Monitoring International Trends

**posted February-March 2018**

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 put financial or other pressures on the Australian sector.

Some recent matters of interest appear on pages 5 to 23. Highlights are listed below :

**Products**

* Aptevo announced that new patient-reported outcomes data for Ixinity [Factor IX (Recombinant)] showed a positive benefit for patients with haemophilia B.
* [Bioverativ](https://www.bioverativ.com/homepage.aspx) announced that [Eloctate](https://www.eloctate.com) use in immune tolerance induction therapy shows promise in high-risk patients with severe haemophilia A and inhibitors treated for the first time.
* [AGC Biologics](https://www.agcbio.com/) will produce the [haemophilia B](https://hemophilianewstoday.com/hemophilia-type-b/) clotting therapy [CB 2679d](http://www.catalystbiosciences.com/pipeline/hemostasis/factor-ix/) that [Catalyst Biosciences](http://www.catalystbiosciences.com/) will test in a Phase IIb trial in the third quarter of 2018.
* Haematologist Mark Walters says that the gene-editing technology CRISPR-Cas9 may soon be applied to humans for the first time to treat sickle cell disease.
* Gang Bao has detailed a series of tests exploring the use of CRISPR to fix the single mutation responsible for sickle cell disease. Bao’s team gathered both stem and progenitor cells from patients with sickle cell disease. They managed to repair between 20 per cent and 40 per cent of the cells. Another team then injected the edited cells into the bone marrow of mice, where they persisted after 19 weeks.
* The first patient has been treated in Biotest’s Phase III study of its fibrinogen concentrate BT524 in cases of acquired fibrinogen deficiency.
* In paroxysmal nocturnal haemoglobinuria, Alexion said its new treatment performed well in Phase III trials while [Ra Pharmaceuticals, Inc.](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Frapharma.com%2F&esheet=51756852&newsitemid=20180212005448&lan=en-US&anchor=Ra+Pharmaceuticals%2C+Inc.&index=1&md5=06151822586287af0bfe45be36f13dcf) announced the completion of dosing and topline data for its Phase II clinical program evaluating RA101495 SC.
* Intravenous immunoglobulin (IVIg) is the initial therapy for Kawasaki disease (KD). Around 20 per cent of patients do not respond adequately. Infliximab, an anti-TNF agent, has been suggested as a potential treatment. Results of a small study of infliximab versus an additional dose of IVIg for treatment-refractory KD patients*,* showed that infliximab improved the defervescence rate within 48 hours compared with IVIg, and that infliximab was well tolerated.
* Sisu Global Health’s device, Hemafuse, permits doctors to recycle a patient’s own blood lost through traumatic internal bleeding. Hemafuse has regulatory approval in Kenya and Ghana which were selected for the initial launch of the device.
* A low-cost portable system to separate blood into its main components without a centrifuge is being developed at the University of Houston.
* Improvised Explosive Devices caused many traumatic injuries during conflicts in Afghanistan and Iraq. A team from Strathclyde University has developed a new three-stage battlefield treatment technique they hope could reduce the need for amputations. The team has also developed a blood salvaging technique, HemoSep, which allows blood lost in surgery to be transfused directly back to the patient.
* Phase III results showed that lanadelumab, Shire’s hereditary angioedema drug, reduced monthly attack rates and improved quality of life compared with placebo.
* Patients with primary immunodeficiency who received Hizentra, a 20 per cent subcutaneous immunoglobulin, said they were highly satisfied with their treatment.

**Safety and Patient Blood Management**

* A study of the applicability of ROTEM (rotational thromboelastometry) in obstetrics has concluded that “there still remains limited data on reference ranges in normal pregnancies and subsequently limited understanding of the effects of complicated pregnancies on ROTEM interpretation. Additional research is required to further define the optimal role of viscoelastic testing in major obstetric haemorrhage.”
* Americans are receiving fewer blood transfusions. From 1993 until about 2011, the rates of plasma and red blood cell transfusions tended to rise. From 2011, they started to come down and continued to decline or level off through 2014.
* Blood stored longer may be less safe for patients with massive blood loss and shock as it may have adverse effects, according to a recent report.
* Researchers concluded that diagnosing and treating antenatal anaemia before delivery may reduce the rates of postnatal red blood cell transfusions.
* Researchers in Denmark tested the feasibility of giving intravenous iron to blood donors. Those who received a full dose of intravenous iron had higher haemoglobin levels compared with the placebo group before the second and third blood donations.
* Meta-analysis has shown that dialysis patients receiving more or less than 200 mg per month of intravenous iron had similar risks of death, infection, cardiovascular disease, and hospitalization.
* A study found that, for older patients with concomitant chronic kidney disease and a new diagnosis of atrial fibrillation, anticoagulants are associated with increased risk of ischemic stroke and haemorrhage, but with reduced risk of all-cause mortality.
* Ferring Pharmaceuticals announced the completion of a global clinical trialof heat-stable carbetocin as a mode of preventing excessive bleeding after childbirth.
* In the US, the first clinical practice guidelines aimed at standardizing the use of blood thinners during heart surgery have emphasised optimal heparin dosing during bypass, the identification of contraindications to heparin use and heparin alternatives, and reversal of anticoagulation.
* Various venous thromboprophylaxis treatments are now available in total joint replacement and hip fracture surgery. A US report has shown use of low-molecular-weight heparin resulted in less major bleeding and deep vein thrombosis and lower venous thromboembolic outcomes after total hip and knee replacement.
* Researchers in St Petersburg have found a way to stop internal bleeding by magnetically driven nanoparticles containing thrombin.
* Johnson & Johnson presented a study showing that, compared with solo aspirin, Xarelto reduced the incidence of major limb problems among peripheral artery disease patients—and decreased amputations, deaths and hospitalizations.
* **Regulatory matters**
* The European Commission granted marketing authorization for Hizentra, CSL’s human subcutaneous immunoglobulin, for maintenance therapy to treat chronic inflammatory demyelinating polyneuropathy.
* The US Food and Drug Administration (FDA) approved hydroxyurea tablets (Siklos, from Addmedica) for the treatment of sickle cell anaemia in paediatric patients aged 2 years and older.
* Emmaus announced that the company’s Marketing Authorisation Application for Xyndari (oral L glutamine) is being assessed by the European Medicines Agency (EMA) for the treatment of sickle cell disease.
* Shire PLC said the FDA had received its Cinryze (C1 esterase inhibitor [human]) supplemental Biologics License Application to expand the currently approved indication to include children aged 6 years and older with hereditary angioedema.
* Grifols received approval from the FDA for a higher potency formulation of its HyperRAB rabies immune globulin [human] for rabies post exposure prophylaxis.
* The Medicines and Healthcare Products Regulatory Agency granted permission for Europe's first *in vivo* genome editing study, allowing patient enrolment in an ongoing Phase I/ II clinical trial evaluating Sangamo’s SB-FIX, a zinc finger nuclease (ZFN)-mediated treatment for haemophilia B.
* Novo Nordisk announced the submission of a Biologics License Applications to the FDA and a Marketing Authorisation Application to the EMA for N8-GP, an extended half-life factor VIII for treatment of haemophilia A.
* The FDA approved the use of the Trevo clot retrieval device to treat certain stroke patients up to 24 hours after symptom onset, rather than the previous 6 hours.

**Company news**

* Grifols has broken ground on a new $US 120 million facility, part of a planned $US 320 million investment in Clayton, North Carolina by 2022.
* In the half year ended December 2017, CSL’s revenue was $US 4.1 billion, up 13 per cent on the prior corresponding period; profit rose 35 per cent to $US 1.1 billion.
* Shortly after announcing it would acquire Bioverative, Sanofi announced that it would buy the Belgium-based antibody drug developer Ablynx,

**Country news**

* The Republic of Ireland says it is the first country in Europe where everyone with haemophilia can access extended half-life therapies.
* A US trauma surgeon who served in Iraq and Afghanistan says three procedures are among those responsible for saving the most lives: greater use of tourniquets, improvements in transfusion therapy and hypothermia prevention.
* Non-invasive foetal RhD genotyping can identify which RhD negative women are carrying RhD positive babies and therefore require antenatal anti-D prophylaxis therapy. A recent cost-effectiveness study has concluded RhD genotyping to be “an economically sound option for Australia”.

**Research not included elsewhere**

* Allan Doctor of Washington University School of Medicine in St. Louis, and his team have received $US 5 million in grants to develop their freeze-dried, powdered blood substitute, ErythoMer, consisting of nano-scale synthetic red blood cells.
* Researchers have reported on a promising experimental broad spectrum antiviral drug that could inhibit a range of coronaviruses.

**Infectious diseases**

* Scientists at Johns Hopkins Malaria Research Institute report that deleting a single gene from mosquitoes can make them highly resistant to the malaria parasite and less likely to transmit it to humans.
* Shionogi has approval in Japan for a drug that is claimed to eliminate the influenza virus in just 24 hours.
* Inovio says that using a collection of synthetic DNA antigens, its experimental vaccine generated (in animals) broad protective antibody responses against all major deadly strains of H1 influenza viruses from the last 100 years.
* Two clinical trials testing an experimental vaccine against H7N9 influenza have been enrolling volunteers across the US.
* On 14 February, China’s National Health and Family Planning Commission notified WHO of the first case globally of human infection with avian influenza A(H7N4) virus.
* By mid-March, WHO had received globally reports of 2144 laboratory-confirmed cases of MERS-CoV and 750 deaths. Saudi Arabia had reported 734 fatalities.
* Themis has been awarded $US 37.5 million to develop new vaccines against MERS and Lassa fever, based on research by the Paul Ehrlich Institut and Institut Pasteur.
* In the US the Defense Threat Reduction Agency’s Chemical and Biological Technologies Department has collaborated with the US Army Medical Research Institute of Infectious Diseases and Merck to develop a vaccine against Ebola.
* ZMapp was used to treat humans during the 2014 West Africa Ebola outbreak before human clinical trials. The Texas Biomedical Research Institute in San Antonio now has a $US 2 million contract from Mapp Biopharmaceutical to test the therapy in primate models, as a step towards FDA licensure.
* Singapore eDevelopment’s subsidiary Global BioLife has completed the initial Zaire Ebola research portion for the study of new anti-viral drug LB2.
* GeoVax Labs says it has **demonstrated** that a single intramuscular dose of its Ebola vaccine (GEO-EM01) provided 100 per cent protection in rhesus macaques.

