Monitoring International Trends

posted January-February 2016

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:

- CSL Behring has sought European marketing approval for its investigational recombinant factor VIII single-chain (rVIII-SingleChain) for the treatment of haemophilia A (Section 1).
- Dimension Therapeutics announced the initiation of a phase I/II study of DTX101, for the treatment of patients with haemophilia B (Section 1).
- Health Canada approved Bayer's Kovaltry Antihaemophilic Factor (Recombinant) for use in adults and children with haemophilia A (Section 2).
- Novo Nordisk submitted its long-acting factor IX product nonacog beta pegol for approval in Europe, with a US filing to follow in the next few months (Section 2).
- The European Commission granted marketing approval to Biotest for the early use of its hepatitis B immunoglobulin Zutectra after liver transplantation (Section 2).
- Cerus Corporation announced that LifeShare Blood Centers had signed a purchase agreement for the INTERCEPT Blood System, its pathogen reduction technology, for platelets and plasma. Cerus also announced a partnership with the American Red Cross (Section 3).
- Janssen Research & Development have agreed to collaborate with researchers at the University of California at San Diego have agreed to identify medications to combat Chagas disease (Section 3).
- CSL reported a 3.8 per cent increase in interim profit to $US 718.8 million (Section 3).
- UK patients with haemophilia A can now access Sobi and Biogen's Elocta, the first haemophilia A treatment approved in Europe that offers prolonged protection against bleeding episodes through prophylactic injections every three to five days (Section 4).
- Until recently, gene therapy was laborious, crude and unsafe for human testing. Now new technology, called CRISPR-Cas9, acts as a microscopic scalpel, performing genomic surgery with a precision, efficiency and affordability (Section 5).
- The European Court of Human Rights in Strasbourg ruled in January that Italy must provide compensation to more than 350 people who contracted viruses, including HIV and hepatitis C, from contaminated blood products (Section 6).
- The mosquito-borne Zika virus was declared by the World Health Organisation (WHO) to be a public health emergency, following reports from Brazil that it may be associated with a specific birth defect, microcephaly (Section 7). Responses have included:
    1. Establishing studies to confirm the alleged link
    2. Travel alerts
    3. Advice to delay pregnancy
    4. Protection for national blood supplies, once transmission-transfusion was confirmed
    5. Advice on safe sex, once sexual transmission was confirmed

6. A rush to develop vaccines and diagnostic tests
7. Enhanced mosquito control

- China continues to notify human cases of A(H7N9) influenza (Section 7).
- In the northern hemisphere, a predominance of influenza A(H1N1)pdm09 viruses has characterized the 2015-2016 influenza season in most countries Section 7).
- A draft report from the US National Science Advisory Board for Biosecurity was discussed as part of the process to re-evaluate federal funding of "gain of function" studies in the light of controversial studies with A(H5N1) viruses (Section 7).
- Scientists at the Walter Reed Army Institute of Research began testing the safety and immune response in people of a vaccine candidate to prevent MERS (Section 7).
- Testing of vaccines and treatments for Ebola continued (Section 7).

Table of Contents

1. Product news

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

a) Octapharma USA announced the commercial availability of Nuwiq an antihaemophilic factor (recombinant indicated for the treatment and control of bleeding, perioperative (surgical) management, and routine prophylaxis in adults and

children with haemophilia A. The company said Nuwiq is the first and only fourth generation recombinant FVIII produced in a human cell line without any chemical modification or protein fusion. Octapharma is conducting clinical studies of the dosing process (GENA-21 and GENA-21b) to improve protection against bleeding episodes and reduce the frequency of dosing with personalized prophylaxis. In the GENA-21 study, adult patients began on infusions every other day or three times per week. Subsequent dosing intervals were then determined based on individual pharmacokinetic data, which resulted in a median dosing interval of 3.5 days and with 58 per cent of patients on a twice a week or fewer infusion schedule.

b) Dimension Therapeutics announced the initiation of a phase I/II study of DTX101[1], for the treatment of patients with haemophilia B. DTX101 is designed to deliver stable expression of blood clotting factor IX . Dimension also received a positive opinion from the European Commission, acting on the positive recommendation from the European Medicines Agency Committee for Orphan Medicinal Products, designating DTX101 (adeno-associated viral vector serotype rh10 containing the gene for human factor IX) as an orphan medicinal product[2] for the treatment of haemophilia B. Dimension already had orphan drug designation and fast track status from the US Food and Drug Administration (FDA) for DTX101 in haemophilia B.

c) Dutch human gene therapy specialist uniQure NV announced data in early January indicating its experimental treatment for haemophilia B increased blood clotting ability in two patients. The company said the therapy, AMT-060, was designed to fix a genetic flaw caused by missing or defective factor IX. The two adult patients received a low dose of the treatment. Factor IX rose to 5.5 per cent and 4.5 per cent of the normal level from less than 2 per cent in the patients. Three other people who received a low dose of the therapy in the trial hadn't yet reached the full 12 weeks of follow-up at the time of the announcement. The company said that four of the five patients, including the first two patients, had achieved the secondary endpoint of full discontinuation of prophylactic recombinant Factor IX therapy. uniQure said that it would shortly present a more comprehensive analysis of data from this low-dose cohort and initiate patient enrolment in a high-dose cohort, subject to approval by its data monitoring committee.

d) CSL Behring has sought European marketing approval for its investigational recombinant factor VIII single-chain (rVIII-SingleChain) for the treatment of haemophilia A[3]. In the pivotal clinical trial, rVIII-SingleChain met all primary endpoints. The Marketing Authorisation Application was based on the AFFINITY clinical development programme, which includes a phase I/III open-label, multi-centre trial examining safety and efficacy. The pharmacokinetics of rVIII-SingleChain compared with recombinant human antihaemophilic factor VIII (octocog alfa) was also studied[4]. CSL says that, specifically designed for greater molecular stability,

---

[1] Dimension's phase 1/2 clinical trial of DTX101 is a single arm, open-label, multi-centre study, designed to evaluate the safety, dose and early efficacy of DTX101 in adult patients with moderate/severe to severe haemophilia B. Information about the study may be found at www.ClinicalTrials.gov, using Identifier NCT: NCT02618915.

[2] Orphan drug designation by the European Commission provides regulatory and financial incentives for companies to develop and market therapies that treat a life-threatening or chronically debilitating condition affecting no more than five in 10,000 persons in the European Union (EU), and where no satisfactory treatment is available. In addition to a 10-year period of marketing exclusivity in the EU after product approval, orphan drug designation provides incentives for companies seeking protocol assistance from the EMA during the product development phase, and direct access to the centralized authorization procedure.

[3] In July 2015, the US Food and Drug Administration (FDA)accepted for review CSL Behring's Biologics License Application for rVIII-SingleChain.

