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:

* Both Health Canada and the US Food and Drug Administration have approved Sobi and Biogen’s Alprolix (a bioengineered version of blood coagulation factor IX, Fc fusion protein). This is the first long-acting haemophilia B therapy to be approved (page 3).
* Baxter International announced it is splitting into two companies, focussing on biopharmaceuticals and medical products respectively (page 4).
* The Netherlands is revising its regulatory regime for biological research after Dutch scientists changed an avian influenza virus so it would be more contagious (page 5).
* A study has shown that “the susceptibility of stored red blood cells to erythrophagocytosis[[1]](#footnote-1) significantly increased with longer storage time of the red blood cell units (page 7).
* Researchers are questioning on ethical grounds routine treatment of pregnant women who are Rhesus D (RhD) negative with Anti D immunoglobulin; now that it is possible to determine foetal blood group by testing the mother’s blood (page 7).
* Professor Marc Turner, medical director at the Scottish National Blood Transfusion Service, announced that testing of mature red blood cells made from human induced pluripotent stem cells will begin in 2016 (page 8).
* The World Health Organization (WHO) issued a statement responding to a spike in MERS-CoV cases, admitting “Approximately 75 per cent of the recently reported cases are secondary cases, meaning that they are considered to have acquired the infection from another case through human-to-human transmission” (page 11).
* The emergence of Ebola Virus Disease in Africa remains a concern (page 11).

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# 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.*

* 1. Bluebird bio has begun US clinical trials of a modified blood stem cell infusion it hopes will treat the inherited blood disorder beta-thalassemia major. The first of a Phase I/II trial of just up to 15 patients has received the drug LentiGlobin, or BB305. Standard treatment involves regular blood transfusions and iron chelation therapies, while LentiGlobin is designed to restore haemoglobin production. A trial in seven patients with both beta-thalassemia major and sickle cell disease was initiated in France in December.
	2. Israel-based Kamada’s drug Alpha-1 Antitrypsin (AAT) will be tested in a new round of clinical trials for [**cystic fibrosis**](http://bionews-tx.com/news/news-tags/cystic-fibrosis/) **in the second half of 2014. Meanwhile an AAT trial for AAT Deficiency, evaluating the safety and efficacy of the inhalable version of the drug in a** double-blind, placebo-controlled study, should be ready to report top-line data by May.
	3. Emmaus Life Sciences reported that 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 met both primary and secondary endpoints. The trial enrolled 230 patients aged from 5 years upwards. The randomized, double-blind, placebo-controlled trial suggested a significant reduction in the median frequency of sickle cell crises over a 48-week period and a statistically significant reduction in the median frequency of hospitalizations over a 48-week time period. The company intends to submit a New Drug Application to the FDA in mid-2014 for marketing approval. The treatment has orphan drug designation in the US and Europe, and fast track designation from the FDA.

# Regulatory

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

* 1. Swedish Orphan Biovitrum (Sobi) and its partner Biogen Idec announced on 21 March that Health Canada had approved Alprolix (a bioengineered version of blood coagulation factor IX, Fc fusion protein), rFIXFc, for the control and prevention of bleeding episodes and for prophylaxis in patients aged 12 and older, with haemophilia B[[2]](#footnote-2). Alprolix is the first approved long-acting haemophilia B therapy and is indicated to prevent or reduce the frequency of bleeding episodes with prophylactic treatment scheduled once weekly or once every 10-14 days, rather than two or three times weekly as with current treatments. This was the first regulatory approval worldwide for Alprolix, which was also under review by regulatory authorities in several other countries, including the United States, Australia and Japan. A week after the Canadian approval, Alprolix received approval from the US Food and Drug Administration (FDA). Thomson Reuters estimates that Alprolix may generate sales of about $US 286 million annually by 2019 and Eloctate, a FVIII product being developed by the same partnership, may generate $1.1 billion annually. Before filing for EU approval, the partners need to complete paediatric trials, a phase III study called Kids B-LONG.
	2. Fenwal, a Fresenius Kabi company, received FDA approval to include new clinical data in the product label of its platelet additive solution, InterSol. A medical chart review of 14,000 transfusions examined at adverse events from platelet transfusion, with and without the additive solution. The review found platelet transfusions using InterSol led to a 0.55 per cent adverse event reaction rate, while transfusions using plasma platelets led to a 1.37 percent adverse event reaction rate.
	3. The FDA’s Blood Products Advisory Committee (BPAC) unanimously voted to recommend approval of Immucor's HEA Molecular BeadChip Test as safe and effective for the molecular typing of human erythrocyte antigen (HEA) phenotypes in 35 blood group systems[[3]](#footnote-3). The test received the CE Mark in July 2010 and is commercially available in Europe and other international markets, but in the US is available for Research Use Only. More than 700,000 tests have been processed with Immucor's HEA assay worldwide.The FDA will take into account the BPAC's advice in making its decision on whether to approve the HEA BeadChip Test for blood group typing in the US. A decision is expected later this year.

