Monitoring International Trends

**posted July 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:

* rEVO Biologics is building a rabbit centre in Massachusetts to house 1200 genetically engineered rabbits raised to produce milk containing Factor VIIa (FVIIa) (page 3).
* The US Food and Drug Administration (FDA) cleared the Sobi/Biogen drug [Eloctate (long life FVIII)](http://email.seekingalpha.com:80/track?type=click&mailingid=1790173&messageid=EM_2900&databaseid=&serial=EM_2900O1790173O1402174606.ff5a3146445ef75ed22ed4f561214664&emailid=susan.bambrick%40nba.gov.au&userid=2550971&extra=&&&3000&&&http://www.biogenidec.com/therapies_eloctate.aspx?ID=20259) for some patients (page 3).
* Two patients given Bluebird Bio’s gene therapy for beta-thalassemia were able to stop receiving blood transfusions within 12 days of receiving the treatment (page 4).
* Bayer and Dimension have agreed develop a gene therapy for haemophilia A (page 5).
* Grifols opened its new **fractionation facility in North Carolina** (page 5).
* Researchers suggest that the use of drains in total hip or total knee arthroplasty) increased blood loss, transfusion, and total cost (page 8).
* The AABB’s updated guidelines on red blood cell (RBC) transfusion thresholds recommend that clinicians employ a restrictive transfusion strategy (page 9).
* The American College of Physicians released recommendations for RBCtransfusion and use of erythropoiesis-stimulating agents in coronary heart disease (page 9).
* A trial in patients with severe head trauma suggests that aggressively treating their anaemia may do more harm than good (page 10).
* Researchers suggest that injecting haemostatic nanoparticles can slow bleeding and improve survival following blast trauma (page 10).
* An international study suggests that pathogen reduction treatment can activate blood platelets and trigger the release of their RNA so they are less effective (page 11).
* Researchers at the University of Essex are working with haemoglobin-based oxygen carriers that mimic the properties of actual haemoglobin (Hb) (page 11).
* Chikungunya has had a major impact in the Caribbean and locally-acquired cases have now appeared in the US (pages 13-14).
* Middle East Respiratory Syndrome (MERS) remains a concern in the Middle East, with some other countries concerned about it returning home with pilgrims (page 15).
* Ebola virus disease in West Africa is proving hard to contain (page 16).

Contents

1. [Products 2](#_Toc393887709)

[Haemophilia treatments 2](#_Toc393887710)

[Sickle Cell treatments 3](#_Toc393887711)

[Beta-thalassemia treatments 3](#_Toc393887712)

[Devices and Services 4](#_Toc393887713)

[Other 4](#_Toc393887714)

1. [Market structure and company news 4](#_Toc393887715)
2. [Country-specific events 6](#_Toc393887716)

[United States 6](#_Toc393887717)

[Canada 7](#_Toc393887718)

[Other countries 8](#_Toc393887719)

1. [Safety and patient blood management 8](#_Toc393887720)

[Appropriate transfusion 8](#_Toc393887721)

[Other. 10](#_Toc393887722)

1. [Research 11](#_Toc393887723)

[Manufacturing blood 11](#_Toc393887724)

[Other 12](#_Toc393887725)

1. [Legal actions and enquiries 13](#_Toc393887726)
2. [Infectious diseases 13](#_Toc393887727)

[Mosquito-borne diseases: dengue, chikungunya and malaria 13](#_Toc393887728)

[Influenza: strains, spread, prevention and treatment 14](#_Toc393887729)

[Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) 15](#_Toc393887730)

[Ebola Virus Disease (EVD) 16](#_Toc393887731)

[Other diseases: occurrence, prevention and treatment 16](#_Toc393887732)

# 1. Products

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

### Haemophilia treatments

* 1. French biotechnology company LFB, through its US-based subsidiary rEVO Biologics[[1]](#footnote-1) will expand its farm in Charlton, Massachusetts, building a rabbit centre to house up to 1200 genetically engineered rabbits raised to produce milk containing factor VIIa (FVIIa), a blood-clotting agent for patients with haemophilia. LFB and rEVO already operate an adjacent property as a farm for genetically altered goats that produce a therapeutic protein in their milk[[2]](#footnote-2). LFB has already produced some FVIIa in the milk of rabbits in France. It announced in May that it had begun a pivotal study of its FVIIa product in adolescents and adults with antibodies that inhibit certain other clotting proteins. The company also plans pivotal studies in children and in surgical patients.
	2. The US Food and Drug Administration (FDA) cleared the Sobi/Biogen drug [Eloctate](http://email.seekingalpha.com:80/track?type=click&mailingid=1790173&messageid=EM_2900&databaseid=&serial=EM_2900O1790173O1402174606.ff5a3146445ef75ed22ed4f561214664&emailid=susan.bambrick%40nba.gov.au&userid=2550971&extra=&&&3000&&&http://www.biogenidec.com/therapies_eloctate.aspx?ID=20259) (antihaemophilic factor (recombinant) Fc fusion protein) for the control and prevention of bleeding episodes, for [perioperative](http://email.seekingalpha.com:80/track?type=click&mailingid=1790173&messageid=EM_2900&databaseid=&serial=EM_2900O1790173O1402174606.ff5a3146445ef75ed22ed4f561214664&emailid=susan.bambrick%40nba.gov.au&userid=2550971&extra=&&&3000&&&http://en.wikipedia.org/wiki/Perioperative) management and for routine prophylaxis in adults and children with haemophilia A. It was the first recombinant therapy to give haemophilia patients the option of increasing the time interval between prophylactic infusions. The recommended starting prophylactic regimen is 50 IU/kg every four days. In a 165-patient Phase III clinical trial of males 12 years and older with severe hemophilia A, prophylactic treatment with Eloctate achieved a statistically significant reduction of bleeding episodes compared with on-demand treatment. One or two Eloctoate infusions controlled 98 per cent of bleeding episodes. This was the first regulatory approval globally for Eloctate, although an application was also with regulatory authorities in Canada, Japan and Australia. For approval of a marketing application in Europe, the European Medicines Agency required the inclusion of paediatric study data. The successful completion of the Kids A-LONG study in April 2014 was therefore an important step in this process.
	3. Acella Pharmaceuticals was granted FDA approval for its tranexamic acid injection 1000mg/10mL (100mg/mL) for short-term use[[3]](#footnote-3) in haemophilia A patients to reduce or prevent haemorrhage and reduce the need for replacement therapy during and following tooth extraction. The FDA determined that the product is bioequivalent and hence therapeutically equivalent to the reference listed drug, Cyklokapron-tranexamic acid injection solution. Acella’s injection will be manufactured by Bioindustria in Italy.

### Sickle Cell treatments

* 1. Mast Therapeutics initiated patient enrolment in a sub-study within EPIC, its Phase III study of MST-188 in sickle cell disease, to quantify the effect of MST-188 on tissue oxygenation, using a non-invasive, FDA-approved device. MST-188 has already been shown to reduce viscosity and adhesive frictional forces in blood and improve microvascular blood flow. Improvements in the flow of oxygen-carrying blood to tissues are expected to reduce the duration of vaso-occlusive crises, and to limit tissue damage and organ dysfunction and failure.
	2. Another investigational drug to treat vaso-occlusive crises has been found to be safe following a clinical trial at the University of California at Davis. The Phase I trial found GMI 1070 maintained adequate blood concentrations[[4]](#footnote-4). While the study did not focus on efficacy there was evidence that it did improve blood flow and reduced the markers of cell activation, said Ted Wun, of the University’s School of Medicine. “White blood cells bind to inflamed blood vessel walls and sickle red cells stick to white cells, but interestingly the initiating event is the white cells….If we could interrupt that white cell interaction, we could stop the cycle that leads to vaso-occlusions”. GMI 1070 (trade name Rivipansel) is produced by GlycoMimetics, based in Gaithersburg, Maryland. The company sponsored the trial.