[4] Results from the phase I/III study presented in 2015 at the International Society on Thrombosis and Haemostasis (ISTH) congress in Toronto showed that patients treated prophylactically had a median

rVIII-SingleChain is the first and only recombinant single-chain factor VIII (FVIII) product in late-stage development for the treatment of haemophilia A. rVIII-SingleChain has a strong affinity for von Willebrand factor, leading to greater stability and integrity of factor VIII in circulation. The stability of rVIII-SingleChain leads to a longer-lasting therapeutic effect with reduced dosing frequency

Other products

e) Scinovia of North Carolina is developing a new imaging system to help surgeons monitor patients' blood flow during operations. It will test a mobile prototype in animal surgeries at the North Carolina State University School of Veterinary Medicine in March and then hopes to have ten surgeons on its medical advisory board test it in clinics and hospitals in the US. The system is a non-invasive, mobile device allowing surgeons to visualize blood-flow speeds in real time, verify their work, and correct if necessary. Scinovia will initially target cardiac bypass surgeries.

f) Kamada announced further 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). The trial is being conducted in collaboration with Baxalta and the Fred Hutchinson Cancer Research Center in Seattle.

g) Protalex announced dosing of the first patient in its European phase Ib study of PRTX-100 in adults with persistent/chronic immune thrombocytopenia (ITP) (the PRTX-100-203 Study). PRTX-100 is a highly purified form of staphylococcal protein A (SpA), which was granted Orphan Drug Designation in Europe and the US for the treatment of ITP. A similar Phase I/II clinical study of PRTX-100 is underway in the US. (the PRTX-100-202 Study).

2. Regulatory

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

a) The European Commission granted marketing approval to Biotest for the early use of its hepatitis B immunoglobulin Zutectra after liver transplantation. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) had adopted a positive opinion[5] for the modification of the indication in November 2015. Previously Zutectra could be administered 6 months after liver transplantation. Now, the subcutaneous hepatitis B immunoglobulin can be applied one week after liver transplantation.

---

annualized bleeding rate (ABR) of 1.14 and a median annualized spontaneous bleeding rate (AsBR) of 0.00. The data also showed that, of 848 bleeds treated in the study, 94 per cent were controlled with no more than two infusions of rVIII-SingleChain, with 81 per cent controlled by one infusion. Moreover, haemostatic control of a bleeding event treated with rVIII-SingleChain was assessed by the investigator as excellent or good 94 per cent of the time (835 assessed bleeding events).The results presented at ISTH included data on more than 14,000 exposure days in 146 patients on prophylaxis and 27 patients treated on demand for a bleeding event. In total, 120 patients were treated for more than 50 days of exposure; 52 had more than 100 days of exposure. In the prophylaxis group, 32 per cent of patients were dosed twice weekly and 54 per cent received treatment three times per week; the regimen was determined by the investigator. The most common adverse events were naso-pharyngitis, arthralgia, and headache. No inhibitors were reported.

[5] The positive assessment is based on the clinical results of the Zutectra-Early-Use-Study (ZEUS) demonstrating the effective use of Zutectra in the early phase after liver transplantation. It was found to contribute significantly to safe, more time efficient, less costly patient care and better convenience for the patient, who can be trained for self-medication during hospitalisation.

b) Novo Nordisk submitted its long-acting factor IX product nonacog beta pegol for approval in Europe[6], with a US filing to follow in the next few months. Nonacog beta pegol will compete on the market with Biogen's long-acting Factor IX product Alprolix (eftrenonacog alfa), which was approved by the FDA in 2014 and filed in Europe by Biogen and Sobi last June. Another long-acting factor IX candidate- CSL Behring's CSL654-has been filed in the US, Europe and Japan[7].
c) Health Canada approved Kovaltry Antihaemophilic Factor (Recombinant) for use in adults and children with haemophilia A for routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes, control and prevention of episodic bleeding, and peri-operative management (surgical prophylaxis). Canada is the first country to give regulatory approval of Kovaltry, which is Bayer's third generation recombinant FVIII product. Kovaltry contains the same amino acid sequence as Kogenate FS[8].
d) Pluristem Therapeutics announced that the FDA had cleared the company's Investigational New Drug (IND) application to begin its Phase I trial of PLX-R18 cells to treat incomplete hematopoietic recovery following Hematopoietic Cell Transplantation (HCT). The clinical trial is expected to begin in the first half of 2016.
e) The US Food and Drug Administration (FDA) cleared Fate Therapeutics' investigational new drug (IND) application for ProTmune, a programmed cellular immunotherapy consisting of donor-sourced mobilized peripheral blood cells which have been functionally modulated using two small molecules. With the IND active, Fate Therapeutics plans to initiate in 2016 a multi-centre, randomized, controlled Phase I/II clinical trial in adult patients with haematologic malignancies undergoing mobilized peripheral blood (mPB) hematopoietic cell transplantation (HCT)[9].
f) BD (Becton, Dickinson and Company) announced US Food and Drug Administration (FDA) 510(k) clearance and European CE marking for a new safety blood collection set (the BD Vacutainer UltraTouch Push Button Blood Collection Set) that uses

---

[6] The filing is based on the results from the PARADIGM clinical trial programme, which involved 115 patients with severe or moderately-severe haemophilia B. Novo Nordisk's drug was shown to be effective in preventing bleeding episodes, as well as on-demand treatment of bleeding episodes. Once-weekly administration of nonacog beta pegol maintained Factor IX activity levels above 15 per cent and reduced the median annualised bleeding rate (ABR) to 1.0, with data suggesting it could prevent bleeds in target joints. Patients also reported an improvement in quality of life during the trial, said Novo Nordisk.

[7] Alprolix extends the half-life of the clotting factor by linking it to an antibody fragment, while CSL654 does so by joining it to albumin protein.

[8] The extensive LEOPOLD program (Long-Term Efficacy Open-Label Program in Severe Hemophilia A Disease) evaluated safety, efficacy and pharmacokinetics of Kovaltry in three open-label, multicentre clinical trials. A total of 204 male previously treated patients (PTPs) with severe haemophilia A (≤ 1% FVIII activity) were included in the trial program.[1] There were 153 subjects aged ≥ 12 years old, and 120 of them had ≥ 50 exposure days (EDs) in the clinical trial.[1] There were 51 subjects aged < 12 years old, and 50 of them had ≥ 50 EDs in the clinical trial. The recommended adult dose for routine prophylaxis is 20 to 40 IU of Kovaltry per kg of body weight two or three times per week.[1] In children ≤ 12 years old, the recommended dose for routine prophylaxis is 20 to 50 IU of Kovaltry per kg body weight twice weekly, three times weekly, or every other day according to individual requirements.[1] Kovaltry is administered using the Vial Adapter reconstitution set.