# 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.*

* 1. CSL won the award for top listed Australian company at the Corporate Performance Awards in Sydney. Fund managers approved of its wise choice of acquisitions and its dominance over its competitors. CSL’s market capitalisation increased from $20 billion five years ago, to $34 billion currently. Sales increased from $3.8 billion in 2008 to $5.5 billion in 2013, while earnings per share rose 54 per cent, attributable to rising profits and share buybacks[[4]](#footnote-4). Shareholders have earned an average annual return of 28.5 per cent over the last decade. The CEO Paul Perreault attributes CSL’s success to “international expansion, clear strategy and focused approach”. He said the company “has affiliates in close to 30 countries, and there is still plenty of room for the company to grow both in developed and emerging markets”.
	2. Anthony Farina, a former journalist who led global public affairs at DuPont, has moved to CSL Limited as vice president of communications and corporate affairs. Farina is based in King of Prussia, Pennsylvania. He was previously in the Delaware statehouse, as press secretary and executive director of communications for Gov. Tom Carper, who is now a Democratic US senator.
	3. At the end of March, Baxter announced it was splitting into two companies, focussing on biopharmaceuticals and medical products respectively. Baxter CEO Robert Parkinson will head the medical-products company, which will retain the Baxter International name. It was responsible for $US9 billion in sales in 2013. It sells intravenous (IV) solutions and nutritional therapies, drug-delivery systems and administration sets, premixed and other injectable drugs, inhalation anaesthetics and hospital-based biosurgery products. The biopharmaceuticals business generated 2013 annual revenues of $US 6illion and develops treatments for haemophilia and other bleeding disorders, immune deficiencies, burns and shock. This business aims to improve diagnosis, treatment and standards of care, enhance capacity to meet growing demand for biotherapeutics, leverage expertise into new emerging therapeutics through acquisitions and collaborations, and develop a new product pipeline focused on new and effective treatments that address unmet medical needs. Baxter will make a tax-free distribution of shares in the biopharmaceuticals business to its shareholders, completing the transaction by mid-2015. The company expects to complete the transaction by mid-2015. Current president of BioScience, Ludwig Hantson, will run the biopharmaceuticals firm. Baxter expects the split will facilitate efficient management focus on distinct businesses, effective commercialization of new products, allocation of resources to growth areas, and improved profitability. The corporate headquarters of both companies will be located in northern Illinois.
	4. Biotest increased its sales by 13.8 per cent last year. Sales rose the 500 million euro mark for the first time, up from 440 million euros in the previous financial year. Biotest's US launch of Bivigam meant sales in the therapy segment rose 16.7 per cent from 330.9 million euros to 386.2 million euros. Sales in Germany rose 4.5 per cent during 2013. Biotest increased its operating profit by 20.4 percent, from 44.7 million euros in 2012 to 53.8 million euros in 2013. Biotest’s Board of Management expects sales and operating profit in the financial year 2014 to grow about ten per cent.
	5. Shares of **Haemonetics Corporation**, a US blood management solutions company, slumped by round 10 per cent when it announced it had not been considered by the American Red Cross for a new supply contract for certain whole blood collection kits. Haemonetics has been supplying 1.8 million in-line whole blood collection kits to the American Red Cross per annum.
	6. Genzyme, a Sanofi company, exercised its right to buy 344,448 shares of Alnylam’s common stock. In January 2014, Alnylam and Genzyme formed a collaboration for the development and commercialization of RNAi therapeutics as genetic medicines.
	7. Cerus Corporation reported that the Humanitarian Foundation Swiss Red Cross has granted funds to Swiss Tranfusion SRC to adapt the INTERCEPT Blood System for red blood cells for pathogen inactivation and transfusion of whole blood for sub-Saharan African countries. The initial funding of 1.5 million Swiss francs is for the project’s feasibility phase and for the completion of in vitro studies to support patient clinical trials. It is common practice in many African countries to transfuse whole blood, whereas in developed countries platelets, plasma or red cells are more often transfused[[5]](#footnote-5). In addition to the transfusion-transmitted pathogens such as HIV HBV HCV and bacteria, there are risks in Africa due to endemic infections such as dengue, malaria, chikungunya and Leishmania for which screening assays may not be available. William ‘Obi’ Greenman, Cerus’ president and chief executive officer, said: “By leveraging our experience using the S-303 pathogen inactivation technology in red cell components we hope to be able to develop a system for whole blood that does not require electricity to inactivate pathogens or leukocytes that may be present in whole blood. Maternal mortality in sub-Saharan Africa is commonly a function of haemorrhagic complications from childbirth and we believe that this technology has the potential to play a meaningful role in improving blood safety and availability in the region and correspondingly improve patient outcomes.”

