Monitoring International Trends

**posted February 2014**

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:

* Bayer announced positive results from the PROTECT VIII trial of BAY 94-9027, its long-acting PEGylated recombinant human factor VIII compound. Trial data will be presented at the 2014 World Federation of Haemophilia Conference in Melbourne. (page 3)
* [Alnylam Pharmaceuticals](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com%2F&esheet=50787964&newsitemid=20140122005518&lan=en-US&anchor=Alnylam+Pharmaceuticals&index=1&md5=c33840d4e206e7fc6588d3434cd68905) has begun a Phase I trial of ALN-AT3, a subcutaneously administered RNAi therapeutic targeting antithrombin. The company said ALN-AT3 has demonstrated efficacy in animal models of haemophilia. (page 3)
* CSL’s plasma-derived drug CSL 112 is being developed for use in preventing recurring heart attacks and other coronary events. (page 3)
* Baxter expects to file for regulatory approval for BAX 855 (its investigational extended half-life rFVIII) in the US before the end of 2014. (page 5)
* The Centers for Disease Control and Prevention ([CDC](http://links.mkt1985.com/ctt?kn=48&ms=ODI3MDM1NQS2&r=MTg5NDA2MTYxOTgS1&b=0&j=MjA0ODc4NzUxS0&mt=1&rt=0)) and the Pentagon will fund the US effort in the Global Health Security Agenda, which aims to strengthen disease-monitoring links between countries, to limit the number of laboratories that handle dangerous microbes and to boost vaccination programs. (page 6)
* In the UK a House of Commons committee is enquiring into the screening of blood and organ donations. (page 6)
* An analysis of every birth in NSW over a decade found that the rate of haemorrhage recorded had almost doubled. The rate of blood transfusions had increased by 33 per cent. (page 7)
* Japanese researchers have found a way to create functional platelets from human induced pluripotent stem cells. (page 8)
* Scientists are working on commercializing a new technology for freezing donated blood for storage in a way which allows it to be made available for transfusion more quickly than by current methods. (page 8)
* At 13 February, Queensland Health reported the dengue case count in Cairns had reached 74 since December. Cases had also been reported in Port Douglas, Innisfail, and Townsville. (page 11)
* In 2013 there were 127 cases of chikungunya reported amongst Australians, an increase from the 19 in 2012. (page 11)
* In early February, the H7N9 influenza outbreak case total passed 300 (with 67 deaths) since the disease emerged in humans, with up to 10 cases a day being reported from Chinese provinces. By 12 February, there had been five confirmed cases in Hong Kong, which appeared to arise from travel to China. Malaysia confirmed in mid-February its first case of H7N9 in a Chinese tourist. (page 11)
* On 7 February, WHO said that since September 2012 it had been informed of 182 laboratory-confirmed cases of MERS, associated with 79 deaths. (page 13)

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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. Bayer HealthCare announced positive results from the PROTECT VIII trial of BAY 94-9027, its long-acting PEGylated recombinant human factor VIII compound. In the trial, the PEGylated factor VIII helped protect against bleeds whether used prophylactically at seven day intervals, at five day intervals, or twice per week. The current standard for prophylaxis is infusion every two or three days. The company said BAY 94-9027 was also effective for treatment of acute and breakthrough bleeds with 91 per cent of events resolving with one or two infusions. Trial data will be presented at the World Federation of Haemophilia Conference in May 2014 in Melbourne. Bayer will submit marketing authorization applications to regulators in the second half of 2015. Paediatric studies, and evaluation of BAY 94-9027 during major surgery, are continuing. Bayer is also planning a study in previously untreated patients.
	2. [Alnylam Pharmaceuticals](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.alnylam.com%2F&esheet=50787964&newsitemid=20140122005518&lan=en-US&anchor=Alnylam+Pharmaceuticals&index=1&md5=c33840d4e206e7fc6588d3434cd68905) has begun a Phase I trial of ALN-AT3, a subcutaneously administered RNAi therapeutic targeting antithrombin. The company said ALN-AT3 has demonstrated efficacy in animal models of haemophilia, including in non-human primate models of induced haemophilia. Alnylam hopes to present initial data from the Phase I trial before the end of this year.
	3. CSL is continuing development of its plasma-derived drug CSL 112[[1]](#footnote-1) which is thought to have potential use in preventing recurring heart attacks and other coronary events. Three distinct analyses of data from a Phase IIa study were presented at the American Heart Association 2013 Scientific Sessions, covering safety and tolerability, pharmacokinetics and lipid biomarker profile, and potential antiplatelet effects in addition to dual antiplatelet therapy. The company said that overall the Phase IIa studies demonstrated for CSL 112 a favourable safety profile, good tolerance and increased cholesterol efflux capacity in stable atherothrombotic patients.
	4. Rockwell Medical has completed its large-scale, long-term safety study of Triferic, in support of a New Drug Application (NDA) for marketing approval. Triferic is an iron-replacement drug for chronic kidney disease patients receiving hemodialysis.
	5. Chimerix presented at the 16th Annual BIO CEO & Investor Conference on 10 February in New York. The company says its lead product, brincidofovir (CMX001), has demonstrated broad-spectrum antiviral activity against all five families of double-stranded DNA that affect humans, including cytomegalovirus, adenovirus, and herpes simplex viruses. Chimerix is working with the US Biomedical Advanced Research and Development Authority (BARDA) to develop brincidofovir as a medical countermeasure against smallpox.
	6. A team led by [Jeffrey Karp](http://www.karplab.net/), a bioengineer at the Brigham and Women's Hospital in Boston, and [Pedro del Nido](http://www.ctsnet.org/home/pdelnido), a cardiac surgeon at Boston Children’s Hospital, has developed and tested a new type of surgical glue: it sticks well to wet tissue, it repels blood and water, and it can bind major blood vessels even when under the pressure of flowing blood. They have demonstrated that the glue can seal the carotid artery and stick to the heart wall during surgery in pigs[[2]](#footnote-2). The glue will next be tested for its ability to seal the holes created by sutures during cardiac surgery. Then would come trials using it to bring vessels together or close holes in the heart without the presence of sutures.
	7. Kamada expects a positive outcome from its Phase II/III clinical trial in Europe of its inhaled Alpha-1 Antitrypsin (AAT-IH) for the treatment of AAT deficiency, and plans to file in the second half of 2014 with the European Medicines Agency for regulatory approval.
	8. Kamada expects to initiate a Phase II/III trial of Glassia in children newly diagnosed with type 1 diabetes to test its efficacy in halting disease progression.