### Beta-thalassemia treatments

* 1. Two patients who were given Bluebird Bio’s experimental gene therapy for beta-thalassemia were able to stop receiving blood transfusions within 12 days of receiving the treatment. An earlier version of the treatment allowed one beta-thalassemia patient to remain free of blood transfusions for six years[[5]](#footnote-5), but that patient was not able to stop transfusions until 12 months after receiving the therapy. Marina Cavazzana, of Paris Descartes University, France, presented data on the two patients at a haematology conference in Milan. Cavazzana reported that the treatment led to relatively few side effects, which could be treated.
	2. Celgene and Acceleron have been granted orphan drug designation for beta-thalassemia by the FDA. They have two drugs in joint development.

### Devices and Services

1. Prototype products featured at a Singapore trade exhibition in June included the BioSenze biometrics device. When the device is plugged into a mobile phone, it powers up to sample blood or saliva. A phone app can then interpret the data within ten minutes, to detect whether a user has, say, dengue fever.

### Other

* 1. GlaxoSmithKline (GSK) began a Phase III study to evaluate the platelet supportive care effects of eltrombopag (Promacta/Revolade) in combination with azacitidine (the current standard of care) compared with placebo in high risk patients with myelodysplastic syndromes (MDS)[[6]](#footnote-6). The trial will determine the proportion of patients who do not require platelet transfusion during the first four cycles of treatment.
	2. Alnylam Pharmaceuticals and The Alpha-1 Project (TAP), the venture philanthropy subsidiary of the Alpha-1 Foundation, are collaborating in the continued development of ALN-AAT, a subcutaneously administrated RNAi therapeutic for the treatment of alpha-1 antitrypsin (AAT) deficiency-associated liver disease.
	3. A small and preliminary study has suggested Xarelto (the oral FXa inhibitor from Bayer/Janssen Pharmaceuticals) may have similar clinical benefit to vitamin K antagonists in the treatment of cerebral venous thrombosis[[7]](#footnote-7).
	4. The FDA approved the first recombinant C1-Esterase Inhibitor product (Ruconest) for the treatment of acute attacks of hereditary angioedema[[8]](#footnote-8) in adult and adolescent patients with (HAE). Ruconest is purified from the milk of genetically modified (transgenic) rabbits. It is manufactured by Pharming Group NV, in the Netherlands, and will be distributed in the US by Santarus.

# 2. 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. Earlier in 2014 Bayer announced plans to invest over € 500 million at two manufacturing sites to prepare for the production of two investigational treatments for haemophilia. Now Bayer has reached agreement with Dimension to develop a gene therapy for haemophilia A in a deal that could be worth about $US250 million to Dimension. Dimension chief executive Thomas Beck said the company’s adeno-associated virus vector technology permits systemic intravenous insertion of the clotting factor gene *in vivo*, which has been shown in preclinical studies to target the liver “resulting in long-lasting expression of FVIII protein at therapeutic levels”. Dimension, which was formed in 2013, will be responsible for pre-clinical development and the phase I/IIa study.
	2. [CSL Behring](http://www.cslbehring.com/) announced Bart C.Jacob (Erasmus University Medical Centre, Rotterdam) as the recipient of its 2014 award for research in neuroimmunology. This annual award provides funds and/or product supply to researchers whose proposals are likely to advance innovative medical research and knowledge about the potential role of immunoglobulin therapy in the treatment of neurological disorders. Dr Jacobs' plans to investigate the efficacy of intravenous immunoglobulin (IVIg) treatment in patients with mild Guillain-Barre syndrome (GBS)[[9]](#footnote-9).
	3. In June, Grifols opened its new **$US 370 million facility in Clayton, North Carolina.** Grifols' North Fractionation Facility will be the world's largest. It will increase production capacity in Clayton from 3.2 million litres of plasma a year to 6 million in 2015 when it is expected to be fully operational. Grifols’ sales in North America totalled €1,708 million in 2013, representing 62.3 per cent of company turnover. Grifols’ profit this year is expected to rise 81 per cent, followed by an 11 per cent increase in 2015.
	4. Grifols share price was under pressure at the end of June after *Compliance Week*, a corporate governance publication out of Boston, reported Grifols had launched an internal investigation into "potential irregular practices" in Europe and the Middle East. The US Foreign Corrupt Practices Act of 1977 makes it illegal for companies to pay foreign government officials to obtain business. Its definition of connection with the United States is broad and Grifols has said its investigation began before it bought US company Talecris in 2011.
	5. **For the first quarter of 2014 Cerus Corporation had a 19 per cent decrease in product revenue over the same quarter in the previous year.**
	6. Massachusetts-based companyrEVO Biologics, owned since 2010 by France’s LFB Biotechnologies, plans to list on the NASDAQ under the symbol RBIO. It has filed for a $US75 million initial public offering (IPO). Its sales of its recombinant protein for the 12 months ended March 31, 2014, amounted to $US33 million.
	7. Pharmaco-Kinesis Corporation was awarded a grant by the US Department of Defense for development of its "Carbon Nanotube Based Biosensor for Organ Injury Detection". Detection of organ injury by the device is enabled through measurement of kidney and liver injury biomarkers, such as albumin and glutathione-S-transferase, in urine and blood.
	8. Pittsburgh-based [ALung Technologies](http://www.massdevice.com/company/alung-technologies-inc) has raised a further $US10 million to continue commercializing its Hemolung respiratory assist device. This is an extracorporeal system that removes carbon dioxide and delivers oxygen directly to a patient's blood via a small catheter inserted into the jugular or femoral vein. The company says the product has been tested and validated by physicians at 43 hospitals in 13 countries.
	9. [Endomedix](http://endomedix.com) received a $US1.49 million grant from the [National Institute of Neurological Disorders and Stroke to develop a sealant and applicator device to control bleeding in brain surgery.](http://www.ninds.nih.gov/) The sealant is a hydrogel that includes two processed biocompatible polysaccharides. They are simultaneously mixed and sprayed onto a surgical site.
	10. Pluristem Therapeutics announced that Russia's Federal Service for Intellectual Property has granted the company a patent titled "Methods of Treating Inflammatory Colon Diseases". The patent covers methods for treating ulcerative colitis or Crohn's disease using placenta-derived cells. Pluristem already holds a matching South African patent and has applications in other jurisdictions.
	11. Swedish Orphan Biovitrum (Sobi) is reviewing preclinical data and considering adding a future haemophilia A candidate to its collaborative agreement with Biogen Idec. The preclinical program is based on the proprietary XTEN technology of Amunix with whom Biogen signed a worldwide license agreement last April[[10]](#footnote-10).
	12. China Biologic Products, a major plasma-based biopharmaceutical company in China, filed a preliminary prospectus supplement in connection with its public offering of shares of its common stock. The Company says it will use the proceeds from the offering for general corporate purposes but may also in the future acquire or invest in complementary products, technologies or businesses.
	13. ProMetic Life Sciences of Quebec received a further order under its supply agreement with Octapharma, relating to the purchase of PrioClear, a proprietary prion capture resin incorporated into Octapharma's manufacturing process for its solvent/detergent treated plasma product, OctaplasLG. OctaplasLG is currently approved for marketing in the US and several European countries. The order should be delivered during the rest of 2014.