# 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.*

* 1. The Netherlands is revising its regulatory regime for biological research after Dutch scientists changed an avian influenza virus so it would be more contagious. The new regime will incorporate "lessons learned" from a continuing dispute over the H5N1 gain-of-function research of virologist Ron Fouchier[[6]](#footnote-6), according to Ayse Aydin, from the Dutch Foreign Affairs Ministry's nonproliferation and disarmament division. Aydin said authors of the policy would consider findings from a December [report](https://www.knaw.nl/en/news/news/early-assessment-of-science-versus-security-vital-for-biosecurity) by the Royal Netherlands Academy of Arts and Sciences. One of its recommendations called for the establishment of a government panel to issue nonbinding guidance on research proposals with biological-weapon implications.
	2. The Indonesian government has received a grant from German-based banking institution KfW to strengthen its avian influenza prevention and control system for animal health. The grant has been used to construct and equip a state-of-the-art Bio-Safety Level (BSL) 3 facility at the National Veterinary Drug Assay Laboratory (NVDAL) in Bogor, West Java province.
	3. A US study[[7]](#footnote-7), of patients hospitalized with [myocardial infarction](http://www.renalandurologynews.com/cardiovascular-disease-cvd/section/627/), showed the incidence of [hospital-acquired anaemia (HAA)](http://www.renalandurologynews.com/anemia/section/624/) varies considerably between hospitals. Adam C. Salisbury, M.D., from Saint Luke's Mid-American Heart Institute in Kansas City, Mo., and colleagues examined the incidence of HAA in a cohort of 17,676 patients with acute myocardial infarction without anaemia at admission. They concluded: "we observed significant variability in the incidence of HAA across hospitals and found a lower risk of HAA at teaching centers, suggesting that qualitative studies of the relation between HAA and processes of care are needed to identify targets for quality improvement".
	4. Another US study[[8]](#footnote-8) identified considerable variation across US hospitals in the rate of major bleeding events among patients with non-STEMI or "non-ST segment elevation myocardial infarction"[[9]](#footnote-9). It included 99,200 patients (at 267 hospitals) enrolled in the National Cardiovascular Data Registry (NCDR) Acute Coronary Treatment and Intervention Outcomes Network Registry between January 2007 and June 2010.
	5. In Ontario, Canada Health Minister Deb Matthews introduced [legislation](http://www.thespec.com/news-story/4424277-province-moves-to-halt-pay-for-plasma-clinics/) on 20 March to ban pay-for-plasma clinics in Ontario and urged her counterparts in other provinces to do the same)[[10]](#footnote-10). The Krever Commission (into the blood contamination that left 30,000 Canadians with HIV and hepatitis C), recommended in 1997 that donors of blood and plasma should not be paid except in rare circumstances. For the past three decades Cangene Corporation in Winnipeg has been licensed by Health Canada to pay donors for specialised plasma. Canada imports the majority of its plasma products from the US, where some donors are paid. Now Health Canada and Canadian Blood Services support the introduction of privately owned pay-for-plasma clinics in Canada.
	6. Researchers found patient factors and treatments explained less than one-third of hospital-level variation. They concluded: “A better understanding of etiologies of hospital variation in bleeding complications may help institutions target high-risk patients and provide optimal care in this population.

# Safety and patient blood management

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

* 1. A study published in *Vox Sanguinis* in April[[11]](#footnote-11) concluded that “the susceptibility of stored red blood cells (RBCs) to erythrophagocytosis[[12]](#footnote-12) significantly increased with longer storage time of the RBC units. Storage duration of RBCs had a greater influence on in vitro erythrophagocytosis than the chronological age of the RBCs at donation.”
	2. Research at the University of Alabama[[13]](#footnote-13) has examined adherence to a restrictive transfusion policy in [gynaecologic](file:///C%3A%5Csearch_results.php%3Fsearch_term%3Dgynecologic%26cat%3Da) [oncology](file:///C%3A%5Csearch_results.php%3Fsearch_term%3Doncology%26cat%3Da) patients. They undertook a retrospective chart review of 582 patients[[14]](#footnote-14) undergoing 2,276 transfusions with packed red blood cells from December 2008 to September 2011. Cancer type and stage, surgical procedure, [haemoglobin](file:///C%3A%5Csearch_results.php%3Fsearch_term%3Dhemoglobin%26cat%3Da) values, transfusions with packed red blood cells, intraoperative blood loss, and [postoperative](file:///C%3A%5Csearch_results.php%3Fsearch_term%3Dpostoperative%26cat%3Da) complications were considered. Transfusions were identified as compliant or noncompliant. Gynaecologic oncologists were 81.1per cent compliant with the restrictive transfusion policy. Noncompliant transfusions were usually given on the day of surgery when intraoperative blood loss was less than 1500 cc, and for [asymptomatic](file:///C%3A%5Csearch_results.php%3Fsearch_term%3Dasymptomatic%26cat%3Da) [anaemia](file:///C%3A%5Csearch_results.php%3Fsearch_term%3Danemia%26cat%3Da). Transfusions ordered in single unit increments represented 64.7 of the total. Compliant and noncompliant transfusions showed no significant difference in postoperative infections, thrombotic events, and mortality. The majority of gynaecologic oncology patients received transfusions compliant with the restrictive transfusion policy. Researchers concluded “Efforts to improve compliance should focus on limiting transfusions when the hemoglobin is >= 7 g/dL and transfusing in single packed red blood cell unit increments."
	3. Beginning in the 1960s a number of countries have given pregnant women who are Rhesus D (RhD) negative Anti D immunoglobulin to reduce the incidence of haemolytic disease of the foetus and new-born[[15]](#footnote-15). This routine was adopted as it was not then possible to identify the foetal blood group. Since 1997 it has been possible to determine foetal blood group by testing the mother’s blood and researchers are now questioning on ethical grounds routine treatment with Anti D immunoglobulin[[16]](#footnote-16).
	4. Daiichi Sankyo reported data from two pre-specified subgroup analyses of East Asian patients[[17]](#footnote-17) with venous thromboembolism (VTE) or non-valvular atrial fibrillation (NVAF) enrolled in two Phase III edoxaban studies. The findings of the two subgroup analyses of 1,101 East Asian patients enrolled in the Hokusai-VTE study and 1,943 East Asian patients enrolled in the ENGAGE AF-TIMI 48 study were consistent with findings in global study populations. These showed edoxaban was comparable with warfarin for the treatment and prevention of VTE and for the prevention of stroke or systemic embolic events in NVAF patients.
	5. Portola Pharmaceuticals began a Phase II proof-of-concept study to evaluate its Factor Xa inhibitor reversal agent andexanet alfa as a reversal agent for Daiichi Sankyo's oral, once-daily, direct Factor Xa inhibitor edoxaban in healthy volunteers. Andexanet alfa has been designated a breakthrough therapy by the FDA.

