

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:

- rEVO Biologics will build a colony of white rabbits in Massachusetts which will produce Factor VIIa in their milk. (page 3)
- Novo Nordisk announced positive results from the first phase III trial of its long-acting recombinant factor VIII for haemophilia A. (page 3)
- Health Canada approved Alprolix, Biogen Idec's long-acting recombinant FIX for haemophilia B. (page 4)
- Fresenius Kabi is building a manufacturing centre in Melbourne. (page 5)
- Bayer is creating additional capacity in Germany for manufacturing its recombinant FVIII products currently in development. (page 5)
- A study suggests perioperative blood transfusions with surgery for nonmetastatic renal cell carcinoma lowers chance of survival. (page 7)
- Another study found that blood transfusion during angioplasty may increase the risk of stroke, heart attack or death. (page 7)
- A third study suggests that in patients undergoing percutaneous coronary intervention, anaemia increases the risk of major bleeding despite use of bivalirudin. (page 8)
- A Canadian study of hospital births from 2003 to 2010 found increasing rates of postpartum haemorrhage and transfusion. (page 8)
- Anaemia has been found to increase the risk of stroke. (page 8)
- The US National Institutes of Health has awarded a grant to Case Western Reserve University to develop injectable artificial platelets. (page 9)
- Mosquito-borne Zika fever, dengue and chikungunya have been raging in various countries in warmer regions round the world. (pages 10,11)
- Avian influenza H7N9 which originated in China and MERS-CoV originating in the Middle East remain under watch for global infectivity (pages 12 to 14)

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1. Products

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

Clotting factors

- a) French company LFB and its US-based subsidiary rEVO Biologics will build a colony of over 1000 New Zealand white rabbits in Massachusetts. They will be able to produce Factor VIIa in their milk¹. The first production there is expected in 2015. Production of the drug for clinical trials has been undertaken in France. The third and final phase of trials in humans is being undertaken this year². If the product receives regulatory approval, the product will be marketed as a treatment for haemophilia A and B patients who have developed inhibitors, or antibodies, to other clotting proteins (Factor VIII or Factor IX).
- b) Novo Nordisk announced positive results from PathfinderT2, the first phase III trial with long-acting recombinant factor VIII, N8-GP (turoctocog alfa pegol) for haemophilia A patients. PathfinderT2 evaluated safety and efficacy when N8-GP was administered to patients 12 years and older for prophylaxis and on-demand treatment. Of the 186 patients in the trial, one who responded well to prophylactic treatment developed inhibitors. The three remaining trials in the program, to conclude within the next 12 months, investigate N8-GP as a treatment for paediatric patients, surgical procedures and as once-weekly prophylaxis.
- c) At the European Association for Haemophilia and Allied Disorders (EAHAD) meeting in Brussels, Baxter presented data on clinical experience of prophylactic treatment with Advate, showing that over half of patients on prophylaxis had fewer than two bleeding episodes per year, with a median annual bleed rate of 1.1. Of these patients, 51 per cent experienced no bleeds over a year of treatment.

Sickle Cell treatment

- d) Emmaus Life Sciences announced positive preliminary top-line results of its Phase III clinical trial evaluating the safety and efficacy of its treatment for sickle cell anaemia and sickle beta-0 thalassemia. The company intends to submit a New Drug Application to the US Food and Drug Administration (FDA) in mid-2014.

Hereditary Angiodema

- e) At the 2014 American Academy of Allergy, Asthma & Immunology (AAAAI) Annual Meeting. CSL Behring introduced data that showed that current hereditary angioedema treatment options³, such as C1 Esterase Inhibitor concentrate, are giving greater patient satisfaction, encouraging higher rates of home treatment and reducing the number of hospitalizations

¹ Transgenic animal production is accomplished by injecting human genes into an early animal embryo, then carried by a surrogate mother. The young so produced carry the desired human protein in their genes and breed normally to produce animals with the human code. The company is already using genetically engineered goats in producing the anti-thrombin III product ATryn, launched in 2009.

² LFB SA, through its rEVO Biologics subsidiary, announced on 3 March the initiation of the global Phase III program for LR769, a novel recombinant form of human Factor VIIa, in patients with congenital haemophilia A or B with inhibitors. This initial Phase 3 clinical trial is an open-label, multicentre study to evaluate the efficacy, safety and pharmacokinetics of LR769 in adolescent and adult hemophilia A and B patients with inhibitors. There will be two dosing regimens for the treatment of bleeding episodes. Initial results are expected in the second half of this year. A second study to start early in 2015 will assess the efficacy of LR769 for the treatment of bleeding episodes in paediatric haemophilia patients with inhibitors. The third study, also to start early in 2015, will evaluate the prevention of bleeding complications in patients undergoing surgery.

³ HAE is a rare, sometimes fatal swelling disorder caused by a deficiency of C1 Esterase Inhibitor (C1-INH).

and visits to Emergency. The findings came from an online survey of physicians, not of patients.

- f) An international study (COMPACT)⁴ begun by CSL Behring is the world's first placebo-controlled phase III trial to examine subcutaneous administration of C1-esterase inhibitor (C1-INH) for use in treating frequent hereditary angioedema attacks.

Other

- g) Kamada has completed enrolment in its phase II/III clinical trial in the US of its human rabies immune globulin KamRAB as a post-exposure prophylaxis for rabies. KamRAB is currently marketed in six other countries. For the clinical development and marketing of KamRAB in the US Kamada has a strategic agreement with Kedrion.
- h) The Blood Products Advisory Committee (BPAC) of the FDA recommended approval of Immucor's HEA Molecular BeadChip™ Test for the molecular typing of human erythrocyte antigen (HEA) phenotypes in 35 blood group systems. The test received the CE Mark in 2010.