# 3. 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. US health policy think tank the Commonwealth Fund examined the healthcare systems of the eleven countries in relation to access and equity, quality and efficiency, and population health indicators such as infant mortality. The US ranked lowest[[11]](#footnote-11), with the UK top overall[[12]](#footnote-12), followed by Switzerland[[13]](#footnote-13), then Sweden[[14]](#footnote-14), Australia, Germany, The Netherlands[[15]](#footnote-15), New Zealand, Norway, France[[16]](#footnote-16), Canada. The report noted that “the Netherlands, UK and Germany provide universal coverage with low out-of-pocket costs while maintaining quick access to specialty services.” Healthcare spending per head in 2011 was highest in the US (at $US 8,508) followed by Norway ($US 5,099) and Switzerland ($US 5,643); and it was lowest in New Zealand ($US 3,182). The UK was second lowest ($US 3,405), Australia third lowest ($US 3800).
	2. With a Presidential Executive Order on Open Data and the Department of Health and Human Services Health Data Initiative, open FDA is expected to make the FDA’s publicly available data accessible, on a needs basis, in a structured, computer readable format that will make it possible for technology specialists and researchers to search, query, or download public information directly from FDA datasets. The FDA decided to phase in open FDA beginning with an initial program involving the reports of drug adverse events and medication errors submitted to the FDA from 2004 to 2013. The adverse events data made available will not contain any data that could be used to identify individuals. This pilot will later be expanded to include the FDA’s databases on product recalls and product labelling.
	3. The US National Institutes of Health (NIH) awarded $US25 million over five years to the J. Craig Venter Institute[[17]](#footnote-17) to back an initiative to study infectious diseases like malaria and influenza at the genetic level to help find better treatments and preventive measures. The establishment of the Genome Center for Infectious Diseases will allow study of the genetic secrets of a wide range of bacteria, viruses and parasites, the recipients said. This will include genetic sequencing of a number of pathogens and research on genetic mechanisms behind the emergence of antibiotic resistance. The parasite research will focus on malaria and also toxoplasmosis. Viruses to be studied include: influenza from human, avian and swine sources, respiratory syncytial virus (RSV), rotavirus, West Nile virus and Eastern equine encephalitis virus. In the bacterial research, the program aims to perform genetic sequencing on more than 1,700 strains of three disease-causing types: klebsiella, acinetobacter and enterobacter.
	4. Since 9 June, all babies born in Illinois hospitals are being tested for the inherited disorder severe combined immunodeficiency (SCID)[[18]](#footnote-18). Babies born with the disorder are not usually diagnosed immediately, but may die during their first year. If SCID is diagnosed before the onset of infection, a bone marrow transplant can successfully treat the disorder. SCID testing is on the US Department of Health and Human Services’ recommended core list. Illinois is the 18th state to test for SCID. Illinois now tests newborns for 40 disorders.
	5. Scientists reported[[19]](#footnote-19) that US residents bitten by a blacklegged tick can be exposed to more than one pathogen simultaneously—the bacterium that causes Lyme disease and the protozoan that causes babesiosis. They found the agents of Lyme disease and babesiosis together in 7 per cent of the thousands of blacklegged ticks they collected from over 150 sites in Dutchess County, New York State. The ticks had fed on infected wildlife, including birds, rodents, opossums, and raccoons.
	6. This year’s variant Creutzfeldt-Jakob disease (vCJD) fatality in Texas was the fourth reported case of vCJD in the US, but the CDC judged it likely that infection had not occurred in the US. One preventive measure the US takes is that the US Department of Agriculture (USDA) requires that spinal tissue (dorsal root ganglia) be extracted from slaughtered cattle older than 30 months be disposed of. A Missouri meat company recently had to recall meat because there was no paperwork to certify that nerve tissue was removed, although visual inspection had suggested the cattle were free of bovine spongiform encephalopathy (BSE).
	7. Health officials in California advised in mid-June that the state’s whooping cough (Pertussis) cases were at epidemic levels.

### Canada

* 1. Blood donations have fallen to a five-year low. In recent months, twenty per cent of donors have missed their appointments.
	2. The Public Health Agency (PHAC) sought bids from funeral directors for transporting the bodies of people suspected of having died from CJD. Its tender notice said the successful bidder would collect the deceased from hospitals, institutions and homes throughout Canada and transport them "by ground, air or rail" to pathologists for brain autopsies. The notice suggested case numbers could be 60 or more each year. This program is part of PHAC's Creutzfeldt-Jakob Disease Surveillance System. Michael Coulthart, director of the surveillance program, said "There is a huge fear out there from funeral directors about doing anything with CJD, but this has no basis in fact for transport”. However, pathologists must wear protective gear while performing an autopsy—due to exposure to brain and spinal-cord tissue where the infectious prions reside—and embalming isn't recommended because of a small risk of transmission.
	3. Some Canadians are asking whether their blood supply could already be contaminated by Lyme disease, which appears to be of increasing incidence, although some of this could arise from increasing awareness and better diagnosis.

### Other countries

* 1. The UK National Blood Transfusion Committee’s Patient Blood Management recommendations are now available at: <http://www.transfusionguidelines.org.uk/uk-transfusion-committees/national-blood-transfusion-committee/patient-blood-management>
	2. There is concern in Ireland that as many as 22,000 citizens are unaware they are suffering from haemochromatosis, with its potential to damage organs such as the liver. The hereditary illness is unusually common in Ireland due to its Celtic heritage[[20]](#footnote-20).

# 4. Safety and patient blood management

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

### Appropriate transfusion

* 1. Surgeons at the University of Pittsburgh Medical Center are preparing to test a new treatment for patients with stab or gunshot wounds. These patients may have suffered such heavy blood loss that they go into cardiac arrest shortly after arriving at hospital. Surgeons have very little time to repair their wounds before brain damage occurs, and a significant proportion die. In a clinical trial, surgeons will inject ice cold saline water directly into their hearts to try to produce hypothermia. Research leader Samuel Tisherman, a visiting professor from the University of Maryland said: "The cooling is to decrease their need for oxygen in the brain and other organs and it's all just to buy time for surgeons to operate on them and stop the bleeding". He said patients "won't have a pulse, they won't be breathing, there wouldn't be any brain waves and no brain activity. But they're not at a point where we would say that they're dead and we would stop all measures to help them". After surgery patients will be re-warmed using a heart-lung machine–already in use in cardiac surgeries. Inducing hypothermia in patients with cardiac arrest is not a new technique, it’s the testing on trauma patients that is novel. The trial is looking initially for only ten patients, and may take up to a year, as the subjects will be only those who are admitted with “catastrophic penetrating trauma,” who have gone into cardiac arrest, and who are very close to death. After reviewing the experience with ten patients and adjusting techniques if necessary, the trial will continue with a further ten patients. Tisherman concedes that since the technique is untried in trauma patients, the risk of brain damage is unknown.
	2. A study[[21]](#footnote-21) has found that the use of drains in patients having primary unilateral total hip arthroplasty (THA) and total knee arthroplasty (TKA) increased blood loss, increased transfusion, and increased total costs. Researchers included 536 THAs and 598 TKAs. They considered gender, age, procedure, surgeon, length of stay, preoperative haemoglobin, all recorded postoperative haemoglobin values, length of hospital stay, amount and type of all blood products transfused, and presence of a drain with any associated output. Researchers calculated the use of a postoperative drain was associated with $US538 additional cost per THA and $US455 per TKA. The use of a drain increased hospital length of stay for THA, but not for TKA. Use of a drain increased estimated blood loss and the volume of allogeneic blood transfused in both procedures. The researchers commented: “Additional data regarding surgeon’s justification for drain use, including visualized intraoperative bleeding and patient-specific concern for post-operative bleeding would provide useful information not available in a retrospective analysis.”
	3. In 2012 the AABB published guidelines addressing red blood cell (RBC) transfusion thresholds[[22]](#footnote-22). The updated guidelines[[23]](#footnote-23) recommend that clinicians employ a restrictive transfusion strategy. They recommend transfusion for ICU patients with haemoglobin ≤7g/dL. In post-operative surgical patients and post-operative patients with symptomatic anaemia, the guidelines recommend a transfusion threshold haemoglobin of ≤8g/dL. They recommend that both symptoms and haemoglobin level should be considered. The authors suggest that a future trial to compare these two transfusion triggers would be helpful.
	4. The American College of Physicians (ACP) released its recommendations fo**r** red blood cell transfusion, and use of erythropoiesis-stimulating agents for patients with coronary heart disease[[24]](#footnote-24). It advised restrictive transfusion with a haemoglobin threshold of 7-8 g/dL in hospitalized patients[[25]](#footnote-25) and advised against using erythropoiesis-stimulating agents for mild to moderate anaemia in patients with congestive heart failure or coronary heart disease[[26]](#footnote-26).
	5. In a narrative review**[[27]](#footnote-27)**, researchers reported on anaemia and RBC transfusion in hospitalized adults and children (other than premature babies) with cardiac disease. They say the appropriate threshold haemoglobin level for unstable cardiac patients is not known, nor is the optimal transfusion strategy in cardiac patients, for the threshold where the risk of anaemia outweighs the risk of transfusion is undefined. They recommend further study on these matters.
	6. A study reviewed data on suspected perioperative transfusion-related acute lung injury (TRALI) cases reported to Canadian Blood Services between 2001 and 2012**[[28]](#footnote-28)**. Researchers found the perioperative group represented a large proportion of TRALI cases. The largest surgical group was patients who had cardiac surgery involving cardiopulmonary bypass (25 per cent). Orthopaedics surgical patients represented (12.5 per cent).
	7. A clinical trial suggests that although patients with severe head trauma may develop anaemia, aggressively treating that anaemia may be ill-advised. Giving blood transfusions, and in some cases, erythropoietin, did not improve long-term recovery for patients with brain injury, and an aggressive transfusion policy increased the risk of blood clots. Lead researcher Dr Claudia Robertson[[29]](#footnote-29) said the results "will probably change clinical practice."
	8. A study by Pablo Perel, from the London School of Hygiene & Tropical Medicine, and colleagues[[30]](#footnote-30), suggests that trauma patients who have the highest predicted risk of death on arrival at a trauma hospital enjoy most benefit from red blood cell transfusions. Conversely those predicted to have with the lowest mortality risk at baseline red blood cell transfusion have an associated higher chance of death[[31]](#footnote-31). The authors commented: “However, as our study was observational, important biases cannot be ruled out, and we cannot claim a causal link. Therefore, this hypothesis should be prospectively evaluated in a randomised controlled trial."

