Biotherapeutics began construction on its biopharmaceutical facility on the Montréal Technoparc's Saint-Laurent Campus in Canada. (Section 3)
- The New Zealand Blood Service announced that it is not able to collect enough plasma for its immunoglobulin needs. It will be importing immunoglobulin made from foreign source plasma. (Section 4)
- In Ireland a 5 year old cow on a dairy farm in county Louth died of mad cow disease.
- In the US, the Department of Health and Human Services has selected nine health departments together with partner hospitals to become special regional treatment centres for severe, highly infectious diseases, including Ebola. (Section 4)
- Cerus Corporation and the SunCoast Blood Bank of south-west Florida announced that the first pathogen reduced platelet units had been produced in the continental US. (Section 4)
- The American Academy of Orthopaedic Surgeons Annual Meeting was told that, among patients who underwent either total knee or total hip replacement, intraoperative use of tranexamic acid significantly reduced the need for blood transfusion. (Section 5)
- Researchers found that high doses of tranexamic acid helped to control blood loss and reduce the need for transfusion in patients having corrective spine surgery. (Section 5)
- A study by Canadian Blood Services has found that women who donate blood more than two or three times a year are twice as likely as those who don't donate to be iron deficient. (Section 5)
- The US International Trade Commission is investigating claims that Danish company Novo Nordisk plans to import into the US haemophilia drugs that infringe patents held by Baxter International. (Section 7)
- In Brisbane, the Supreme Court ruled that a young boy requiring a liver transplant may be given a blood transfusion despite parental objection on religious grounds. (Section 7)
- Between 15 December last year and 29 May this year the US Department of Agriculture (USDA) confirmed more than 200 findings of birds infected with highly-pathogenic avian influenza (HPAI) A (H5N2), (H5N8), and (H5N1) viruses. Most were in backyard and commercial poultry. As the crisis expanded, millions of birds were euthanased, eggs were rationed and egg prices rose. (Section 8)
- Human cases of H7N9 avian flu continue to be reported from China.
- By 7 June South Korea had announced 64 MERS cases and five deaths. By 24 June, the total number of MERS cases had reached 179, with 27 deaths. (Section 8)
- Researchers in Hong Kong found that South Korea's MERS outbreak was fanned by three human "superspreaders". At least three-quarters of the cases can be attributed to clusters in hospitals started by three highly infectious people. (Section 8)
- As of 7 June, WHO's total case count for the current Ebola outbreak was 27,237, with the number of deaths 11,158. 68 of these had occurred in the previous 21 days (38 in Guinea and 30 in Sierra Leone). In mid-June, Sierra Leone introduced new curfews for two northern districts after a spike in cases, and that was followed by the discovery of three new cases in Liberia. (Section 8)

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.

Haemophilia treatments

- Bayer HealthCare presented data on haemophilia A at the International Society on Thrombosis and Haemostasis (ISTH) 2015 Annual Congress[1]. More than 20 company abstracts had been accepted for presentation, including five oral[2] and 18 poster[3]

[1] held June 20-25 in Toronto

[2] oral presentations included *BAY 81-8973 Prophylaxis Efficacy in Patients With Severe Hemophilia A: Analyses of Annualized Bleeding Rate Outcomes in the LEOPOLD I Trial*; *LEOPOLD Trial Results: Correlation of von Willebrand Factor Antigen Level With BAY 81-8973 Pharmacokinetic Parameters of*

presentations. "We are eager to share clinical data from our LEOPOLD trials on the investigational product BAY 81-8973 and from the SPINART trials on Kogenate FS antihemophilic factor (recombinant)," said Dario Mirski, Vice President and Head of US Medical Affairs, Bayer HealthCare Pharmaceuticals.

- Alnylam Pharmaceuticals presented new data on ALN-AT3 at the International Society on Thrombosis and Haemostasis (ISTH) 2015 Congress[4]. ALN-AT3 is an investigational RNAi therapeutic for the treatment of haemophilia and rare bleeding disorders (RBD). Data included new interim Phase 1 clinical data and additional pre-clinical study results. John Maraganore, Chief Executive Officer of Alnylam, said: "….our presentation of initial Phase 1 clinical data for ALN-AT3 is aimed at providing safety and preliminary clinical activity results from about a dozen subjects with severe haemophilia." [5]
- Biogen presented 23 company-sponsored platform and poster presentations at the International Society on Thrombosis and Haemostasis (ISTH) 2015 Congress[6]. Data presentations included a platform presentation from the Kids B-LONG study detailing the safety and efficacy of Alprolix [Coagulation Factor IX (Recombinant), Fc Fusion Protein] in children with haemophilia B, the first time the full results from the Kids B-LONG study will be publicly presented. There was also an interim ASPIRE study[7] analysis of the long-term safety and efficacy of Eloctate [Antihemophilic Factor (Recombinant), Fc Fusion Protein] for the prevention and treatment of bleeding in previously treated adults and adolescents with haemophilia A.

Patients with Severe Hemophilia A; *SPINART 3-Year Analyses: Patient-and Joint-Level Changes in Colorado Adult Joint Assessment Scale and Magnetic Resonance Imaging Scores With Bayer's Sucrose-Formulated Recombinant Factor VIII in Adolescents and Adults;* and *SPINART 3-Year Results with Bayer's Sucrose-Formulated Recombinant Factor VIII: Relationship Between Bleeding Frequency and Joint Health in Adults With Severe Hemophilia A Using Prophylaxis*

[3] poster presentations included: *Poster #293: Prophylactic Efficacy of Twice-Weekly Versus 3-Times-Weekly BAY 81-8973 in Severe Hemophilia A: Results of the LEOPOLD I and II Clinical Trials;* and *Poster #292: Bleeding Events in Chinese Children with Severe Hemophilia A Receiving Standard Prophylaxis vs On-Demand Treatment With Bayer's Sucrose-Formulated Recombinant Factor VIII.*

[4] June 20 – 25, 2015 in Toronto

[5] Presentations by Alnylam scientists at the meeting included: an oral presentation, *Antithrombin Reduction Improves Coagulation in Rare Bleeding Disorder Plasma*, during the Rare Platelet Disorders session; an oral presentation, *A Subcutaneously Administered Investigational RNAi Therapeutic (ALN-AT3) Targeting Antithrombin for Treatment of Hemophilia: Interim Phase 1 Study Results in Patients with Hemophilia A or B*, during the Hemophilia – Novel Treatments session; a poster presentation titled Thrombin Generation in Human Hemophilia Plasma at Reduced Antithrombin Levels and *Concomitant Factor or Bypass Agent Addition*, during the Coagulation Factor VIII-Factor IX–II session; and a poster presentation, *Safety Evaluation of Chronic Antithrombin Silencing in Non-Human Primate and Expanded Therapeutic Index in a Hemophilia A Mouse Model*, during the Animal Models-III session.