# 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.*

* 1. Marc Turner, medical director at the Scottish National Blood Transfusion Service, is leading a £5 million project at the University of Edinburgh which aims to underpin the manufacturing of blood on an industrial scale. He recently announced: “We have made red blood cells, for the first time, that are fit to go in a person's body.” Testing of mature red blood cells made from human induced pluripotent stem cells will begin in 2016. The trial is expected to involve three patients with thalassemia who will receive about 5ml of blood to start with to check the cells behave normally in the body.
	2. A study[[18]](#footnote-18) by FDA researchers[[19]](#footnote-19) could assist in designing a therapy for diseases where red cells fracture eg in some complications of sickle cell anaemia and malaria. The work might also facilitate development safe and effective haemoglobin-based oxygen carriers for treating blood loss due to trauma. The blood protein haptoglobin could be used to block the destructive chemical reactions set off by haemoglobin escaping fractured red blood cells. Haptoglobin occurs naturally. It binds strongly to free haemoglobin and prevents it from producing tissue-damaging molecules in the bloodstream. The haemoglobin instead damages the attached haptoglobin. The immune system then eliminates them both.
	3. Using a University of Pennsylvania-designed device to monitor cerebral blood flow (CBF) non-invasively and continuously in acute stroke patients, researchers are studying how head of bed (HOB) positioning affects the flow of blood to the brain. Most people hospitalised l with an acute stroke are kept flat for at least 24 hours in the hope of increasing CBF in areas round the damaged tissue. Researchers reported in the journal *Stroke* that, while this practice increased CBF in the affected hemisphere in the majority of stroke patients, about one quarter of the patients had highest CBF with their head elevated. "This study illustrates the potential of using advanced technology to make individualized treatment decisions in real time" said senior author John A. Detre, professor of Neurology and Radiology in the Perelman School of Medicine at the University of Pennsylvania. "While, on average, our findings support current guidelines to lay patients flat following stroke, they also suggest that for some stroke patients, lying flat may be either unnecessary or even harmful. Future studies examining clinical outcomes after stroke and using optical CBF measurements to guide management will be needed to confirm this."
	4. To give researchers a tool to analyse how blood cells turn cancerous, scientists have located the regions which make a specific gene active or silent in a blood cell, regions called enhancers and promoters". Until now, researchers could only recognise the unique signatures of enhancers and promoters, however, their exact location, as well as the association of specific enhancers to specific blood cells, remained unclear," said Alistair Forrest of the RIKEN Centre for Life Science Technology in Yokohama. Blood stem cells give rise to erythrocytes (red blood cells), leukocytes (white blood cells), and thrombocytes (platelets). The gene expression changes that occur in the stem cell to dictate what type of blood cell it becomes, or even if it develops a genetic mutation, are not completely understood. Forrest says: "Now that we have these incredibly detailed pictures of each of these cell types, we can now work backwards to compare cancer cells to the cells they came from originally to better understand what may have triggered the cells to malfunction." The study appeared in the journal *Blood,* the Journal of the American Society of Hematology.
	5. **A new study**[[20]](#footnote-20) **by** Sarkis Mazmanianhis team at the California Institute of Technology (Caltech) in Pasadena **suggests that intestinal bacteria play an important role in the development of white blood cells that help the body's immune system fight infection.**
	6. Researchers at the Johns Hopkins Children's Center have described a protein that regulates the body's immune response to cytomegalovirus (CMV), which is a disease particularly devastating to neonates and those the immunocompromised-including organ transplant recipients.
	7. Researchers led from University College, London have reported that long-term brain damage from stroke could be lessened by saving cells known as pericytes that control blood flow in capillaries. Theresearch, published in Nature, suggests pericytes are the main regulator of blood flow to the brain, and tighten and die around capillaries after stroke. Specific chemicals reduce pericyte death in the laboratory, and might be developed into drugs to treat stroke victims.