### Other.

* 1. A study on using hemostatic nanoparticles to improve survival following blast trauma has been published in The Proceedings of the National Academy of Sciences*[[32]](#footnote-32)*. Researchers developed and tested a type of synthetic platelet, which can be injected into the body to speed the formation of blood clots. These nanoparticles may prove to be an important tool in slowing internal bleeding. The researchers say there is still a great deal of work to do, but they are encouraged by the length of the survival period the nanoparticles induce.
	2. A relatively new method of electrocautery, the radiofrequency bipolar haemostatic sealer (RBHS), uses saline-cooled delivery of energy, to seal blood vessels rather than burning them. An assessment of the benefits of RBHS in adult patients undergoing multilevel spinal fusion surgery found the method can conserve blood, promote higher haemoglobin levels, and reduce transfusion-related costs[[33]](#footnote-33).
	3. The FDA granted Boehringer Ingelheim Pharmaceuticals its breakthrough therapy designation[[34]](#footnote-34) for idarucizumab, an investigational fully humanized antibody fragment, or Fab, being studied as a specific antidote for Pradaxa (dabigatran). Sabine Luik, the company’s senior vice president, Medicine & Regulatory Affairs, said: "We are committed to innovative research and to advancing care in patients taking Pradaxa. We continue to investigate the potential of idarucizumab as a therapeutic option should a patient experience uncontrolled bleeding or need to undergo emergency surgery or another invasive procedure." Boehringer Ingelheim plans to seek an accelerated approval pathway for idarucizumab[[35]](#footnote-35).
	4. Researchers have reported that presurgical prophylaxis for [venothromboembolism (VTE)](file:///C%3A%5CCardiology%5CVenousThrombosis%5C) appeared to reduce the risk of thrombosis in cancer patients without increasing the risk of bleeding episodes.[[36]](#footnote-36).
	5. An international study[[37]](#footnote-37) suggests that pathogen reduction treatment can activate blood platelets and trigger the release of RNA. "The processes that are used target the genetic material of pathogenic organisms," explains Patrick Provost. "They were developed more than 20 years ago, before we understood the importance of the [genetic material](http://medicalxpress.com/tags/genetic%2Bmaterial/) contained in platelets…..The platelets end up depleted of RNA so, once transfused, they're unable to do what they normally would".
	6. Thrombolytic drugs are prescribed to prevent pulmonary embolism. Researchers analyzed data from 16 trials involving use of the drugs and concluded that the risk of major bleeding, especially in the brain, remains a concern. Lead author Dr. Jay Giri of the University of Pennsylvania said the "potential benefit must be balanced against potential bleeding risks in the individual patient." He said the research[[38]](#footnote-38) suggests patients younger than 65 might be at less risk for bleeding from clot-busting drugs.

# 5. Research

*A wide range of scientific research has some potential to affect the use of blood and blood products. However, research projects have time horizons which vary from “useful tomorrow” to “at least ten years away”. Likelihood of success of particular projects varies, and even research which achieves its desired scientific outcomes may not lead to scaled-up production, clinical trials, regulatory approval and market development.*

### Manufacturing blood

* 1. Tang Ruikang, a Zhejiang University professor, is with his research team developing an approach to manufacturing “universal” human blood by “cloaking” red blood cells (RBCs)[[39]](#footnote-39). Team member Wang Ben said they attempted to create a cloaked cell with different functions and characteristics. They eventually targeted polydopamine (PDA), which is native to the human body and can mimic dopamine to modify the RBC surface. *In vitro* experiments demonstrated that the antigenic response during blood mismatching does not occur, and the structural and functional characteristics of the modified RBCs are unchanged. *In vivo* experiments in mice revealed that PDA-RBCs behave like native cells. Their life span is similar, and even after multiple transfusions they do not trigger an immune response from the mice.
	2. Researchers at the University of Essex have received a grant to work on developing an artificial blood that can be stored at room temperature. Study leader Professor Chris Cooper says: “There would be no need for blood group typing and a longer shelf life means you are able to stockpile the supplies necessary for major disasters”. Researchers say the product they are planning **will be easy to detect if it’s used for doping.** Their project, Haem02, relies on haemoglobin-based oxygen carriers (HBOC) to mimic the properties of actual haemoglobin (Hb)[[40]](#footnote-40).

### Other

* 1. A study determined the range of antibodies to tetanus, diphtheria, measles and varicella in IVIg products and the levels of these antibodies in patients undergoing IVIg treatment[[41]](#footnote-41). Researchers studied over a year 21 patients with primary antibody deficiencies who were receiving regular IVIg therapy. Blood samples were collected quarterly before immunoglobulin infusion. Samples were taken from the IVIg preparation the patients received at their previous infusions. Researchers found that antibody levels to the four selected diseases showed considerable variation between different IVIg lots, but they were similar when compared between commercial preparations. All patients presented had protective levels of antibodies specific for tetanus, measles and varicella, but some had suboptimal diphtheria antibody levels.
	2. Scientists at King's College London have reported a genetic variant associated with an increased risk of heart attack and stroke[[42]](#footnote-42). The variant is found in platelets which are critical in the formation of [blood clots](http://medicalxpress.com/tags/blood%2Bclots/). This finding may assist in the identification of patients at particularly high risk of [stroke](http://medicalxpress.com/tags/stroke/) or heart attack so they may be encouraged to reduce risk factors such as high blood pressure and smoking.
	3. The US Defense Advanced Research Projects Agency (DARPA) is funding researchers at the Whitehead Institute to develop a way to attach chemical payloads to red blood cells. DARPA’s interest is in developing treatments or vaccines for biological weapons, but it is possible any technique developed could be used more generally carrying anti-inflammatory antibodies to sites of inflammation, suppressing unwanted immune responses to protein-based therapies, removing cholesterol from the bloodstream, and ferrying clot-busting proteins to blocked blood vessels.
	4. Humacyte completed patient enrolment in two multi-centre, studies to assess the safety and efficacy of HumaGraft, its bioengineered blood vessel.
	5. French researchers claim to have developed a blood test that can detect vCJD in both humans and animals during the early phases of infection[[43]](#footnote-43). They say the test identified three out of four vCJD patient samples, and that no false positives were reported in 114 healthy controls. Olivier Andréoletti of the Ecole Nationale Vétérinaire de Toulouse said: “There are many potential blood donors in the UK and other countries that are currently incubating asymptomatically. Each of them could be a source of contamination.”
	6. Researchers at the University of Minnesota are commencing trials in California to determine if medical marijuana can alleviate the chronic pain of sickle cell disease.