[9] Scott Wolchko, President and Chief Executive Officer of Fate Therapeutics, said: "Programming donor immune cells *ex vivo* to enhance therapeutic function upon adoptive transfer is a highly-differentiated therapeutic paradigm, which is easily integrated into current clinical practice and avoids costly and time-consuming measures, such as genetic engineering, cell expansion and cell separation. We believe the use of ProTmune as the donor cell source for HCT can meaningfully improve patient outcomes, decrease hospital length of stay by mitigating use of in-hospital drug treatments, and substantially reduce the overall cost of care."

proprietary needle technology[10] to help enhance the patient experience. The company says that when combined with BD RightGauge technology, which increases the needle's inner diameter and enables clinicians to select a smaller gauge needle without sacrificing sample quality and blood flow, this new device has been shown to reduce penetration forces substantially.

3. Market structure and company news

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

a) Dublin-based Shire arranged to acquire Baxalta for approximately $US 32 million in cash and stock. Its unsuccessful bid in July was for $US 30 billion all-stock.
b) Baxalta's CEO Ludwig Hanson is rumoured to be collecting tens of millions of dollars in cash and Shire stock[11], with Baxalta reimbursing any federal excise tax due on the exit payment[12].
c) Flemming Ornskov, Shire's CEO, will lead the combined company, which will remain headquartered in Dublin. Shire runs its US operations out of Lexington, Massachusetts, and the company will maintain its American hub there. Omskov and most other senior executives are based in Lexington.
d) Baxalta's operations will face a lower tax rate by being taken over by Shire, which is registered in Jersey but based for tax purposes in Ireland. US-based Baxalta had projected a tax rate of 23 per cent in 2016. A combination would yield an effective tax rate of 16 per cent to 17 per cent by 2017, Shire said.
e) Cerus Corporation announced that LifeShare Blood Centers had signed a purchase agreement for the INTERCEPT Blood System, its pathogen reduction technology, for platelets and plasma. LifeShare Blood Centers supplies approximately 16,000 platelet and 79,000 plasma units for patient transfusion annually as the sole provider of blood products over100 medical facilities in Louisiana, East Texas, and Southern Arkansas. Cerus was also able to announce a partnership with the American Red Cross.
f) Chimerix shares fell heavily after a last- stage clinical trial of the antiviral drug brincidofovir in 452 bone marrow transplant recipients showed that more patients

[10] PentaPoint Comfort 5-bevel needle technology. This design creates a flatter, thinner surface to help penetrate the skin with significantly greater ease.

[11] Securities and Exchange Commission records show that in August Hanson owned 217,221 Baxalta shares, worth about $US 9.9 million at the buyout price of approximately $US 45.57 a share. A filing in July showed Hantson also held 1.5 million stock options with exercise prices ranging from $US 24.83 to $US 31.50 per share. At the buyout price, that's $US 22 million after deducting exercise prices. Severance pay would be equal to twice annual salary and bonus.

[12] Baxalta used to have an explicit policy against such "tax gross-up" payments to departing executives, but reversed that policy on 11 January, the same day it announced its sale to Shire. Shareholder rights advocates object to gross-up payments. Firstly, the payments encourage severance arrangements which encourage a CEO to sell a company when this may not be in the interest of shareholders. Secondly, there is the question of equity. Should shareholders pay a CEO's taxes? Critics of the deal point to Hanson's comments in August that "we do not believe that a combination of our two companies would be strategically complementary, or that our respective product portfolios would benefit from such a combination".

given the therapy died after treatment than did those given a placebo[13]. Chimerix paused enrolment in late-stage trials in kidney transplant recipients.

g) Emmaus Life Sciences, of California, raised approximately $US 1.7 million in gross proceeds from the sale of common shares to Korea Bio Medical Science Institute as part of a collaboration agreement between the two companies. Part of the capital will be used to advance Emmaus' pharmaceutical grade L-glutamine treatment (PGLG), under clinical development having completed its Phase III trial for the management of sickle cell disease.
h) Researchers at the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California at San Diego have agreed on collaboration with Janssen Research & Development (a subsidiary of Johnson & Johnson) to identify medications to combat Chagas disease. Janssen will provide Skaggs dean James McKerrow with funding and access to a screening library of compounds. McKerrow said his team will use a new robotic drug screening facility at the School of Pharmacy to test the thousands of Janssen R&D compounds for their ability to kill or inhibit *Trypanosoma cruzi*, the parasite that causes Chagas disease.
i) KEDPlasma, a subsidiary of Kedrion Biopharma, announced the acquisition of two plasma collection centres from ImmunoTek Bio Centers. KEDPlasma collects plasma for its parent company, which produces plasma-derived medicinal products. The two new centres, located in Dothan, Alabama and Hattiesburg, Mississippi bring KEDPlasma's total to twelve US collection centres, and are part of a five year plan to increase the number of centres the company operates. ImmunoTek had, been supplying Kedrion Biopharma with plasma from these centres since they were opened in 2014. They are FDA licensed and approved by the European Authority. KEDPlasma currently operates twelve plasma collection centres in the US, four in Germany and three in Hungary, with all having approval by European authorities and/or the US Food and Drug Administration. The company's collection centre in Buffalo, New York is specialized in collecting hyper-immune Anti-D human plasma for the manufacture of an Anti-D immunoglobulin pharmaceutical product for the prevention of haemolytic disease of the foetus and newborn.
j) CSL reported a 3.8 per cent increase in interim profit to $US 718.8 million.
k) Biotest announce the appointment of Kedrion Biopharma as the exclusive distributor of its intravenous immunoglobulin product, Bivigam in the US.

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) UK patients with haemophilia A can now access Sobi and Biogen's Elocta, the first haemophilia A treatment approved in Europe that offers prolonged protection against bleeding episodes through prophylactic injections every three to five days. Elocta can be used in the UK for both prophylaxis and on-demand treatment of bleeding.
b) In Canada, the federal National Democratic Party wants the national government to ban plasma clinics that pay donors. Ontario and Quebec moved to ban such clinics, but Saskatchewan's health minister says he has no objections.

[13] Those given brincidofovir had fewer infections while on the drug than those given placebo. However, I the ten weeks following treatment they were more likely to develop the infection or die than the placebo group, The higher rates of infection and death in patients given brincidofovir was driven by graft-versus-host disease, where the patient's body begins attacking transplanted cells. The increase in graft-versus-host also meant significantly more patients given brincidofovir were given corticosteroids, which increases risk of infection.

c) Canada's Héma-Québec announced that the black community has high rates of sickle-cell anaemia, treated through regular blood transfusions, and it is using Black History Month to seek out more blood donors from the black community.
d) Cerus Corporation announced mid-January that AABB had granted the first requests of US blood centres and hospitals to use Intercept pathogen reduction in place of irradiation to satisfy AABB's requirement to reduce the risk of transfusion-associated graft versus host disease (TA-GVHD)[14].
e) In the US, AABB[15] and The Joint Commission[16] announced a collaborative partnership to provide a joint hospital certification program for patient blood management. This voluntary certification is based on the AABB Standards for a Patient Blood Management Program. Mark G. Pelletier, COO, Accreditation and Certification Operations of The Joint Commission, said: "Blood transfusion continues to be one of the most frequently performed procedures in hospitals, and although great strides have been made to make blood usage as safe as possible, transfusion complications and adverse outcomes can still occur. Our goal in collaborating with AABB on this certification is to help ensure that patient blood management programs maximize their potential to reduce risk to patients and help organizations save on costs through more structured blood management."