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# Products and treatments

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

## Treating haemophilia

* + On 12 March Aptevo Therapeutics announced in Seattle that new patient-reported outcomes data for Ixinity [Coagulation Factor IX (Recombinant)] were presented at the Thrombosis and Hemostasis 2018 Summit of North America, supporting a positive benefit for Ixinity in patients with haemophilia B. The study was designed to generate a descriptive analysis of patient experiences on the drug. It asked clinical and quality of life questions. Limitations included small sample size, a potential for selection bias and recall bias among participants, and the use of non-validated outcomes measures. Patients reported a high level of satisfaction with low annualized bleed rates and low impact on quality of life scores[[1]](#footnote-1). Dr Scott Stromatt, Chief Medical Officer for Aptevo, said: “Anecdotal reports from patients who have switched their factor IX therapy to Ixinity appear to suggest some clinical and quality of life benefit associated with Ixinity therapy”. Ixinity was launched in the US in 2015; it is an intravenous therapeutic for use in people 12 years of age or older.
	+ [Bioverativ](https://www.bioverativ.com/homepage.aspx) announced[[2]](#footnote-2) that [Eloctate](https://www.eloctate.com) use in immune tolerance induction (ITI) therapy shows promise in high-risk patients with severe haemophilia A and inhibitors treated for the first time. The company also says the results support a potential benefit for some patients who tried and failed ITI with other factors[[3]](#footnote-3). Maha Radhakrishnan, senior vice president (medical) at Bioverativ, said in a [press release](https://www.bioverativ.com/newsroom/haemophilia-publishes-a-retrospective-analysis-investigating-the-use-of-eloctate%C2%AE-for-immune-tolerance-induction-in-people-with-inhibitors-and-severe-hemophilia-a.aspx): “The results of this analysis are encouraging and support the need for additional and ongoing scientific research on Eloctate in ITI to determine whether an Fc-based recombinant factor VIII therapy can rapidly tolerize patients with inhibitors”. [Swedish Orphan Biovitrum](https://www.sobi.com/en) (SOBI) and [Bioverativ](https://www.bioverativ.com/homepage.aspx) launched two Phase IV clinical trials ([NCT03093480](https://clinicaltrials.gov/ct2/show/NCT03093480?term=NCT03093480&rank=1) and [NCT03103542](https://clinicaltrials.gov/ct2/show/NCT03103542?term=NCT03103542&rank=1)), currently recruiting participants, to investigate further the performance of Eloctate in ITI in patients with severe haemophilia A and inhibitors.
	+ [AGC Biologics](https://www.agcbio.com/) has agreed to produce the [haemophilia B](https://hemophilianewstoday.com/hemophilia-type-b/) clotting therapy that [Catalyst Biosciences](http://www.catalystbiosciences.com/) is testing in clinical trials. The next step in testing [CB 2679d](http://www.catalystbiosciences.com/pipeline/hemostasis/factor-ix/) will be a Phase IIb trial in the third quarter of 2018. Catalyst’s South Korean partner, ISU Abxis, began a Phase I/II trial ([NCT03186677](https://clinicaltrials.gov/ct2/show/NCT03186677)) of CB 2679d in June 2017[[4]](#footnote-4). [Interim results](https://hemophilianewstoday.com/2017/09/20/catalysts-cb-2679d-shown-to-outperform-benefix-in-phase-1-2-trial-hemophilia-b/) were reported to show that an IV dose of CB 2679d was nearly 22 times more potent than a similar dose of [BeneFIX](http://www.benefix.com/), [Pfizer](http://www.pfizer.com/)’s standard Factor IX replacement therapy. Also reported was that CB 2679d remained in the blood an average of 34 hours, compared with 25 for BeneFIX. Final results are expected in 2018, Catalyst said. The [European Union](https://hemophilianewstoday.com/2017/06/30/europe-grants-orphan-drug-status-to-hemophilia-b-therapy-cb-2679d/) [granted CB 2679d orphan drug status](https://hemophilianewstoday.com/2017/10/02/hemophilia-b-recombinant-factor-ix-variant-wins-fda-orphan-drug-status-catalyst-says/) in June 2017 and the FDA [in September 2017](https://hemophilianewstoday.com/2017/10/02/hemophilia-b-recombinant-factor-ix-variant-wins-fda-orphan-drug-status-catalyst-says/).

## Treating beta thalassemia and sickle cell disease

* + Paediatric haematologist Mark Walters hopes that the gene-editing technology CRISPR-Cas9 may soon be applied to humans for the first time to treat sickle cell disease[[5]](#footnote-5). He says the first clinical trials could begin within the next couple of years. He is leading the project through The University of Southern California (UCSF)[[6]](#footnote-6).
	+ Sickle cell disease is [caused by a single mutation](https://ghr.nlm.nih.gov/gene/HBB#conditions) in the gene that codes for beta-globin, a component of red blood cells. At the American Association for the Advancement of Science’s annual meeting, Gang Bao, a bioengineering professor at Rice University, detailed a series of tests exploring the use of CRISPR to fix this mutation. With colleagues from Baylor College of Medicine and Texas Children’s Hospital, Bao’s team gathered both stem and progenitor cells from patients with sickle cell disease. They managed to repair between 20 per cent and 40 per cent of the cells[[7]](#footnote-7). A team at Matt Porteus’s lab at Stanford then injected the edited cells into the bone marrow of mice, where they persisted after 19 weeks.
	+ Vertex Pharmaceuticals [teamed up](https://www.fiercebiotech.com/biotech/updated-vertex-pays-105m-to-kick-off-gene-editing-pact-crispr-therapeutics) with CRISPR Therapeutics in 2015, and recently [licensed](https://www.fiercebiotech.com/biotech/vertex-licenses-blood-disorder-gene-therapy-from-crispr-therapeutics) the first CRISPR-based treatment to come out of the partnership: a therapy for beta thalassemia and sickle cell.
	+ Imara dosed the first patient in its Phase IIa clinical trial to evaluate the safety, pharmacokinetics and pharmacodynamics of escalating doses of IMR-687 in adult patients with sickle cell disease (SCD). IMR-687 has Rare Pediatric Disease designation from the US Food and Drug Administration (FDA. The drug is being developed as a once-daily oral therapy with the intention of addressing both the underlying red and white blood cell pathologies associated with the condition.

## Other products

* + The first patient has been treated in Biotest’s Phase III study of its fibrinogen concentrate BT524 in cases of acquired fibrinogen deficiency. The ADFIRST (**Ad**justed **Fi**brinogen **R**eplacement **St**rategy) study recruits patients who lose fibrinogen due to significant blood loss during a planned spinal surgery. The efficacy and safety of BT524 are being assessed in comparison with fresh frozen plasma. The study will include about 200 patients over 15 study sites in Germany, Spain, Belgium, Switzerland and Poland.[[8]](#footnote-8)
	+ Alexion announced that its new treatment for paroxysmal nocturnal haemoglobinuria (PNH) performed well in Phase III trials, demonstrating noninferiority to eculizumab (Soliris, from Alexion) and cutting the number of infusions significantly. Alexion expects to make regulatory submissions for ALXN1210 in PNH in the US, EU and Japan in the second half of 2018.
	+ [Ra Pharmaceuticals, Inc.](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Frapharma.com%2F&esheet=51756852&newsitemid=20180212005448&lan=en-US&anchor=Ra+Pharmaceuticals%2C+Inc.&index=1&md5=06151822586287af0bfe45be36f13dcf) announced the completion of dosing and topline data for its Phase II clinical program evaluating RA101495 SC for the treatment of paroxysmal nocturnal haemoglobinuria (PNH).
	+ Intravenous immunoglobulin (IVIg) is the initial therapy for Kawasaki disease (KD), an acute febrile disorder that primarily affects children aged 5 years or less. As it can cause coronary artery abnormalities and acquired heart disease in children, it is critical to suppress acute inflammation within 10 days of the disease’s onset if coronary artery lesions (CAL) are to be prevented. Around 20 per cent of patients do not respond adequately to IVIg. IVIg-refractory KD may be treated with an additional dose, but half of refractory patients may still not respond. Since serum tumour necrosis factor (TNF) is high in patients with KD, infliximab, an anti-TNF agent, has been suggested as a potential treatment for IVIG-refractory KD. Results of a small study[[9]](#footnote-9) of infliximab versus an additional dose of IVIg for treatment-refractory patients with KD, showed that infliximab improved the defervescence[[10]](#footnote-10) rate within 48 hours compared with IVIg, and that infliximab was well tolerated[[11]](#footnote-11). The researchers concluded that as anti-TNF therapy directly improves endothelial cell function and reduces inflammation, treating KD with infliximab may contribute to preventing development of coronary artery abnormalities. They recommended larger and longer studies to confirm the longer-term outcomes of administering infliximab.
	+ Baltimore medical device firm Sisu Global Health was founded in 2014. Its first device, Hemafuse, permits doctors to recycle a patient’s own blood lost through traumatic internal bleeding. It filters and cleans the blood, removing any clots so it can be immediately transfused to the same patient. The device is intended for use in emergency situations in which a fresh supply of donor blood may not be readily available. It is also intended to be a cost efficient donor blood alternative, with cost of one use of Hemafuse ranging from about $US 80 to $US 200. Hemafuse has regulatory approval in Kenya and Ghana which were selected for the initial launch of the device.
	+ A low-cost system to separate blood into its main components without a centrifuge is being developed at the University of Houston. According to a proof-of-concept [study](http://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0190827&type=printable) published in the journal PLoS ONE, the system is portable and would need minimal training to operate.
	+ Improvised Explosive Devices led to a high number of traumatic injuries during conflicts in Afghanistan and Iraq. A team from Strathclyde University has developed a new three-stage battlefield treatment technique they hope could reduce the need for amputations. It involves a new type of tourniquet[[12]](#footnote-12) and a cooling "sock" which preserves the limb from further damage until the casualty can be evacuated. On arrival at the field or base hospital, the limb is placed inside a protective box which provides it with decontaminated air and maintains its blood supply while medics attempt a repair. The team has also developed a blood salvaging technique, HemoSep, which allows blood lost in surgery to be transfused directly back to the patient, reducing the need for donated blood. The research was funded by the UK’s Defence Science and Technology Laboratory. After appropriate trials the sytem is expected to be available commercially.
	+ Newly released phase III results[[13]](#footnote-13) have shown that lanadelumab, Shire’s experimental hereditary angioedema (HAE) drug, reduced monthly attack rates and improved quality of life compared with placebo. Lanadelumab is under priority review by the FDA, with a decision expected by 26 August. Lanadelumab has been also been granted accelerated assessment by the European Medicines Agency.
	+ Patients with primary immunodeficiency who received Hizentra, a 20 per cent subcutaneous immunoglobulin, were highly satisfied with their treatment, according to real-world survey data presented at the 2018 Joint Congress of the American Academy of Allergy, Asthma & Immunology and World Allergy Organization[[14]](#footnote-14).