# 6. 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. The Scottish Government initially allowed £3 million to fund the Penrose inquiry to investigate how hundreds of Scots were given contaminated NHS blood in the 1970s and 1980s. Following delays, the estimate of cost by the time the inquiry reports later this year will have risen to at least £11.7m.

# 7. Infectious diseases

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

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

* 1. By 5 June 35 cases of dengue fever had been confirmed in Queensland in 2014, eighteen in Charters Towers and seventeen from Townsville. Researchers, wanting to release *Wolbachia*-infected mosquitoes in Townsville (in a bid to eradicate dengue), met with community leaders on 16 June. Professor Scott O’Neill ( Monash University and his team have successfully run trials elsewhere.
	2. Sanofi Pasteur’s phase III trial in Asia of its dengue vaccine showed an efficacy of 56.5 per cent against dengue infections in children aged 2 to 14[[44]](#footnote-44). Annelies Wilder-Smith, of Nanyang Technological University in Singapore, who was not involved in this particular trial, said: "That is much less than we would have hoped”...but admitted "If we can reduce 50 percent of the world's dengue infections, that in itself is already a breakthrough". Jonas Schmidt-Chanasit, head of the virus diagnostics department at Bernhard-Nocht Institute for tropical Medicine in Hamburg, said: "We waited a long time on the results of this study". While he saw the fact that the vaccine had no adverse effects as good news, he commented: "The efficacy of the vaccine, though, has to be regarded with suspicion". He warned that the protection was not equally good for all four subtypes of the dengue virus, and that could be dangerous. Maria Rosario Capeding from the Research Institute for Tropical Medicine in the Philippines (and lead author of the study) said: "This candidate vaccine has the potential to have a significant impact on public health in view of the high disease burden in endemic countries". Sanofi hopes to market the vaccine from 2015.
	3. The Caribbean Public Health Agency said in mid-June that the chikungunya virus had been detected in twenty countries and territories. Case numbers were being estimated in hundreds of thousands. The number had tripled in a month.
	4. France is concerned that chikungunya may become endemic on the mainland. Some 400,000 people from Guadeloupe and Martinique live there but holiday in the islands. They could return to France carrying the virus, and be bitten by the tiger mosquito, which transmits it. This mosquito is already present.
	5. By early June US authorities were publicly expressing concern that dengue fever and chikungunya were posing a serious threat to Florida. In the previous week dengue fever had been confirmed in 24 people and chikungunya confirmed in 18 people. All of the infected people in Florida at that stage had travelled to the Caribbean or South America. By 15 July, 234 chikungunya cases had been reported in the continental US, 230 in people returning from the Caribbean and South America, three from the Pacific Islands and one from Asia.
	6. By mid-July many US states were reporting chikungunya, but so far only in those who had been in the Caribbean. On July 17, the CDC reported a locally acquired case in Florida, the first case in the continental US[[45]](#footnote-45). Another soon followed.
	7. A prophylactic vaccine against chikungunya fever has been developed by an Austrian company, Themis Bioscience. A phase I study has shown the vaccine to be safe, and that it induces a significant neutralizing immune response. The vaccine uses a standard anti-measles vaccine as a vector.
	8. Seattle BioMed researchers have developed a next generation genetically attenuated parasite that might lead to a highly protective malaria vaccine[[46]](#footnote-46).

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

* 1. On 12 June Hong Kong lowered the response level of the Preparedness Plan for Influenza Pandemic from "Serious" to "Alert". The level had been raised to "Serious" upon the detection of the first confirmed case of human infection with avian influenza A(H7N9) imported from the mainland last December. Hong Kong had by 12 June 10 confirmed 10 cases, all imported. The surveillance system of the local public and private hospitals had not detected any new case for two months. When the wholesale poultry market had resumed operation on February 19, the Government had further suspended the import of live poultry from the mainland for four months. The Food and Health Bureau said it would ask a consultant to recommend whether or not live poultry sales should be maintained in Hong Kong.
	2. An international study[[47]](#footnote-47) has identified five Asian countries which could join China as targets for H7N9. Parts of Bangladesh, India, Indonesia, the Philippines and Vietnam as at risk because they have live bird markets in densely-populated areas.
	3. Novartis’ Holly Springs facility is the first pandemic-ready site licensed by the FDA to produce cell-culture influenza vaccines. The facility is a result of a joint partnership between Novartis and the US Department of Health and Human Services, Biomedical Advanced Research and Development Authority.
	4. Researchers developed a potentially lethal virus resembling the 1918 Spanish flu strain that killed an estimated 50 million people[[48]](#footnote-48). [Lord May](http://www.zoo.ox.ac.uk/people/view/may_r.htm), the former President of the Royal Society and once chief science adviser to the UK government, said: “The work they are doing is absolutely crazy. The whole thing is exceedingly dangerous." Of the justification given by the US researchers involved-that the experiments were essential to an appreciation of the pandemic risk posed by viruses currently circulating in wild birds-Lord May said: "Yes, there is a danger, but it's not arising from the viruses out there in the animals, it's arising from the labs of grossly ambitious people." [Marc Lipsitch](http://www.hsph.harvard.edu/marc-lipsitch/), professor of epidemiology at Harvard School of Public Health, said: "I am worried that this signals a growing trend to make transmissible novel viruses willy-nilly, without strong public health rationale. This is a risky activity, even in the safest labs. Scientists should not take such risks without strong evidence that the work could save lives”. He did not consider that the Kawaoka paper provided this. A significant proportion of global work on creating dangerous viruses is funded by the US NIH. [Simon Wain-Hobson](https://www.pasteur.fr/ip/easysite/pasteur/en/research/scientific-departments/virology/units-and-groups/molecular-retrovirology), a virologist at the Pasteur Institute in Paris, worries that governments and funding bodies will take the risks seriously only when an accident happens. Following almost immediately on this debate, the CDC found itself subject to criticism over carelessness in handling dangerous material, as did the NIH.