# Infectious diseases

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

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

* 1. In contrast with a number of other countries round the tropics, the Philippines has recorded a drop in dengue cases so far this year. It reported 11,000 dengue cases to 1 March, a 52 per cent decrease over the same period last year. 40 fatalities were reported in the first two months of this year.
	2. There has been a continuing high incidence of dengue in West Jakarta..
	3. Britain's wet winter and warm spring has raised dengue fears as Aedes aegypti mosquitoes are known to be present.
	4. There is concern in Japan that rising temperatures are expanding the habitat of the dengue-carrying tiger mosquito across the northern part of the country and that dengue may have returned for the first time in six decades. It appears that a German traveller contracted dengue in January.
	5. Transmission of dengue relies on mosquitoes (Aedes aegypti) living long enough for the virus to infect the salivary glands. Survival rates of wild mosquitoes are difficult to measure. Hon Mieu Island in central Vietnam has been the site of a pilot release of Aedes aegypti infected with a strain of Wolbachia pipientis bacterium that induces virus interference and mosquito life-shortening. The bacterium was initially studied as a dengue control in Queensland, and has also been deployed in Indonesia. In the Vietnam trial, mosquito survival was found to be highest in the dry/cool (January-April) and dry/hot (May-August) seasons, when more of the Hon Mieu mosquitoes survived to an age that they were able to transmit dengue. The work led to season specific Aedes aegypti survival models to improve mosquito control strategies to break the dengue transmission cycle.[[21]](#footnote-21)
	6. Sanofi Pasteur hopes to be first to market with a dengue vaccine in 2015[[22]](#footnote-22). It began producing the vaccine last July to ensure it is ready to ship if the product is approved by regulators. Based on earlier clinical trial results, approval may not be assured. Data released in 2012 from a trial in Thailand showed Sanofi’s vaccine did not protect against one the disease’s four strains, which was the most prevalent in the country at the time. The vaccine, which is given in three shots six months apart, is currently being tested in 20,000 children aged 9-16 in Latin America and in 10,000 children aged 2-14 in southeast Asia. Guillaume Leroy, who heads the dengue vaccine project at Sanofi Pasteur, said the results of this final trial would start “trickling in” from mid-year Sanofi hopes to present consolidated clinical results at a conference on tropical diseases in November. Where will Sanofi market first if results are positive? “It’s hard to predict which one could be first, but one can easily imagine it’ll be one of the bigger countries, such as Brazil, Mexico, Malaysia, maybe the .Philippines,” Leroy said.
	7. Takeda, Merck, GlaxoSmithKline and Novartis are also working on dengue vaccines, but these are not yet in phase III trials.
	8. Researchers at the Florida campus of The Scripps Research Institute have a $US2.3 million grant to study a family of viruses (“flavivirus”) that cause dengue fever, West Nile, yellow fever and other diseases spread by mosquitoes and ticks. These diseases cause flulike symptoms, severe pain and sometimes encephalitis. Flaviviruses are estimated to affect 2.5 billion people globally each year and cause hundreds of thousands of deaths each year. There are no treatments but a small number of vaccines provide protection against a few.
	9. The University of Alabama at Birmingham has been awarded $35 million from the US National Institute of Allergy and Infectious Diseases (NIAID) to establish a research centre developing new drugs for global infectious disease threats. The Antiviral Drug Discovery and Development Center, or AD3C, will focus on four virus types: flaviviruses, coronaviruses[[23]](#footnote-23), alphaviruses and influenza.
	10. Chikungunya is an alphavirus, first isolated from the blood of a febrile patient in Tanzania in 1953, and has since caused epidemics in Africa and Asia and has been seen in limited areas of Europe. This year it has spread to the Caribbean. The European Centre for Disease Prevention and Control (ECDC) on 28 March reported that the number of confirmed and suspected chikungunya cases in the Caribbean was continuing to increase; so far there had been 3211 confirmed chikungunya cases reported, including 5 deaths, and there had been 15 282 suspected cases. The US is expecting locally acquired cases of **chikungunya in the next year or two.**
	11. AT 26 March, the European Centre for Disease Prevention and Control (ECDC) estimated that more than 30,000 people in French Polynesia had sought medical care for Zika-like symptoms since the outbreak began in October[[24]](#footnote-24). By then there were 8,600 confirmed cases.
	12. In New Caledonia, the first locally acquired case of Zika was reported in mid-January. The number of confirmed cases by 18 March was 276.
	13. By 25 March there had been 49 confirmed cases of Zika virus (a flavivirus) in the Cook Islands, while 630 people were believed to have suffered from the mosquito-borne disease.
	14. The Bill & Melinda Gates Foundation has awarded $U23 million over five years for University of Notre Dame research that seeks to prevent malaria and dengue fever.