2. Regulatory

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

Plasma and recombinant products

- a) Health Canada approved Alprolix, Biogen Idec's long-acting recombinant FIX product for haemophilia B. The drug was approved for controlling and preventing bleeding and for routine prophylaxis in patients over twelve years of age. Biogen is currently seeking approval for Alprolix from the FDA, expecting feedback in the second quarter of 2014, along with feedback on Eloctate, its candidate for haemophilia A. The company is conducting paediatric studies on both Alprolix and Eloctate.
- b) Biotest voluntarily recalled specific lot numbers of BIVIGAM (Immune Globulin Intravenous (Human), 10% Liquid), 100 ml because there was the potential that some of the vials may have an integrity defect.

Other

- c) rEVO Biologics asked the FDA for approval to test its drug ATryn in 120 women, yet to be located and enrolled, who have preeclampsia and are 24 to 28 weeks pregnant⁵. rEVO hopes to show that in early pre-term preeclampsia the drug can prolong pregnancy. A Tryn, which is made from the milk of genetically engineered goats, was approved in 2009 to treat serious blood clots in pregnant women.

⁴ COMPACT=Clinical Studies for Optimal Management in Preventing Angioedema with Low-Volume Subcutaneous C1-inhibitor Replacement Therapy).

⁵ Preeclampsia is a sudden spike in blood pressure.

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.

Company results, forecasts and plans

- a) Grifols reported a 34.6 percent year-on-year rise in 2013 net profit to 345.6 million euros, boosted by overseas sales. Barcelona-based Grifols generates most of its sales outside Spain.
- b) In announcing 2013 results for Cerus Corporation, the president and CEO said "we anticipate a possible second-half approval decision for INTERCEPT plasma in the United States, and prepare for a possible INTERCEPT platelet approval decision in 2015.... We expect operating expenses will increase during 2014 as we decide to bring on additional resources with evolving insight into the United States approval process and possible subsequent commercial launch for our platelet and plasma products, and as we make decisions around the speed of enrolment for our European red blood cell clinical trials and the license-enabling manufacturing development work needed to obtain CE mark for our red blood cell product candidate." INTERCEPT plasma and platelet applications will be filed with Health Canada in the first half of 2014.
- c) Preliminary figures suggest Biotest increased earnings after taxes by 38.5 per cent in 2013 over the previous year. The main factors for this profit increase were significantly higher sales in the US and in Asia. Biotest will publish final results for the Financial Year 2013 and the annual report on March 25th, 2014. The Annual General Meeting of Biotest AG will take place on May 7th, 2014 in Frankfurt.
- d) Swedish Orphan Biovitrum (Sobi) reported a fourth-quarter loss of 13.4 million Swedish kronor compared with a loss of 142.7 million kronor in the same quarter last year. Total revenues for the fourth quarter were 610.8 million kronor, up 29 per cent from 471.9 million kronor in the prior year quarter. For 2014, Sobi expects operating costs to increase as the company continues to prepare for the planned launch of the three phase III pipeline programmes.
- e) CSL Behring has opened a Washington office, headed by an experienced lobbyist and political staffer.

New capacity

- f) Fresenius Kabi is investing \$A 47 million building a pharmaceutical manufacturing centre in the western suburbs of Melbourne, creating 120 jobs in Derrimut. It is expected to be operational by 2016, producing intravenous bags and delivery systems for Australian hospitals. The centre is being built with a grant from the State Government. It will have the capability to operate 24 hours a day.
- g) Bayer currently manufactures Kogenate only in California. The company is now investing over 50 million euros at its sites Wuppertal and Leverkusen, Germany, to create additional capacity for manufacturing its recombinant FVIII products currently in development. These are its long-acting BAY 94-9027 and its plasma protein-free BAY 81-8973. Both the products are in Phase III trials.

Contracts

- h) Novavax extended its contract with the US Department of Health and Human Services, Biomedical Advanced Research and Development Authority (BARDA) for the advanced development of Novavax' recombinant seasonal and pandemic influenza vaccines. These funds will support the Phase II trial for an H7N9 vaccine candidate and activities relating to a quadrivalent seasonal influenza vaccine.

Other

- i) Swedish Orphan Biovitrum has won the EURORDIS Company Award 2014 which recognises pioneering companies developing treatments for rare diseases. EURORDIS is the largest European Patient Organisation in rare diseases, representing over 600 rare disease organisations in 58 different countries and more than 4,000 rare diseases. EURORDIS claims to speak for 30 million patients.