### Middle East Respiratory Syndrome-Coronavirus (MERS-CoV)

* 1. Osama Felali, chair of Saudi Arabia’s Haj and Umrah Committee, said the number of Umrah pilgrims arriving from different countries had not been restricted because of MERS, which had by then killed nearly 300 people in the Kingdom alone[[49]](#footnote-49). He said there was a 10 per cent increase in the number of Umrah pilgrims this year, compared with 2013. More than three million foreign pilgrims were expected during Ramadam.
	2. In mid-June, the World Health Organization (WHO) said efforts to prevent the spread of MERS needed to be increased before the start of the Muslim pilgrimage season. The Philippines government in July urged 6,500 Filipinos who are set to join the annual Hajj pilgrimage in October to go next year instead. Morocco's health minister in June advised the country's Muslims not to make pilgrimages to Saudi Arabia in 2014.
	3. Researchers in Saudi Arabia have identified key defining characteristics of MERS in CT imaging of patients confirmed as having the disease. They found that the most common CT finding in hospitalized patients with MERS infection is suggestive of an organizing [pneumonia](file:///C%3A%5Chealth%5CPneumonia.aspx) pattern. "A few studies have described variable degrees of lung opacities in patients with MERS, but did not clearly address their exact distribution," said Amr M. Ajlan, the corresponding author of the study. "Because we evaluated the CT findings in this laboratory-confirmed group of MERS patients, we had the ability to better characterize the nature and distribution of the abnormalities”. Recognizing this pattern in acutely ill patients living in or traveling from endemic areas may help in the early diagnosis of MERS[[50]](#footnote-50).
	4. Scientists are investigating antibody immunotherapy for treating MERS. Amongst them are Wayne **Marasco,** scientific director of the Center for Human Antibody Therapies at Dana-Farber Cancer Institute and his colleagues[[51]](#footnote-51). Marasco, who has worked on MERS since 2012 at the request of the US Department of Defense, said effective drugs may already be available and amongst the 35 antibody drugs approved by the FDA for other diseases. Researchers from the University of Maryland, the NIH, the US Army Medical Research Institute of Infectious Diseases and Zalicus Inc., have identified 27 compounds with activity against both MERS and [severe acute respiratory syndrome](http://www.healio.com/infectious-disease/emerging-diseases/news/online/%7Bb17430d9-479f-47da-8b2a-c2fd2bab69fc%7D/sars-10-years-later-gaps-in-global-capacity-coordination-remain) (SARS)[[52]](#footnote-52).
	5. **Scientists are confident they have evidence that MERS spreads from camels to people. There are suggestions the virus moved into camels from bats. Experience shows that at least in health care settings, if appropriate infection control is not undertaken the virus spreads between people.** One report in Eurosurveillance[[53]](#footnote-53) provided further details on the confirmation of MERS-CoV in camel milk, and another provided more evidence that the virus or its close relative has been circulating in Saudi Arabian camels since the early 1990s.

### Ebola Virus Disease (EVD)

* 1. From 15-17 Jul 2014, 67 new cases of EVD, including 19 new deaths, were reported in Liberia (22 new cases and 10 deaths and Sierra Leone (45 new cases and 9 deaths). The outbreak in Guinea showed a declining trend. By 17 July the cumulative number of cases in the three countries stood at 1048, including 632 deaths.
	2. On 4 July 2014 the Philippine Overseas Employment Administration had temporarily suspended the processing and deployment of newly hired overseas Filipino workers (OFWs) bound for three West African nations-Guinea, Liberia and Sierra Leone-as Ebola virus disease [EVD] outbreak in the region had worsened.

### Other diseases: occurrence, prevention and treatment

* 1. By mid-July, Victoria had the highest number of measles notifications for fifteen years, with 57 cases since the beginning of the year. Tasmania had confirmed its first measles case in five years. The ACT had announced its first case this year. Two cases of measles had been confirmed in Cairns, the second in a passenger recently arrived from Papua New Guinea.
	2. For two Australian men, levels of HIV fell to undetectable levels after bone marrow transplants at St Vincent’s Hospital, Sydney. Researchers say the virus may only be dormant and could return unless HIV medications are continued.
	3. On 4 June, health authorities in Queensland announced an outbreak of parechovirus infection in infants, with the first eleven 11 cases of the virus ever reported in the state. By then 46 babies had been confirmed nationally with the virus[[54]](#footnote-54).
	4. A report released by Eastern Sydney Medicare Local in June revealed a 290 per cent increase in gonorrhoea notifications in the four years between 2008 and 2012. The local government area with the highest increase was Woollahra, with a population of 52,581 in 2011, and a median weekly income twice the national average[[55]](#footnote-55).
1. Known as GTC Biotherapeutics before it was acquired by LFB in 2010 [↑](#footnote-ref-1)
2. ATryn, for patients with an inherited deficiency in the anti-clotting agent antithrombin III, was launched in 2009. [↑](#footnote-ref-2)
3. 2 to 8 days [↑](#footnote-ref-3)
4. Published online in the journal Public Library of Science ONE (PLoS ONE) [↑](#footnote-ref-4)
5. Report appeared in *Nature* in 2010. [↑](#footnote-ref-5)
6. MDS is a cancer where the bone marrow does not produce sufficient healthy blood cells and there are abnormal (blast) cells in the bone marrow and/or blood. Sufferers usually display anaemia (fatigue), neutropenia (infections), or thrombocytopenia (bleeding). MDS may become acute myeloid leukaemia (AML) in close to half of patients. [↑](#footnote-ref-6)
7. [Christina Geisbüsch](http://stroke.ahajournals.org/search?author1=Christina+Geisb%C3%BCsch&sortspec=date&submit=Submit), [Daniel Richter](http://stroke.ahajournals.org/search?author1=Daniel+Richter&sortspec=date&submit=Submit), [Christian Herweh](http://stroke.ahajournals.org/search?author1=Christian+Herweh&sortspec=date&submit=Submit), [Peter A. Ringleb](http://stroke.ahajournals.org/search?author1=Peter+A.+Ringleb&sortspec=date&submit=Submit), and [Simon Nagel](http://stroke.ahajournals.org/search?author1=Simon+Nagel&sortspec=date&submit=Submit), “ Novel Factor Xa Inhibitor for the Treatment of Cerebral Venous and Sinus Thrombosis: First Experience in 7 Patients”, *Stroke* 24 June 2014. [↑](#footnote-ref-7)
8. Patients with hereditary angioedema can experience rapid swelling of the hands, feet, limbs, face, intestinal tract, or airway. This can occur spontaneously, or can be triggered by surgery, infection or stress. Immediate treatment may be required to prevent death. [↑](#footnote-ref-8)
9. GBS is an inflammation of the peripheral nerves characterized by the rapid onset of weakness and, often, paralysis of the legs, arms, breathing muscles and face. IVIg is recommended in severe GBS. [↑](#footnote-ref-9)
10. Biogen Idec and Sobi are already collaborators in the development and commercialisation of Eloctate (haemophilia A) and Alprolix (Haemophilia B). Biogen leads development, and has manufacturing rights. Sobi has the right to opt in to assume final development and commercialisation in Europe, including Russia, the Middle East and Northern Africa. Biogen holds commercialisation rights in the rest of the world. [↑](#footnote-ref-10)
11. The US healthcare system was the most expensive but underperformed. It ranked very low on efficiency, access and equity and did not achieve better health outcomes. [↑](#footnote-ref-11)
12. The UK led in quality of care, efficiency and access, was second for equity, third for timeliness of care and tenth for healthy lives. [↑](#footnote-ref-12)
13. Switzerland was first in timeliness of care and equity, and third in terms of healthy lives. [↑](#footnote-ref-13)
14. Sweden was second in terms of healthy lives. [↑](#footnote-ref-14)
15. The Netherlands was second in terms of timeliness of care. [↑](#footnote-ref-15)
16. France was first in terms of healthy lives [↑](#footnote-ref-16)
17. of Maryland and California [↑](#footnote-ref-17)
18. According to the US Centers for Disease Control and Prevention, this occurs in one out of every 40,000 to 75,000 births. [↑](#footnote-ref-18)
19. Online in the journal PLoS One [↑](#footnote-ref-19)
20. In Ireland the chance of developing haemochromatosis is estimated to be one in 83 whereas in Europe the estimate is one in 400. [↑](#footnote-ref-20)
21. [Bjerke-Kroll BT](http://www.ncbi.nlm.nih.gov/pubmed?term=Bjerke-Kroll%20BT%5BAuthor%5D&cauthor=true&cauthor_uid=24360337), [Sculco PK](http://www.ncbi.nlm.nih.gov/pubmed?term=Sculco%20PK%5BAuthor%5D&cauthor=true&cauthor_uid=24360337), [McLawhorn AS](http://www.ncbi.nlm.nih.gov/pubmed?term=McLawhorn%20AS%5BAuthor%5D&cauthor=true&cauthor_uid=24360337), [Christ AB](http://www.ncbi.nlm.nih.gov/pubmed?term=Christ%20AB%5BAuthor%5D&cauthor=true&cauthor_uid=24360337), [Gladnick BP](http://www.ncbi.nlm.nih.gov/pubmed?term=Gladnick%20BP%5BAuthor%5D&cauthor=true&cauthor_uid=24360337), [Mayman DJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Mayman%20DJ%5BAuthor%5D&cauthor=true&cauthor_uid=24360337),”The increased total cost associated with post-operative drains in total hip and knee arthroplasty”, [*J Arthroplasty*.](http://www.ncbi.nlm.nih.gov/pubmed/24360337) 2014 May;29(5):895-9. doi: 10.1016/j.arth.2013.10.027. [↑](#footnote-ref-21)
22. [Carson JL](http://www.ncbi.nlm.nih.gov/pubmed?term=Carson%20JL%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Grossman BJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Grossman%20BJ%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Kleinman S](http://www.ncbi.nlm.nih.gov/pubmed?term=Kleinman%20S%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Tinmouth AT](http://www.ncbi.nlm.nih.gov/pubmed?term=Tinmouth%20AT%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Marques MB](http://www.ncbi.nlm.nih.gov/pubmed?term=Marques%20MB%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Fung MK](http://www.ncbi.nlm.nih.gov/pubmed?term=Fung%20MK%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Holcomb JB](http://www.ncbi.nlm.nih.gov/pubmed?term=Holcomb%20JB%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Illoh O](http://www.ncbi.nlm.nih.gov/pubmed?term=Illoh%20O%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Kaplan LJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Kaplan%20LJ%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Katz LM](http://www.ncbi.nlm.nih.gov/pubmed?term=Katz%20LM%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Rao SV](http://www.ncbi.nlm.nih.gov/pubmed?term=Rao%20SV%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Roback JD](http://www.ncbi.nlm.nih.gov/pubmed?term=Roback%20JD%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Shander A](http://www.ncbi.nlm.nih.gov/pubmed?term=Shander%20A%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Tobian AA](http://www.ncbi.nlm.nih.gov/pubmed?term=Tobian%20AA%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Weinstein R](http://www.ncbi.nlm.nih.gov/pubmed?term=Weinstein%20R%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Swinton McLaughlin LG](http://www.ncbi.nlm.nih.gov/pubmed?term=Swinton%20McLaughlin%20LG%5BAuthor%5D&cauthor=true&cauthor_uid=22751760), [Djulbegovic B](http://www.ncbi.nlm.nih.gov/pubmed?term=Djulbegovic%20B%5BAuthor%5D&cauthor=true&cauthor_uid=22751760); [Clinical Transfusion Medicine Committee of the AABB](http://www.ncbi.nlm.nih.gov/pubmed?term=Clinical%20Transfusion%20Medicine%20Committee%20of%20the%20AABB%5BCorporate%20Author%5D); with 23 collaborators, “Red blood cell transfusion: a clinical practice guideline from the AABB”**,** [*Ann Intern Med*.](http://www.ncbi.nlm.nih.gov/pubmed/22751760) 2012 Jul 3;157(1):49-58. doi: 10.7326/0003-4819-157-1-201206190-00429. [↑](#footnote-ref-22)
23. ###  Jonathan Bortinger, Alexander R. Carbo, “When to Order Red Blood Cell Transfusion for Patients with Anemia”, [The Hospitalist, June 2014](http://www.the-hospitalist.org/details/print/6202431/June_2014.html)