[6] Including: *Safety and Efficacy of Recombinant Factor VIII Fusion Protein (rFVIIIFc) for the Prevention and Treatment of Bleeding in Previously-Treated Adult and Adolescent Subjects with Hemophilia A: Interim Analysis of the ASPIRE Study* – Poster #235; *Treatment of Bleeding with Recombinant Factor VIII Fc Fusion Protein in Previously-Treated Pediatric Subject with Hemophilia A in the Phase 3 Kids A-LONG Study* – Poster #239; *Indirect Comparisons of Factor Consumption, Bleeding Rates, and Infusion Frequencies During Routine Prophylaxis with Recombinant Factor VIII Fc Fusion Protein and Other Recombinant Factor VIII Products* – Poster #170; *Study of Recombinant Factor IX Fc Fusion Protein in Children with Hemophilia B* – Late Breaking Oral Session #009; *Indirect Comparisons of Factor Consumption, Bleeding Rates, and Infusion Frequencies During Routine Prophylaxis with Recombinant Factor IX Fc Fusion Protein and Other Recombinant Factor IX Products* – Poster #171; and *A retrospective study on the current treatment practice of haemophilia A and B in the United Kingdom*-Poster #299

[7] ASPIRE is a multi-year extension study for people who completed the pivotal, phase 3 A-LONG or Kids A-LONG studies.

Sickle Cell treatments

- Bluebird Bio has released early safety and efficacy data based on long-term follow up of the first patient with severe sickle cell disease (SCD) treated with the company's LentiGlobin BB305. It regards the data as promising. The proportion of anti-sickling haemoglobin being produced by this patient treated with gene therapy is rising steadily and accounted for 45 per cent of all haemoglobin production at the patient's six-month visit post-drug product infusion. This is above the 30 per cent threshold defined as necessary to have a disease-modifying clinical effect. Bluebird Bio also announced that the trial patient had been free of transfusions for more than three months without complications or hospitalisations for SCD-related events, and with improvement in haemolysis markers.

Treatment of Alpha-1 Antitrypsin Deficiency (AATD)[8]

- Kenneth R. Chapman**,** director of the Asthma and Airway Centre of the University Health Network in Toronto, said in a press release about a recent study[9] relevant to patients with Alpha-1 Antitrypsin Deficiency: "Our findings provide additional evidence that treatment with an $Alpha_1$-Proteinase Inhibitor may slow the accelerated loss of lung tissue that is a characteristic of this potentially debilitating disease". Chapman and colleagues conducted a multicentre, double blind, placebo-controlled study on 180 non-smokers aged 18 to 65 years to compare the efficacy and safety of CSL Behring's Zemaira ($Alpha_1$-Proteinase Inhibitor) with placebo[10].
- Kamada reported on the discussion of the updated data from its European and Canadian Phase II/III clinical study of inhaled alpha-1 antitrypsin (AAT) to treat alpha-1 antitrypsin deficiency (AATD) during a panel discussion[11] entitled, "New Treatment Prospects for AATD Patients: Results from a Phase 2/3 Inhaled AAT Trial," which was held during the American Thoracic Society (ATS) 2015 International Conference in Denver in May. The slides from the presentation and a video of the panel discussion were made available on www.kamada.com. While the trial did not achieve statistical significance in one primary endpoint, there were some encouraging results[12]. David Tsur, CEO of Kamada, said: "We continue with our plans to submit a Marketing Authorization Application with the European Medicines Agency for approval of our inhaled AAT by year-end 2015 and are confident that the totality of this data set will support our efforts to bring inhaled AAT to the market place.

[8] AATD is a hereditary condition marked by a lack of the alpha-1 antitrypsin protein, whose main function is to protect the lungs from inflammation.

[9] The RAPID study=Randomized, Placebo-controlled Trial of Augmentation Therapy in Alpha-1 Proteinase Inhibitor Deficiency

[10] Prof Kenneth R Chapman, on behalf of the RAPID Trial Study Group, "Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial". Published online in *The Lancet*, 27 May 2015. DOI: http://dx.doi.org/10.1016/S0140-6736(15)60860-1

[11] chaired by Robert A. Sandhaus, Director of the Alpha1-Antitrypsin Deficiency Program at National Jewish Health Hospital in Denver, Colorado, and the Clinical Director of the Alpha-1 Foundation.

[12] Kenneth R. Chapman, Director, Canadian Registry Alpha-1 Antitrypsin Deficiency, Asthma and Airway Centre, Toronto Western Hospital, said "The lung function results seen in this study are striking and the change is quite rapid. This is the first time a controlled randomized study in AATD has demonstrated actual efficacy in lung function, the gold standard endpoint in respiratory trials." Gerry McElvaney, Professor of Medicine at the Royal College of Surgeons in Ireland (RCSI) said: "These results reinforce the known anti-inflammatory effects of AAT on neutrophil migration and elastase release, and thereby, on inflammation in the lung. This is a very important finding as it could be applicable in a number of respiratory conditions where lung inflammation exists."