5. 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) Chemical engineers at the Massachusetts Institute of Technology have used carbon nanotubes in a new method for detecting proteins, including fibrinogen[17]. If developed into an implantable sensor, this method could be used for continuous monitoring of patients taking blood thinners.
b) Scientists have reported[18] a new human virus confirmed from genetic screenings of blood samples that appears to be linked to hepatitis C but it is unknown whether it can cause disease. Called the human pegivirus-2 (HPgV-2), the novel virus was discovered by a team of researchers from Abbott Laboratories, the University of Chicago and University of California at San Francisco. "We are just beginning to

[14] Also, in letters received by Blood Bank of Delmarva, SunCoast Blood Bank, the National Institutes of Health and Community Blood Center, the AABB's Blood Bank and Transfusion Services Standards Program Unit (BBTS SPU) wrote that, "based on the evaluation of relevant data and current use of the Intercept Blood System for pathogen reduction, it is the intent of the BBTS SPU to propose an interim standard to the 29th edition allowing for the practice described." Issuance of the interim standard would mean blood centres and hospitals would not need to request a variance to use the Intercept Blood System for platelets in place of irradiation.
[15] AABB, formerly the American Association of Blood Banks, is an international, not-for-profit association representing individuals and institutions involved in transfusion medicine, cellular therapies and patient blood management.
[16] The Joint Commission is a non-profit organisation founded in 1951 to continuously improve health care for the public, in collaboration with other stakeholders, by evaluating health care organizations and inspiring them to excel in providing safe and effective care of the highest quality and value.
[17] Gili Bisker et al., "Protein-targeted corona phase molecular recognition"*. Nature Communications (2016).* doi:10.1038/ncomms10241
[18] In the journal *PLoS Pathogens.* The authors note in an addendum that while their paper was under review, another study published in the journal *mBio* reported on the discovery of a novel virus named "hepegivirus 1" that was found in serum samples from people given blood transfusions. It was about 96 per cent identical to the HPgV-2 virus index case in their study.

explore the clinical ramifications," study coauthor Andrew Aronsohn, a liver specialist and assistant professor of medicine at the University of Chicago comments in the article. "Does it make a difference to the infected person's health? Does it work with hepatitis C to make patients even sicker? We don't yet know. We only know that a blood-borne virus, never before detected, is out there."

c) Biophysicists have created a mathematical model to predict arterial thrombus formation–the main cause of heart attacks and strokes. They derived equations allowing them to reproduce platelet aggregation, which they described as being similar to the computer game *Tetris*. The process was found to resemble a travelling wave in which platelets flow in blood plasma. In this state the platelets can change from a free-flowing state to one where they are deposited in the blood vessels[19].

d) Until recently, gene therapy was laborious, crude and unsafe for human testing. But the new technology, called CRISPR-Cas9[20], acts as a microscopic scalpel, performing genomic surgery with a precision, efficiency and affordability. Research at the Stanford School of Medicine, led by Dr Matthew Porteus, is part of an accelerating research movement made possible using the new technique to try to cure genetic diseases such as sickle cell anaemia and muscular dystrophy. These labs are steadily advancing through cell-based and animal trials, as biotech companies raise large sums of money needed to bring the therapies to market[21]. "Now, with lots of people working with CRISPR, this means the possibility of actually finding a way to cure patients of disease increases dramatically," said Porteus, an associate professor of paediatrics and a pioneer in gene editing. The Stanford team aims to start human trials in 2018. The researchers are targeting two severe blood diseases, sickle cell anaemia and beta thalassemia, and several diseases of the immune system.

e) Researchers at Duke University are in a team using the same approach to fix a muscle gene, restoring function in mice with an incurable type of muscular dystrophy[22]. Boston researchers are deploying the tool to treat a rare inherited eye disease that can cause blindness[23]. Other teams are working to fix the genes that cause Huntington's disease, Sanfilippo syndrome and cystic fibrosis.

f) Scientists at the Wyss Institute for Biologically Inspired Engineering at Harvard University have created a better assay for testing blood's clotting tendency[24], which could prove to be a lifesaver for patients with abnormal blood coagulation and platelet function. The approach subjects blood to what it would experience inside a patient's vascular network. The team led by Donald Ingber developed a novel microfluidic device in which blood flows through a lifelike network of small "vessels." It is here that it's subjected to true-to-life shear stresses and force gradients of the human vascular network. Using automated pressure sensors and a proprietary algorithm developed by

---

[19] The study involved researchers from Russia and Germany and was published in *PLOS ONE.*

[20] CRISPR stands for "clustered regularly interspaced short palindromic repeats," or clusters of brief DNA sequences that read similarly forward and backward. It works like the search-and-replace function of a computer. CRISPR has caused some controversy because of its potential to rearrange the basic building blocks of life. In December, experts gathered in Washington, D.C., to urge limits to its use in creating dangerous new organisms or "designer babies."

[21] In December 2015, the biotech firm CRISPR Therapeutics received a $US 335 million investment from German pharmaceutical giant Bayer AG to form a joint venture that will research CRISPR-based treatments.

[22] Their findings were published in the journal *Science*.

[23] In November 2015, the Cambridge, Massachusetts, biotech startup Editas Medicine, cofounded by the Massachusetts Institute of Technology's Dr. Feng Zhang, announced that it planned to test a CRISPR-based gene therapy technique in hopes of curing a rare form of blindness by fixing a gene that controls the eye's photoreceptor cells. It has raised $120 million from investors, including Bill Gates and Google Ventures, on top of $43 million raised in 2013.

[24] Reported in Nature Communications

the Wyss team, data acquired from the device is analyzed in real time, precisely predicting when a certain blood sample will obstruct the blood vessel network.

6. 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) A US law firm in January announced an investigation for shareholders in Baxalta on whether officers and directors of Baxalta breached their fiduciary duties owed to NYSE:BXLT investors in connection with the proposed acquisition. The investigation concerns whether the Baxalta Board of Directors undertook an adequate sales process, adequately shopped the company before entering into the transaction, maximized shareholder value by negotiating the best price, and acted in the shareholders' best interests in connection with the proposed sale.

b) The European Court of Human Rights in Strasbourg ruled in January that Italy must pay £7.7million to more than 350 people who contracted viruses, including HIV and hepatitis C, from contaminated blood products. The court ruled that victims were entitled to compensation because "the causal link between the transfusion of infected blood and their contamination has been proved".

c) The ruling increased pressure on the British Government. There, 7,500 people were affected, of whom 2,000 have since died. The Prime Minister, David Cameron, announced last March £25million to "support any transitional arrangements to a better payments system", but so far no money has been paid.