 [↑](#footnote-ref-23)
24. ###  Qaseem A, Humphrey LL, Fitterman N, Starkey M, Shekelle P. “Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians”, *Ann Intern Med.* 2013;159(11):770-779; or Julieann F. Grant, D’Anna Saul, Alexis N. Lopez, Anita L. Hart, Mark A. McQuillan, “American College of Physicians Releases Clinical Practice Guideline for Treating Anemia in Heart Disease Patients, [The Hospitalist, June 2014](http://www.the-hospitalist.org/details/print/6202431/June_2014.html)

 [↑](#footnote-ref-24)
25. This was described as a weak recommendation based on evidence of low quality [↑](#footnote-ref-25)
26. This was described as a strong recommendation, based on evidence of moderate quality [↑](#footnote-ref-26)
27. GeneviÃ¨ve Du Pont-Thibodeau, Karen Harrington, Jacques Lacroix, “Anemia and red blood cell transfusion in critically ill cardiac patients”, *Annals of Intensive Care* 2014, 4:16 [↑](#footnote-ref-27)
28. Asim Alam, Mary Huang, xQi-Long Yi, Yulia Lin, Barbara Hannach.Published Online: April 18, 2014 DOI: <http://dx.doi.org/10.1016/j.transci.2014.04.008> [↑](#footnote-ref-28)
29. Claudia Robertson, professor, neurosurgery, Baylor College of Medicine, Houston,Texas; July 2, 2014, *Journal of the American Medical Association.* [↑](#footnote-ref-29)
30. Perel P, Clayton T, Altman DG, Croft P, Douglas I, et al. (2014) “Red Blood Cell Transfusion and Mortality in Trauma Patients: Risk-Stratified Analysis of an Observational Study”. *PLoS Med* 11(6): e1001664. [DOI: 10.1371/journal.pmed.1001664](http://dx.doi.org/10.1371/journal.pmed.1001664) [↑](#footnote-ref-30)
31. The researchers used data from the CRASH-2 trial which evaluated the effect of tranexamic acid in reducing blood loss in patients with trauma. This covered 20,127 patients with significant bleeding from 274 hospitals in 40 countries. The researchers evaluated the association between receiving versus not receiving RNCs with all-cause mortality by 28 days post trauma. They stratified their findings by predicted risk of death based on clinical observations at admission. They found that those at greatest predicted risk of dying (>50%) had a smaller chance of death from all causes if they were given RBCs. For those in the 21%–50% risk group there was found to be no significant difference in their chance of dying based on whether they were given RBCs or not. However, for those predicted to have a 6%–20% chance of death their observed chance of death was higher if they received RBCs. For those whose predicted risk was below 6%, the actual odds of dying associated with receiving RBCs was even higher. In absolute figures, compared with no RBC transfusion, transfusion was associated with 5.1 more deaths per 100 patients in the patient group with the lowest predicted mortality risk but with 11.9 fewer deaths per 100 patients in the group with the highest predicted mortality risk. [↑](#footnote-ref-31)
32. [Margaret M. Lashof-Sullivan](http://www.pnas.org/search?author1=Margaret+M.+Lashof-Sullivan&sortspec=date&submit=Submit), [Erin Shoffstall](http://www.pnas.org/search?author1=Erin+Shoffstall&sortspec=date&submit=Submit), [Kristyn T. Atkins](http://www.pnas.org/search?author1=Kristyn+T.+Atkins&sortspec=date&submit=Submit), [Nickolas Keane](http://www.pnas.org/search?author1=Nickolas+Keane&sortspec=date&submit=Submit), [Cynthia Bir](http://www.pnas.org/search?author1=Cynthia+Bir&sortspec=date&submit=Submit), [Pamela VandeVord](http://www.pnas.org/search?author1=Pamela+VandeVord&sortspec=date&submit=Submit), and [Erin B. Lavik](http://www.pnas.org/search?author1=Erin+B.+Lavik&sortspec=date&submit=Submit), “Intravenously administered nanoparticles increase survival following blast trauma”, doi: 10.1073/pnas.1406979111 [↑](#footnote-ref-32)
33. Steven M Frank, Jack O WaseyIan, M Dwyer, Ziya L Gokaslan, Paul M Ness, Khaled M Kebaish, in *Journal of Orthopaedic Surgery and Research* 2014, 9:50 [↑](#footnote-ref-33)
34. The FDA established this designation to accelerate the development and review of drugs for serious or life-threatening conditions if preliminary clinical evidence indicates the therapy may demonstrate a substantial improvement over existing therapies on one or more clinically significant endpoints. [↑](#footnote-ref-34)
35. The company presented phase I data at the American Heart Association Scientific Sessions in 2013. [↑](#footnote-ref-35)
36. Cregg J, et al. "Venothromboembolism Prophylaxis" AANP 2014 (American Association of Nurse Practitioners) [↑](#footnote-ref-36)
37. led by Dr Patrick Provost of Université Laval's Faculty of Medicine and the CHU de Québec Research Center, and published in the journal *Platelets* [↑](#footnote-ref-37)
38. Published June 18 in the *Journal of the American Medical Association* [↑](#footnote-ref-38)
39. ##  Ben Wang, Guangchuan Wang, Binjie Zhao, Jiajun Chen, Xueyun Zhang and Ruikang Tang, “[Antigenically shielded universal red blood cells by polydopamine-based cell surface engineering](http://pubs.rsc.org/en/content/articlelanding/2014/sc/c4sc01120a)”, in the May 15, 2014, issue of *Chemical Science*, the journal of the Royal Society of Chemistry (RSC). **DOI:** 10.1039/C4SC01120A