Other

- At the European Haematology Association's 20th congress[13] Alnylam presented what it describe as promising early results from an ongoing Phase I/II study evaluating Its drug ALN-CC5. This is a first-in-class C5 synthesis inhibitor for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH)[14]. Phase II enrolment is expected to commence by the end of the year.
- Double-blind randomized controlled trials (DBRCTs) are the gold standard for evaluating drugs. They were designed to determine the efficacy of a treatment free from patient or doctor bias, however they take no account of the effects of patient behaviours, such as diet and lifestyle. A meta-analysis of six such trials was led by Erik Snowberg, professor of economics and political science at Caltech, and included Sylvain Chassang from Princeton and Ben Seymour from Cambridge University. It found that behaviour can have a serious impact on effectiveness[15]. The researchers suggested what they called a two-by-two trial. [16] Snowberg and his colleagues found that with this new trial design, they can identify the effects of behaviour, the effects of treatment, and the interaction of behaviour and treatment. Their trial method randomises not only treatment, but also the probability of treatment. In a two-by-two trial, patients are first randomly assigned to either a "high probability of treatment" group or a "low probability of treatment" group. The patients in the high probability group are then randomly assigned to either the treatment (70 per cent) or the control (30 per cent) group. Patients in the low probability group are also randomly assigned to treatment or control, with their likelihood of receiving the treatment being 30 per cent. The patients are then informed of their probability of treatment.
- In a trial, a lens-free microscope invention from the UCLA California Nano Systems Institute enabled a pathologist to detect cancers and other cellular abnormalities at 99 per cent accuracy[17]. The device is coupled with a smartphone.

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

- The European Medicines Agency (EMA) has released its draft *Guideline on epidemiological data on blood transmissible infection*. In the EU, companies are required to submit scientific data for blood-or plasma-derived products using the plasma master file (PMF) certification procedure[18]. The PMF is then incorporated into the companies' marketing authorization(s), and is updated annually. Companies "are

[13] in Vienna in June

[14] PNH is a debilitating disorder marked by the breakdown of red blood cells with releases of hemoglobin in the urine. It's cause is a defect in the formation of surface proteins on red blood cells. Current treatment is Alexion Pharmaceuticals' Soliris (eculizumab) which earned $US 2.2 billion in sales in 2014. It is the world's second most expensive drug.

[15] Eg One patient may by their organised nature follow dosing requirements exactly while another may be less reliable on timing or dosing. The random assignment of patients between the treated group and the control (placebo) group can also affect outcomes eg a patient who has only a fifty per cent chance of being in the treated group may do less to support a good outcome, exercise to encourage weight loss for example, than if their probability of receiving the trial drug were higher.

[16] The study was published online on June 10 in the journal PLOS ONE.

[17] Alon Greenbaum,Yibo Zhang, Alborz Feizi, Ping-Luen Chung, Wei Luo, Shivani R. Kandukuri and Aydogan Ozcan, "Wide-field computational imaging of pathology slides using lens-free on-chip microscopy", *Science Translational Medicine* 17 Dec 2014: Vol. 6, Issue 267, pp. 267ra175. DOI: 10.1126/scitranslmed.3009850 Corresponding author. E-mail: ozcan@ucla.edu

[18] *Directive 2003/63/EC*

required to include the epidemiological data on the local viral epidemiology" for the collection centres responsible for the blood/plasma in the PMF. The new guideline follows public consultation in 2014[19].

- Biogen has submitted a Marketing Authorisation Application (MAA) for Alprolix (rFIXFc)[20] to the EMA. Swedish Orphan Biovitrum AB (Sobi) has an opt-in right to assume final development and commercialisation of Alprolix in Europe, Russia, certain countries in the Middle East, and North Africa.
- The FDA accepted for review BPL's amended Biologics License Application for Coagadex for hereditary factor X deficiency. The FDA has assigned a Prescription Drug User Fee Act (PDUFA) goal date of October 27 2015. Coagadex is a high purity human factor X concentrate. It has already received FDA orphan drug designation for the treatment of hereditary factor X deficiency. The FDA is reviewing data from two Phase III trials. BPL has also submitted a Marketing Authorization Application to the EMA.
- At the end of May, Baxter submitted a Marketing Authorization Application to 17 authorities in Europe seeking approval of its 20 per cent concentration subcutaneous immune globulin treatment for patients with primary immunodeficiencies.
- Health Canada approved a new, low-volume presentation size for the existing indications of Berinert[21], a plasma-derived, pasteurized and nanofiltered C1-esterase inhibitor (C1-INH) concentrate. The new Berinert 1500 IU format is reconstituted with 3 mL vial of Sterile Water for Injection (Diluent). This vial size can be prepared and administered faster than the same dose using the existing vial size of 500 IU. This is particularly significant for patients who weigh more than 50 kilograms.
- CSL Behring announced that the EMA Committee for Medicinal Products for Human Use (CHMP) has recommended granting marketing authorisation for Respreeza[22], a highly purified alpha-1 protein derived from human plasma, indicated to treat patients with severe alpha-1 antitrypsin deficiency (AATD)[23]. Respreeza replaces the protein that these patients are missing and raises the alpha-1 antitrypsin levels in their blood, which can help to protect the lungs from damage due to inflammation. The CHMP positive opinion will be transmitted to the European Commission (EC) to start the EC decision-making process. The EC may then grant a centralised European marketing authorisation for Respreeza as a maintenance treatment to slow the progression of emphysema in adults with documented severe alpha-1 proteinase inhibitor deficiency.

[19] http://www.raps.org/Regulatory-Focus/News/2015/06/03/22606/EMA-Releases-Draft-Guideline-on-Epidemiological-Data-Requirements-for-Plasma-Derived-Products/#sthash.8nVsDdFm.dpuf

[20] Alprolix (rFIXFc) is a long-acting recombinant factor IX Fc fusion protein product candidate for people with haemophilia B. Alprolix [Coagulation Factor IX (Recombinant), Fc Fusion Protein] is approved for the treatment of haemophilia B in the US, Canada, Australia, and Japan.

[21] In Canada, Berinert is indicated for the treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema (HAE) of moderate to severe intensity. Berinert, licensed since 2010, is the first C1-INH available in Canada.