4. Country-specific events

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

United States

- a) In the US, a report from the Agency for Healthcare Research and Quality says that 29 per cent of all US hospitalizations in 2011 included a surgical procedure but hospitalizations involving surgery accounted for nearly half of all hospital costs. Spinal fusion surgeries earned the most hospital revenue because of their higher cost per hospital stay and frequency, followed by knee arthroplasty, and percutaneous coronary angioplasty.
- b) At least 2.7 million Americans currently have hepatitis C⁶. Many are not aware they are infected. More people in the US now die from infection with hepatitis C than from HIV, the virus that causes AIDS. Risk factors for hepatitis C include intravenous drug use, and having received a blood transfusion before 1992. With Baby Boomers being six times more likely than others to be infected with hepatitis C, the Centers for Disease Control and Prevention (CDC) recommends one-time screening for people born between 1945 and 1965. Screening, together with more effective and better tolerated medication becoming available, could reduce the death rate significantly.
- c) The FDA's Vaccines and Related Biological Products Advisory Committee voted 16 to 0 that the 2014-2015 trivalent influenza vaccine should retain the three strains included in the current vaccine: an A/California/7/2009 (H1N1)-like virus and an A/Texas/50/2012 (H3N2)-like virus, and a B/Massachusetts/2/2012-like virus, a B/Yamagata lineage strain, as the influenza B strain. For the quadrivalent vaccine, the panel unanimously recommended that the B/Victoria lineage strain contained in the current quadrivalent vaccine, a B/Brisbane/60/2008-like virus, be retained as the second influenza B strain. During the 2012-2013 season, the quadrivalent vaccine accounted for about 20 per cent of the total doses distributed, and is expected to account for more than half of the doses distributed during next season. Dr Lisa Grohskopf, of the CDC's National Center for Immunization and Respiratory Diseases, told the meeting that influenza activity peaked in late December and early January and that influenza A (H1N1) viruses have predominated. As of 15 February, there had been 52 influenza-associated paediatric deaths reported, which is fewer than the number reported last season.
- d) A new study⁷ reported that over one-third of community hospital patients with serious bloodstream infections received inappropriate antibiotic treatment.
- e) The Medical Advisory Committee of the Immune Deficiency Foundation issued guidelines for vaccines in immunodeficient patients⁸.

⁶ . Dr. David Bernstein, chief of hepatology at North Shore University Hospital in Manhasset, N.Y said: "Our methods of estimating the true prevalence of the disease is flawed. All [federal government] reports underestimate the true prevalence of hepatitis C infection as they do not include the homeless or the incarcerated -- two large populations with a high prevalence of hepatitis C infection."

⁷ published March 18 in the journal *PLoS One*

United Kingdom

- f) UK patients who suffer narcolepsy or cataplexy since receiving Glaxo Smith Kline's Pandemrix vaccine against swine flu will share in approximately £60 million to be paid out by the UK government.
- g) Allegations emerged that information from patients' NHS records had been sold to a major insurance body to help insurers refine their premiums.

Other

- h) A team of US academics and disease experts from the World Health Organization (WHO) has warned that Indonesia's rate of economic growth could be adversely affected by its high rate of tropical diseases⁹, including leprosy, dengue and schistosomiasis.
- i) Nearly ten per cent of Egypt's population suffers from thalassemia. Now the health ministry has launched an awareness-raising campaign. Along with the Egyptian Thalassemia Association, the haematology unit at Zagazig University's paediatric hospital, the paediatric-haematology unit at Cairo University and Novartis Pharma Egypt. The campaign will also encourage those not affected to donate blood for those who do.
- j) The Ontario Health Minister said the province would not license Canadian Plasma resources to open clinics in Toronto and Hamilton that would pay \$C 25 to people for each plasma donation. She said she did not wish to jeopardise the volunteer-based collection system.
- k) A recent study¹⁰ found the management of patients with common variable immunodeficiency varies across Europe, with implications for outcome measures.

5. Safety and patient blood management

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

Appropriate transfusion

- a) A US study¹¹ suggests that patients who receive perioperative blood transfusions relating to their surgery for nonmetastatic renal cell carcinoma (RCC) have a lower chance of survival than those who do not.
- b) A new study has found that receiving a blood transfusion while undergoing angioplasty may raise the patient's risk of heart attack, stroke or death¹². It noted variation between transfusion practice between US hospitals and suggested randomized trials of transfusion strategies to guide practice.

⁸ They recommended that clinicians educate parents and physicians about the need for maintaining herd immunity in the population at large; that they avoid avoid live viral and bacterial vaccines in all patients with significant T-and beta-cell deficiencies; that they determine the degree of immune reconstitution in patients treated with HCT, enzyme therapy, or gene therapy before live vaccine treatment; and that they balance the exposure to infection from live vaccines and close contact-transmitted vaccine-derived infection in the immunoreconstituted child.

⁹ "An Emerging Market Economy Beset by Neglected Tropical Diseases", *PLoS One*

¹⁰ Gathmann B. *J Allergy Clin Immunol.* 2014;[doi:10.1016/j.jaci.2013.12.1077](https://doi.org/10.1016/j.jaci.2013.12.1077).

¹¹ Linder, B. J., Thompson, R. H., Leibovich, B. C., Cheville, J. C., Lohse, C. M., Gastineau, D. A. and Boorjian, S. A. (2014), "The impact of perioperative blood transfusion on survival after nephrectomy for non-metastatic renal cell carcinoma (RCC)". *BJU International*. doi: 10.1111/bju.12535

¹² Matthew Sherwood, of the Duke Clinical Research Institute and colleagues, in *Journal of the American Medical Association* Feb. 26, 2014

- c) Another study¹³ suggested that in patients undergoing percutaneous coronary intervention, baseline anaemia substantially increases the risk of major bleeding despite use of bivalirudin; and that in-hospital bleeding predicts higher long-term mortality primarily in anaemic patients, and particularly those given blood transfusions.
- d) A Canadian study¹⁴ of hospital births from 2003 to 2010 found postpartum haemorrhage increased from 5.1 per cent of deliveries in 2003, to 6.2 per cent in 2010¹⁵. Postpartum haemorrhage with blood transfusion increased from 36.7 to 50.4 per 10 000 deliveries, while postpartum haemorrhage with hysterectomy increased from 4.9 to 5.8 per 10 000 deliveries. Postpartum haemorrhage with uterine suturing, or ligation/embolization of pelvic arteries, increased from 4.1 to 10.7 per 10 000 deliveries. A rising trend in postpartum haemorrhage has been noted in a number of high-income countries, including the US, Australia, Norway and Sweden. In this Canadian study, none of the potential risk factors examined (an increase in older mothers giving birth, a previous caesarean section or twin or multiple pregnancies) explained the increase, according to lead author Azar Mehrabadi, a perinatal epidemiologist in the School of Population and Public Health at the University of British Columbia. "Really, we don't know what's driving it at this point. But a lot of hospitals know this is happening," he said.