7. 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).

Zika Virus

a) The mosquito-borne Zika virus[25], which has been spreading round the warmer regions of the world, was considered primarily as a very unpleasant inconvenience by otherwise healthy people, rather than as a major global health threat. That changed when it began ravaging Brazil, and reports suggested that it may be associated with a specific birth defect, microcephaly — babies born with abnormally small heads[26] and associated problems.

b) The US Centers for Disease Control and Prevention (CDC) issued a travel alert following the reports of microcephaly(http://www.cdc.gov/ncbddd/birthdefects/microcephaly.html) and other poor pregnancy outcomes in babies of mothers who were infected with Zika virus while pregnant. It said "additional studies are needed to further characterize this

[25] Zika is a flavivurus, as are dengue, chikungunya, West Nile, yellow fever, Japanese encephalitis and tick-borne encephalitis

[26] Brazil's Health Ministry says 3530 babies born between October 2015 and mid-January this year have microcephaly, while only 150 cases were recorded in 2014.

relationship" and that "More studies are planned to learn more about the risks of Zika virus infection during pregnancy[27]."

c) Meanwhile, the CDC[28] issued questions and answers on Zika virus infection and pregnancy, pointing out that there is no vaccine to prevent infection, or medicine to treat Zika. It recommended that "Until more is known, and out of an abundance of caution" pregnant women and women trying to become pregnant should take special precautions[29]. It also said that "At this time, and for several reasons, we do not recommend routine Zika virus testing in pregnant women who have traveled to a country with known transmission. First, there can be false-positive results due to antibodies that are made against other related viruses. Second, we do not know the risk to the fetus if the mother tests positive for Zika virus antibodies. We also do not know if the risk is different in mothers who do or do not have symptoms due to Zika virus infection."
d) The forthcoming Olympics in Rio is recognised as a vehicle for hastening the global spread of ZIka. The Australian Olympic Committee warned its athletes of the need to avoid mosquito bites.
e) The World Health Orgnisation (WHO) declared the spread of the Zika virus to be a public health emergency.
f) Dr Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases within the US National Institutes of Health (NIH), said NIH researchers have begun some initial work towards a vaccine against Zika[30], and that the agency also plans to boost funding to some Brazilian scientists to accelerate Zika-related research. The University of Texas Medical Branch in Galveston has agreed to collaborate with the Brazilian Ministry of Health on developing a Zika vaccine and finding other ways to fight the outbreak of the virus.
g) Scientists have created a new strain of 'super-infected' mosquitoes that could potentially help fight dengue fever and the Zika virus. Researchers created a strain of *Aedes aegypti* mosquitoes in the lab that has been infected with two types of Wolbachia, a bacterium that can reduce the risk of dengue spreading to humans. The new strain is more effective at blocking dengue than the singly-infected insect, researchers from University of Melbourne said[31].
h) British firm Oxitec released test results suggesting that genetically modified mosquitoes could help battle the Zika virus. Tests begun in April 2015 showed that the release of genetically modified sterile male mosquitoes succeeded in reducing a variety of disease-transmitting mosquito larvae by 82 per cent by year's end in an area of the city of Piracicaba.
i) GlaxoSmithKline is evaluating whether its vaccine technology is suitable for the Zika virus. A GSK spokeswoman said vaccine development typically takes ten to fifteen years. Sanofi, which has its dengue vaccine approved in some countries, is reviewing applying its technology to Zika. Pfizer, Johnson and Johnson and Merck said they were evaluating their technologies or existing vaccines for their potential to combat Zika.

---

[27] A study by US and Brazilian researchers has begun in the state of Paraiba.

[28] National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Vector-Borne Diseases (DVBD)

[29] These include*:* Pregnant women in any trimester should consider postponing travel to the areas where Zika virus transmission is ongoing. Pregnant women who do travel to one of these areas should talk to their doctor or other healthcare provider first and strictly follow steps to avoid mosquito bites during the trip. Women trying to become pregnant or who are thinking about becoming pregnant should consult with their healthcare provider before traveling to these areas and strictly follow steps to prevent mosquito bites during the trip. Pregnant women were advised to see their healthcare provided if they developed a fever, rash, joint pain, or red eyes within two weeks after traveling to a country where Zika virus cases had been reported, being sure to tell their health care provider where they travelled.

[30] The aim is to have a vaccine in a Phase I clinical trial by late in the northern hemisphere summer.

[31] The findings were published in the journal *PLOS Pathogens.*

j) Amongst the many other companies working to develop a vaccine against the Zika virus are Protein Sciences of Meriden, Connecticut; GeoVax Labs of Atlanta, Georgia; Bharat Biotech, based in Hyderabad, India; NewLink Genetics' Infectious Disease Division, based in Devens, Massachusetts; and Inovio Pharmaceuticals of Plymouth Meeting, Pennsylvania;
k) A team from the University of South Australia have been working with biotech company Sementis to develop a vaccine for the mosquito-borne Chikungunya virus. With pre-clinical studies showing the vaccine to be effective, they believe it could be adapted to prevent Zika.
l) After Brazil reported its first known cases of Zika transmission via blood transfusion, a number of countries have asked blood donors who have visited areas where Zika is active to defer their donations, usually for 21 or 28 days. Cerus used the Zika scare to emphasise the value of its pathogen reduction technology for blood products[32]. The FDA called for blood banks in areas of the US where the virus is transmitted locally (like Puerto Rico and the US Virgin Islands) to import whole blood and red blood cells from regions without an outbreak instead of using local donations.
m) A number of cases of sexual transmission of the Zika virus have been observed and precautionary measures advised..
n) With so much attention on the ZIka virus and the possibility it may cause birth defects, a number of interest groups have taken the opportunity to raise awareness of the widespread cytomegalovirus or CMV, which is known to be a significant cause of major birth defects.
o) GenArraytion of Rockville, Maryland, announced it had developed a molecular test that can identify Zika virus in mosquitoes before they infect humans.
p) Researchers in Germany have developed a diagnostic test that can accurately detect the Zika virus in humans, with test kits already sent to Brazil. The tests, developed by German biotechnology company, Genekam, not only reveal the presence of Zika pathogens in a blood sample but also provide information on the quantity in the patient's blood. Sudhir Bhartia, a Genekam researcher, said the test brings quick results. "Our test examines DNA and works with chemicals that react to the Zika virus only. Similar pathogens like Dengue fever won't show up in the results," Bhartia said. However, Bhartia stressed the tests can only be administered in specialized medical facilities and laboratories that have the appropriate equipment and personnel with sufficient know-how[33].
q) There are at least eight other companies working to develop a Zika tes.
r) Cases of Guillaume-Barre syndrome have been widely reported to be associated with the Zika virus.