[22] The CHMP positive opinion is based upon data from CSL Behring's RAPID (randomised, placebo-controlled trial of augmentation therapy in alpha-1 proteinase inhibitor deficiency) study. According to the trial results, patients with AATD treated with alpha-1 proteinase inhibitor therapy showed a lower annual rate of lung density decline compared with placebo, when measured using chest computed tomography, at full inspiration. This demonstrated that Respreeza significantly slows the progression of emphysema in these critically ill patients.

[23] Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show evidence of progressive lung disease (e.g. lower forced expiratory volume per second (FEV1) predicted, impaired walking capacity or increased number of exacerbations).

Other

- When the FDA does not approve marketing applications by drug companies it sends them what are termed *complete response letters*. Companies do not necessarily share the contents of these in full with the public (including their own investors). Now a cross sectional study has compared the content of non-public complete response letters with the content of subsequent press releases issued by the companies concerned[24]. The study was led by Peter Lurie, associate commissioner for public health strategy and analysis with the FDA[25]. All 61 applications for which FDA's Center for Drug Evaluation and Research initially issued complete response letters between 11 August 2008 and 27 June 2013 were included. 48 per cent of complete response letters cited deficiencies in both the safety and efficacy domains, and only 13 per cent cited neither safety nor efficacy deficiencies. No press release was issued for 18 per cent of complete response letters, and 21 per cent of press releases did not match any statements from the letters. Press release statements matched 14 per cent of the 687 statements made in the letters. Of 32 complete response letters that called for a new clinical trial for safety or efficacy, 59 per cent had matching press release statements. Seven complete response letters of the 61 reported higher mortality rates in treated participants; only one associated press release mentioned this fact.
- Data from the US national babesiosis[26] surveillance program together with annually reported transfusion-transmitted babesiosis (TTB) cases show that the TTB-risk to US blood supply is rising[27]. The FDA's Blood Products Advisory Committee (BPAC) has been considering a number of questions eg if licensed tests are available should antibody testing be national[28] or only in endemic areas like the Northeastern, mid-Atlantic and upper Midwestern states? Should NAT testing be performed all year or seasonally?
- Verax Biomedical gained FDA clearance to expand the use of its rapid test that screens for bacterial contamination in blood platelets. The FDA approved the test in 2007 and 2009 to screen single-donor platelets and whole blood-derived platelets. Now the test can also be used to screen pre-storage pool and apheresis platelets.
- The FDA granted orphan drug designation[29] for Apitope's pre-clinical drug candidate ATX-F8-117 which is designed to prevent or treat inhibitors in patients with haemophilia A. It received orphan drug designation from the EMA last year.

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[24] Peter Lurie, Harinder S Chahal.,Daniel W Sigelman, Sylvie Stacy, Joshua Sclar,Barbara Ddamulira, "Comparison of content of FDA letters not approving applications for new drugs and associated public announcements from sponsors: cross sectional study" BMJ 2015; 350 doi: http://dx.doi.org/10.1136/bmj.h2758 (Published 10 June 2015) Citation BMJ 2015;350: h27581

[25] Office of Public Health Strategy and Analysis, US Food and Drug Administration, Office of the Commissioner, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA

[26] Babesiosis, transmitted by a tick-vector, is caused by infections of humans with intraerythrocytic protozoa of the genus *Babesia*. Babesiosis can also be transmitted by transfusion of blood and blood products collected from an infected donor.Babesiosis is characterized by a wide spectrum of clinical manifestations that depend on the host's age and immunological and health status. In children and young healthy adults, *Babesia microti* infection leads to asymptomatic or mild disease. However, disease may be severe and even fatal in neonates, the elderly and the immuno-compromised, including cancer patients, with fatality rates of 5-20 per cent reported.

[27] The FDA is reported to consider Babesia microti as the highest-ranking transfusion-transmitted pathogen for which no donor screening carried out.

[28] Instituting NAT testing in the top five highly endemic states (Connecticut, Massachusetts, Rhode Island, New York and New Jersey) year-round in addition to antibody testing in all states plus DC is estimated to reduce TTB risk by 95%, in the best case scenario, when compared to the current no testing scenario.

[29] Such orphan drug designation is for novel drugs and biologics directed towards the safe and effective treatment, diagnosis or prevention of disorders or diseases that affect fewer than 200,000 people in the US. Amongst other benefits the designation provides market exclusivity for a time.

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.

- Baxter International announced on 5 June that its board of directors had approved the planned separation of its biopharmaceuticals operations. Baxalta was to begin trading as an independent company beginning 1 July, 2015 on the New York Stock Exchange (NYSE) under the ticker symbol BXLT. Following the separation, Baxalta will provide treatments for people with rare conditions, chronic diseases or limited treatment options. Baxalta's broad pipeline is built on innovation in bleeding disorders and immunology, and is expanding to address areas of oncology, as well as technology platforms such as gene therapy.
- BPL Plasma opened its newest collection centre in Phoenix, Arizona.
- ProMetic Life Sciences of Quebec is purchasing Emergent BioSolutions' plasma collection centre in Winnipeg. The centre is an FDA and Health Canada licensed facility. The centre is close to the existing Emergent Winnipeg based cGMP manufacturing facility, which was recently announced as providing ProMetic with up to 250,000 litres of annual plasma processing capacity.
- A new business intelligence report[30] says the global albumin excipient market was valued at $US 704.9 million in 2013 and is expected to grow at a compound annual growth rate of 2.3 per cent from 2014 to 2020, reaching an estimated value of $US 828.2 million by 2020. North America dominates the market because of demand for albumin in drug formulations, and research and development activities. The albumin market in the region was valued at $US 253.8 million in 2013. Research focus is on using albumin as a carrier for micro-and nanoparticles for sustained-release injectable drugs. The US FDA approved paclitaxel nano-particulate formulation containing albumin as a carrier in September 2013.
- A market research report on blood plasma[31] says while North America dominates the global market, Asia and Europe will experience high growth rates in the next five years. China is expected to be the fastest growing.
- A market report was also released recently on the current state of the blood transfusion industry globally[32].
- Pfizer received a request for additional information from the US Federal Trade Commission (FTC) with respect to its previously announced proposal to acquire Hospira. The request for information from the FTC, known as a "second request," was anticipated as part of the regulatory process under the Hart-Scott-Rodino Antitrust Improvements Act of 1976 (HSR Act).
- Kedrion announced that in 2014, one third of its revenues came from the US, which has become the company's largest market. A state-of-the-art production line for the manufacturing of anti-D immunoglobulin was recently completed at Kedrion's facility in Melville, New York.
- In the US, The National Hemophilia Foundation (NHF) has awarded CSL Behring its 2015 Corporate Leadership Award in recognition of "the company's longstanding and unwavering commitment to advancing science and improving the care of the bleeding disorders community".