Treating iron deficiency

- e) Researchers at Imperial College London have discovered that iron deficiency increases the stickiness of platelets and can add to stroke risk¹⁶.

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.

Stem cells

- a) A trial to involve 3000 heart attack patients across 11 European countries will test whether stem cell treatment can cut death rates and repair damaged tissue. Patients will have standard treatment to widen their narrowed arteries. This involves inserting a stent. Then half the patients will have stem cells taken from their bone marrow and injected into their heart. "This is the definitive trial," said chief investigator Prof Anthony Mathur, director of cardiology at Barts Health NHS Trust and chief investigator for the trial. "After 15 years of research we will now have a clear answer".

¹³ Ali ZA, Poludasu S, Qureshi YH, et al. "Impact of major bleeding on long-term mortality in anemic versus nonanemic patients undergoing percutaneous coronary intervention using bivalirudin." *Am J Cardiol.* 2014;Epub ahead of print.

¹⁴ Azar Mehrabadi, Shiliang Liu, Sharon Bartholomew, Jennifer A. Hutcheon, Michael S. Kramer, Robert M. Liston, K.S. Joseph, for the Maternal Health Study Group of the Canadian Perinatal Surveillance System (Public Health Agency of Canada); "Temporal Trends in Postpartum Hemorrhage and Severe Postpartum Hemorrhage in Canada From 2003 to 2010", *Journal of Obstetrics and Gynaecology Canada*, January 2014

¹⁵ Most of the increase was due to "uterine atony," loss of tone in the muscles of the uterus so they don't contract adequately to stop excess blood flow after delivery.

¹⁶ C. Shovlin et al. "Ischaemic strokes in patients with pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia: associations with iron deficiency and platelets." *PLoS One*, 19 February 2014. dx.plos.org/10.1371/journal.pone.0088812

Sickle Cell Disease

- b) Sickle cell disease is an inherited disease, passed down by both parents, mostly of African, Hispanic, Mediterranean and Middle Eastern descent. Normal, oval-shaped red blood cells lose oxygen and collapse into sickle shapes. They can become stuck in veins, causing excruciating pain, anaemia, fatigue, respiratory distress and organ failure. In 1973, life expectancy after diagnosis was estimated to be 14 years in the US, but it is now higher because of early use of antibiotics, improved pain management, and the use of a relatively cheap drug, hydroxyurea, approved by the FDA to reduce pain crises in some patients. It increases the production of foetal haemoglobin, which improves oxygen transport by the blood.
- c) Bone marrow transplants are another option, albeit a risky one. About 500 bone marrow transplants have been performed on sickle cell patients in the US, mostly involving children. “The transplant worked 95 percent of the time in kids who have a perfect match,” said John Tisdale, a senior investigator with the Molecular Clinical and Hematology Branch of the National Heart, Blood, and Lung Institute, “but a matched sibling is found only about 10 percent of the time”. Tisdale transplanted mice with sickle cell disease with donor stem cells that were genetically only half a match, then tried it in humans. “We have transplanted 11 adults with half a match,” Tisdale said. A similar human trial at Johns Hopkins has also given encouraging results.
- d) At the frontier in treatment is gene therapy. Using mice, Stuart Orkin at the Dana-Farber Center is switching off the mechanism in haemoglobin that changes it from foetal to adult.
- e) At the La Jolla Institute for Allergy and Immunology in California a short-acting anti-inflammatory drug, Lexiscan, is being tested. It reduces the production of white cells produced when sickle cells start to block blood vessels. Inhibiting the inflammation response appears to ease the vessel blockage, reduce organ damage and ease pain.
- f) Yutaka Niihara is a UCLA haematologist and head of the biopharmaceutical company Emmaus Medical. He says that a type of amino acid, L-glutamine, can reverse the oxidation that leads to sickling, and that patients who have taken oral doses had fewer pain crises and reported more energy.

Artificial platelets

- g) Scientists led from Case Western Reserve University, in collaboration with the Cleveland Clinic Foundation, have been awarded \$US 1.9 million by the US National Institutes of Health to develop injectable artificial platelets that will stick to bleeding sites and signal natural platelets to join them. Anirban Sen Gupta is an assistant professor of biomedical engineering at Case Western, and lead researcher. He says the grant will allow the team to refine the design with respect to shape, size and molecular surface, to mimic key form and function aspects of natural platelets, and to test the resulting artificial platelets in animal models.

Other

- h) Scientists from Austria, Hungary and Croatia claim¹⁷ to have identified a biomarker in blood plasma as an accurate predictor of malignant pleural mesothelioma survival and as a guide to whether aggressive surgery will extend life. They say that higher levels of fibrinogen meant shorter survival periods, and that patients with the highest fibrinogen levels would benefit more from palliative care than surgery.
- i) Scientists from Finland and Estonia report after studying blood samples from 17,000 generally healthy people that they have discovered biomarkers that strongly indicate risk of dying from underlying illnesses in the next five years¹⁸. They identified as significant the

¹⁷ in the *British Journal of Cancer*

¹⁸ *PLOS Medicine* 2014;11:e1001606, DOI: [10.1371/journal.pmed.1001606](https://doi.org/10.1371/journal.pmed.1001606)

levels of albumin, alpha-1-acid glycoprotein, citrate and the size of very-low-density lipoprotein particles.