### Influenza: strains, spread, prevention and treatment

#### H7N9

* 1. As of 29 March, 393 human cases of H7N9 had been confirmed on the Chinese mainland. A Hong Kong government spokesman said "All boundary control points have implemented disease prevention and control measures. Thermal imaging systems are in place for body temperature checks of inbound travellers. Random temperature checks by handheld devices have also been arranged. Suspected cases will be immediately referred to public hospitals for follow-up investigation….. Regarding health education for travellers, display of posters in departure and arrival halls, in-flight public announcements, environmental health inspection and provision of regular updates to the travel industry via meetings and correspondence are proceeding.” China continued to report cases throughout April, with, for example, two each on 17, 21 and 23 April. Taiwan and Hong kong reported imported cases.

#### H1N1

* 1. New Zealand has had a pre- winter surge in influenza, the A (H1N1) flu strain, that caused the 2009 swine flu pandemic, infecting 800,000 New Zealanders.

### MERS-CoV

* 1. WHO announced that genetic data show the MERS-CoV isolates in camels and humans are closely linked and "suggest the current observed pattern of disease in humans is the result of repeated introductions into human populations from camels, with subsequent limited human-to-human transmission, rather than sustained community transmission among humans. As such, discovery of the route of transmission between camels and humans remains critical to stopping the initial introduction into human populations."
	2. From September 2012 to1 April 2014, WHO was informed of a global total of 207 laboratory-confirmed cases of infection with MERS-CoV, including 87 deaths.
	3. During April, the MERS-CoV experience gained momentum. On 26 April, Saudi Arabia had confirmed 10 cases in 24 hours. The Saudi Health Minister had already been removed. The World Health Organization (WHO) had already issued a statement responding to the MERS spike, admitting “Approximately 75 per cent of the recently reported cases are secondary cases, meaning that they are considered to have acquired the infection from another case through human-to-human transmission.”

### Ebola Virus Disease (EVD)-originating in West Africa

* 1. As of 31 March 2014, Guinea’s Ministry of Health had reported 122 clinically compatible cases of EVD, of which 24 were laboratory confirmed, and 98 were probable (78) or suspected (22) cases. The total included 80 deaths, of whom 13 have been laboratory confirmed for EVD with the remaining 67 regarded as probable. As of 30 March 2014, 20 patients were in isolation. Eleven health care workers were among the probable and suspected cases. Efforts were being made to prompt community awareness about the importance of hand washing, and using personal protective equipment when handling potentially contaminated blood and body fluids and during environmental and disinfection. Safe burial is a major concern[[25]](#footnote-25). This is the first Ebola epidemic to strike Guinea. Guinea has banned the sale and consumption of bats and other bush meat. It has banned public funerals forvictims. Volunteers from the Guinean Red Cross have been dealing with infected bodies and disinfecting the homes of victims.
	2. At 1 April 2014 Liberia’s Ministry of Health had reported eight clinically compatible cases of EVD, including two laboratory-confirmed cases. Two patients had died.
	3. Sierra Leone’s Ministry of Health said it is vigilant following the deaths of two probable cases of EVD in one family who died in Guinea but whose bodies were repatriated to Sierra Leone.