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[30] Published by Transparency Market Research and titled *Albumin (Excipient) Market – Global Industry Analysis, Size, Share, Volume, Growth, Trends and Forecast, 2014 – 2020* http://www.transparencymarketresearch.com/albumin-market.html

[31] http://www.persistencemarketresearch.com/market-research/blood-plasma-market.asp

[32] *The Global Blood Transfusion Industry Report 2015* http://www.orbisresearch.com/contacts/request-sample/14536

- Green Cross Biotherapeutics began construction on its biopharmaceutical facility on the Montréal Technoparc's Saint-Laurent Campus. The $C315 million project includes the only intravenous immunoglobulin (IVIg) and albumin manufacturing plant in Canada. This project was realized through the Canada-Korea Free Trade Agreement. Established in 2014, GCBT is a Canada-based member of the Green Cross family and will also be serving as Green Cross' North American headquarters.

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.

- The New Zealand Blood Service announced that it is not able to collect enough plasma for its immunoglobulin needs. It will be importing immunoglobulin made from foreign source plasma. Dr Peter Flanagan, medical director for NZBS, said "Those products will be manufactured from plasma that has been collected from paid donors. Nonetheless, the systems used for their manufacture assure safety and I'm sure that they will be entirely suitable for use in the New Zealand context."
- On 14 June, World Blood Donor Day, the New Zealand Blood Service issued a plea for more Maori and Pacific Islanders to register as blood donors[33].
- In Bahrain, over 220 sickle cell patients have died over the last six years from complications. In January, US experts (from the Johns Hopkins Medicine International Sickle Cell Centre for Adults) visited Bahrain's Hereditary Blood Disorder Centre, and submitted a number of recommendations. Health Minister Sadiq Al Shehabi announced at the opening of a sickle cell workshop in June that hydroxyurea, which breaks down cells prone to sickle, will be available at all government-run health centres. It was previously available only at the country's main hospital, Salmaniya Medical Complex (SMC).
- Authorities in Ireland expected tests to show that a 5 year old cow on a dairy farm in county Louth died of mad cow disease. If confirmed, it would be the first mad cow disease case nationally in two years. National and international reference organisations and the European Commission have been alerted. Confirmation could affect Ireland's "negligible risk status" from the World Organisation for Animal Health (OIE) and Ireland would revert to "controlled risk status" and have to practise a range of controls for some years.
- In the US, the Department of Health and Human Services (HHS) has selected nine health departments together with partner hospitals[34] to become special regional

[33] Few Maori are registered as donors, which makes it difficult to match donors for people needing bone marrow transplants. It was explained to those who might contemplate answering the call that bone marrow transplants no longer involved drilling into the hip bones, but people were medicated for three days to bring cells from the middle of the bones into the bloodstream from which the donation was taken.

[34] Massachusetts Department of Public Health in partnership with Massachusetts General Hospital in Boston, Massachusetts; New York City Department of Health and Mental Hygiene in partnership with New York City Health and Hospitals Corporation/HHC Bellevue Hospital Center in New York City; Maryland Department of Health and Mental Hygiene in partnership with Johns Hopkins Hospital in Baltimore, Maryland; Georgia Department of Public Health in partnership with Emory University Hospital and Children's Healthcare of Atlanta/Egleston Children's Hospital in Atlanta, Georgia; Minnesota Department of Health in partnership with the University of Minnesota Medical Center in Minneapolis, Minnesota; Texas Department of State Health Services in partnership with the University of Texas Medical Branch at Galveston in Galveston, Texas; Nebraska Department of Health and Human Services in partnership with Nebraska Medicine-Nebraska Medical Center in Omaha, Nebraska; Colorado Department of Public Health and Environment in partnership with Denver Health

treatment centres for severe, highly infectious diseases, including Ebola. The Office of the Assistant Secretary for Preparedness and Response (ASPR) has awarded $US 20 million through its Hospital Preparedness Program to upgrade the regional treatment centres' capabilities to manage patients with Ebola or other highly infectious diseases[35]. ASPR will provide an additional $US 9 million to these recipients in the next four years to sustain their readiness. This funding comes from the $US 339.5 million Congress appropriated to enhance state and local public health and health care system preparedness following cases of Ebola in the US arriving from the 2014 Ebola epidemic in West Africa. In addition to the nine regional facilities, there are another 46 Ebola treatment centres and their associated health departments which may be expected to handle one or more simultaneous clusters of patients. HHS is still working with Arizona, California, Hawaii, Nevada and the Pacific island territories and freely associated states, to identify a regional treatment centre.