- j) A new study compared the level of contamination on physicians' hands and stethoscopes¹⁹. Researchers found that the stethoscope and the fingertips were more contaminated than all other parts of the physicians' hands, with bacteria in general and with MRSA (methicillin-resistant *Staphylococcus aureus*) in particular. They also noted that the contamination level of the stethoscope increased with contamination of the hands. "Hand hygiene remains the primary measure for the prevention of hospital infections, and appropriate handling of stethoscopes (their cleansing immediately after use) should be part of good patient care practices," said Dr Didier Pittet, director of the Infection Control Program at University of Geneva Hospitals.

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).

Mosquito-borne diseases: zika, dengue, chikungunya and malaria

- a) Zika fever is a disease of arboviral origin, expanding its geographic area. It usually presents as an influenza-like illness with skin rash²⁰. The virus is mosquito borne. As of 7 March there were outbreaks on at least 15 Polynesian islands, including Tahiti and Bora Bora. The European Centre for Disease Prevention and Control also confirmed one case and reported 40 suspected cases on Easter Island. The virus is thought to have come with tourists from other islands, picked up by local *Aedes aegypti* mosquitos. Chilean health authorities who have responsibility on Easter Island decided not to raise a health alert, claiming the outbreak was contained and under control. However, experts fear the spread of the virus by unknowing tourists to a wide range of localities with host mosquitos.
- b) One confirmed case of Zika in French Polynesia led to hospitalisation for Guillain-Barre syndrome (GBS). The patient also had serological markers of resolute dengue which raised the question of a sequential arboviral immune stimulation. There had been observed an unusual clustering of GBS cases during concurrent circulation of Zika [virus] and 2 dengue [virus] serotypes. Experts warned that "in endemic areas, clinicians should be aware of the risk of diffuse demyelinating disorders [disorders involving damage to the myelin sheath of neurons] in case of Zika [virus] infection"²¹.
- c) The European Centre for Disease Prevention and Control estimated that more than 29,000 people in French Polynesia sought medical care for Zika-like symptoms from when the outbreak began in October to the beginning of March.

¹⁹ The study results were published 27 February in the journal *Mayo Clinic Proceedings*.

²⁰ Zika is asymptomatic in 80 per cent of cases. When the infection is symptomatic it may be mistaken for other arboviral infections like dengue or chikungunya. Symptoms include a low grade fever, arthralgia, myalgia, headache, conjunctivitis and skin rash. Post-infection weakness is usual.

²¹ Oehler E, Watrin L, Larre P, Leparac-Goffart I, Lastere S, Valour F, Baudouin L, Mallet HP, Musso D, Ghawche F. Zika virus infection complicated by Guillain-Barre syndrome-case report, French Polynesia, December 2013. *Eurosurveillance*, Volume 19, Issue 9.

- d) As at 11 March, Queensland Health reported that so far this season there had been 17 confirmed cases of dengue type 3 in Port Douglas, 117 Confirmed cases of dengue type 1 in Cairns/Innisfail and 10 confirmed cases of dengue type 1 in Townsville.
- e) The Secretariat of the Pacific Community, or SPC, says the number of dengue fever outbreaks in the region over the past year is unprecedented. Four types of dengue fever have circulated in the region at different times. It is two decades since dengue three circulated widely so people have been particularly susceptible to it. New Zealand is concerned that its northern areas, including Auckland, may experience more dengue cases. Australia has donated \$A1.5 to help Fiji fight dengue.
- f) Malaysia had 18,047 dengue cases and 36 deaths reported for the first two months of 2014 compared with 4,250 cases and eight deaths for the first two months of 2013. Experts are predicting 60,000 cases this year. The strain currently circulating is dengue type 2, a more virulent strain than usual.
- g) The Government of Hong Kong tested its preparedness for the possible community outbreak of dengue fever on 3 March in "Exercise Coral", organised by the Centre for Health Protection of the Department of Health in collaboration with government departments.
- h) Brazil, which had over one million cases of dengue reported last year, is to host football's World Cup during the dengue season this year.
- i) The *Aedes aegypti* mosquito, which spreads dengue fever and other diseases, has reappeared around Darwin Harbour, after it was eradicated in 1969, and Asian tiger mosquitoes (*Aedes albopictus*) have also been trapped. They are thought to have arrived on cargo vessels. The port area was sprayed and "fogged".
- j) *Aedes aegypti* have been found at Melbourne airport in the plastic, water-filled bollards used for traffic management.
- k) Researchers at the University of North Carolina, in the labs of Dr Ralph Baric, and Dr Aravinda de Silva, showed that a molecular hinge where two regions of a protein connect is where natural human antibodies attach to the dengue 3 virus to disable it²². Now Drs Baric and de Silva are collaborating with vaccine developers at two pharmaceutical companies to test potential dengue vaccines now in clinical trials. If these investigational vaccines don't bind to their molecular hinge, then they will probably be less effective than desired.
- l) De Silva and Baric are also attempting to deal with dengue's particular phenomenon called antibody dependent enhancement. People infected with one type of dengue usually develop a natural immune response that overcomes the virus and prevents a repeat infection. But if they are later infected with a second type of dengue, the virus is enhanced because of that first immune response. This can result in dengue haemorrhagic fever and death. A large clinical trial of a dengue vaccine, conducted in Thailand in 2011, therefore contained a mix of the four types of dengue then known. However the vaccine proved only partially protective. If these researchers can isolate the major epitopes (binding sites) for each dengue type, they know from their experiments so far that they could modify a virus with all the epitopes and have the basis for a vaccine against all types²³.
- m) A major outbreak of chikungunya in the Caribbean has concerned US authorities expecting it to spread to their southern states.
- n) The Asian Development Bank has established a Regional Malaria and Other Communicable Disease Threats Trust Fund. Australia contributed \$US 16 million.