# Regulatory

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

* 1. Late in 2013, the FDA approved the use of Baxter’s FEIBA (Factor Eight Inhibitor Bypassing Activity) for prophylaxis in patients with haemophilia A or B who have developed inhibitors. A randomized controlled trial showed it could provide safe prophylaxis and reduce bleeding compared with on-demand treatment. The results, originally published online August 1, 2013, have now appeared in the January print issue of *Haemophilia[[3]](#footnote-3)*.
	2. The FDA granted GlaxoSmithKline breakthrough therapy designation[[4]](#footnote-4) for eltrombopag (Promacta/Revolade) for the treatment of cytopaenias in patients with severe aplastic anaemia who have experienced inadequate response to immunosuppressive therapy[[5]](#footnote-5).
	3. AMAG Pharmaceuticals received a complete response letter from the FDA for its supplemental new drug application for Feraheme (ferumoxytol) injection for intravenous use beyond its current indication for chronic kidney disease, to include all adult iron deficiency anaemia patients who have failed or cannot tolerate oral iron treatment. The FDA recommended AMAG obtain further clinical trial data in the proposed extended patient population with emphasis on hypersensitivity/anaphylaxis, cardiovascular events, and death.
	4. The FDA’s Cardiovascular and Renal Drugs Advisory Committee voted 10-0, with one abstention, against the approval of rivaroxaban (Xarelto) in combination with standard antiplatelet therapy to reduce the risk of thrombotic cardiovascular events in patients with acute coronary syndrome. The FDA then issued a complete response.
	5. The Cardiovascular and Renal Drugs Advisory Committee also voted against recommending approval of The Medicine Company’s intravenous antiplatelet agent cangrelor in patients undergoing cardiac stent procedures or those needing bridging from oral antiplatelet therapy to surgery.
	6. Before the Winter Olympics, a number of drug companies—including Roche, Amgen and GlaxoSmithKline—provided confidential information on experimental drugs to the World Anti-Doping Authority to assist officials to stay ahead of drug cheats.

# 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. In mid-February, CSL announced its half-year profit had risen by 3.4 per cent compared with profit in the first half of the previous year. Net profit was US $646 million in the six months to December 31. There were strong sales for Kcentra (prothrombin complex concentrate), approved by the FDA in April 2013 for the urgent reversal of warfarin therapy in adult patients with acute major bleeding.
	2. Biogen Idec reported a successful 2013. Total revenue was $US 6.9 billion, an increase of twenty six per cent over the previous year. According to the company, this performance was driven by significant growth in the multiple sclerosis franchise. Two haemophilia treatments will be launched in 2014. Biogen Idec has signed an exclusive agreement with UCB for the latter to commercialize Biogen’s products in South Korea, Hong Kong, Thailand, Singapore, Malaysia, and Taiwan, and both develop and commercialize products in China.
	3. Baxter reported income and revenue for the fourth quarter of 2013 which was higher than expected because of its haemophilia and dialysis products.
	4. Baxter International and Xenetic Biosciences have restructured their agreement for the development of BAX 826, a recombinant Factor VIII. Their previous, exclusive, worldwide agreement was to develop novel forms of polysialylated blood coagulation factors, including Factor VIII, using Xenetic's proprietary polysialic acid (PSA) technology. Under the new agreement Baxter will take equity in Xenetic and will make contingent milestone payments as well as pay royalties on future sales.
	5. Baxter expects to file for regulatory approval for BAX 855 (an investigational extended half-life rFVIII) in the US before the end of 2014. A Phase I/II open-label clinical trial to assess the safety and optimal dosing schedule of BAX 335 is in progress. Baxter 335 is an investigational Factor IX gene therapy treatment which provides a mechanism for the patient's own liver to begin producing Factor IX following a single dose.
	6. Cangene Corporation’s shareholders approved the previously announced acquisition by Emergent BioSolutions. Cangene shareholders will receive US$3.24 per share in cash, for a total purchase price of US$222 million.
	7. Sanofi Pasteur and the University of Melbourne have agreed to fund jointly proof-of-concept studies for technologies developed by the University which the company can use to develop immune-boosting substances and vaccines against infectious diseases. Sanofi Pasteur will have the first right-of-refusal to acquire exclusive, worldwide licenses to develop and commercialise the technology.
	8. St Louis start-up company Pulse Therapeutics has raised $US1.03 million from three private investors to work on a device that uses magnet technology to break up blood clots.
	9. TetraLogic Pharmaceuticals Corporation of Pennsylvania has entered into a research collaboration with the Walter and Eliza Hall Institute of Medical Research of Melbourne to examine TetraLogic's birinapant in viral infections.

# 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

* 1. The Centers for Disease Control and Prevention ([CDC](http://links.mkt1985.com/ctt?kn=48&ms=ODI3MDM1NQS2&r=MTg5NDA2MTYxOTgS1&b=0&j=MjA0ODc4NzUxS0&mt=1&rt=0)) and the Pentagon will fund the US effort in the Global Health Security Agenda, which aims to strengthen disease-monitoring links between countries, to limit the number of laboratories that handle dangerous microbes and to boost vaccination programs. The Agenda involves 26 countries, and the World Health Organization (WHO); it follows on from a 2005 agreement by 194 countries to improve their disease detection and response by a June 2012 deadline, which many failed to meet. The Obama administration will spend $US40 million in 10 countries this year to upgrade laboratories and communications networks. [Thomas Frieden](http://topics.bloomberg.com/thomas-frieden/), director of the CDC, said the President will seek another $US45 million next year.
	2. Researchers used the Agency for Healthcare Research and Quality-sponsored Kids' Inpatient Database to examine over 123,000 trauma discharges[[6]](#footnote-6). They found that for patients with chronic conditions the incidence of medical errors was 4.04 per 100 discharges, compared with 1.07 per 100 discharges for patients without chronic conditions. Amongst chronic conditions, diseases of the blood and blood-forming organs had an incidence of 10.88 per 100 discharges, while diseases of the circulatory system had an incidence of 9.91 per 100 discharges and immunity disorders 9.37 per 100 discharges.
	3. CDC figures show quadrivalent flu vaccines enjoy a significant price premium over trivalent vaccines.
	4. A study found that the majority of children in the US at risk for tuberculosis were either born outside the US or born in the US to parents born outside the country[[7]](#footnote-7).
	5. CDC researchers have estimated health care costs and productivity loss from West Nile Virus to have been $US778 million from 1999 to 2012 inclusive[[8]](#footnote-8).