- In the US, the Agency for Healthcare Research and Quality (AHRQ) found that while the top medical conditions for overall spending have generally remained static for a decade, the amount being spent on these ailments has risen substantially. The AHRQ adjusted spending numbers to constant 2012 dollars. Cardiac condition spending rose from $US 83.5 billion in 2002 to $US 101 billion in 2012. Spending on trauma-related injuries rose from $US 68.9 billion to $US 93.1 billion. Cancer had the highest percentage increase, from $US 59.8 billion to $US 87.5 billion, a 48 per cent increase. Asthma rose from $US 55.9 billion to $US 75.9 billion. Spending on mental health disorders went up from $US 58.6 billion to $US 83.6 billion. Diabetes spending, particularly for children, also rose. Per capita expenses were fairly steady for cancer, mental disorders and cardiac conditions, but they rose significantly for traumas, from $US 1,933 to $US 2,609. Per capita asthma expenses rose, from $US 1,113 to $US 1,681.
- Cerus Corporation and the SunCoast Blood Bank of south-west Florida announced that the first pathogen reduced platelet units had been produced in the continental US, following Cerus' FDA approvals received for the INTERCEPT Blood System for platelets and plasma in December 2014.
- In China, 12.99 million people voluntarily donated blood in 2014, a 40-fold increase on 1998 when China enacted a Blood Donation Law, but difficulties in ensuring a safe blood supply persist. A *China Daily* report in January cited an HIV/AIDS specialist as saying that each year about ten people in China are infected with HIV/AIDS via infected blood "due to limited screening technology."
- In Cambodia, a trial of a novel method of reducing anaemia appears positive. Lumps of iron in the shape of a smiling fish[36] are boiled in water or soup, releasing iron, and when lemon juice is added this aids absorption.
- In 2011, Germany began requiring drug companies to demonstrate whether a new drug provided clinical benefits over existing drugs. Four years on, this has lowered the government's drug bill and resulted in lower prices in Germany than elsewhere in the EU.

Medical Center in Denver, Colorado; Washington State Department of Health in partnership with Providence Sacred Heart Medical Center and Children's Hospital in Spokane, Washington.

[35] Regional Ebola treatment centres will be required to accept patients within eight hours of being notified; have the capacity to treat at least two Ebola patients at the same time; have respiratory infectious disease isolation capacity or negative pressure rooms for at least 10 patients; be able to treat paediatric patients with Ebola or other infectious diseases or partner with a neighbouring facility to do so; be able to handle safely highly contaminated infectious waste; conduct quarterly trainings and exercises; and receive an annual readiness assessment from the yet-to-be-established National Ebola Training and Education Center, composed of experts from health care facilities that have safely and successfully cared for patients with Ebola in the US, and funded by ASPR and the Centers for Disease Control and Prevention, to ensure clinical staff are adequately prepared and trained to safely treat patients with Ebola and other infectious diseases.

[36] A symbol of good luck in the national culture

- In Sweden, blood donors are sent automatic text messages telling them when their blood has actually been used. This is in addition to the 'thank you' text they receive when they give blood.
- Canadian Blood Services is planning to make it easier for older donors to give blood, saying it will drop a requirement that all first-time donors 61 years of age and older submit a doctor's letter confirming they are fit to donate. It will also drop the same requirement for repeat donors between the ages of 67 and 71 who have not donated in the past two years, and for repeat donors 71 and over who are currently required to get an annual physician assessment. There are about 420,000 blood donors in Canada at any given time, but about 170,000 donors drop out every year, either because they have to or they choose to stop. Older donors tend to give more blood. A third of all donors are over 50, but that group produces about 45 per cent of donations, said Dr. Mindy Goldman, medical director, donor and clinical services.
- Canadian Blood Services has eliminated 16 mobile clinics, nine of them in Saskatchewan, as a cost-cutting measure.
- In the Solomon Islands, the blood bank at the National Referral Hospital is continuously running low on blood, according to the hospital's Medical Lab Manager, Donald Tahani. He said one of the main hindrances to a blood donation programme in a Melanesian society is the culture of blood line. "Most people will only donate blood if the patient who is in need of blood is a family relative".
- Amref Health Africa, the Ministry of Health of the Republic of South Sudan (RSS) and partners will manage a five-year $US 6 million Centers for Disease Control and Prevention (CDC) grant to build the capacity of national laboratory and blood transfusion services.
- The Dubai Health Authority (DHA) has issued guidelines for Platelet Rich Plasma (PRP) therapy[37]. This treatment, which is claimed to accelerate regeneration and healing using one's own blood, has gained popularity. The guidelines specify professional experience and training requirements required of health care professionals offering the therapy, and aim to ensure safe procedures and patient education.

5. Safety and patient blood management

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

Appropriate transfusion

- The American Academy of Orthopaedic Surgeons Annual Meeting was told that, among patients who underwent either total knee or total hip replacement, intraoperative use of tranexamic acid significantly reduced the need for blood transfusion[38]. Joseph Styron (of the Cleveland Clinic) and colleagues examined retrospectively data from 883 patients who underwent total hip arthroplasty (THA) or total knee arthroplasty (TKA). 553 patients underwent surgery after a comprehensive preoperative blood management protocol was introduced, and also intraoperative treatment with TXA, while 330 were not treated with TXA intraoperatively.

[37] PRP therapy involves injecting a person's own platelet-rich plasma into a targeted area.Platelets contain growth factors, which are claimed to stimulate tissue recovery by increasing collagen production, enhancing stem cell proliferation, stimulating blood flow and causing the cartilage to become more resilient.

[38] Styron JF, et al. Paper #591. American Academy of Orthopaedic Surgeons Annual Meeting; March 24-28, 2015; Las Vegas.

- Researchers found that high doses of tranexamic acid helped to control blood loss and reduce the need for transfusion in patients having corrective spine surgery, especially those undergoing posterior vertebral column resection[39].

Treating iron deficiency

- A study by Canadian Blood Services has found that women who donate blood more than two or three times a year are twice as likely as those who don't donate to be iron deficient (one-in-three women have low ferritin levels, but frequent donors have a two-in-three chance of low ferritin). In the general population men do not often present with iron deficiencies but if they donate blood more than three times a year they have a one-in-three chance of suffering low ferritin levels. Dr Mindy Goldman, author of the report and medical director for donor and clinical services said CBS has begun randomly sampling ferritin levels of 12,000 to 15,000 donors across Canada after a pilot study of 550 donors in Ottawa showed high iron deficiency rates among frequent donors, said Goldman. Donors with low ferritin levels are sent a letter recommending they see their doctor and consider iron supplements, and then receive a follow-up call. Dr Goldman said the information from the current (larger) survey will be used to see if better education is needed on iron for donors and their GPs, and to consider whether the maximum number of donations annually should be changed[40]. She admitted room to move on this was limited. "We cannot make a big change in criteria without being aware of the effect it would have on the blood supply," she said.