# Safety and patient blood management

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

## Appropriate Transfusion

* + ROTEM (rotational thromboelastometry) allows rapid coagulation assessment at point-of-care. It delivers on-screen information on all coagulation steps and fibrinolysis in real time. Its usefulness as an adjunct to cardiac and liver surgery is well recognised but it is not so well established in obstetrics. Researchers in a recent study commented that: “Much of the data is extrapolated from other settings such as trauma or cardiac surgery and haemostatic derangements in these settings are likely to differ from those in post-partum haemorrhage (PPH)”[[15]](#footnote-15). They went on to examine just what these derangements might be[[16]](#footnote-16), and thus the potential for ROTEM use in bleeding associated with obstetrics. They concluded that “there still remains limited data on reference ranges in normal pregnancies and subsequently limited understanding of the effects of complicated pregnancies on ROTEM interpretation. Additional research is required to further define the optimal role of viscoelastic testing in major obstetric haemorrhage.”
	+ the 2018 North American Robotic Urology Symposium[[17]](#footnote-17) researchers reported[[18]](#footnote-18) that robotic radical cystectomy (RRC) with intracorporal urinary diversion is safe and feasible in octogenarians with bladder cancer. Compared with open radical cystectomy, RRC was associated with significantly lower estimated blood loss and perioperative transfusions with equivalent pathological and oncological outcomes. RRC was found to be an independent protective predictor for needing a transfusion after controlling for confounders.
	+ In a paper[[19]](#footnote-19) presented at the meeting of the American Academy of Orthopaedic Surgeons in New Orleans[[20]](#footnote-20), researchers recommended that orthopaedic surgeons performing shoulder arthroplasty may want to consider tranexamic acid (TXA). They found the use of TXA decreased the risk of transfusion and was associated with a shorter hospital stay. Shawn G. Anthony, assistant professor of orthopaedics at the Icahn School of Medicine at Mount Sinai and shoulder and sports medicine surgeon at Mount Sinai West, said: “While utilization of TXA has become very common in total hip and knee arthroplasty, TXA is still used in less than 50% of patients undergoing shoulder arthroplasty as of 2016. Utilization is increasing but continued education is important. The use of TXA presents one more way to improve the safety of shoulder arthroplasty for patients.”
	+ Aaron Tobian, director of transfusion medicine at Johns Hopkins University's School of Public Health, is senior author of a new study[[21]](#footnote-21) that found Americans are receiving fewer blood transfusions. The researchers looked at trends in transfusion from 1993 to 2014. From 1993 until about 2011, the rates of plasma and red blood cell transfusions tended to rise. From 2011, they started to come down and continued to decline or level off through 2014. Red blood cell transfusions decreased from nearly 7 per cent to less than 6 per cent from 2011 to 2014, the study found. Plasma transfusions dropped from 1.0 percent to 0.87 percent during that same time. Platelet transfusions remained stable. The reduction in red blood cell transfusions was seen in both sexes, all races/ethnicities, different severities in patient conditions, various types of payers (private insurance, government insurance or no insurance) and different reasons for admission. The red blood cell transfusion decrease was significantly greater in patients coming in for elective surgery compared with non-elective surgery (a drop of 26 per cent versus 14 per cent, respectively). Tobian said when people have elective surgery, they have pre-operative blood work done. At that time, the doctor can see what a patient's haemoglobin level is. If it's low, the doctor can recommend taking iron to raise those levels before surgery to avoid the need for a transfusion.
	+ Blood stored longer may be less safe for patients with massive blood loss and shock as it may have adverse effects, according to a recent report.[[22]](#footnote-22)

## Recognising and treating anaemia

* + Researchers wanting to determine whether anaemic pregnant women were more likely to receive postpartum red blood cell (RBC) transfusions analysed the association between haemoglobin levels and transfusions in 8039 pregnant women from a tertiary care maternity hospital[[23]](#footnote-23). Of the 8039 women, 1562 (19.4 per cent) were anaemic, and 106 (1.3 per cent) received a postpartum RBC transfusion. Among the anaemic women, 3.6 per cent received a blood transfusion compared with 0.76 per cent of the non-anaemic women. Anaemia during pregnancy increased the risk of postpartum RBC transfusions for both vaginal deliveries and caesarean sections. The authors concluded that diagnosing and treating antenatal anaemia before delivery may reduce the rates of postnatal RBC transfusions.
	+ Researchers in Denmark tested the feasibility of giving intravenous iron to blood donors[[24]](#footnote-24). They randomized 85 first-time female blood donors in a double-blind, prospective clinical trial contrasting iron isomaltoside (1000 mg) with a placebo (saline infusion). The 41 donors who received a full dose of intravenous iron had higher haemoglobin levels compared with the placebo group before the second and third blood donations. Ferritin and iron levels were also higher in the women who received the intravenous iron. No serious adverse events, were recorded and side effects were similar between the two arms of the trial.
	+ Meta-analysis has shown that dialysis patients receiving more or less than 200 mg per month of intravenous iron had similar risks of death, infection, cardiovascular disease, and hospitalization[[25]](#footnote-25).

## Other

* + A study[[26]](#footnote-26) found that, for older patients with concomitant chronic kidney disease and a new diagnosis of atrial fibrillation, anticoagulants are associated with increased risk of ischemic stroke and haemorrhage, but with reduced risk of all-cause mortality. Shankar Kumar, from University College London, and colleagues conducted a propensity-matched population-based cohort analysis from January 2006 through December 2016. They wrote: "Giving anticoagulants to older people with concomitant atrial fibrillation and chronic kidney disease was associated with an increased rate of ischemic stroke and haemorrhage but a paradoxical lowered rate of all-cause mortality…………Careful consideration should be given before starting anticoagulants in older people with chronic kidney disease who develop atrial fibrillation."
	+ The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) communicated a [positive trend vote](https://seekingalpha.com/pr/17079712-portola-pharmaceuticals-announces-results-chmp-oral-explanations-andexanet-alfa-betrixaban) backing approval for Portola Pharmaceuticals' andexanet alfa, a Factor Xa inhibitor used as a reversal agent for patients on anticoagulant therapy who experience Factor Xa-related bleeding. CHMP sought additional data, which will delay the release of its opinion[[27]](#footnote-27). For Factor Xa inhibitor betrixaban the vote trend was negative for the proposed indication of preventing venous thromboembolism (VTE) in adult patients hospitalized for acute illness at risk of VTE. A positive opinion is therefore unlikely when CHMP votes formally, and the Committee may seek a further study to prove the drug’s benefit/risk balance in the target population[[28]](#footnote-28).
	+ **Ferring Pharmaceuticals and Merck (*t***hrough MSD[[29]](#footnote-29) for Mothers) **announced the completion of CHAMPION (Carbetocin Haemorrhage Prevention), a global clinical trial conducted by the Human Reproduction Program at the World Health Organization (WHO).** CHAMPION, involving nearly 30,000 women in 10 countries, is the largest clinical trial ever conducted in postpartum haemorrhage (PPH). It has been testing Ferring’s heat-stable carbetocin as a mode of preventing excessive bleeding after childbirth. The CHAMPION trial has compared the effectiveness and safety of carbetocin versus the current standard of care, oxytocin. Heat-stable carbetocin could address a significant limitation associated with oxytocin – the need for refrigeration during shipping and storage, to prevent degradation in temperatures above 8°C. Carbetocin may remain active long-term in hot and humid climates. It could therefore reduce the incidence of PPH in regions where cold storage is difficult to achieve and where most of maternal deaths due to PPH currently occur. Results from the trial are expected to be made available during the second half of 2018. If the results are favourable, Ferring will seek registration of carbetocin on a broad basis around the world, manufacture the drug and sell it to the public sector of low- and lower-middle-income countries at an acceptable price.
	+ In the US, the first-ever clinical practice guidelines aimed at standardizing the use of blood thinners during heart surgery have emphasised optimal heparin dosing during bypass, the identification of contraindications to heparin use and heparin alternatives, and reversal of anticoagulation. [The guidelines](https://doi.org/10.1016/j.athoracsur.2017.09.061) were developed by representatives of the Society of Thoracic Surgeons (STS), the Society of Cardiovascular Anesthesiologists (SCA), and the American Society of ExtraCorporeal Technology (AmSECT). The document was published concurrently in the journals Annals of Thoracic Surgery, Anesthesia & Analgesia, and the Journal of Extra Corporeal Technology. Lead author was Linda-Shore-Lesserson, director of Cardiovascular Anesthesiology at North Shore University Hospital in Manhasset, New York.
	+ A number of venous thromboprophylaxis treatments are now available in total joint replacement and hip fracture surgery. In the US an updated Agency for Healthcare Research and Quality Effective Health Care Program report showed use of low-molecular-weight heparin resulted in less major bleeding and deep vein thrombosis and lower venous thromboembolic outcomes after total hip and knee replacement[[30]](#footnote-30).
	+ Researchers from ITMO University in St Petersburg have found a way to stop internal bleeding by magnetically driven nanoparticles containing thrombin. These can be injected intravenously and delivered straight to the site of a vascular injury. The researchers reported this can accelerate local clot formation and reduce overall blood loss by 15 times. The nanoparticles are not toxic to humans[[31]](#footnote-31).
	+ At the American College of Cardiology's 67th Annual Scientific Session, Johnson & Johnson presented a new study showing that, compared with solo aspirin, Xarelto reduced the incidence of major limb problems among peripheral artery disease patients by 43 per cent—and decreased amputations, deaths and hospitalizations. The results are part of a new analysis of the Compass trial, which last August showed that a Xarelto-aspirin combination could beat aspirin alone at reducing the likelihood of cardiovascular events in patients with PAD and/or coronary artery disease (CAD). Putting Xarelto into the mix slashed the combined risk of death, stroke and heart attack by 24 per cent.