### United Kingdom

* 1. In the UK, a House of Commons science and technology select committee has been told the country’s blood banks are “a ticking time-bomb” because donations are not properly screened for mad cow disease[[9]](#footnote-9).
	2. Kent, Surrey and Sussex Air Ambulance said its doctors and paramedics had performed 69 emergency blood transfusions since this became possible a year ago.

### Australia

* 1. Queensland researchers believe that surveillance and mapping of internet searches and social media topics would provide more up to date information on developing epidemics than the current method, which relies on physicians reporting relevant patient visits[[10]](#footnote-10). Google publishes search data for flu and dengue[[11]](#footnote-11), but does not publish search terms. The Queensland researchers are working on their own system, which they hope will encompass all communicable diseases recognised in Australia, about 65. They believe Australia offers an ideal trial site, because of high internet penetration and high dependence on Google.

### Germany

* 1. German officials identified a cow with a case of bovine spongiform encephalitis (BSE), the country’s first reported case since 2009. The cow was killed and its body destroyed, with none of the meat entering the human food chain.

# Safety and patient blood management

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

* 1. Jane Ford, from the Kolling Institute at the University of Sydney led a team which analysed every birth in NSW over a decade. They found that the rate of haemorrhage recorded had almost doubled, from 4 per cent to 7 per cent of births. The rate of blood transfusions had increased 33 per cent, to 1.6 per cent of mothers. Experts say one reason is that the "third stage" of labour, after the baby is delivered, is not being managed well. President of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, Michael Permezel[[12]](#footnote-12), said he had seen a trend for some women to refuse medication after labour that encourages the body to deliver the placenta safely. "Women who go for a so-called 'natural' delivery of the placenta have double the rate of transfusion," he said. "In the developing world, it's a well-known fact that women die every minute [because they cannot access this medication]." Jonathan Morris[[13]](#footnote-13), the director of the Kolling Institute, commented that measures that reduced transfusion were not being used. These included testing for iron deficiency before birth and treating it, and massaging the uterus after birth to stimulate contractions.
	2. In January, a two day workshop, *Strategies to Address Hemolytic Complications of Immune Globulin Infusions* was jointly sponsored by the FDA’s Center for Biologics Evaluation and Research, the Plasma Protein Therapeutics Association and the US National Heart, Lung and Blood Institute, The sessions included Epidemiology and Risk Factors for IG-related Hemolysis[[14]](#footnote-14), Pathogenesis of Hemolysis[[15]](#footnote-15), Anti-A and Anti-B Haemagglutinins in IG Products[[16]](#footnote-16), Other Product Risk Factors for Hemolysis[[17]](#footnote-17), Donor plasma and anti-A/anti-B levels[[18]](#footnote-18), and Immune Globulin manufacturing and clearance of isoagglutinins[[19]](#footnote-19).
	3. The Institute for Patient Blood Management, Englewood Hospital and Medical Center, New Jersey, had over 1,000 registrations for its seminar “Making Wise Healthcare Choices” on 10 February. Speakers included physicians and surgeons from multiple clinical areas, including patient blood management, radiology, gynaecology, neurology, gastroenterology, and cardiology.

# 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. Japanese researchers have found a way to create functional platelets from human induced pluripotent stem cells. They genetically manipulated these stem cells to become stable immortalized lines of platelet-producing cells (megakaryocyte progenitors). The megakaryocyte progenitors could produce large quantities of platelets with clotting capabilities similar to those of donated platelets. The immortalized megakaryocyte progenitors could be expanded and frozen for long-term storage.[[20]](#footnote-20)
	2. Researchers at the Children's Medical Center Research Institute at the University of Texas Southwestern and Baylor College of Medicine have found that, in mice, blood-forming stem cells divide more frequently in females than in males due to higher oestrogen levels[[21]](#footnote-21). Dr Sean Morrison said "In female mice, estrogen increases the proliferation of blood-forming stem cells in preparation for pregnancy. Elevated estrogen levels that are sustained during pregnancy induce stem cell mobilization and red cell production in the spleen, which serves as a reserve site for additional red blood cell production……… If estrogen has the same effect on stem cells in humans as in mice, then this effect raises a number of possibilities that could change the way we treat people with diseases of blood cell-formation. Can we promote regeneration in the blood-forming system by administering estrogen? Can we reduce the toxicity of chemotherapy to the blood-forming system by taking into account estrogen levels in female patients? Does estrogen promote the growth of some blood cancers? There are numerous clinical opportunities to pursue."
	3. Research at the Riken Centre for Developmental Biology in Japan has led to a method of creating stem cells by “shocking” red blood cells of mice in an acid bath[[22]](#footnote-22). Dr Haruko Obokata from the Centre, said she was "really surprised" that cells could respond to their environment in this way. The next step is to test the method with human blood cells. Professor Chris Mason, Professor of Regenerative Medicine at University College London, said “If this works in people……., it looks faster, cheaper and possibly safer than other cell reprogramming technologies—personalised reprogrammed cell therapies may now be viable".
	4. Scientists at the University of Warwick are working on commercializing a new technology for freezing donated blood for storage in a way which allows it to be made available for transfusion more quickly than by current methods. They are looking to polyvinyl alcohol to prevent the formation of cell-rupturing ice crystals from forming as the blood thaws. The volume required is about 0.1 percent of the volume of the blood, and it is considered safe to be left in the blood to be transfused[[23]](#footnote-23).
	5. Scientists at Saint Louis University[[24]](#footnote-24) are studying whether abciximab, currently used to open blocked arteries in heart patients undergoing angioplasties, could help children and young adults in severe pain from sickle cell disease. Abciximab deals with the proteins that influence the stickiness of platelets and the flow of red blood cells through the walls of the blood vessels.
	6. Scientists have found that an injectable antibody, known as 3F7, protected rabbits from developing blood clots but did not cause bleeding complications. They hope to move to a small phase I study to test the drug’s safety in humans[[25]](#footnote-25).
	7. Australian bat lyssavirus and rabies are amongst fifteen known species of lyssavirus. They are usually transmitted to humans through animal bites and scratches, and there is a fatality rate of 100 percent where the infection is not treated quickly through injections of inactivated vaccines and immunoglobulin. Researchers from Monash University; Institut Pasteur, Université Paris Diderot and CNRS, in France; and Gifu University, in Japan, have identified the region in a lyssavirus protein that inhibits immune responses, and developed a mutated lyssavirus that may be a step towards developing new live rabies vaccines. Dr Greg Moseley, the team leader from the Monash Department of Biochemistry and Molecular Biology, said: “Live vaccines can be grown easily in large quantities, and delivered as a single oral dose, unlike existing ‘killed’ rabies vaccines that must be injected several times over an extended period, limiting their application in resource-poor countries.”  Monash University has filed an Australian provisional patent application to facilitate future clinical development.[[26]](#footnote-26)
	8. Two characteristics of prion infections which have been largely unexplained are their long incubation periods (up to fifty years), and the time lag between the accumulation of misfolded prion protein in the brain and the appearance of symptoms. Now University of Alberta researchers have identified a mechanism in brain cells that may keep neurological diseases in check for an extended period.[[27]](#footnote-27)
	9. A study has found that, although the risk of thrombosis for women after childbirth is highest in the first six weeks, the risk remains significantly raised for at least a further six weeks[[28]](#footnote-28).
	10. Canadian researchers led by Dr [John Dick](http://www.theprincessmargaret.ca/en/findaperson/pages/scientistprofile.aspx?personid=344) of [Princess Margaret Cancer Centre](http://www.theprincessmargaret.ca/Pages/home.aspx) in Toronto have discovered a pre-leukemic stem cell that may be at the root of acute myeloid leukemia, may evade chemotherapy and may then trigger a relapse in patients who have gone into remission. They found about 25 per cent of patients have a mutation in a specific gene that causes the development of pre-leukemic stem cells, which function like normal blood stem cells but grow abnormally[[29]](#footnote-29). Dick assumes subsequent genetic sequencing studies will probably find other mutated pre-disease-causing stem cells in the remaining 75 per cent of patients. The research raises the possibility that these primordial stem cells could be targeted by a drug that could stop the disease early.
	11. Harvard Apparatus Regenerative Technology (HART) of Boston makes synthetic windpipes by growing a patient’s own stem cells on a lab-made scaffold. The company is working with the FDA to test the system and is currently conducting trials in Russia.
	12. MIT chemical engineers, funded by Alnylam Pharmaceuticals and the US National Institutes of Health, have designed nanoparticles that can deliver short strands of RNA into cells and turn off disease-causing genes. The technique is known as RNA interference (RNAi). These new particles encase short strands of RNA within a sphere of fatty molecules and proteins, and can silence target genes in the livers of mice. Daniel Anderson, an associate professor of chemical engineering and a member of MIT’s Koch Institute for Integrative Cancer Research, said: “What we’re excited about is how it only takes a very small amount of RNA to cause gene knockdown in the whole liver. The effect is specific to the liver — we get no effect in other tissues where you don’t want it.”[[30]](#footnote-30) The team also found the nanoparticles could silence genes in nonhuman primates. The technology has been licensed for commercial development.
	13. Canadian researchers have found that fever-reducing medications help to spread influenza[[31]](#footnote-31). Dr David Earn, a researcher with the Michael G. DeGroote Institute for Infectious Disease Research (IIDR) and professor of mathematics at McMaster University, said: "Because fever can actually help lower the amount of virus in a sick person's body and reduce the chance of transmitting disease to others, taking drugs that reduce fever can increase transmission”.