²² The finding was published in the *Proceedings of the National Academy of Sciences*,

²³ de Silva and Baric's also believe their research could be relevant in other fields where there is no vaccine..

"The general idea is that a complex protein-interaction site can now be moved from one virus to another," de Silva said. For instance, an epitope from a virus like hepatitis C could be moved onto the live virus used in the measles vaccine. This new chimeric virus would simultaneously offer people protection against hepatitis C and measles. He went on to suggest that a virus might not even be needed. "We might just need to create the epitope that we know antibodies can bind to. And that would serve as the vaccine."

Influenza: strains, spread, prevention and treatment

H7N9

- a) In January and February of 2014, 72 people died from H7N9 in China, more than in the whole of 2013²⁴. Total cases in China had been 226 in those two months.
- b) By the first week of March, Hong Kong had confirmed its sixth case of H7N9, with infection identified once more as having occurred on the mainland in a live poultry market. Hong Kong had banned live poultry imports from the mainland. Given that for 2013 and 2014 combined, 389 cases of H7N9 had been confirmed on the mainland up to 10 March, Hong Kong implemented other border protection measures²⁵ and offered advice for travellers²⁶. The Centre for the Health Protection of the Hong Kong Department of Health continued to advise anyone visiting China to avoid live poultry markets and to cook poultry and eggs thoroughly.
- c) By the end of February South China's Guangdong province had selected Guangzhou, Shenzhen and Foshan as pilot cities to allow only frozen poultry to be sold at markets. In the Zhejiang province capital of Hangzhou city officials closed the main poultry markets on February 15, some permanently, with those in two outlying districts closed for 3 months. The city also banned the transport of live poultry on public transport and the raising of poultry in urban areas. To allay consumers' concerns, authorities are developing a tag for frozen poultry to show that it has passed rigid inspection and quarantine.
- d) A Chinese vaccine for H7N9 may be available by May, according to Li Lanjuan, of the Chinese Academy of Engineering. Adimmune, Taiwan's human vaccine producer, will launch the second phase of human trials of its H7N9 vaccine in March and expects to begin mass production in June. It will be able to make 3 million doses of vaccine per month. In March, Novavax announced in the US the initiation of a Phase I/II clinical trial of its H7N9 avian influenza VLP (virus-like particle) vaccine candidate.
- e) The European Centre for Disease Prevention and Control provided a risk assessment of human avian influenza A infection in China, dated 24 February. It said the faster pace of human infections in the second wave might point to enhanced transmissibility of the virus, a larger wild or domestic bird reservoir, an increase in the number of exposed people, a seasonal pattern, or multiple influences.
- f) The Public Health Agency of Canada (PHAC) noted that in the second wave, cases were less skewed towards the elderly, though males still predominated. Limited person-to-person transmission was noted with close contact, but PHAC said that could change.
- g) In the northern Spring of 2013 H7N9 virus was isolated from a seemingly healthy tree sparrow in a Shanghai park, highlighting the need to monitor the presence of the virus in a number of species²⁷.
- h) Chinese researchers suggested online in *The Lancet* that H9N2 avian flu appears to be an "incubator" for flu viruses of wild bird origin so that culling poultry infected with H9N2 might curb human infection. They noted that H10N8, which recently killed two people in Jiangxi

²⁴ In 2013 there were 144 cases and 46 deaths recorded.

²⁵ A spokesperson said: "All boundary control points have implemented disease prevention and control measures. Thermal imaging systems are in place for body temperature checks of inbound travelers. Random temperature checks by handheld devices have also been arranged. Suspected cases will be immediately referred to public hospitals for follow-up investigation."

²⁶ Through airport posters, in-flight announcements, health inspections and advice to the travel industry. Travellers returning from avian-flu infected regions with fever or respiratory symptoms were asked to wear masks, seek medical attention and reveal their travel history. Healthcare professionals were asked to question whether presenting patients had had contact with poultry, other birds or their droppings

²⁷ Zhao B, Zhang X, Zhu W, Teng Z, Yu X, Gao Y, et al. "Novel avian influenza A(H7N9) virus in tree sparrow, Shanghai, China, 2013" in *Emerging Infectious Diseases* 20 (5), May 2014

province, has a genetic lineage similar to H7N9, including internal genes from H9N2 in poultry. They called on health officials everywhere to close live poultry markets or disinfect them regularly.

- i) A report funded in part by the US Geological Survey²⁸ says the North Atlantic region is a significant pathway to allow the movement of avian influenza between Europe and North America in either direction. Birds congregate in Iceland's wetlands during migration, providing opportunities for transmission and comingling of viruses.