# Regulatory

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

* + The European Commission granted marketing authorization for Hizentra, CSL’s human normal immunoglobulin, the first subcutaneous immunoglobulin (SCIg), for maintenance therapy to treat chronic inflammatory demyelinating polyneuropathy (CIDP)[[32]](#footnote-32). Hizentra received approval as maintenance therapy to prevent relapse of neuromuscular disability and impairment. Approval was based on data from the phase III Polyneuropathy and Treatment with Hizentra (PATH) study[[33]](#footnote-33).
	+ The US Food and Drug Administration (FDA) approved hydroxyurea tablets (Siklos, from Addmedica) for the treatment of sickle cell anaemia in paediatric patients aged 2 years and older. The approval was based on efficacy and safety data from the Escort-HU study[[34]](#footnote-34). The treatment was approved for use in Europe in 2007.
	+ Emmaus announced that the company’s Marketing Authorisation Application for Xyndari (oral L glutamine) is being assessed by the European Medicines Agency (EMA) for the treatment of sickle cell **disease**[[35]](#footnote-35)**. It is being** reviewed by the EMA under the centralised licensing procedure for all 28 members of the European Union, together with Norway and Iceland[[36]](#footnote-36).
	+ Shire PLC announced on 15 February that the FDA had received its Cinryze (C1 esterase inhibitor [human]) supplemental Biologics License Application to expand the currently approved indication to include children aged 6 years and older with hereditary angioedema (HAE)[[37]](#footnote-37). The submission has been given Priority Review designation by the FDA, which is expected to provide a decision on the expanded indication by 20 June 2018, based on the Prescription Drug User Fee Act V action date. The plasma-derived drug has been approved in the US since October 2008 for routine prophylaxis against attacks in adolescents and adults living with HAE. The submission is supported by data from two open-label studies and two paediatric clinical studies[[38]](#footnote-38).
	+ Grifols has received approval from the FDA for a higher potency formulation of its HyperRAB rabies immune globulin [human] for rabies post exposure prophylaxis (treatment of a person immediately after exposure to the rabies virus)[[39]](#footnote-39). The new formulation doubles the potency (300 IU/mL) of currently available rabies immune globulin options, meaning fewer injections or reduced volume in each dose. The most common adverse reactions during clinical trials were injection-site pain and headache.
	+ To help reduce the risk of transfusion-transmitted babesiosis in the US, the FDA approved new donor screening tests[[40]](#footnote-40).
	+ Quidel Corporationannounced that it had received 510(k) clearance from the FDA to market its Sofia Lyme FIA to be used with the Sofia 2 Fluorescent Immunoassay Analyzer for the rapid differential detection of human IgM and IgG antibodies to *Borrelia burgdorferi* from serum and plasma specimens from patients suspected of *B. burgdorferi* infection. The test is intended to aid in the diagnosis of Lyme disease.
	+ Shionogi announced that the New Drug Application (NDA) for lusutrombopag (S-888711), an investigational, once-daily, orally administered, small molecule thrombopoietin (TPO) receptor agonist, had been accepted for filing and had been granted Priority Review by the FDA. Shionogi is seeking FDA approval of lusutrombopag for the treatment of thrombocytopenia in patients with chronic liver disease who are at increased risk for bleeding associated with invasive procedures[[41]](#footnote-41). The submission is based on two Phase III clinical trials, L-PLUS1 and L-PLUS2, in which lusutrombopag met the pre-specified primary and all key secondary endpoints with statistically significant results. The EMA has validated for review Shionogi’s standard Marketing Authorization Application (MAA) for lusutrombopag. In Europe, the MAA submission is based on the same two Phase III clinical trials as the FDA filing.
	+ The Medicines and Healthcare Products Regulatory Agency (MHRA) granted permission for initiation of Europe's first in vivo genome editing study. This Clinical Trial Authorisation (CTA) allows patient enrolment in an ongoing Phase I/ II clinical trial evaluating Sangamo’s SB-FIX, a zinc finger nuclease (ZFN)-mediated in vivo genome editing treatment for haemophilia B.
	+ On 27 February Novo Nordisk announced the submission of a Biologics License Applications to the FDA) and a Marketing Authorisation Application to the EMA for N8-GP, an extended half-life factor VIII for treatment of people with haemophilia A.
	+ Protagonist Therapeutics announced that the FDA had granted Orphan Drug Designation for PTG-300, the company's sub-cutaneous injectable hepcidin mimetic for the treatment of beta-thalassemia[[42]](#footnote-42). Protagonist had completed a Phase I study of PTG-300 that generated pharmacodynamic-based clinical proof-of-concept by achieving dose-related and sustained decreases in serum iron levels in normal healthy volunteers. It was well tolerated with no serious adverse events or dose-limiting toxicities. The company will conduct a global clinical trial with PTG-300 in patients with beta-thalassemia.
	+ The FDA approved the use of the Trevo clot retrieval device to treat certain stroke patients up to 24 hours after symptom onset. The device was previously approved for use in patients for six hours after symptoms began. The device is used as an initial therapy for strokes due to blood clots (known as an acute ischemic stroke) to reduce paralysis, speech difficulties and other stroke disabilities and only as an addition to treatment with a medication that dissolves blood blots, called tissue plasminogen activator (t-PA).
	+ AMAG Pharmaceuticals announced that the FDA had approved the use of Feraheme (ferumoxytol injection) for all eligible adult patients with iron deficiency anaemia (IDA) who are intolerant of or have not responded adequately to oral iron therapy. Feraheme was previously approved in the US to treat IDA in adults with chronic kidney disease.
	+ Baxter International announced FDA approval of Bivalirudin in 0.9 per cent Sodium Chloride Injection. Bivalirudin is a specific and direct thrombin inhibitor indicated for use as an anticoagulant in patients undergoing percutaneous coronary intervention, a common non-surgical procedure to treat blocked or narrowed blood vessels in the heart.