# Legal actions and enquiries

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

* 1. In the US a federal appeals court has maintained that culturing a patient’s stem cells for therapeutic use falls within the purview of the FDA and must be regulated as a drug.

# Infectious diseases

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

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

* 1. At 13 February, Queensland Health reported the dengue case count in Cairns had reached 74 since December. The strain has been DENV 1. A DENV 1 case had been confirmed in Innisfail with a second likely. The Miallo/ Port Douglas case count was stable at 17 and the strain has been DENV 3. Townsville confirmed one case.
	2. Since dengue fever infects only humans, scientists have not had animal models on which to work in their search for vaccines and treatments. Now researchers from MIT and the Singapore-MIT Alliance for Research and Technology (SMART) have developed a “humanized mouse” that mimics features of the human immune system. The team may have found the cause of one of the major symptoms of dengue—the depletion of the blood platelets essential to clotting. The researchers found that in the bone marrow of dengue-infected humanized mice, cells that eventually become platelets (megakaryocytes) were also depleted[[32]](#footnote-32).
	3. Following field trials in Far North Queensland and Vietnam of mosquitoes carrying *Wolbachia* bacterium to stop the spread of dengue, trials are in progress in Indonesia.
	4. A team of scientists at the University of Michigan and Purdue University has described for the first time the structure of a protein (NS1) which is produced inside infected cells and helps flaviviruses such as dengue and West Nile replicate and spread infection. Team leader Janet Smith of the University of Maryland Life Sciences Institute said: "Seeing the design of this key protein provides a target for a potential vaccine or even a therapeutic drug." [[33]](#footnote-33)
	5. In 2013 there were 127 cases of chikungunya reported amongst Australians, an increase from the 19 in 2012. The disease is now prevalent in South East Asia, Papua New Guinea and the Pacific, leading to a spike in cases among Australians travelling to these countries. There is also a danger that the virus could cross the Torres Strait, with the short distance and frequent population movements between Papua New Guinea and Cape York.

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

### H7N9

* 1. In early February, the H7N9 outbreak case total passed 300 (with 67 deaths) since the disease emerged in humans, with up to 10 cases a day being reported from Chinese provinces[[34]](#footnote-34). WHO said the most active calendar year for the continuing H5N1 strain, 2006, saw 115 cases[[35]](#footnote-35).
	2. By 12 February, there had been five confirmed cases in Hong Kong, which appeared to arise from travel to China. Malaysia confirmed in mid-February its first case of H7N9 in a Chinese tourist.
	3. The United Nation's Food and Agriculture Organization (FAO) warned on 5 February that cross-border spread was increasingly likely.
	4. In early February the *South China Morning Post* reported that China's poultry industry wanted public health agencies to cease reporting individual H7N9 cases, to "avoid excessively detailed reports" of H7N9 infections, and to refer to "H7N9 flu" or "H7N9 virus" rather than "H7N9 bird flu." The industry was anxious to reduce consumer concern about buying and eating poultry.
	5. Vivaldi Biosciences and the US National Institute of Allergy and Infectious Diseases (NIAID) have signed a cooperative research and development agreement to develop and evaluate in preclinical studies live attenuated influenza vaccines against H7N9.
	6. China’s Sinovac Biotech in January announced the acceptance by the China Food and Drug Administration of its clinical trial application for its H7N9 vaccine.