Other.

h) Researchers from the University of Antwerp reported[41] that intensive care patients have very high levels of phthalates (particularly DEHP) and bisphenol A (BPA) in their blood and urine, because of their exposure to plastic medical devices. Patients on kidney replacement therapy, or lung and heart support, showed serum levels that were 100-or 1,000-times higher than in the general population. The researchers concluded that more research into the health effects of DEHP and BPA is needed[42].

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) British scientists have found red blood cells and collagen fibres in dinosaur bones from the Cretaceous period, 75 million years ago. The fossils were poorly conserved, said study co-author Sergio Bertazzo from Imperial College London, but the find boosted expectations of prising organic remains from a much wider range of fossils.

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[39] Jingming Xie, Lawrence G. Lenke, Tao Li, Yongyu Si, Zhi Zhao, Yingsong Wang, Ying Zhang, Jie Xiao, "Preliminary investigation of high-dose tranexamic acid for controlling intraoperative blood loss in patients undergoing spine correction surgery", *The Spine Journal,* April 1 2015, Volume 15, Issue 4, Pages 647–654. DOI: http://dx.doi.org/10.1016/j.spinee.2014.11.023

[40] An Italian study in 2013 listed Canada and the US as the only two countries that allow donations up to six times a year, once every 56 days, for women. Six other countries allow men to donate up to six times yearly but women are limited to two-to-four times a year.

[41] in the science journal *Environment International*

[42] US research has found that premature babies had serum BPA levels 16-32 times those in the general infant population. Another US study found that DEHP exposure in neonates in intensive care was thousands of times higher than levels necessary to avoid reproductive and hepatic toxicity.

b) The Drugs for Neglected Diseases initiative (DNDi) and four pharmaceutical firms, Eisai, Shionogi, Takeda and AstraZeneca have announced plan to accelerate and cut the cost of early stage drug discovery for leishmaniasis and Chagas disease. The 'Neglected Tropical Diseases Drug Discovery Booster' consortium will circumvent early stage commercial barriers between the four pharmaceutical participants, allowing DNDi to search millions of unique compounds simultaneously.

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.

- The US International Trade Commission is investigating claims that Danish company Novo Nordisk plans to import into the US haemophilia drugs that infringe patents held by Baxter International. The ITC statement said that it has voted to launch an investigation of certain recombinant factor VIII products.
- In Brisbane, the Supreme Court has ruled that a young boy requiring a liver transplant may be given a blood transfusion despite parental objection on religious grounds.

8. Infectious diseases

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

Mosquito-borne diseases: dengue, chikungunya and malaria

- In Singapore the Agency for Science, Technology and Research (A*STAR) is collaborating with biotechnology company Visterra to further development of an antibody to treat dengue fever. VIS513 is designed to neutralise all four serotypes of the dengue virus. It demonstrated in pre-clinical (animal) studies a rapid reduction in the concentration of virus. A*STAR's Drug Discovery and Development unit (D3) and Visterra will also work with infectious disease experts at Duke-National University of Singapore to generate additional data necessary to initiate clinical trials. D3 and Visterra will then conduct clinical trials in humans in Singapore.
- Researchers in Australia and Scotland have found that a highly resistant malaria parasite hijacks resources in immature red blood cells to defend itself against the impact of anti-malarial drugs[43] .

Influenza: strains, spread, prevention and treatment

- Between 15 December last year and 29 May this year the US Department of Agriculture (USDA) confirmed more than 200 findings of birds infected with highly-pathogenic avian influenza (HPAI) A (H5N2), (H5N8), and (H5N1) viruses. Most were in backyard and commercial poultry. Over 40 million birds had been either infected or exposed across 20 states. The US Centers for Disease Control and Prevention (CDC)

[43] Published 5 June in *PLoS Pathogens*. Co-author Malcolm McConville, Professor of biochemistry at The University of Melbourne.

on 4 June issued an alert on the potential for human infection and to describe the agency's recommendations for patient investigation and testing, infection control including the use of personal protective equipment, and antiviral treatment and prophylaxis. By then 29 million birds had been euthanized in Iowa alone. The US was experiencing an egg shortage and rationing, and was importing from Europe. Egg prices were rising.

- Human cases of H7N9 avian flu continue to be reported from China.
- In Australia, the first five months of 2015 were the worst on record for influenza cases, with 8914 laboratory-confirmed cases.
- Researchers at Kansas State University say they have developed vaccines for two strains of avian flu, H5N1 and H7N9[44].
- Harris vaccines of Iowa is testing a vaccine for avian flu on turkeys, with the Agriculture Department at its National Veterinary Services Laboratories in Ames. A second test is being undertaken on chickens and ducks at the government's Southeast Poultry Research Laboratory in Georgia.

MERS-CoV

g) By 7th June South Korea had announced 64 MERS cases and five deaths. There was some political squabbling about how the outbreak had been handled and had taken off quite as rapidly as it had. One particular hospital was receiving most of the blame. WHO had despatched a team to Seoul after the fourth death.

h) By 14 June, 230 organizations and more than 25,000 people had called off blood donations scheduled for between June 3 and July 15, apparently scared by MERS. The Korean Red Cross also cancelled its blood drive scheduled for 12 and 13 June in central Seoul, over MERS. The blood drive was to mark World Blood Donor Day on 14 June.

i) The World Health Organisation (WHO) in a visit at that time noted that the MERS virus hadn't spread outside hospitals or become easier to transmit between humans. It was spreading in hospital patients, visiting family members and medical staff. WHO Assistant Director Keiji Fukuda said overcrowded emergency rooms and hospital wards might have contributed to a wider-than-expected transmission of the virus. He said South Korea's habit of "doctor shopping"-visiting multiple facilities to treat the same infection-and having many friends and family members visiting hospital patients might also have contributed. Fukuda called on the South Korean government to continue with strong control measures, including tracing patients' contacts and preventing suspected cases from travelling. About 2,900 schools and kindergartens had been temporarily closed, but WHO advised they could be re-opened. More than 4,000 people had been isolated after possible contact with those infected. Cellphones were being used to track people under quarantine. Two hospitals had been temporarily closed after MERS patients were found to have been in contact with hundreds of people before diagnosis.

j) By 24 June, South Korea announced it would draw up a supplementary budget of around $US 9 billion[45] to cope with the cost of dealing with the MERS outbreak and the consequent economic slump. At that time, the total number of MERS cases had reached 179, with 27 deaths. Only 5 cases had been infected by unknown transmission routes outside hospitals. Samsung Hospital, where 90 people had contracted the virus, had suspended services on 14 June for ten days, but then the shutdown was extended "indefinitely". Heir apparent to the Samsung group, Jay Y. Lee had publicly apologised on 23 June for "causing great pain and concern". Konkuk University Medical Center stopped admitting new patients on 24 June after four cases were reported.