### Other diseases: occurrence, prevention and treatment

* 1. Health workers in Papua New Guinea fear a galloping **tuberculosis** epidemic, health workers say 15,000 new cases are recorded annually. WHO says a quarter of those are fatal. .UNAIDS PNG coordinator Stuart Watson reports that it is people living with HIV in PNG who are most at risk of contracting TB. He said multi-drug resistant (MDR) and extra-drug resistant (XDR) TB are increasing in PNG.
	2. India and China together account for almost 40 per cent of the world's known TB cases India had an estimated 2.8 million people infected with TB in 2012, whereas China had half that number.
	3. Of the 40 000 TB cases recorded in Bombay in 2013, more than ten per cent were relapse cases. The annual count of relapse cases has remained constant for a number of years. Over the last three years, the count of MDR and extensively drug resistant (XDR) TB cases has increased substantially[[26]](#footnote-26).
	4. Experts have reassured UK members of parliament that very few cases of **vCJD** are missed by doctors. However, as there has been no test for it, the precise number of people with the degenerative brain disease remains uncertain. This human form of bovine spongiform encephalopathy (BSE), appeared after widespread exposure to BSE prions in the late 1980s and early 1990s through contaminated meat. A recent study published in the *BMJ*[[27]](#footnote-27) estimated that 1 in 2000 people in the UK carried vCJD proteins, although only 177 clinical cases had occurred thus farWHO South-East Asia Region [SEARO], home to a quarter of the world's population, was certified **polio**-free on 27 March 2014 by an independent commission under the WHO certification process. It is the fourth of six WHO Regions to be certified, one more towards global polio eradication. Eighty per cent of the world's population now resides in certified polio-free regions.
	5. With continuing incidence of polio in the Syrian Arab Republic with international transmission, the polio outbreak response in the Middle East remains in place to contain regional spread.
	6. In the autumn of 1348 the Black Death reached Britain from central Asia and by late spring the following year it had killed sixty per cent of London’s population. Scientists extracted the DNA of the bacterium, Yersinia pestis, from teeth in skulls found during excavations and compared the strain of **bubonic plague** with the strain that recently killed 60 people in [Madagascar](http://www.theguardian.com/world/madagascar). Tthe fourteenth century strain was no more virulent than the modern disease. The DNA codes were an almost coinccident. Some scientists believe that for the plague to spread so fast it must have invaded the lungs of victims and was transmitted by coughs and sneezes, and was therefore a pneumonic plague as well as a bubonic plague. Infection was transmitted human to human, not just by the rat fleas that bit a sick person and transmitted the plague to the next victim. "As an explanation [rat fleas] for the Black Death in its own right, it simply isn't good enough. It cannot spread fast enough from one household to the next to cause the huge number of cases that we saw during the Black Death [epidemics](http://www.theguardian.com/world/epidemics)," said Dr Tim Brooks, who put his theory in a Channel 4 [documentary](http://www.theguardian.com/tv-and-radio/documentary), Secret History: The Return of the Black Death. . Antibiotics can today prevent rodent flea-associated bubonic plague the disease from becoming pneumonic.
1. Cellular destruction of erythrocytes [↑](#footnote-ref-1)
2. The Health Canada approval of Alprolix rested on results from the global, phase III B-LONG study. This showed that Alprolix safely and effectively prevented, or reduced, bleeding episodes with prophylactic injections given weekly or once every 10-14 days in adults and adolescents with severe haemophilia B. In acute treatment, more than 90 per cent of bleeding episodes were controlled by a single Alprolix injection. [↑](#footnote-ref-2)
3. The HEA BeadChip product is an in vitro diagnostic test and is Immucor's core molecular test for extended typing of red blood cell antigens from a DNA sample. The product is designed to predict the phenotypes of the Rh (C,c,E,e), Kell (K, k, Kpa, Kpb, Jsa, Jsb), Duffy, Kidd, MNS, Lutheran, Dombrock (Doa, Dob, Hy, Jo), Landsteiner-Wiener, Diego, Colton, and Scianna blood group systems. The test is also designed to detect a mutation (HgbS 173 A > T) in the Beta Globin gene. [↑](#footnote-ref-3)
4. eg when US competition regulators knocked back CSL’s $US3.1 billion bid for Talecris Biotherapeutics, the company handed much of the cash back to shareholders through share buybacks. [↑](#footnote-ref-4)
5. “We believe pathogen inactivation for whole blood has the potential to improve the safety of transfusions in sub-Saharan Africa where diminished blood availability due to severe anaemia from malaria HIV and obstetric bleeding is common” said Dr. Rudolf Schwabe chief executive officer of the Swiss Red Cross. “Based on our experience over the past three years with the INTERCEPT System we have seen first-hand the substantial impact that pathogen inactivation has had in reducing transfusion transmitted infectious risk in platelets and plasma; this technology should be made available to developing countries such as those in sub-Saharan Africa where the risk of bacterial contamination is about 2500 times greater than in Switzerland and ten to fifteen percent of HIV infections are caused by contaminated transfusions.” [↑](#footnote-ref-5)