### H10N8

* 1. A study published in *The Lancet* on 4 February reported that a strain of the H10N8 avian flu had mutated and could now be carried by humans. H10N8 flu had been found in three people in China up to 14 February. Two of them had died. The study said the new strain had genetic similarities to H5N1 and H7N9, and that since it hasn’t been responsible for major reported outbreaks in poultry it could be spreading silently in birds. The study said that H10N8 was not then known to have been transmitted from person to person but warned: “The pandemic potential of this novel virus should not be underestimated”.

### H5N1

* 1. H5N1 can circulate in vaccinated birds without causing obvious disease. A Canadian woman who recently died of H5N1 had visited Beijing, which has not reported a case of H5N1 for some years.
	2. A Japanese man has been found to have an antibody against H5N1, although he has no record of bird flu symptoms and no human infection with H5N1 has been reported in Japan. A research team led by Yoshikazu Kurosawa, president of Fujita Health University in Toyoake, believes the man had previously been infected with three different types of flu viruses, with two of them resembling the H5N1 strain.[[36]](#footnote-36)
	3. At the American Society for Microbiology Biodefense meeting in Washington DC in January the University of Alabama at Birmingham and Hemispherx's presented a poster entitled "Seasonal Influenza Vaccine and a TLR-3 Agonist, Rintatolimod (Ampligen(R)), Given Intranasally Produced Cross-Reactive IgA Antibodies Against Pathogenic H5N1 Influenza HA”. The presenter was Dr. E. Turner Overton, an infectious disease expert at UAB. Researchers hope that the use of Ampligen as an adjuvant combined with approved commercial vaccine FluMist may offer advantages. FluMist , due to its intranasal administration, imitates the natural entry of the influenza virus, to generate local 'first-line' immunity as well as traditional systemic immunity. The stimulation of cross-protection against pre-pandemic H5N1 avian influenza strains is an ongoing clinical research goal and the proposed "vaccine cocktail" will enable potentially wider immunity against a variety of highly pathogenic influenza viruses.

### H5N8

* 1. South Korean authorities have culled 3 million birds with no human cases reported.

### Miscellaneous Influenza:

* 1. Israel’s BiondVax Pharmaceuticals announced the completion of tests on its flu vaccine which show it is “universal” and suited to new flu strains that have appeared in the past few years, including H5N1, H5N8, H6N1, H7N7, H7N9 and H10N8. BiondVax says its new vaccine contains small doses of the flu virus, sufficient to teach the immune system to recognize all flu strains.
	2. *New Scientist* on 31 January carried a report on the H9N2 virus, which it says gave rise to H5N1, H7N9 and H10N8. Robert Webster of St. Jude Children's Research Hospital in Memphis, Tennessee, told *New Scientist* that “closing Asia's ubiquitous live poultry markets would be the key to controlling N9N2, as this is where H9N2 and its spin-off viruses spread, mingle and evolve – and where humans catch them. Beijing, Shanghai and three cities in Zhejiang Province temporarily closed their live poultry markets. Some reports suggest live markets in major cities may be banned permanently. Zhang Yonghui, head of the Guangdong Centre for Disease Prevention and Control, told China's official news service Xinhua that the government [should](http://news.xinhuanet.com/english/china/2014-01/27/c_126071190.htm) change the country over to industrial chicken slaughter.

### MERS-CoV (formerly known as Middle East Respiratory Syndrome, novel coronavirus)

* 1. On 7 February, WHO said that since September 2012 it had been informed of 182 laboratory-confirmed cases of MERS, associated with 79 deaths.
	2. Researchers led by Stanley Perlman, a microbiologist at the University of Iowa, have created the first mouse model for MERS-CoV for testing of drugs and vaccines.
	3. An editorial in the journal *Annals of Internal Medicine* said the spread of MERS in hospitals is a significant problem, as was the case with SARS[[37]](#footnote-37). Health workers have made up around twenty per cent of cases, and some have been asymptomatic. In the same issue was a report on the disease course and outcomes of 12 intensive care patients in Saudi Arabia, three of whom were health workers[[38]](#footnote-38). A WHO report on 20 January said “more than half of all laboratory-confirmed secondary cases have been associated with health care settings. These include health care workers treating MERS-CoV patients, other patients receiving treatment for conditions unrelated to MERS-CoV, and people visiting MERS-CoV patients”.
	4. Camels have been seen as a possible source of MERS-CoV[[39]](#footnote-39). Now researchers have found another coronavirus in dromedary camels in the United Arab Emirates[[40]](#footnote-40).
	5. While MERS CoV is the coronavirus of current concern, as was SARS-CoV a decade ago, there are other coronaviruses, some not yet known to infect humans[[41]](#footnote-41).