[45] By the end of June this was reported to be worth $US 13.5 billion

k) On 28 June South Korea reported its 32nd death from MERS as the virus's mortality rate continued to rise even as the pace of the outbreak appeared to slow. The mortality rate by then was 17.5 percent[46]. The total number of infections remained unchanged at 182 and fifteen patients were in critical condition, the health ministry said. Of the first 24 fatal cases none were healthcare workers, nineteen were aged 60 or more and 17 were male. A total of 2,562 people were under quarantine either at state facilities or at home. South Korea had by then passed a law authorising prison terms of up to two years for people who defy quarantine orders or lie about their potential exposure to an infectious disease.

l) Researchers in Hong Kong found that South Korea's MERS outbreak was fanned by three human "superspreaders" and followed a pattern of transmission similar to the SARS epidemic more than a decade ago. At least three-quarters of the cases can be attributed to clusters in hospitals started by three highly infectious people. The index patient spread the virus to 27 people in one hospital alone. The superspreader identified as case No. 14 contracted the disease from the index case and passed the virus to at least 70 others in the emergency room of one of Seoul's five largest hospitals. Case No. 16 spread it to 24 others.

m) Superspreaders all presented with symptoms of pneumonia when they first visited hospitals though their MERS diagnosis was delayed, Jacob Lee, a professor of infectious disease at Hallym University Kangnam Sacred Heart Hospital, told a government briefing. He identified five patients as superspreaders and said it took an average of 8.2 days from the day they started showing symptoms until they were confirmed to be carrying MERS, whereas the average for 93 patients was 4.6 days.

n) At 7 June China had one MERS case, a man who had travelled there from Korea having broken his quarantine. His virus had been completely genome-sequenced, and pronounced not to have mutated from the virus causing infections in assault Arabia.

o) Inovio Pharmaceuticals will move its DNA vaccine for MERS into a Phase I clinical trial in healthy volunteers in collaboration with GeneOne Life Science Inc. In preclinical tests, INO-4500 demonstrated robust and durable immune responses. Third party support and resources would be needed for further development and commercialisation.

Ebola

p) As of 7 June, WHO's total case count for the current Ebola outbreak was 27,237, with the number of deaths 11,158. 68 of these had occurred in the previous 21 days (38 in Guinea and 30 in Sierra Leone). In mid-June, Sierra Leone introduced new curfews for two northern districts after a spike in cases in June.

q) The Obama administration has a $US1.8 million contract with a Pennsylvania company to develop a quick-and-easy test for Ebola that could deliver results in a field setting or doctor's office within twenty minutes. The Health and Human Services Department said diagnosis might require only a drop of the patient's blood or saliva on a test strip.

r) A nurse who contracted Ebola in Sierra Leone and recovered in Rome was given a product from China, MIL77, which had also been given to a British Army nurse who recovered from Ebola at a London hospital in March. It is similar to a cocktail of antibodies known as ZMapp, the result of a collaboration between the US and Canada. This was considered promising early in the Ebola outbreak[47], but the few doses available were rapidly used up. A small private Chinese company, Beijing

[46] World Health Organization figures have put the mortality rate for the disease at around 36 per cent.
[47] It had already been shown to save monkeys injected with what would otherwise have been a lethal dose of the virus.

Mabworks, then produced about 100 doses of MIL77[48]. Now US officials have patent infringement concerns[49] and there are also disagreements over when experimental Ebola therapies should be offered to patients only in carefully controlled studies and when they should be made more available for compassionate reasons. Feng Li, chief executive of Beijing Mabworks, said his company had made a licensing agreement with the holder of intellectual property rights to ZMapp. ZMapp is being tested in a clinical trial in the US and Sierra Leone. Doctors Without Borders and some other aid groups have baulked at participating in the ZMapp trial because it is randomized and patients have only a 50 per cent chance of receiving the treatment. At Royal Free Hospital in London where MIL77 has been used for a number of patients, the decision was made not to participate in the American-run clinical trial of ZMapp because of the randomizing requirement. It instead keeps a supply of MIL77.

Other diseases: occurrence, prevention and treatment

n) Spain has had its first known case of diphtheria for 28 years, in an unvaccinated six year old boy.

o) Scientists from The University of Texas Medical Branch (UTMB) at Galveston have successfully tested in animal models a vaccine to address Chagas disease[50], widespread in Latin America and spreading elsewhere through travel and migration. The US is particularly prone to it in the southern states. It is caused by a parasite, *T.cruzi.*

[48] The scarcity of ZMapp was “a spark, like lightning to me,” said Boyan Zhang, chief scientific officer at Beijing Mabworks. With Chinese government grants, the company had already developed mammalian cells capable of quickly producing antibodies targeted against cancer and viral diseases in humans, and the same process was considered appropriate for developing an Ebola treatment. Within three months, using information in ZMapp’s patent, Dr. Li and his colleagues had copied the active part of ZMapp and produced the antibodies using the company’s specialized cells. In another month, with the help of the pharmaceutical company Hisun, they had 100 doses.

[49] The US government holds a patent on one of the antibodies in ZMapp, which was developed with support from American and Canadian military research agencies because of Ebola’s potential as a biological weapon.

[50] See *PLoS Pathogens*