# 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.*

* + Life Sciences Pennsylvania presented its *2018 Patient Impact Award* to CSL Behring for Haegarda, C1 Esterase Inhibitor Subcutaneous (Human), which has been shown to reduce hereditary angioedema (HAE) attacks [[43]](#footnote-43)by 95 per cent versus placebo (median). It is administered subcutaneously rather than intravenously, so patients can manage their own treatment. Haegarda, which is a plasma-derived concentrate, has Orphan Drug Exclusivity in the US granted for seven years by the FDA.
	+ Spanish company Grifols has broken ground on a new $US 120 million facility, part of a planned $US 320 million investment in Clayton, North Carolina by 2022. This latest addition will be a purification and filling facility for its haemotherapy products and is expected to begin production in 2022. Grifols already has a $US 90 million plasma fractionation facility under construction in Clayton. Last December, the company purchased enough land to triple the size of its Clayton site for future expansion.
	+ Swedish Orphan Biovitrum (Sobi) reported in February a bigger fourth-quarter 2017 profit jump than expected[[44]](#footnote-44) but suggested a slightly slower profit growth in 2018 than was being estimated by analysts. The share price had risen on 22 January when Sanofi announced it had agreed to buy Bioverativ for $US 11.6 billion.
	+ Oxford BioMedica will partner with Bioverativ to develop and manufacture lentiviral vectors designed to treat haemophilia. Bioverativ—which is [being acquired by Sanofi for approximately $US 11.6 billion](https://www.genengnews.com/gen-news-highlights/sanofi-snaps-up-bioverativ-for-116b-boosting-hemophilia-and-rare-disease-offerings/81255406)—has agreed to license Oxford BioMedica’s LentiVectorEnabled technology, as well as its industrial-scale manufacturing technology[[45]](#footnote-45). Oxford BioMedica agreed in July 2017 to deliver commercial and clinical supplies of lentiviral vectors for Novartis’ chimeric antigen receptor T-cell (CAR-T) treatment Kymriah(tisagenlecleucel)[[46]](#footnote-46) and other undisclosed CAR-T products. Novartis will pay Oxford BioMedica up to $US 100 million over three years—with $US 10 million upfront. That agreement can be extended to five years if both companies agree. Oxford BioMedica also has partnership agreements with Sanofi, GC LabCell, GlaxoSmithKline, and Immune Design.
	+ The Octapharma Group reported its result for 2017, with sales of €1.72 billion – €120 million (7.5 per cent) more than 2016’s figure (on a constant currency basis, the growth rate was 9.4 per cent). Gross profit in 2017 was €592 million. €87 million was invested in research and development (R&D) and €201 million in the extension of production capacity and infrastructure[[47]](#footnote-47).
	+ In the half year ended December 2017, CSL’s revenue was $US 4.1 billion, up 13 per cent on the prior corresponding period, while profit rose 35 per cent to $US 1.1 billion. CSL chief executive Paul Perreault said: “Our immunoglobulin products Hizentra and Privigen continued to deliver strong performance. To some extent their growth has been masked by atypical market conditions in the prior comparable period when some competitors experienced supply constraints.” CSL Behring, the group’s largest business unit (ahead of Seqirus), reported revenue of $US 3.4 billion, up 8 per cent in constant currency terms. CSL said it expects to report constant currency profit in the range of between $US 1.55 billion and $US 1.6 billion for its 2018 financial year. Mr Perreault commented: “An uneven profit profile for CSL is expected for the first and second half results, due to the seasonality of the influenza business and the timing of expenses – particularly research and development”.
	+ Sanofi announced that it would buy the Belgium-based antibody drug developer Ablynx for $US 4.8 billion in cash. Sanofi outbid the Danish company [Novo Nordisk, which offered $3.1 billion](https://cen.acs.org/articles/96/i3/Investment-flows-JP-Morgan-Healthcare.html) for Ablynx. The deal is Sanofi’s second in two weeks for a company involved in blood diseases. On 22 January Sanofi said it would [spend $11.6 billion](https://cen.acs.org/articles/96/i5/Drug-industry-deal-making-starts.html) to acquire Bioverativ.

# Specific country events

* + The Republic of Ireland announced it was the first country in Europe where every person with haemophilia could access the newest generation of treatments, extended half-life therapies, under new supply contracts signed between the HSE (Health Services Executive) and Swedish Orphan Biovitrum. A new contract for the supply of Elocta (efmoroctocog alfa), for the treatment of haemophilia A was signed in January 2018. It followed an earlier contract for the supply of Alprolix (eftrenonacog alfa), for the treatment of haemophilia B. Both contracts are for two years.
	+ New Zealand saw many holidaymakers return from Samoa, Tonga and Fiji in January and February with dengue. Two residents did not return, one dying in Samoa and one in Tonga.
	+ On 5 March Britain's prime minister called for the UK to remain part of the European Medicines Agency (EMA) after Brexit. The proposal was in accord with the wishes of the biopharma industry, but whether the European Union proved receptive to the idea remained to be seen. More than one country in continental Europe had expressed a desire to host the EMA when it relocated from London. Theresa May in her [speech](https://www.gov.uk/government/speeches/pm-speech-on-our-future-economic-partnership-with-the-european-union) said she wanted to “explore ... the terms on which the UK could remain part of” the EMA and certain other European agencies.
	+ Romania’s health minister Sorina Pintea decided on 5 March to activate the European civil protection mechanism to ensure the necessary immunoglobulin quantities for Romanian patients. Producers and distributors have reportedly left the market as the state’s price fixing policy has made sales unprofitable. “We haven’t been able to convince distributors and producers to bring this type of medicine although we decided to suspend the clawback tax for these drugs for a period of two years,” said the health minister. She added that Romania had no immunoglobulin in stock and asked other EU states to provide about 5,000 doses.
	+ In the US, following the 2012 massacre at Sandy Hook Elementary School in Newtown, Connecticut, President Barack Obama called for an effort to enhance public resilience to mass casualty events. The American College of Surgeons responded with the Hartford Consensus, in 2013, which called for [training the public in bleeding-control techniques](http://bulletin.facs.org/2013/09/hartford-consensus-ii/#.WnJPD5M-dUM). “The most common cause of preventable death following injury is hemorrhage,” said Babak Sarani, a trauma surgeon at George Washington University Hospital. “The longer someone bleeds, the higher the chance that they are going to die. … The first person who can help that victim, inevitably, is another civilian.” Surgeons developed a training course for people with no medical background, and the course was offered by volunteer instructors. The American College of Surgeons estimates that 120,000 people have taken a Stop the Bleed course, but one group of military veterans thought more people should be trained. In September 2017 a Facebook group called [Next Generation Combat Medic](https://www.facebook.com/nextgencombatmedic/) decided to create the National Stop the Bleed Day[[48]](#footnote-48). They chose March 31, 2018, coordinated with the American College of Surgeons and began the awareness campaign, encouraging people to sign up for free Stop the Bleed courses at [bleedingcontrol.org](https://cms.bleedingcontrol.org/class/search). Following the Florida school shooting, there was public discussion about schools needing to be equipped and trained with Stop the Bleed kits.
	+ Colonel Shawn C. Nessen[[49]](#footnote-49), a trauma surgeon who served in Iraq in 2003 and Afghanistan from 2006 to 2008, says three trauma care procedures are among those responsible for saving the most lives. All three have to do with haemorrhage control: greater use of tourniquets, improvements in transfusion therapy and hypothermia prevention.
	+ A. Barocas**,** an infectious disease physician at Massachusetts General Hospital and instructor of medicine at Harvard University Medical School, and his colleagues, suggest that expanding hepatitis C virus testing to everyone aged 18 years and older in the US would likely be a cost-effective way to improve HCV outcomes. The authors claimed in the journal Clinical Infectious Diseases that the strategy would also identify more than a quarter million more HCV cases than the current CDC-recommended strategy of screening baby boomers (those born between 1945 and 1965).
	+ Non-invasive foetal RhD genotyping can identify which RhD negative women are carrying RhD positive babies and therefore require antenatal anti-D prophylaxis therapy. A recent cost-effectiveness study[[50]](#footnote-50) has concluded RhD genotyping to be “an economically sound option for Australia”[[51]](#footnote-51). Associate Professor Catherine Hyland, from the Australian Red Cross Blood Service’s research and development team in Brisbane, said it is a challenge to maintain anti-D supplies under the current universal prophylaxis program: “There are only approximately 150 to 200 donors who currently contribute to the anti-D program. Anti-D is not found naturally in blood donors under normal circumstances. In that sense it is very rare. The gift these donors provide for RhD negative pregnant women is invaluable.” National screening programs for all RhD negative pregnant women to guide anti-D prophylaxis already exist in Denmark, the Netherlands and Finland while smaller programs are underway in England and Sweden. Associate Professor Hyland said: “One barrier for introducing a screening program in Australia is the size of the country, because the samples have a limited storage time, and require refrigerated transport”. Foetal RhD genotyping is already available in Australia on request from attending obstetricians.

# Research not included elsewhere

*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.*

* + Researchers at [Emory University School of Medicine](http://med.emory.edu/main/index.html) have produced a small-scale model to study bleeding and clotting of wounds, and the alterations observed in [haemophilia A](https://hemophilianewstoday.com/hemophilia-type-a/) patients[[52]](#footnote-52). They found that an anti-platelet drug, Integrilin (eptifibatide), used to deter blood clot formation, did not actually affect bleeding time (a fact which had already been observed), but worked by lowering platelet density within the clot. In addition, supplying the microsystem with haemopilia A patients’ blood increased bleeding time and resulted in abnormal blood clot formation. “The vascularized microfluidic bleeding model presented here recapitulates a true mechanical injury and enables the use of human (and therefore patient) blood samples, while the experiments themselves are relatively inexpensive and simple to conduct,” the team wrote. The system physically models only the microvasculature and does not reproduce aspects of larger blood vessels.
	+ Researchers at the US National Institutes of Health have cured mice with a life-threatening disorder that involves the overproduction of red blood cells[[53]](#footnote-53). They treated the mice using [Tempol](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2854323/), an experimental drug for treatment of diabetes, cancer and other diseases. The research suggests that Tempol or a similar drug may treat [polycythemias](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2696729/) that affect humans, such as [mountain sickness](https://www.ncbi.nlm.nih.gov/pubmed/20417340)—a blood complication in low-oxygen, high-altitude settings[[54]](#footnote-54).
	+ Scientists at the Universities of Bayreuth and Marburg have created high-definition images of human blood vessels magnified thousands of times. Using virtual reality glasses (from computer games), they could take virtual exploratory tours through a complex mesh of tiny blood vessels. They made new discoveries about the spleen[[55]](#footnote-55).
	+ Scientists have discovered a specific gene that plays an important role in the development of blood cells may also cause blood diseases and disorders. The Pi4Ka gene is necessary for blood cell growth, but it can also cause various types of blood cancer and anaemia when disrupted*[[56]](#footnote-56)*.
	+ [Allan Doctor, MD](http://research.peds.wustl.edu/Faculty/doctor_a), professor of paediatrics at Washington University School of Medicine in St. Louis, and his research team have received $US 5 million in grants to develop artificial red blood cells. The grants are from the US Department of Defense and the National Institutes of Health (NIH). The team is developing a freeze-dried, powdered blood substitute, ErythoMer, comprised of nano-scale synthetic red blood cells that can deliver oxygen throughout the body. The artificial red cells contain purified human haemoglobin. The haemoglobin is encapsulated in a polymer shell that regulates oxygen capture and release and prevents adverse interactions between haemoglobin and vasoactive molecules in blood plasma, which might otherwise lead to vessel narrowing and critically limited blood flow. Freeze-dried ErythoMer can be stored at ambient temperatures for extended periods. Doctor said: “ErythroMer can be stocked on an ambulance shelf, carried in a backpack in austere environments such as a battlefield or a remote village, and it easily can be stored in depot fashion in anticipation of civilian disasters. ErythroMer then can be reconstituted with water at the point of care and used as a life-saving, stopgap measure until the patient can be brought to a field hospital or medical center.” The blood substitute has been tested successfully in mice and rats. The new funding will support further study in larger animals.
	+ A research team centred at Osaka University has used newly identified blood vessel stem cells to repair injured blood vessels and treat vascular disorders.[[57]](#footnote-57)
	+ A report from a study conducted on mice[[58]](#footnote-58) suggests that Vitamin D may protect heart tissue and prevent heart failure after a heart attack.
	+ Researchers have reported on a promising experimental broad spectrum antiviral drug that could inhibit a range of coronaviruses[[59]](#footnote-59).
	+ The protein albumin in nature appears as a solution only when dissolved in water. Now chemists at Martin Luther University Halle-Wittenberg have developed a method of producing various albumin-based gels[[60]](#footnote-60).
	+ Harmke A. Polinder-Bos, from the University of Groningen in the Netherlands, and colleagues have reported[[61]](#footnote-61): "Conventional hemodialysis induces a significant reduction in global and regional cerebral blood flow (CBF) in elderly patients. Repetitive intradialytic decreases in CBF may be one mechanism by which hemodialysis induces cerebral ischemic injury."
	+ A Phase 1 clinical trial has been awarded $US 5.74 million to evaluate an innovative blood [stem cell transplant](https://sicklecellanemianews.com/stem-cell-transplant-sickle-cell-disease/) procedure for adults with severe [sickle cell disease](https://sicklecellanemianews.com/). The [California Institute for Regenerative Medicine](http://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.cirm.ca.gov%2F&esheet=51767786&newsitemid=20180302005770&lan=en-US&anchor=California+Institute+for+Regenerative+Medicine&index=1&md5=4bdfbd9fa297dc5823d4f0283108f570) (CIRM) granted the funding to [City of Hope](http://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.cityofhope.org%2Fhomepage&esheet=51767786&newsitemid=20180302005770&lan=en-US&anchor=City+of+Hope&index=2&md5=1b05c58f7ac696a90327f9645931ebdf), where the research will be conducted, and will enable testing the new treatment in six adults.