[32] Cerus said its research shows it can successfully deactivate the Zika virus- see *Transfusion, August 2015.*

[33] In Brazil, researchers offered a method to blood banks that wish to screen transfusion blood for pregnant women and in cases of intrauterine transfusion. There is a suspicion that Zika could cause foeatuses to develop microcephaly, a condition in which babies are born with small heads and brains. The initiative is led by São Paulo's blood bank Fundação Pró-Sangue/Hemocentro, with support from the research foundation Fapesp. Headed by molecular biologist José Eduardo Levi, it is making available a method that uses real-time polymerase chain reaction (PCR) in combination with the protocols developed by the Centers for Disease Control and Prevention (CDC) in the US to detect Zika. The CDC protocol, which includes specific reagents, primers and probes, underwent adaptations for local use, Levi said in a press statement. Validation is done with isolates of lab-grown viruses supplied by researchers at Rede Zika, an emergency network established to deal with the crisis and its possible link with microcephaly. Further validation is carried out in the plasma of the receiver of the transfusion. Levi added that, for now, the monitoring of transfusion blood will focus on those two types of situations that account for only 0.16 percent of the total.

Other mosquito-borne diseases: malaria, chikungunya, dengue, Ross River virus

a) A group of researchers from Nicaragua, the US and the U.K. have collaborated on a study into the correlation between antibody titres and protection from symptomatic infection with dengue. They have published their results in the *Proceedings of the National Academy of Sciences*[34]. They found that higher pre infection neutralizing antibody titres correlate with a lower probability of symptomatic infections in children.

b) A dengue vaccine, TV003, was developed by scientists in the laboratory of Stephen Whitehead at NIH's National Institute of Allergy and Infectious Diseases (NIAID). The Butantan Institute, a non-profit producer of immune biologic products for Brazil, licensed the NIAID dengue vaccine technology and is sponsoring a placebo-controlled, multi-centre phase III trial using test vaccine produced in Sao Paulo. It will be tested on 17,000 volunteers.

c) The La Jolla Institute for Allergy and Immunology will share in a $US 18 million grant to study the human immune system's response to dengue virus and tuberculosis. The grant will fund the collection, shipping, and processing of thousands of samples from a network of clinical sites in Sri Lanka, Nicaragua, Peru and Sweden. A team led by the institute's Alessandro Sette is one of four that will share the grant as part of the Human Immune Profiling Consortium under the direction of the US National Institutes of Health. The consortium will identify groups of genes expressed in T cells, a key white blood cell type, associated with protection from or susceptibility to the two diseases. "By comparing and contrasting the gene expression signatures associated with disease and protection from disease, we will better understand what kind of immune responses vaccines should induce in order to be protective," said Bjoern Peters, an associate professor at the institute who is spearheading the tuberculosis project in addition to performing the bioinformatics analysis for both pathogens.

d) Malaysia had over 120,000 confirmed dengue cases in 2015. The number has increased each year since 2011. There were 322 dengue related fatalities, 100 more than in the previous year. The World Health Organization (WHO) estimates there may be 50–100 million dengue infections worldwide every year. Estimates from the University of Oxford and the Wellcome Trust, using cartographic approaches, suggest 390 million dengue infections per year worldwide**.**

e) Australian scientists[35] have found why people with malaria don't develop immunity during infection. Malaria parasites cause an inflammatory reaction that sabotages the body's ability to protect itself against the disease. Dr Diana Hansen said: "With many infections, a single exposure to the pathogen is enough to induce production of antibodies that will protect you for the rest of your life. However, with malaria it can take up to 20 years for someone to build up sufficient immunity to be protected. During that time people exposed to malaria are susceptible to reinfection and become sick many times, as well as spreading the disease….."This research opens the door to therapeutic approaches to accelerate development of protective immunity to malaria and improve efficacy of malaria vaccines."

f) A team of researchers lauded a clip-on repellent device that could actually kill or knock the *Aedes aegypti* mosquito down. The OFF! Clip-On prevents mosquito bites by releasing a vapour-like insecticide through a battery-operated fan, producing an insecticide "cloud" around the device wearer. Researchers Christopher Bibbs and Rui-De Xue of Florida's Anastacia Mosquito Control District conducted an outdoor test to see how the device will work against hungry mosquitoes. They discovered that

[34] "Neutralizing antibody titers against dengue virus correlate with protection from symptomatic infection in a longitudinal cohort". *PNAS* 2016 ; published ahead of print January 4, 2016, DOI: 10.1073/pnas.1522136113

[35] From the Walter and Eliza Hall Institute, Melbourne, publishing in the journal *Cell Reports.*

the clip-on caused high mosquito death and knockdown rates up to 0.3 meters away from the device – considered enough to protect the wearer.

Influenza: strains, spread, prevention and treatment

a) China notified 19 additional human cases of H7N9 between 21 December and 25 January, bringing the total number of human cases on the mainland to 702 since 2013. The World Health Organisation (WHO) reported 28 cases in China between 5 and 11 February, 2016. Most had been exposed to live poultry or live poultry markets. Hong Kong on 23 February announced its first case of H7N9 for the year, in a patient who entered Hong Kong from the mainland.
b) A study[36] of H7N9 infections concluded that advanced age, as well as a delay in confirmation of diagnosis and start of antiviral treatment, were the greatest contributory factors to a high risk of death, but that certain genetic mutations observed were associated with increased fatality rate.
c) In January, China announced its first human case of H5N1 flu this year. Since 2003 the country has confirmed 52 cases and 31 deaths[37]. France has detected outbreaks in poultry.
d) In the northern hemisphere, a predominance of influenza A(H1N1)pdm09 viruses has characterized the 2015-2016 influenza season in most countries; this virus subtype may cause more severe disease and deaths in adults aged 15-64 years than A(H3N2) viruses. Most of the viruses characterized so far have been similar to the strains recommended for inclusion in this winter's trivalent or quadrivalent vaccines for the northern hemisphere.
e) Researchers[38] identified a genetic risk that makes people who contract H1N1 flu more likely to develop a hyper inflammatory disorder[39] and perhaps die, and that this may also hold for other infections. "Viruses that cause robust immune responses may be more likely to trigger rHLH in genetically susceptible people," Dr. Randy Cron, a senior study investigator and physician in Pediatric Rheumatology at the University of Alabama-Birmingham (UAB) and Children's of Alabama, said. "Prenatal screening for mutations in common HLH-associated genes may find as much as 10 per cent of the general population who are at risk for HLH when an inflammation threshold is reached from H1N1 or other infectious triggers." The researchers suggested that children should be screened to detect their HLH genes, which would help if they develop a viral infection in the future[40].
f) Two studies published in January[41] by the US Centers for Disease Control and Prevention (CDC) and other researchers noted that the live attenuated influenza vaccine—a nasal spray option—failed to protect adequately from the 2009 H1N1 strain in 2013-14, when it was the predominant circulating strain. CDC researchers involved in both studies noted that reporting of data before publication had enabled MedImmune to change the vaccine. The researchers drilled down into US Influenza Vaccine Effectiveness (Flu VE) Network data.
g) In the US in January a draft report from the National Science Advisory Board for Biosecurity (NSABB) was discussed at a meeting which was part of the Obama administration process put in place in October 1914 to re-evaluate federal funding of "gain of function" (GOF) studies in the light of controversial studies with A(H5N1) vruses. The administration had asked for recommendations, and the January