### Other diseases: occurrence, prevention and treatment

* 1. NSW Health urged everyone planning on travelling to the Philippines to ensure they are up to date with their measles vaccinations before they travel. The Northern Territory Health Department said on 7 February that its nineteenth case of measles in three weeks had been infectious while on a flight from Manila to Darwin.
	2. Novant Health Forsyth Medical Center in Winston-Salem, North Carolina, performed a procedure on a patient with neurological symptoms on 18 January. Subsequent tests revealed he had Creutzfeldt-Jakob disease (CJD). The surgical equipment used in the patient’s procedure was not then sterilized up to the enhanced standards required in CJD cases, since prions can survive routine cleaning procedures. The hospital said in its statement: “There were reasons to suspect that this patient might have had CJD. As such, the extra precautions should have been taken, but were not.” Eighteen neurosurgery patients at the hospital may have been exposed to CJD.
	3. In Afghanistan, Kabul has seen its first polio case since 2001. Polio is regarded as endemic in the rest of Afghanistan, Pakistan and Nigeria. Concerns in the Middle East have recently led to major vaccination campaigns. In 2013 there were 190 cases in Somalia, and multiple cases in Ethiopia, Cameroon and Kenya.
	4. Daiichi Sankyo and UMN Pharma have entered into a collaborative research agreement to develop a vaccine against norovirus, one of the leading causes of infectious gastroenteritis globally[[42]](#footnote-42).
1. The company says “CSL112 is a novel formulation of apolipoprotein A-I (apoA-I), the active component of high-density lipoprotein (HDL). It is purified from human plasma and reconstituted to form HDL particles suitable for intravenous infusion. Studies have shown the infusion of CSL112 rapidly elevates markers of reverse cholesterol efflux, a process by which cholesterol is removed from arteries and transported to the liver for clearance.” [↑](#footnote-ref-1)
2. **N. Lang et al. “A blood-resistant surgical glue for minimally invasive repair of vessels and heart defects”** Science Translational Medicine**, 10.1126/scitranslmed.3006557, 2014.** [↑](#footnote-ref-2)
3. S. V. Antunes, S. Tangada, O. Stasyshyn, V. Mamonov, J. Phillips, N. Guzman-Becerra, A. Grigorian, B. Ewenstein, W.Y.Wong, “Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors”, *Haemophilia,* [Volume 20, Issue 1,](http://onlinelibrary.wiley.com/doi/10.1111/hae.2013.20.issue-1/issuetoc) pages 65–72, January 2014. DOI: 10.1111/hae.12246 [↑](#footnote-ref-3)
4. The breakthrough therapy designation, introduced under the 2012 FDA Safety and Innovation Act, expedites development and review of drugs to treat serious or life-threatening medical conditions when preliminary clinical evidence suggests that the drug may offer substantial improvement on at least one clinically significant endpoint over available therapies. The designation includes all the features of the fast track designation, together with intensive guidance from the FDA on the drug’s clinical development program. [http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.fda.gov%2Fforconsumers%2Fbyaudience%2Fforpatientadvocates%2Fspeedingaccesstoimportantnewtherapies%2Fucm128291.htm&esheet=50795338&newsitemid=20140203005396&lan=en-US&anchor=http%3A%2F%2Fwww.fda.gov%2Fforconsumers%2Fbyaudience%2Fforpatientadvocates%2Fspeedingaccesstoimportantnewtherapies%2Fucm128291.htm&index=4&md5=e22ed08a3c3f3e5b412799b063afd3f4) [↑](#footnote-ref-4)
5. Valdez JM, et al. “Decreased Infection-Related Mortality and Improved Survival in Severe Aplastic Anemia in the Past Two Decades”, *Clinical Infectious Diseases* 2011;52(6):726–735.ii [↑](#footnote-ref-5)
6. [Xiaotong Liu](http://smo.sagepub.com/search?author1=Xiaotong+Liu&sortspec=date&submit=Submit), [Han Yin](http://smo.sagepub.com/search?author1=Han+Yin&sortspec=date&submit=Submit), [Junxin Shi](http://smo.sagepub.com/search?author1=Junxin+Shi&sortspec=date&submit=Submit), [Krista Kurz Wheeler](http://smo.sagepub.com/search?author1=Krista+Kurz+Wheeler&sortspec=date&submit=Submit), [Jonathan I Groner](http://smo.sagepub.com/search?author1=Jonathan+I+Groner&sortspec=date&submit=Submit), and [Huiyun Xiang](http://smo.sagepub.com/search?author1=Huiyun+Xiang&sortspec=date&submit=Submit), “Medical errors in hospitalized pediatric trauma patients with chronic health conditions”,

*SAGE Open Medicine* vol. 2 2050312113519987 [↑](#footnote-ref-6)
7. [Jenny Pang](http://pediatrics.aappublications.org/search?author1=Jenny+Pang&sortspec=date&submit=Submit), [Larry D. Teeter](http://pediatrics.aappublications.org/search?author1=Larry+D.+Teeter&sortspec=date&submit=Submit), [Dolly J. Katz](http://pediatrics.aappublications.org/search?author1=Dolly+J.+Katz&sortspec=date&submit=Submit), [Amy L. Davidow](http://pediatrics.aappublications.org/search?author1=Amy+L.+Davidow&sortspec=date&submit=Submit), [Wilson Miranda](http://pediatrics.aappublications.org/search?author1=Wilson+Miranda&sortspec=date&submit=Submit), [Kirsten Wall](http://pediatrics.aappublications.org/search?author1=Kirsten+Wall&sortspec=date&submit=Submit), [Smita Ghosh](http://pediatrics.aappublications.org/search?author1=Smita+Ghosh&sortspec=date&submit=Submit), [Trudy Stein-Hart](http://pediatrics.aappublications.org/search?author1=Trudy+Stein-Hart&sortspec=date&submit=Submit), [Blanca I. Restrepo](http://pediatrics.aappublications.org/search?author1=Blanca+I.+Restrepo&sortspec=date&submit=Submit), [Randall Reves](http://pediatrics.aappublications.org/search?author1=Randall+Reves&sortspec=date&submit=Submit), and [Edward A. Graviss](http://pediatrics.aappublications.org/search?author1=Edward+A.+Graviss&sortspec=date&submit=Submit), on behalf of the Tuberculosis Epidemiologic Studies Consortium, “Epidemiology of Tuberculosis in Young Children in the United States”, *Pediatrics*, Published online February 10, 2014. doi: 10.1542/peds.2013-2570. [↑](#footnote-ref-7)
8. J. Erin Staples, Manjunath Shankar, James J. Sejvar, Martin I. Meltzer, and Marc Fischer, “Initial and Long-Term Costs of Patients Hospitalized with West Nile Virus Disease” *Am J Trop Med Hyg 13-0206;* Published online February 10, 2014, doi:10.4269/ajtmh.13-0206. [↑](#footnote-ref-8)
9. #  A study of archived appendix samples (published in October 2013) postulated that 1 in 2,000 people in the UK may carry the abnormal prion protein associated with vCJD. **Gill O, Spencer Y, Richard-Loendt A, et al.** “Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey”. BMJ 2013;347.f5675. Also **Salmon R, **“****How widespread is variant Creutzfeldt-Jakob disease?” BMJ 2013;347:f5994