# 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, Zika virus and the tick-borne babesiosis and Lyme disease).*

## Mosquito-borne diseases

* + A study of pregnant women in the Caribbean confirmed that Zika virus causes birth defects, particularly if infection occurs early in pregnancy[[62]](#footnote-62). Researchers reported that about 7 percent of Zika-infected women in French territories of the Caribbean delivered babies that suffered from birth defects of the brain and eyes[[63]](#footnote-63).
	+ Scientists at Johns Hopkins Bloomberg School of Public Health’s Malaria Research Institute have reported[[64]](#footnote-64) that deleting a single gene from mosquitoes can make them highly resistant to the malaria parasite and less likely to transmit the parasite to people.

## Seasonal influenza

* + On 16 February the US Centers for Disease Control and Prevention (CDC) in its Morbidity and Mortality Weekly Report published “Interim Estimates of 2017–18 Seasonal Influenza Vaccine Effectiveness”[[65]](#footnote-65). It showed that flu vaccines were 36 per cent effective overall against influenza A and B, that is, a vaccinated person reduced his or her risk of getting the flu by about one third. However, the vaccine effectiveness against the season's dominant strain, H3N2, was only 25 per cent. The vaccine was 67 per cent effective against the A(H1N1) pdm09 viruses and 42 per cent effective against influenza B viruses. Of the 63 children who had died by that stage of the season, three-quarters had not been vaccinated. Irrespective of viral strain, vaccine effectiveness was 59 per cent for children aged 6 months to 8 years; 33 per cent for those aged 18 to 49 years; and not significantly effective for those aged 9 to 17 years, 50 to 64 years, or 65 years or older. CDC [recommends antiviral medications](https://emergency.cdc.gov/han/han00409.asp) as an adjunct to vaccination, with their potential public health benefit being increased in the context of low vaccine effectiveness.
	+ Japan approved a drug that can apparently eliminate the influenza virus in just 24 hours. Xofluza is manufactured by Shionogi. This new drug requires just one dose, compared with five doses of Tamiflu.
	+ Inovio Pharmaceuticals announced that its synthetic vaccine approach using a collection of synthetic DNA antigens generated broad protective antibody responses against all major deadly strains of H1 influenza viruses from the last 100 years (including the virus that caused “Spanish Flu” in 1918) in multiple animal models including mice, guinea pigs and non-human primates.

## Avian influenza

*Because of the capacity of influenza viruses for re-assortment, the spread of influenza strains in animals and birds is of interest as one or more strain may eventually develop the potential to cause a pandemic in humans. There are also strains which, while primarily infecting and being transmitted by animals or birds, nevertheless can infect humans, and the concern there is that human-to-human transmission might develop.*

* + Two clinical trials[[66]](#footnote-66) testing an experimental vaccine against H7N9 influenza are enrolling volunteers at sites across the US. The Phase II studies are sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). They will test varied dosages and schedules of an inactivated vaccine known as *2017 H7N9 IIV.*  The trials will also test whether an adjuvant[[67]](#footnote-67) boosts the immune responses of recipients. One of the trials will assess the H7N9 vaccine with adjuvant in conjunction with a quadrivalent seasonal influenza vaccine to see whether either vaccine affects the immune response to the other. The experimental vaccine was developed by Sanofi Pasteur, supported by the Biomedical Advanced Research and Development Authority (BARDA), a component of the US Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response[[68]](#footnote-68).
	+ On 14 February, the National Health and Family Planning Commission (NHFPC) of China notified the World Health Organization (WHO) of one case of human infection with avian influenza A(H7N4) virus. This was the first human case of avian influenza A(H7N4) infection to be reported from anywhere in the world. The patient had reported a history of exposure to live backyard poultry before onset of symptoms. Genetic sequencing of this A(H7N4) virus shows that all the virus segments originated from avian influenza viruses.

## MERS

* + By mid-March, the World Health Organization (WHO) had received globally reports of 2144 laboratory-confirmed cases of MERS-CoV, including at least 750 deaths.
	+ As at 20 March, 1814 of these had been in Saudi Arabia, with 734 reported fatalities.
	+ A case of MERS in Oman round that time brought the total number in that country to 11. The previous laboratory confirmed case in Oman occurred in November 2017.
	+ The Coalition for Epidemic Preparedness Innovations (CEPI), the public-private vaccine initiative launched in 2017, has signed its first company agreement, granting Themis up to $US 37.5 million to develop new vaccines against MERS and Lassa fever. The grant will be spread over five years and will support Themis through phase II testing, providing safety and immunological data, plus the manufacturing of investigational supplies for efficacy trials or emergency deployment during outbreaks. Research by the Paul Ehrlich Institut and Institut Pasteur are the basis for Themis’ MERS and Lassa candidates, respectively. The institutions have identified antigens for inclusion in vaccine compositions and have demonstrated proof of concept in animal studies. Themis will apply its measles vector platform used in the company's lead program for chikungunya, which is in phase II trials in 600 patients in the US and Europe, and in its Zika candidate which has begun testing in humans.

## Ebola

* + A research team led by Robert Stahelin of Purdue University has concluded that it may be possible to stop the replication of Ebola virus by mutating its most important protein[[69]](#footnote-69).
	+ In the US the Defense Threat Reduction Agency’s Chemical and Biological Technologies Department has collaborated with the US Army Medical Research Institute of Infectious Diseases (USAMRIID) and Merck to develop a vaccine against the Ebola virus. USAMRIID scientists have so far conducted four non-human primate studies to evaluate the efficacy of Merck's V920. The vaccine has also been tested in clinical trials in North America, Europe and Africa. Data will eventually form part of licence applications to the FDA and the EMA.
	+ ZMapp is a monoclonal antibody combination therapy[[70]](#footnote-70) that was used to treat humans during the 2014 West Africa Ebola outbreak before human clinical trials[[71]](#footnote-71). The drug was later tested in its first randomized, controlled human trial as an accompanying therapy to standard care (oral favipiravir) versus monotherapy favipiravir in humans infected with a virus strain diagnosed in West Africa by polymerase-chain-reaction-assay[[72]](#footnote-72). Now the Texas Biomedical Research Institute in San Antonio will begin clinical trials[[73]](#footnote-73). The institute was granted a $US 2 million contract by Mapp Biopharmaceutical to test the therapy in primate models, as a step towards FDA licensure.
	+ Singapore eDevelopment announced on 1 March that biomedical subsidiary Global BioLife had completed the initial Zaire Ebola research portion for the study of new anti-viral drug LB2, part of its new universal therapeutic drug platform, Linebacker. Dr. Roscoe Moore, previously Assistant Surgeon General of the US serves as Scientific Advisor to the Linebacker Project. He commented: "The results validate our core belief that the Linebacker platform can be a major entry as an effective small molecule anti-infective - effective, and at the same time, with a good safety profile." In addition to Ebola, the LB2 drug demonstrates similar broad efficacy against SARS, MERS, H5N1 Avian Bird Flu, MRSA, and Cholera. Global BioLife expects in future to show positive results from the LB2 drug against ZIKA, Malaria, and the influenza pandemic.
	+ GeoVax Labs published its manuscript titled “A Single-Dose of Modified Vaccinia Ankara Expressing Ebola Virus Like Particles Protects Nonhuman Primates from Lethal Ebola Virus Challenge” in [***Scientific Reports by Nature Research***](https://www.nature.com/articles/s41598-017-19041-y)***.*  This demonstrated** that a single intramuscular dose of GeoVax’s Ebola vaccine (GEO-EM01) provided 100 per cent protection in rhesus macaques challenged with a lethal dose of Ebola virus.