H5N1

- j) Bird flocks, wild and farmed, continue to be found in a number of countries to be infected with H5N1, sometimes with associated culls²⁹. Occasional human cases occur where there has been some association with infected birds. To the beginning of March, Cambodia had reported six cases this year, some fatal.
- k) The Japanese Ministry of Health, Labour and Welfare last August awarded a cell culture vaccine production facility capacity building grant to the Daiichi Group in the expectation that H5N1 vaccine would be supplied by the end of March 2014. The company found that vaccine yields declined during the purification process and this has delayed the achievement of its goal.

H1N1

- l) A(H1N1) or swine flu which caused a pandemic scare in 2009 has been the dominant flu strain during the US winter and has been experienced in other northern hemisphere countries. It can be expected to be around to some extent also during the Australian flu season. Queensland Health has already confirmed several cases on Palm Island.
- m) Another study has examined disparate ethnic experience with 2009 pandemic H1N1 influenza, this time using data from Ontario³⁰. While the study concluded that pH1N1 cases were more likely to come from certain ethnic groups compared with test-negative controls³¹, further work is needed to establish whether these disparities arise due to social or biological factors, and to develop approaches to reduce the burden of a future influenza pandemic.

Influenza: general

- n) US firm VaxInnate has begun a Phase I trial of its recombinant quadrivalent vaccine for seasonal flu.

²⁸ Robert J. Dusek, Gunnar T. Hallgrimsson, Hon S. Ip, Jón E. Jónsson, Srinand Sreevatsan, Sean W. Nashold, Joshua L. TeSlaa, Shinichiro Enomoto, Rebecca A. Halpin, Xudong Lin, Nadia Fedorova, Timothy B. Stockwell, Vivien G. Dugan, "North Atlantic Migratory Bird Flyways Provide Routes for Intercontinental Movement of Avian Influenza Viruses", *PlosOne*, March 19, 2014. DOI: 10.1371/journal.pone.0092075

²⁹ The website of the US Geological Survey lists round 170 bird species as affected by H5N1. (<http://www.nwhc.usgs.gov/disease_information/avian_influenza/affected_species_chart.jsp>).

³⁰ Debeka Navaranjan, Laura C Rosella, Jeffrey C Kwong, Michael Campitelli and Natasha Crowcroft, "Ethnic disparities in acquiring 2009 pandemic H1N1 influenza: a case-control study", *BMC Public Health* 2014, **14**:214 doi:10.1186/1471-2458-14-214. The electronic version can be found online at: <http://www.biomedcentral.com/1471-2458/14/214>

³¹ Ethnic disparities in hospitalization and death due to pH1N1 were known. This study examined ethnic disparities in acquiring the disease. The researchers found adult cases were more likely than controls to be self-classified as East/Southeast Asian, South Asian and Black. Paediatric cases were more likely to be self-identified as Black). However, paediatric cases without risk factors for severe influenza infection were more likely to be South Asian, Black, and West Asian/Arab, Latin American or Multi-racial groups.

- o) A meta-analysis published in *The Lancet Respiratory Medicine*³² suggested Tamiflu reduced the death rate in the 2009 H1N1 pandemic. The research was led by Nyugen-Van-Tam, a professor of health protection at the University of Nottingham, and funded by Hoffman-La Roche, which makes Tamiflu.
- p) Romark Laboratories is sponsoring a Phase III trial of a formulation of mitazoxzide, known as NT-300, alone and in combination with Tamiflu, as treatment for acute but uncomplicated flu.

MERS-CoV

- a) WHO's global MERS tally, updated 14 March, was 196 cases and 83 deaths. Saudi Arabia by then accounted for 157 cases, with the death toll 63.
- b) A study says the MERS virus has been “extraordinarily common” in camels for at least 20 years, and may have been passed directly to humans from the animals³³.
- c) Health experts warned that MERS-CoV infections that may be acquired in healthcare facilities illustrate the need to continue to strengthen infection prevention and control measures³⁴.
- d) WHO issued advice to member states about appropriate response to MERS-CoV³⁵. It has not to date advised special screening at points of entry with regard to this event, nor does it currently recommend the application of any travel or trade restrictions.
- e) Researchers reported in the *Proceedings of the National Academy of Sciences* that they have developed a mouse model for MERS -CoV infection, which could provide an opportunity for early testing of drugs and vaccines.

³² doi:10.1016/S2213-2600(14)70041-4

³³ ³³ Alagaili AN, Briese T, Mishra N, et al: “Middle East respiratory syndrome coronavirus infection in dromedary camels in Saudi Arabia”. *MBio*. 2014; 5(2). pii: e00884-14. doi: 10.1128/mBio.00884-14

³⁴ The advice : *Healthcare facilities that provide care for patients suspected or confirmed with MERS-CoV infection should take appropriate measures to decrease the risk of transmission of the virus to other patients, healthcare workers and visitors. Education and training for infection prevention and control should be provided to all healthcare workers and regularly refreshed. Early identification of the MERS-CoV is important, but not all the cases could be reliably and timely detected, especially when disease is mild or presents atypically. Therefore, it is important to ensure that standard precautions are consistently used for all patients and all work practices all of the time, regardless of suspected or confirmed infection with the MERS-CoV or any other pathogen. Droplet precautions should be added when providing care to all patients with symptoms of acute respiratory infection, and contact precautions plus eye protection should be added when caring for confirmed or probable cases of MERS-CoV infection. Airborne precautions are indicated when performing aerosol generating procedures. When the clinical and epidemiological clues strongly suggest MERS-CoV, the patient should be managed as potentially infected, even if an initial test on a nasopharyngeal swab is negative. Repeat testing should be done when the initial testing is negative, preferably on specimens from the lower respiratory tract.*