 [↑](#footnote-ref-9)
10. [Gabriel J Milinovich](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Gabriel%20J+Milinovich), [Gail M Williams](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Gail%20M+Williams), [Archie C A Clements](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Archie%20C%20A+Clements) and [Wenbiao Hu](http://www.thelancet.com/search/results?fieldName=Authors&searchTerm=Wenbiao+Hu), “Internet-based surveillance systems for monitoring emerging infectious diseases”, *The Lancet Infectious Diseases*, [Volume 14, Issue 2](http://www.thelancet.com/journals/laninf/issue/vol14no2/PIIS1473-3099%2814%29X7064-7), Pages 160-168, February 2014 doi:10.1016/S1473-3099(13)70244-5 [↑](#footnote-ref-10)
11. <https://www.google.org/flutrends/about/how.html> [↑](#footnote-ref-11)
12. Reported in the Sydney Morning Herald 1 February, 2014. [↑](#footnote-ref-12)
13. Ibid. [↑](#footnote-ref-13)
14. With speakers from the Paul Ehrlich Institute, [↑](#footnote-ref-14)
15. With speakers from the US National Institutes of Health Clinical Center, the American Red Cross and the Universities of Ottawa and Toronto. [↑](#footnote-ref-15)
16. With speakers from the University of Toronto, the US National Institute for Biological Standards and Control, Swissmedic, and LFB Biomedicaments. [↑](#footnote-ref-16)
17. With speakers from the Puget Sound Blood Center and George Washington University. [↑](#footnote-ref-17)
18. With speakers from CSL Behring and Baxter Corporation. [↑](#footnote-ref-18)
19. With speakers from CSL Behring and LFB Biomedicaments [↑](#footnote-ref-19)
20. Sou Nakamura, Naoya Takayama, Shinji Hirata, Hideya Seo, Hiroshi Endo, Kiyosumi Ochi, Ken-ichi Fujita, Tomo Koike, Ken-ichi Harimoto, Takeaki Dohda, Akira Watanabe, Keisuke Okita, Nobuyasu Takahashi, Akira Sawaguchi, Shinya Yamanaka, Hiromitsu Nakauchi, Satoshi Nishimura, Koji Eto, “Expandable Megakaryocyte Cell Lines Enable Clinically Applicable Generation of Platelets from Human Induced Pluripotent Stem Cells”, *Cell Stem Cell,* 13 February 2014, 10.1016/j.stem.2014.01.011 [↑](#footnote-ref-20)
21. Daisuke Nakada, Hideyuki Oguro, Boaz P. Levi, Nicole Ryan, Ayumi Kitano, Yusuke Saitoh, Makiko Takeichi, George R. Wendt, Sean J. Morrison.” **Oestrogen increases haematopoietic stem-cell self-renewal in females and during pregnancy”**. Nature, 2014; 505 (7484): 555 DOI: [10.1038/nature12932](http://dx.doi.org/10.1038/nature12932) [↑](#footnote-ref-21)
22. *Nature*, vol. 505, p. 596, published 29 January 2014, doi:10.1038/505596a [↑](#footnote-ref-22)
23. [Robert C. Deller](http://www.nature.com/ncomms/2014/140203/ncomms4244/full/ncomms4244.html#auth-1), [Manu Vatish](http://www.nature.com/ncomms/2014/140203/ncomms4244/full/ncomms4244.html#auth-2), [Daniel A. Mitchell](http://www.nature.com/ncomms/2014/140203/ncomms4244/full/ncomms4244.html#auth-3),and [Matthew I. Gibson](http://www.nature.com/ncomms/2014/140203/ncomms4244/full/ncomms4244.html#auth-4), “Synthetic polymers enable non-vitreous cellular cryopreservation by reducing ice crystal growth during thawing”, *Nature Communications 5***Volume:**

, Article number: 3244 DOI:

doi:10.1038/ncomms4244 [↑](#footnote-ref-23)
24. Led by William Ferguson, director of the Division of Pediatric Hematology and Oncology at Saint Louis University [↑](#footnote-ref-24)
25. Magnus Larsson, Veronika Rayzman, Marc W. Nolte, Katrin F. Nickel, Jenny Björkqvist, Anne Jämsä, Matthew P. Hardy, Marion Fries, Stefan Schmidbauer, Patricia Hedenqvist, Michael Broomé, Ingo Pragst, Gerhard Dickneite, Michael J. Wilson, Andrew D. Nash, Con Panousis, and Thomas Renné, “A Factor XIIa Inhibitory Antibody Provides Thromboprotection in Extracorporeal Circulation Without Increasing Bleeding Risk”, *Sci Transl Med* 5 February 2014 6:222ra17. DOI:10.1126/scitranslmed.3006804.Thomas Renne of the Karolinska Institute, Stockholm, Sweden, and University Hospital Hamburg-Eppendorf, Germany is named as inventor on a patent application covering the use of factor XII as a target of anti-clotting drugs. Several of his co-researchers are employees of CSL, which is developing the 3F7 antibody. Alvin Schmaier is professor of haematology and oncology, Case Western Reserve University, Cleveland, Ohio. [↑](#footnote-ref-25)
26. [L. Wiltzer](http://jid.oxfordjournals.org/search?author1=L.+Wiltzer&sortspec=date&submit=Submit), [K. Okada](http://jid.oxfordjournals.org/search?author1=K.+Okada&sortspec=date&submit=Submit), [S. Yamaoka](http://jid.oxfordjournals.org/search?author1=S.+Yamaoka&sortspec=date&submit=Submit), [F. Larrous](http://jid.oxfordjournals.org/search?author1=F.+Larrous&sortspec=date&submit=Submit), [H. V. Kuusisto](http://jid.oxfordjournals.org/search?author1=H.+V.+Kuusisto&sortspec=date&submit=Submit), [M. Sugiyama](http://jid.oxfordjournals.org/search?author1=M.+Sugiyama&sortspec=date&submit=Submit), [D. Blondel](http://jid.oxfordjournals.org/search?author1=D.+Blondel&sortspec=date&submit=Submit),[H. Bourhy](http://jid.oxfordjournals.org/search?author1=H.+Bourhy&sortspec=date&submit=Submit), [D. A. Jans](http://jid.oxfordjournals.org/search?author1=D.+A.+Jans&sortspec=date&submit=Submit), [N. Ito](http://jid.oxfordjournals.org/search?author1=N.+Ito&sortspec=date&submit=Submit) and [G. W. Moseley](http://jid.oxfordjournals.org/search?author1=G.+W.+Moseley&sortspec=date&submit=Submit), “Interaction of Rabies Virus P-Protein With STAT Proteins is Critical to Lethal Rabies Disease”, *Journal of Infectious Diseases* doi: 10.1093/infdis/jit829 First published online: December 23, 2013 [↑](#footnote-ref-26)
27. Charles E. Mays, Chae Kim3, Tracy Haldiman, Jacques van der Merwe, Agnes Lau, Jing Yang, Jennifer Grams, Michele A. Di Bari, Romolo Nonno, Glenn C. Telling, Qingzhong Kong3, Jan Langeveld, Debbie McKenzie7, David Westaway and Jiri G. Safar, Prion disease tempo determined by host-dependent substrate reduction”, *The Journal of Clinical Investigation*, 2014;124(2):847–858. doi:10.1172/JCI72241. [↑](#footnote-ref-27)
28. Kmietowicz Z. “Risk of thrombosis is raised for 12 weeks after giving birth, finds US study”. *BMJ* 2014;348:g1556 [↑](#footnote-ref-28)
29. Liran I. Shlush, Sasan Zandi, Amanda Mitchell, Weihsu Claire Chen, Joseph M. Brandwein, Vikas Gupta, James A. Kennedy, Aaron D. Schimmer, Andre C. Schuh, Karen W. Yee, Jessica L. McLeod, Monica Doedens, Jessie J. F. Medeiros, Rene Marke, Hyeoung Joon Kim, Kwon Lee, John D. McPherson, Thomas J. Hudson, The HALT Pan-Leukemia Gene Panel Consortium, Andrew M. K. Brown, Quang M. Trinh, Lincoln D. Stein, Mark D. Minden, Jean C. Y. Wang, John E. Dick.” **Identification of pre-leukaemic haematopoietic stem cells in acute leukaemia”**. Nature, 2014; DOI: [10.1038/nature13038](http://dx.doi.org/10.1038/nature13038) [↑](#footnote-ref-29)
30. Anderson is senior author of the paper (in the *Proceedings of the National Academy of Sciences* for the week of 10 February) describing the particles. The research included scientists from Amylam. [↑](#footnote-ref-30)
31. D. J. D. Earn, P. W. Andrews, B. M. Bolker. “**Population-level effects of suppressing fever”.** Proceedings of the Royal Society B: Biological Sciences, 2014; 281 (1778): 20132570 DOI: [10.1098/rspb.2013.2570](http://dx.doi.org/10.1098/rspb.2013.2570) [↑](#footnote-ref-31)
32. A Sridharan, Q [Chen](http://www.ncbi.nlm.nih.gov/pubmed?term=Chen%20Q%5BAuthor%5D&cauthor=true&cauthor_uid=23966397), KF [Tang KF](http://www.ncbi.nlm.nih.gov/pubmed?term=Tang%20KF%5BAuthor%5D&cauthor=true&cauthor_uid=23966397), EE [Ooi](http://www.ncbi.nlm.nih.gov/pubmed?term=Ooi%20EE%5BAuthor%5D&cauthor=true&cauthor_uid=23966397) , ML Hibberd, J [Chen J](http://www.ncbi.nlm.nih.gov/pubmed?term=Chen%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23966397)., “Inhibition of megakaryocyte development in the bone marrow underlies dengue virus-induced thrombocytopenia in humanized mice*”,* [*J Virol.*](http://www.ncbi.nlm.nih.gov/pubmed/23966397) 2013 Nov;87(21):11648-58. doi: 10.1128/JVI.01156-13. Epub 2013 Aug 21. [↑](#footnote-ref-32)
33. D. L. Akey, W. C. Brown, S. Dutta, J. Konwerski, J. Jose, T. J. Jurkiw, J. DelProposto, C. M. Ogata, G. Skiniotis, R. J. Kuhn, J. L. Smith**. “Flavivirus NS1 Structures Reveal Surfaces for Associations with Membranes and the Immune System**.” Science, 2014; DOI: [10.1126/science.1247749](http://dx.doi.org/10.1126/science.1247749) [↑](#footnote-ref-33)
34. 31 patients on the Chinese mainland died from H7N9 in January. Live poultry markets in Hangzhou and Shanghai had been ordered to close permanently. [↑](#footnote-ref-34)
35. Between 2003 and 2013, the bird flu H5N1 is known to have infected 648 people, with 384 deaths. [↑](#footnote-ref-35)
36. Nobuko Ohshima, Ritsuko Kubota-Koketsu, Yoshitaka Iba, Yoshinobu Okuno, and Yoshikazu Kurosawa “Two Types of Antibodies Are Induced by Vaccination with A/California/2009pdm Virus: Binding near the Sialic Acid-Binding Pocket and Neutralizing Both H1N1 and H5N1 Viruses”, *PloS One*, 5 February 2014 DOI: 10.1371/journal.pone.0087305 [↑](#footnote-ref-36)
37. Trish M. Perl, Allison McGeer, and Connie Savor Price, “Medusa's Ugly Head Again: From SARS to MERS-CoV”, Ann Intern Med. Published online 28 January 2014 doi:10.7326/M14-0096 [↑](#footnote-ref-37)
38. Yaseen M. Arabi, Ahmed A. Arifi, Hanan H. Balkhy, Hani Najm, Abdulaziz S. Aldawood, Alaa Ghabashi, Hassan Hawa, Adel Alothman, Abdulaziz Khaldi, and Basel Al Raiy, “Clinical Course and Outcomes of Critically Ill Patients With Middle East Respiratory Syndrome Coronavirus Infection”, Ann Intern Med. Published online 28 January 2014 doi:10.7326/M13-2486 [↑](#footnote-ref-38)
39. Meyer B, Müller MA, Corman VM, Reusken CBEM, Ritz D, Godeke G-D, et al. Antibodies against MERS coronavirus in dromedary camels, United Arab Emirates, 2003 and 2013. *Emerg Infect Dis* [Internet]. 2014 Apr [print]. <http://dx.doi.org/10.3201/eid2004.131746> [↑](#footnote-ref-39)
40. Woo PCY, Lau SKP, Wernery U, Wong EYM, Tsang AKL, Johnson B, et al. Novel betacoronavirus in dromedaries of the Middle East, 2013. Emerg Infect Dis [Internet]. 2014 Apr [print]. <http://dx.doi.org/10.3201/eid2004.131769> [↑](#footnote-ref-40)
41. Coronaviruses are a large group of RNA viruses that can cause both respiratory and enteric signs of disease in various species. They are further classified into alpha, beta, and gamma coronaviruses based on genetic and serologic difference. The equine coronavirus, a beta coronavirus, has been responsible for a number of recent outbreaks across the US. In horses, this is an enteric disease. So far there has been no association with a respiratory component (although in cattle both enteric and respiratory effects are common). Researchers recently completed a study on equine coronaviruses in mature horses. At the 2013 American Association of Equine Practitioners' Convention, in Nashville, Tennessee, Nicola Pusterla, a professor at the University of California, Davis, School of Veterinary Medicine, presented the results of the study. "We consider this an emerging pathogen," Pusterla said, noting that disease outbreaks associated with ECoV and adult horses have rarely been described in the scientific literature prior to recent years. Coronavirus is spread faeco-orally, Pusterla said, "and likely passed from horse to horse via faecal contamination of the environment from clinically but also asymptomatic shedders. [↑](#footnote-ref-41)
42. Patel MM, et. al. “Systematic Literature Review of Role of Noroviruses in Sporadic Gastroenteritis”, *Emerg Infect Dis.* 2008; 14(8):1224-31. [↑](#footnote-ref-42)