[36] Sha J, Chen X, Ren Y. "Differences in the epidemiology and virology of mild, severe and fatal human infections with avian influenza A (H7N9) virus", *Arch Virol.* 2016 Feb 18. [Epub ahead of print]
[37] As of 14 December, the WHO had confirmed 844 cases globally, including 449 deaths,
[38] From the University of Alabama-Birmingham, Cincinnati Children's Hospital Medical Center and Children's of Alabama.
[39] called HLH, rHLH, or hemophagoytic lymphohistiocytosis
[40] Results were published in *The Journal of Infectious Diseases*
[41] In *Pediatrics* and *The Journal of Infectious Diseases*

meeting included an ethics white paper commissioned to help the Board finalize its report. Risk-benefit assessment was also a significant topic on the agenda.

i) Marc Lipsitch, director of the Center for Communicable Disease Dynamics at the Harvard School of Public Health and part of a group that has urged for a more careful assessment of GOF studies and alternate ways of studying the virus, said the risk-benefit assessment the NSABB used for its draft report underestimated the absolute risk for the GOF studies of most concern.
ii) Jill Taylor, director of the Wadsworth Center at the New York State Department of Health, urged the NSABB to ensure that its policy report includes a mechanism for ensuring that investigators and institutions have a culture of safety and responsibility and to consider if risk mitigation measures are required, a step that would typically involve public health departments.
iii) Yoshihiro Kawaoka, a virologist with the University of Wisconsin, Madison, and lead author of one of the two controversial H5N1 papers published in 2012 that brought the GOF controversy to a head, said oversight mechanisms for GOF studies should be incorporated into existing federal frameworks. A number of participants asked that the final draft include global perspectives, because though the report is intended to guide US policy, it affects the international research community and will likely be used as a blueprint elsewhere.
iv) The second of two National Academies symposia on GOF issues will be held March 10 and 11 2016. The first was held in December 2014, not long after White House announced a research pause on GOF studies, and its charge to the NSABB to provide recommendations.

h) France has had a number of highly pathogenic avian flu outbreaks in poultry flocks. Both H5N1 and H5N2 have been found. Scotland has had an outbreak of low-pathogenic HN1. Vietnam has been battling H5N6 in poultry flocks. Taiwan has had several outbreaks of H5N6 in birds. Hong Kong has also detected H5N6.
i) Avian influenza killed millions of chickens and turkeys in the US in spring and summer 2015, leading to billions in lost revenue for the US poultry industry. Now, scientists at Kansas State University, in collaboration with Garcia-Sastre of the Icahn School of Medicine at Mount Sinai, have developed a vaccine that protects poultry from multiple strains of avian influenza found in the US, including H5N1, H5N2 and H5N8. The vaccine has the potential to be administered through water or into embryonated eggs, making it easier for poultry producers to vaccinate flocks. The vaccine, NDV-H5Nx, also protects poultry against Newcastle disease virus—a virus that naturally affects poultry.
j) Chen Hualan, director of National Avian Influenza Reference Laboratory in China told the Chinese news agency Xinhua that EAH1N1 is the strain most likely to cause next human flu pandemic. Recorded since 1979 usually in pigs, its long term evolution has helped it to transmit efficiently to humans[42].

MERS-CoV (Middle East Respiratory Syndrome-Coronoavirus)

a) The Saudi Arabia Ministry of Health announced that to 23 February 2016 the country had had a total of 1301 cases of laboratory-confirmed MERS-CoV, including 554 deaths.
b) Tests carried out in Riyadh by Sausi Arabia's Agriculture Ministry found 85 per cent of camels were carrying MERS.
c) The cluster of MERS cases in Riyadh last year has been reviewed[43]. The report concluded: "This large MERS outbreak in a major tertiary-care hospital in Riyadh was

[42] Influenza surveillance in China has isolated 228 flu strains from more than 36,000 samples and out of which 139 are found to be belonging to EAH1N1 lineage. The researchers have identified five genotypes that have potential capacity to infect humans.

[43] Balkhy HH, Alenazi TH, Alshamrani MM, Baffoe-Bonnie H, Al-Abdely HM, El-Saed A, et al., "Notes from the field: nosocomial outbreak of Middle East respiratory syndrome in a large tertiary care

thought to be related to emergency department overcrowding, uncontrolled patient movement, and high visitor traffic. The outbreak required institution of multiple measures to interrupt transmission, including almost complete shutdown of the hospital."

d) On 25 January, Thailand announced its second confirmed case of MERS, in an elderly man who had travelled from Oman. The Public Health Ministry was keeping known contacts under surveillance[44]. Airports of Thailand Plc (AoT) had reserved two concourses at Bangkok's Suvarnabhumi airport for flights from the Middle East to effectively screen passengers for MERS. Screening stations equipped with thermal scanners and staffed by experienced officials were observing the condition of each passenger. Airlines had been asked to help pre-screen passengers so those with suspicious symptoms could be treated quickly. Passengers would receive written instructions and warnings related to MERS. Hand sanitisers were distributed in airport areas where travellers gathered, including information booths, form-filling spots and taxi stands. Workers were cleaning surfaces people touched, such as luggage trolleys and handrails.
e) SAB Biotherapeutics of Sioux Falls, South Dakota, announced it has produced a new human antibody therapeutic to treat MERS[45]. The company said research efforts showcasing the effectiveness of the treatment were led by global infectious disease experts at the Naval Medical Research Center and MERS-CoV expert, Matthew B. Frieman, Associate Professor of Microbiology and Immunology at the University of Maryland, School of Medicine, and were published in *Science Translational Medicine*[46]. The new approach protected mice from the infection during the study.
f) Scientists at the Walter Reed Army Institute of Research started vaccinations to test the safety and immune response in people of a vaccine candidate to prevent MERS. Seventy-five participants will receive the vaccine at WRAIR's Clinical Trial Center in Silver Spring, Maryland. The vaccine, GLS-5300, is being co-developed by Inovio Pharmaceuticals and GeneOne Life Science. The vaccine is a DNA vaccine. DNA technology will shorten the time it takes to produce the vaccine in quantity if it's approved by the US Food and Drug Administration (FDA)[47].