³⁵ *WHO encourages all of its member states to continue their surveillance for severe acute respiratory infections (SARI) and to carefully review any unusual patterns. Healthcare providers are advised to maintain vigilance. Recent travelers returning from the Middle East who develop SARI should be tested for MERS-CoV as advised in the current surveillance recommendations. All WHO member states are reminded to promptly assess and notify WHO of any new case of infection with MERS-CoV, along with information about potential exposures that may have resulted in infection and a description of the clinical course. Investigation into the source of exposure should promptly be initiated to identify the mode of exposure, so that further transmission of the virus can be prevented. People at high risk of severe disease due to MERS-CoV should avoid close contact with animals when visiting farms or barn areas where the virus is known to be potentially circulating. For the general public, when visiting a farm or a barn, general hygiene measures, such as regular hand washing before and after touching animals, avoiding contact with sick animals, and following food hygiene practices, should be adhered to. WHO does not advise special screening at points of entry with regard to this event nor does it currently recommend the application of any travel or trade restrictions.*

- f) Scientists have analysed 32 MERS-CoV isolates from Saudi Arabia and found little genomic evidence that the virus is evolving to become more easily transmitted between humans.

Other diseases: occurrence, prevention and treatment

- a) Chimerix announced enrolment of the planned 450 patients in their phase III SUPPRESS trial of brincidofovir is on track to provide results in mid-2015. Positive data would support accelerated approval of brincidofovir for the prevention of cytomegalovirus (CMV), the first approval of an antiviral for the prevention of CMV in recipients of bone marrow transplants.
- b) Dr Graham Jackson, of the University College of London Institute of Neurology, and his colleagues have reported on a blood test screening for infection with the agent responsible for variant Creutzfeldt-Jakob disease (vCJD)³⁶, performing well enough to be used to screen populations at risk for the disease.
- c) Given the spread of microorganisms with the New Delhi metallo-beta-lactamase (NDM) resistance mechanism, both across bacterial species and across geographic boundaries, the Pan American Health Organization/WHO emphasised again the need to establish prevention and infection control in health care settings, as well as surveillance and detection.
- d) An HIV baby born in Los Angeles last April began treatment four hours after birth and is showing no signs of the disease. A child from Mississippi received similar treatment over three years ago and is also reported to be disease free. A clinical trial will be conducted with 60 babies who are born infected put on drugs within 48 hours.
- e) Seattle BioMed, the University of Washington, Seattle Children's Hospital, the Fred Hutchinson Cancer Research Center, and Rockefeller University have together been awarded a grant from NIAID toward developing an HIV vaccine.
- f) Scientists at the University of Illinois have developed a microchip that can diagnose the HIV virus. Their small device takes a drop of blood from a patient³⁷.
- g) The phrase "pertussis paradox" describes the rise in reported cases of pertussis (whooping cough) seen in the developed world after a switch was made to a more tolerable, less reactogenic vaccine³⁸. The US and Spain are amongst countries which have seen increased pertussis cases this year in the northern hemisphere winter. Australian researchers have also looked at the vaccine pressure involved with the continued evolution of the organism³⁹.
- h) To eradicate polio by 2018, WHO recommends that by the end of 2015, all children receive routinely at least one dose of Inactivated Polio Vaccine in over 120 countries that solely use Oral Polio Vaccine. Sanofi Pasteur and the Bill & Melinda Gates Foundation are amongst organizations making financial contributions. Iraq has announced its first polio case in fourteen years.
- i) A consortium including the University of Texas Medical Branch at Galveston (UTMB) has been awarded a grant by NIAID to develop vaccines and treatment for the Ebola and Marburg viruses. Researchers from the US Army Medical Research Institute of Infectious

³⁶ In *JAMA Neurology*, published online 3 Mar 2014, doi:10.1001. They said the assay was of sufficient sensitivity and specificity to warrant a major study comparing vCJD prevalence in the UK with a population unexposed to BSE.

³⁷ Watkins NN, Hassan U, Damhorst G, Ni H, Vaid A, Rodriguez W, Bashir R. "Microfluidic CD4+ and CD8+ T Lymphocyte Counters for Point-of-Care HIV Diagnostics Using Whole Blood." *Science Translational Medicine*. 2013.

³⁸ Lutwick LI, Preis J: "Pertussis": In: *Emerging Infectious Diseases: Clinical Case Studies*. Ergonul O, Can F, Akova M, Madoff L (eds), 2014, Elsevier, (in press)

³⁹ Lam C, Octavia S, Ricafort L, et al: "Rapid increase in pertactin-deficient *Bordetella pertussis* isolates, Australia". *Emerg Infect Dis* 2014; 20(4)

Diseases (USAMRIID) and their industry partners recently showed a small-molecule drug candidate protects macaques against Marburg⁴⁰.

⁴⁰Travis K. Warren, Jay Wells, Rekha G. Panchal, Kelly S. Stuthman, Nicole L. Garza, Sean A. Van Tongeren, Lian Dong, Cary J. Retterer, Brett P. Eaton, Gianluca Pegoraro, Shelley Honnold, Shanta Bantia, Pravin Kotian, Xilin Chen, Brian R. Taubenheim, Lisa S. Welch, Dena M. Minning, Yarlagadda S. Babu, William P. Sheridan, and Sina Bavari. "Protection against filovirus diseases by a novel broad-spectrum nucleoside analog BCX4430": *Nature*, published online 2 Mar 2014 (1800 London time/1300 Eastern US time). DOI: 10.1038/nature13027.