 [↑](#footnote-ref-39)
40. In the US, the FDA has so far declined to approve HBOC. It has said in a statement “… cell free Hb can cause high blood pressure; Hb can also escape the blood vessels and damage the kidneys and other organs ….Therefore, FDA has not approved any HBOCs for use in the United States, and the regulatory agencies of most other countries also have not approved HBOCs.” *Evaluating the Safety and Efficacy of Hemoglobin-based Blood Substitutes,* last updated 14 May 2013. [↑](#footnote-ref-40)
41. [Nobre FA](http://www.ncbi.nlm.nih.gov/pubmed?term=Nobre%20FA%5BAuthor%5D&cauthor=true&cauthor_uid=24952415), [Gonzalez IG](http://www.ncbi.nlm.nih.gov/pubmed?term=Gonzalez%20IG%5BAuthor%5D&cauthor=true&cauthor_uid=24952415), [Simão RM](http://www.ncbi.nlm.nih.gov/pubmed?term=Sim%C3%A3o%20RM%5BAuthor%5D&cauthor=true&cauthor_uid=24952415), [de Moraes Pinto MI](http://www.ncbi.nlm.nih.gov/pubmed?term=de%20Moraes%20Pinto%20MI%5BAuthor%5D&cauthor=true&cauthor_uid=24952415), [Costa-Carvalho BT](http://www.ncbi.nlm.nih.gov/pubmed?term=Costa-Carvalho%20BT%5BAuthor%5D&cauthor=true&cauthor_uid=24952415), “Antibody levels to tetanus, diphtheria, measles and varicella in patients with primary immunodeficiency undergoing intravenous immunoglobulin therapy: a prospective study”**,** [*BMC Immunol.*](http://www.ncbi.nlm.nih.gov/pubmed/24952415) 2014 Jun 21;15:26. doi: 10.1186/1471-2172-15-26. [↑](#footnote-ref-41)
42. “The PlA1/A2 Polymorphism of Glycoprotein IIIa as a Risk Factor for Myocardial Infarction: a Meta-Analysis'” and *“*The PlA1/A2 Polymorphism of Glycoprotein IIIa as a Risk Factor for Stroke: a Systematic Review and Meta-Analysis” in [*PLoS ONE*](http://medicalxpress.com/journals/plos-one/)*.* [↑](#footnote-ref-42)
43. Caroline Lacroux, Emmanuel Comoy, Mohammed, Armand Perret-Liaudet, Séverine Lugan, Claire Litaise, Hugh Simmons, Christelle Jas-Duval, Isabelle Lantier, Vincent Béringue, Martin Groschup, Guillaume Fichet, Pierrette Costes, Nathalie Streichenberger, Frederic Lantier, Jean Philippe Deslys, Didier Vilette, Olivier Andréoletti, “Preclinical Detection of Variant CJD and BSE Prions in Blood”, *PloS Pathogens*, June 12, 2014. DOI: 10.1371/journal.ppat.1004202. [↑](#footnote-ref-43)
44. In the trial, the vaccine reduced the number of severe cases by 88.5 per cent. [↑](#footnote-ref-44)
45. From 2006 to 2013 an average of 28 [returning travellers were](http://http/www.cdc.gov/chikungunya/geo/united-states.html) diagnosed with chikungunya in the US every year. They were usually returning from Asia. [↑](#footnote-ref-45)
46. Their study was published online in the journal *Molecular Therapy.* [↑](#footnote-ref-46)
47. led by scientists at the Free University of Brussels, the International Livestock Research Institute, Oxford University and the Chinese Centre for Disease Control and Prevention and published in the journal *Nature Communications*. [↑](#footnote-ref-47)
48. Researchers at the University of Wisconsin-Madison, led by [Yoshihiro Kawaoka](http://www.vetmed.wisc.edu/people/kawaokay/), used reverse genetics to build the virus from fragments of wild bird flu strains, and mutated it to make it airborne. See Watanabe T, Zhong G, Russel CA, et al. “Circulating avian influenza viruses closely related to the 1918 virus have pandemic potential”, *Cell Host & Microbe*; 15(6): 692-705; available at <<http://dx.doi.org/10.1016/j.chom.2014.05.006>> [↑](#footnote-ref-48)
49. A few days earlier the health ministry had revised statistics back to 2012, and increased the death toll thus far from 190 to 282, while the number of infections had been increased from 575 to 688. [↑](#footnote-ref-49)
50. The study appeared ahead of print online in the *American Journal of Roentgenology* [↑](#footnote-ref-50)
51. [Tang XC. Proc Natl Acad Sci USA. 2014;111:E2018-2016.](http://www.pnas.org/content/111/19/E2018.abstract?sid=d0a15d7e-7e18-4775-9361-b3e812ae1084) [↑](#footnote-ref-51)
52. Their study was published in Antimicrobial Agents and Chemotherapy, a journal from the American Society for Microbiology [Dyall J. Antimicrob Agents Chemother. 2014;doi:10.1128/AAC.03036-14.](http://aac.asm.org/content/early/2014/05/13/AAC.03036-14.full.pdf%2Bhtml) [↑](#footnote-ref-52)
53. A Eurosurveillance report on camel milk in Qatar says that there was MERS-CoV RNA in the milk of five out of seven camels that were shedding the virus. This matched the inference in a report filed earlier by QATAR with the World Organization for Animal health (OIE). In the other Eurosurveillance study, scientists tested recent camel samples from Egypt and Australia, and also Saudi Arabian camel samples collected in 1993. MERS-CoV or a very similar virus existed in camels in 1993. No evidence of MERS-CoV was found in Australian camels. [↑](#footnote-ref-53)
54. Parechovirus usually causes mild respiratory or gastrointestinal symptoms in babies, but in some young infants complications can include hepatitis or encephalitis. Queensland Children's Medical Research Institute paediatric infectious diseases director Professor Theo Sloots said the virus "affects the brains of young children, and in severe cases can result in death." The virus spreads through respiratory droplets, saliva or faeces, with young babies at most risk. [↑](#footnote-ref-54)
55. In 2011 the national notification rate for gonococcal disease for people aged 15 years and over was 65 per 100 000 population, an increase from 40 per 100 000 in 2001

(<[http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/4102.0Main+Features10Jun+2012](http://www.abs.gov.au/AUSSTATS/abs%40.nsf/Lookup/4102.0Main%2BFeatures10Jun%2B2012)>).

More men than women are diagnosed with gonorrhea, and the rate of diagnosis is 21 times greater in Aboriginal and Torres Strait Islander peoples than in the non-indigenous population ( see"Sexually transmissible and blood-borne infections in Australia: the 2013 Surveillance Reports", available at

<<http://www.kirby.unsw.edu.au/news/sexually-transmissible-and-blood-borne-infections-australia-2013-surveillance-reports>>). [↑](#footnote-ref-55)