Ebola virus disease

a) Merck's Ebola vaccine posted interim Phase III data showing 100 per cent efficacy in July 2015[48]. Gavi, the Global vaccine alliance, has awarded $US 5 million late-stage trials, licensure and prequalification by the WHO. Merck expects to submit the vaccine for regulatory approval by the end of 2017[49]. Merck's Phase III trial is ongoing and follows a novel "ring" structure, in which people at risk for Ebola infection were vaccinated with rVSV-ZEBOV.
b) The Walter Reed Army Institute of Research (WRAIR) in January announced the initiation of a Phase II clinical trial to evaluate the safety and immunogenicity of a prime-boost Ebola vaccine regimen in both healthy and HIV-infected study

---

hospital -- Riyadh, Saudi Arabia 2015, CDC. *MMWR Morb Mortal Wkly Rep* 19 Feb 2016; 65(6):163-164

[44] a relative who accompanied the man, 218 crew and passengers, a taxi driver, a hotel employee, and 30 hospital staff.

[45] Cows were bioengineered to produce human antibodies.

[46] Thomas Luke, Matthew B.Frieman, et al: "Human polyclonal immunoglobulin G from transchromosomic bovines inhibits MERS-CoV *in vivo*". *Sci Translational Med*, 17 Feb 2016, Vol 8 Issue 326 326ra21.

[47] No culture system (such as eggs) is necessary

[48] A study published in *The Lancet* medical reported that Merck's vaccine was was tested on more than 4,000 people who were in close contact with Ebola patients in Guinea.

[49] Merck has filed an emergency use application with the Woirld Health Organization so the experimental vaccine might be used in an emergency. Merck plans to provide 300,000 doses starting in May 2016 for use in clinical trials or emergency situations.

volunteers. This study includes two vaccine candidates, Ad26.ZEBOV from Crucell Holland B.V., one of the Janssen Pharmaceutical Companies of Johnson & Johnson, and MVA-BN-Filo from Bavarian Nordic, which will be given sequentially as a "prime boost" regimen. Seventy-five volunteers will receive a prime dose with MVA-BN-Filo followed by a boost with Ad26.ZEBOV at the WRAIR Clinical Trials Center in Silver Spring, Md. WRAIR-affiliated sites in Africa will also begin evaluating this regimen, as well as a vaccination schedule beginning with Ad26.ZEBOV and then boosted with MVA-BN-Filo.

c) GlaxoSmithKline, Johnson & Johnson, and Maryland-based Novavax and Profectus BioSciences[50] also have Ebola candidates in clinical trials. San Diego's Inovio is leading a consortium to develop treatments and a vaccine for Ebola.
d) Scientists at Albert Einstein College of Medicine and the US Army Medical Research Institute of Infectious Diseases (USAMRIID) have engineered the first antibodies that in mice can potently neutralize the two deadliest strains of the virus that causes Ebola haemorrhagic fever. "A broadly effective immunotherapy for Ebola virus would be a tremendous advance, since it's impossible to predict which strain of the virus will cause the next outbreak," said study co-leader Jonathan Lai, associate professor of biochemistry at Einstein. The other study co-leader is John M. Dye, branch chief of viral immunology at USAMRIID[51]. There are currently no plans to further test the new immunotherapy. But if a pharmaceutical company were interested, said Dr Lai, "it could probably move the antibody fairly rapidly along the evaluation process."
e) Researchers from Plymouth University, the US National Institutes of Health and the University of California, Riverside, have shown the ability of a vaccine vector based on expressing Ebola virus glycoprotein, to provide protection against Ebola virus in the experimental rhesus macaque, non-human primate model. This is a critical step before translation of Ebola virus vaccines into humans and other great apes[52].
f) Researchers from the Toronto General Research Institute, University of Toronto, Canadian Blood Services, the National Microbiology Laboratory in Winnipeg and the US National Institutes of Health used a mini-genome system to rapidly evaluate candidate drugs that could inhibit the Ebola virus. The team was led by Dr Eleanor Fish, senior scientist in the Toronto General Research Institute (TGRI) and Dr Donald Branch, senior scientist in the Centre for Innovation - Canadian Blood Services and TGRI. Their results[53] provide details on the procedure for evaluating potential anti-Ebola drugs and comparing the antiviral effectiveness of eight drugs from three different drug classes. Interferons and anti-HIV drugs showed antiviral activity against the Ebola virus in their studies.
g) In mid-January, the World Health Organisation announced no new Ebola cases in the three worst-affected countries for 6 weeks. Then a day later, Sierra Leone reported an Ebola-related death. By then the most recent epidemic had affected over 28,600 people and killed more than 11,300.

Other diseases: occurrence, prevention and treatment

a) The Wesley Hospital in Brisbane again had a patient test positive for legionnaire's disease, and the city's Mater Private Hospital later also had a patient test positive.

[50] Profectus BioSciences, of Baltimore announced in January the launch of a phase I trial of its VesiculoVax-vectored vesicular stomatitis virus (VSV) Ebola vaccine after its success last year in macaques. The dose-escalation study includes 39 volunteers divided into three groups who will receive the injected vaccine. The Phase 1 study will evaluate safety and immune response. The vaccine is supported by the US Department of Defense. In July 2015, a Canadian-developed VSV Ebola vaccine was shown to be highly effective in a ring-vaccination strategy in Guinea.
[51] The study was published online in *Scientific Reports*.The study is titled "Bispecific Antibody Affords Complete Post-Exposure Protection of Mice from Both Ebola (Zaire) and Sudan Viruses."
[52] The study was published 15th February in the online journal *Scientific Reports*.
[53] published in *PLOS Neglected Tropical Diseases* DOI: 10.1038/srep21674

b) At the beginning of January, West Australian health authorities, fearing an outbreak of whooping cough, urged pregnant women to be vaccinated. Most deaths from the disease occur in children under three months of age.
c) The US Department of Agriculture's (USDA) Food Safety and Inspection Service (FSIS) announced the finalization of new federal standards to reduce *Salmonella* and *Campylobacter* in chicken and turkey mince, as well as in raw chicken breasts, legs, and wings. Based on scientific risk assessments, FSIS estimates that implementation of these standards will lead to an average of 50,000 prevented illnesses annually. FSIS has also updated its microbial testing schedule at poultry facilities and will soon begin posting more information online about individual companies' food safety performance. FSIS implemented performance standards for whole chickens in 1996 but has since learned that *Salmonella* levels increase as chicken is further processed into parts. Poultry parts like breasts, wings and others represent 80 percent of the chicken available for Americans to purchase. By creating a standard for chicken parts, and by performing regulatory testing at a point closer to the final product, FSIS can greatly reduce consumer exposure to *Salmonella* and *Campylobacter*.
d) Australia has had a salmonella outbreak associated with pre-packed lettuce grown in Victoria.