6. Fouchier’s research was undertaken at Erasmus Medical Centre, Rotterdam. His team modified the H5N1 virus to spread through the air between mammals, by enabling the agent to bind more readily to their cell receptors. The research had funding support from the US. There was also similar work in Wisconsin, to understand how H5N1 could evolve to be a greater threat to humans. The US National Science Advisory Board for Biosecurity (NSABB) put both studies under the spotlight in 2011, suggesting publication of the studies would allow bioterrorists to initiate a lethal pandemic. Debate continues over regulation of future "gain-of-function" pathogen research. Since gain-of-function studies cultivate pathogens with attributes that do not yet exist in nature, would-be researchers claim they are necessary to prepare for future forms of disease. The Fouchier research controversy has engaged the Dutch legal system. He challenged the Dutch government's right to license sensitive data before it can be internationally transmitted. He lost his bid in September, but appealed to a hugher court in November. Last August, he and some other virologists called for future gain-of-function studies to focus on avian flu H7N9. Meanwhile, Chinse scientists said they had already conducted “gain of function” studies on it. [↑](#footnote-ref-6)
7. published in *The American Journal of Cardiology* [↑](#footnote-ref-7)
8. [Xian Y.,Circ Cardiovasc Qual Outcomes. 2014;doi:10.1161/CIRCOUTCOMES.113.000715.](http://circoutcomes.ahajournals.org/content/early/2014/03/04/CIRCOUTCOMES.113.000715.short?rss=1) [↑](#footnote-ref-8)
9. [Myocardial infarctions](http://heartdisease.about.com/od/heartattack/g/infarction.htm) (heart attacks) occur when a [coronary artery](http://heartdisease.about.com/od/coronaryarterydisease/g/coronary_art.htm) suddenly becomes occluded by a blood clot, causing at least some of the heart muscle being supplied by that artery to die. Myocardial infarctions are of two types, with a NSTEMI being the less severe type. In a NSTEMI, the blood clot only partly occludes the artery, so only part of the heart muscle being supplied by the affected artery dies. [↑](#footnote-ref-9)
10. Quebec had already banned the practice. [↑](#footnote-ref-10)
11. Veale, M. F., Healey, G. and Sparrow, R. L. (2014),”Longer storage of red blood cells is associated with increased in vitro erythrophagocytosis”. *Vox Sanguinis*, 106: 219–226. doi: 10.1111/vox.12095 [↑](#footnote-ref-11)
12. Cellular destruction of erythrocytes [↑](#footnote-ref-12)
13. J.D.Boone, K.H. Kim, M. Marques and J.M. Straughn,“Compliance rates and outcomes associated with a restrictive transfusion policy in gynecologic oncology patients.” *Gynecologic Oncology*, 2014;132(1):227-230. [↑](#footnote-ref-13)
14. The mean age of patients was 55.9 years. Ovarian and [endometrial](file:///C%3A%5Csearch_results.php%3Fsearch_term%3Dendometrial%26cat%3Da) cancers were the most commonin the group. [↑](#footnote-ref-14)
15. This can arise when the blood group of the mother and foetus differ. [↑](#footnote-ref-15)
16. See *Biomedical Central.* **Julie Kent, Anne-Maree Farrell** and **Peter Soothill,”** Routine administration of Anti-D: the ethical case for offering pregnant women fetal RHD genotyping and a review of policy and practice**”** BMC Pregnancy and Childbirth 2014, **14**:87 doi:10.1186/1471-2393-14-87 or <http://www.biomedcentral.com/1471-2393/14/87> There is one Australian-based author: Anne-Maree Farrell is with the Faculty of Law, Monash University. [↑](#footnote-ref-16)
17. From Japan, China, Korea and Taiwan [↑](#footnote-ref-17)
18. “Redox Properties of Human Hemoglobin in Complex with Fractionated Dimeric and Polymeric Human Haptoglobin”,*Free Radical Biology and Medicine* 69 (2014) 265-277 [↑](#footnote-ref-18)
19. from the Office of Blood Research and Review in the Center for Biologics Evaluation and Review. [↑](#footnote-ref-19)
20. Arya Khosravi, Alberto Yáñez, Jeremy G. Price, Andrew Chow, Miriam Merad, Helen S. Goodridge, Sarkis K. Mazmanian, “Gut Microbiota Promote Hematopoiesis to Control Bacterial Infection,” *Cell Host & Microbe* 12 March 2014 - See more at: <http://pilladvised.com/2014/03/good-gut-bacteria-help-fight-infection/#sthash.IugL1Rwm.dpuf> [↑](#footnote-ref-20)
21. Leon E. Hugo, Jason A. L. Jeffery,Brendan J. Trewin, Leesa F. Wockner, Nguyen Thi Yen, Nguyen Hoang Le, Le Trung Nghia, Emma Hine, Peter A. Ryan, Brian H. Kay, “Adult Survivorship of the Dengue Mosquito *Aedes aegypti* Varies Seasonally in Central Vietnam”, *PLOS Neglected Tropical Diseases*, February 13, 2014. DOI: 10.1371/journal.pntd.0002669 [↑](#footnote-ref-21)
22. Sanofi has invested over ($US1.38 billion) in research and development over two decades, and has prepared a dedicated production plant outside Lyon. This will have a capacity of up to 100 million doses per year from late 2017. [↑](#footnote-ref-22)
23. eg Middle East respiratory syndrome-novel coronavirus, or MERS-CoV [↑](#footnote-ref-23)
24. It was recognized some of these could have been dengue. [↑](#footnote-ref-24)
25. People can become infected during burial ceremonies involving close contact with the bodies ofEbola victims. [↑](#footnote-ref-25)
26. From 181 new patients diagnosed with MDR TB and 288 under treatment for it in 2011, the figure rose to 2195 new patients diagnosed with MDR TB and 1935 under treatment the next year. In 2013, 2903 patients were diagnosed with MDR TB and 2604 were on treatment. [↑](#footnote-ref-26)
27. BMJ *2014;* *348* *doi: http://dx.doi.org/10.1136/bmj.g2425* *(Published 28 March 2014)* *Cite this as: BMJ 2014;348:g2425* [↑](#footnote-ref-27)