## Other diseases: occurrence, diagnosis, prevention and treatment

* + Established tests for tick-borne diseases (TBDs) have had limited diagnostic accuracy and have not been able to test for more than one infection simultaneously. Scientists based at Columbia University have now developed the TBD-Serochip, which they say is more accurate than existing tests, and can detect Lyme disease and seven other TBDs[[74]](#footnote-74). The TBD Serochip can determine whether a person is infected with more than one tick-borne pathogen[[75]](#footnote-75). As new tick-borne infectious agents are discovered, the TBD-Serochip can be modified to include them. Senior author W. Ian Lipkin[[76]](#footnote-76) commented: "The TBD Serochip promises to make diagnosis far easier, offering a single, accurate test for eight different TBDs. Early detection of infection enables rapid and appropriate treatment."
	+ In the first six weeks of this year 37 cases of whooping cough had been reported in northern Queensland compared with ten in the same period last year.
	+ As of 6 March, there had been 58 confirmed cases of hepatitis A in Victoria so far this year, with further cases awaiting confirmation. One man had died. The health department said all those so far affected had been adults, with most reporting male-to-male sexual activity. A number of cases had also identified as people who inject drugs.
	+ In mid-March, graziers in Southern Queensland were advised to vaccinate their livestock against anthrax after it was identified in cattle near St George, a year since about 80 head died in the area. At the end of February, anthrax was detected on a property at Swan Hill, In Victoria. The property was quarantined and any at risk livestock vaccinated.
	+ By 16 March five Australians had died in a listeriosis outbreak after eating contaminated rockmelons grown on a farm in southern NSW.
	+ Residents of Duaringa west of Rockhampton are concerned about the health risks (such as transmission of the Lyssa virus posed by a flying fox (bat) infestation of their town. The Central Highlands Regional Council had a count conducted on 27 February and estimated there may be up to 5000 bats in this town of fewer than 300 people.
	+ The US Centers for Disease Control and Prevention (CDC) said researchers found evidence of one patient who didn't develop CJD until 2015, even though the initial exposure was thought to happen in 1985[[77]](#footnote-77). That is the longest latency period for a prion-related disease currently recorded, but future cases may surpass it.
1. 89 per cent of respondents were very satisfied or somewhat satisfied with Ixinity; a majority of respondents reported that they had been somewhat active (56 per cent) or very active (22 per cent) since starting the drug; the median reported annualized bleed rate (ABR) among patients taking Ixinity prophylaxis was 1.6, while the median ABR recorded in the pivotal clinical trial was 1.52; and a majority of respondents reported only slight problems or no problems in aspects of quality of life: mobility, self-care, usual daily activities, pain or discomfort, anxiety or depression. [↑](#footnote-ref-1)
2. The study, “[Recombinant factor VIII Fc fusion protein for immune tolerance induction in patients with severe haemophilia A with inhibitors—A retrospective analysis](http://onlinelibrary.wiley.com/doi/10.1111/hae.13413/full),” was published in the journal [Haemophilia](http://onlinelibrary.wiley.com/journal/10.1111/%28ISSN%291365-2516). [↑](#footnote-ref-2)
3. Researchers evaluated data from 19 patients with severe haemophilia A who received immune tolerance induction therapy using Eloctate – seven were being treated with ITI for the first time, and the remaining 12 had been previously treated. The results showed that tolerization was achieved after a median of 7.8. months in four of the seven first-time immune tolerance induction patients. The remaining three patients continue on Eloctate-ITI therapy, but two patients already show a reduction in the levels of inhibitor. Among the 12 patients who had failed to respond to previous therapies, seven patients achieved a negative inhibitor level in a median 3.3 months, but in four people inhibitors returned. Four rescue patients did not show a response to ITI with Eloctate, and one responded to the therapy and showed a reduction in inhibitor levels. Researchers wrote: “Most rescue patients in this study were still undergoing rFVIIIFc ITI at the time of data collection, and therefore, a longer follow-up is needed to determine their final outcomes.” [↑](#footnote-ref-3)
4. At the beginning of 2018, the South Korean Ministry of Food and Drug Safety agreed to Catalyst’s request to amend the Phase I/II trial plan to shorten its duration. The amendment consisted of eliminating a treatment group and reassigning the participants to another group. The Phase I/II clinical trial is still [recruiting participants](https://clinicaltrials.gov/ct2/show/study/NCT03186677#contacts). [↑](#footnote-ref-4)
5. CRISPR enters a cell and targets its genetic code, identifying mutations and substituting the “correct genes”. Sickle cell disease is caused by a point mutation, so it is considered a good target for CRISPR. [↑](#footnote-ref-5)
6. “You have a Berkeley laboratory doing something new and successful,” Walters said. “(We) worked with our clinical knowledge and (UC Berkeley’s) technical expertise to create an innovative solution.” UCSF supplied clinical materials such as stem cells of affected patients to UC Berkeley’s Doudna Lab and Corn Lab, which specialize in CRISPR. Successful trials have already been performed in mice. [↑](#footnote-ref-6)
7. Bao said: "The idea is to correct that particular mutation, and then stem cells that have the correction would differentiate into normal blood cells, including red blood cells. Those will then be healthy blood cells”. The team is unsure whether correcting 40 per cent of cells is sufficient. [↑](#footnote-ref-7)
8. Information about the study design can be found at [www.clinicaltrialsregister.eu](https://d.docs.live.net/www.clinicaltrialsregister.eu) (EudraCT number: 2017-001163-20). [↑](#footnote-ref-8)
9. [Masaaki Mori](https://www.nature.com/articles/s41598-017-18387-7#auth-1), [Takuma Hara](https://www.nature.com/articles/s41598-017-18387-7#auth-2), [Masako Kikuchi](https://www.nature.com/articles/s41598-017-18387-7#auth-3), [Hiroyuki Shimizu](https://www.nature.com/articles/s41598-017-18387-7#auth-4), [Tomoyuki Miyamoto](https://www.nature.com/articles/s41598-017-18387-7#auth-5), [Satoru Iwashima](https://www.nature.com/articles/s41598-017-18387-7#auth-6), [Tatsuya Oonishi](https://www.nature.com/articles/s41598-017-18387-7#auth-7), [Kunio Hashimoto](https://www.nature.com/articles/s41598-017-18387-7#auth-8), [Norimoto Kobayashi](https://www.nature.com/articles/s41598-017-18387-7#auth-9), [Kenji Waki](https://www.nature.com/articles/s41598-017-18387-7#auth-10), [Yasuo Suzuki](https://www.nature.com/articles/s41598-017-18387-7#auth-11), [Yoshikazu Otsubo](https://www.nature.com/articles/s41598-017-18387-7#auth-12), [Hiroshi Yamada](https://www.nature.com/articles/s41598-017-18387-7#auth-13), [Chikao Ishikawa](https://www.nature.com/articles/s41598-017-18387-7#auth-14), [Taichi Kato](https://www.nature.com/articles/s41598-017-18387-7#auth-15) and [Shigeto Fuse](https://www.nature.com/articles/s41598-017-18387-7#auth-16), “Infliximab versus intravenous immunoglobulin for refractory Kawasaki disease: a phase 3, randomized, open-label, active-controlled, parallel-group, multicenter trial”,*Scientific Reports* volume 8, Article number:1994 (2018) doi:10.1038/s41598-017-18387-7 published online 31 January 2018 [↑](#footnote-ref-9)
10. Rapid lowering of temperature [↑](#footnote-ref-10)
11. 31 patients were randomized to receive either infliximab in a single intravenous dose of 5 mg/kg (n = 16) or intravenous polyethylene glycol-treated human immunoglobulin (VGIH) at a dose of 2 mg/kg (n = 15). The study’s primary outcome was the defervescence rate within 48 hours after treatment, and safety was evaluated through to the 56th day. The researchers found that:

	* The defervescence rate within 48 hours was significantly greater in the infliximab arm at 76.7 per cent versus the VGIH arm at 37.0 per cent.
	* The median febrile period from the start of the study drug administration was 16.0 hours in the infliximab arm and 56.1 hours in the VGIH arm.
	* Axillary body temperature from 4 hours to 20 hours was significantly lower in the infliximab group than in the VGIH group.
	* CALs were found in 1 patient in the infliximab arm and 3 patients in the VGIH arm by day 21, and no patient had a new CAL after day 21.
	* Improvement and resolution of clinical symptoms other than fever were comparable between treatment groups.
	* Adverse events occurred in 93.8 per cent of patients in the infliximab arm and 100 per cent of patients in the VGIH arm, with 1 serious event reported in the VGIH arm. The most commonly reported adverse events were an increase in anti–double-stranded DNA IgM antibodies. [↑](#footnote-ref-11)
12. The new tourniquet applies pressure at different points on the limb, reducing damage to specific areas. [↑](#footnote-ref-12)
13. presented at the 2018 American Academy of Allergy, Asthma, and Immunology meeting [↑](#footnote-ref-13)
14. Romano JM, Mallick R. “High treatment satisfaction with Hizentra, a 20% subcutaneous immunoglobulin (SCIG): real-world survey data”. Presented at the 2018 American Academy of Allergy, Asthma & Immunology/World Allergy Organization Joint Congress; March 2-5, 2018; Orlando, FL. Abstract 844. [↑](#footnote-ref-14)
15. Julie Lee, Kerstin Wyssusek, Jeremy Cohen, Andre van Zundert, “Rotational thromboelastometry (ROTEM) in obstetrics”, *Australasian Anaesthesia*, 2017. This study was in part funded by Australia’s National Blood Authority. [↑](#footnote-ref-15)
16. Not least of which is the increase in hypercoagulability throughout the three trimesters of pregnancy, [↑](#footnote-ref-16)
17. Held 16-17 February in Las Vegas [↑](#footnote-ref-17)
18. “A Contemporary Analysis of Robotic and Open Radical Cystectomy in Octogenarians” was presented by Akbar N. Ashrafi, USC institute of Urology, Keck School of Medicine of USC, University of Southern California. [↑](#footnote-ref-18)
19. “Utilization and Real-World Effectiveness of Tranexamic Use In Shoulder Arthroplasty: A Population-Based Study”. [↑](#footnote-ref-19)
20. 6 to 10 March 2018 [↑](#footnote-ref-20)
21. Results from the study were published 27 February in a letter in the *Journal of the American Medical Association*. [↑](#footnote-ref-21)
22. Brant M. Wagener, Parker J. Hu, Joo-Yeun Oh, Cilina A. Evans, Jillian R. Richter, Jaideep Honavar, Angela P. Brandon, Judy Creighton, Shannon W. Stephens, Charity Morgan, Randal O. Dull, Marisa B. Marques, Jeffrey D. Kerby, Jean-Francois Pittet , Rakesh P. Patel, “Role of heme in lung bacterial infection after trauma hemorrhage and stored red blood cell transfusion: A preclinical experimental study”, *PLOS Medicine,* Published: March 9, 2018. <https://doi.org/10.1371/journal.pmed.1002522> [↑](#footnote-ref-22)
23. [Petty K, Waters JH, Sakamoto SB, and MH Yazer. Antenatal anemia increases the risk of receiving postpartum red blood cell transfusions although the overall risk of transfusions is low. Transfusion 2018; 58; 360-365.](http://onlinelibrary.wiley.com/doi/10.1111/trf.14434/full) [↑](#footnote-ref-23)
24. [Gybel-Brask M, Seeberg J, Thomsen LL, Johansson PI. Intravenous iron isomaltoside improves hemoglobin concentration and iron stores in female iron-deficient blood donors: a randomized double-blind placebo-controlled clinical trial. Transfusion 2018; doi:10.1111/trf.14521](http://onlinelibrary.wiley.com/doi/10.1111/trf.14521/full) [↑](#footnote-ref-24)
25. Hougen I, Collister D, Bourrier M, et al. “Safety of Intravenous Iron in Dialysis: A Systematic Review and Meta-Analysis”. *Clin J Am Soc Nephrol* 2018;13. doi:10.2215/CJN.05390517; editorial comment: Li X and Kshirsagar AV. “Rest Easy with Intravenous Iron for Dialysis Patients? High Dose IV Iron Safety.” *Clin J Am Soc Nephrol* 2018;13. doi:10.2215/CJN.00930118 [↑](#footnote-ref-25)
26. published online 14 February in *The British Medical Journal* [↑](#footnote-ref-26)
27. In the US, AndexXa is currently under FDA review in the U.S. with an action date of 4 May. [↑](#footnote-ref-27)
28. In the US, betrixaban was approved in June 2017 under the brand name Bevyxxa. [↑](#footnote-ref-28)
29. Merck Sharp Dome [↑](#footnote-ref-29)
30. Balk EM, et al. “Venous thromboembolism prophylaxis in major orthopedic surgery: Systematic review update” Available at: [www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and reports/?pageaction=displayproduct&productid=2480](http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and%20reports/?pageaction=displayproduct&productid=2480) [↑](#footnote-ref-30)
31. Emiliya M. Shabanova et al, “Thrombin@Fe3O4 nanoparticles for use as a hemostatic agent in internal bleeding”, *Scientific Reports* (2018). [DOI: 10.1038/s41598-017-18665-4](http://dx.doi.org/10.1038/s41598-017-18665-4) [↑](#footnote-ref-31)
32. CIDP is a rare autoimmune disorder that affects the peripheral nerves and may cause permanent nerve damage. [↑](#footnote-ref-32)
33. Principal investigator for the PATH study was Dr Ivo van Schaik, professor of neurology, University of Amsterdam Academic Medical Centre. The study showed that after switching from intravenous immunoglobulin (IVIg), the percentage of patients with CIDP relapse or withdrawal during SCIg treatment was significantly lower with Hizentra (39% with 0.2 g/kg weekly and 33% with 0.4 g/kg weekly) than with placebo (63%). Most patients preferred SCIg over IVIg treatment, not least because of the convenience of self-administration. [↑](#footnote-ref-33)
34. Ersi Voskaridou, Stephan Lobitz, Uwe Kordes, Regine Grosse, Valentine Brousse, Malika Benkerrou, Mariane De Montalembert, Jean-Antoine Ribeil and Frederic Galacteros, “Comparison of the Safety Profile of Sickle Cell Disease Patients Treated with Hydroxycarbamide in Off-Label Versus in-Label Prescriptions in the Escort-HU Non Interventional, Prospective, Observational Open-Label Cohort Study”, *Blood,* 2016 128:2497 [↑](#footnote-ref-34)
35. The application is supported by results of the company's Phase III randomised, double-blind, placebo-controlled, multi-centre clinical trial of 230 patients aged 5 to 58 years with sickle cell disease who had two or more painful crises within the previous year. Patients who were treated with Xyndari over a 48-week period experienced fewer crisis episodes compared with patients given a placebo, fewer hospitalisations for sickle cell pain, and fewer days in the hospital. Patients on Xyndari also had fewer occurrences of acute chest syndrome, which is a potentially fatal complication of sickle cell disease. The most common adverse reactions were constipation, nausea, headache, abdominal pain, cough, pain in an extremity, back pain and chest pain. [↑](#footnote-ref-35)
36. Xyndari has also received orphan designation and an approved paediatric investigation plan (PIP) from the EMA. [↑](#footnote-ref-36)
37. HAE is a rare, genetic disorder that results in recurring attacks of swelling in the abdomen, face, feet, genitals, hands and/or throat. Swelling of the larynx is particularly dangerous as it can cause asphyxiation if not immediately treated. HAE arises from deficient or dysfunctional C1 Esterase Inhibitor (C1-INH), a protein in the blood that helps to control inflammation in the body. The condition is estimated to affect about 1 in 10,000 to 1 in 50,000 people worldwide. [↑](#footnote-ref-37)
38. US National Institutes of Health. Open-Label C1 Esterase Inhibitor (C1INH-nf) for the Prevention of Acute Hereditary Angioedema (HAE) Attacks (CHANGE 3). Available at [https://clinicaltrials.gov/ct2/show/results/NCT00462709](https://www.globenewswire.com/Tracker?data=eDmlQZSR4FRYnGEBBPY6rBo4_G5lpQUV_ZpYi66DaBg6qZ4xE_bzM9-wvpSjUCGuHXa0Lpd5_OdeuEAywPOtyiK5kPQJBjlUWpRV7gAj9oF6dADYDOII53LDduRQHwboOl1AjGVGJaYb2RbtMPTRh5YQxz-Be5iKVRKhq5048KZSdjhPN0lZUrP_CcbgwZV7).. [↑](#footnote-ref-38)
39. In the US, for patients who have not been vaccinated before, the Advisory Committee on Immunization Practices (ACIP) and Centers for Disease Control and Prevention (CDC) recommend immediate prophylaxis following exposure to rabies, including a rabies immune globulin injection directly into the wound site to prevent the virus from entering the central nervous system, which eventually leads to death. [↑](#footnote-ref-39)
40. The FDA approved the Imugen *Babesia microti* Arrayed Fluorescent Immunoassay (AFIA), for the detection of antibodies to *Babesia microti (B. microti)* in human plasma samples, and the Imugen *Babesia microti* Nucleic Acid Test (NAT), for the detection of *B. microti* DNA in human whole blood samples. These tests are intended to be used as donor screening tests on samples from individual human donors, including volunteer donors of whole blood and blood components, as well as living organ and tissue donors. [↑](#footnote-ref-40)
41. The Prescription Drug User Fee Act (PDUFA) date for an FDA decision is 26 August 2018. [↑](#footnote-ref-41)
42. David Y. Liu, Chief Scientific Officer and Head of Research and Development of Protagonist Therapeutics, said: "Beta-thalassemia is a rare genetic blood disorder that is characterized by impaired red blood cell production that can result in life-threatening chronic anemia, usually requiring regular and life-long blood transfusions for survival. Over time, these transfusions can lead to excessive iron levels in the body which can be toxic and consequently lead to end-stage damage to vital organs such as the liver and the heart. As a hepcidin mimetic, PTG-300 is designed to help reduce these excessive iron levels and thereby it may lead to improvements in anemia and decreased need for blood transfusions and chelation therapy." [↑](#footnote-ref-42)
43. U.S. National Institutes of Health. CINRYZE for the Treatment of Hereditary Angioedema Attacks in Children Under the Age of 12.  Available at [https://clinicaltrials.gov/ct2/show/results/NCT01095510](https://www.globenewswire.com/Tracker?data=eDmlQZSR4FRYnGEBBPY6rBo4_G5lpQUV_ZpYi66DaBg6qZ4xE_bzM9-wvpSjUCGuKNcyFx05bX_DO_rKQkwuqTSMWX2tUCWrjaqn_WVZW9mcc_ivvM-GVdjnpjb2oADxTssHafcEslxr_FYIFm8uePnlbxW4lBoDvqkcBgQVMKxoJVSTPJcLZ0wDWkHufpkv).

U.S. National Institutes of Health. Safety and Efficacy Study of CINRYZE for Prevention of Angioedema Attacks in Children Ages 6-11 With Hereditary Angioedema. Available at [https://clinicaltrials.gov/ct2/show/NCT02052141?recrs=e&cond=Hereditary+Angioedema&cntry=US&age=0&draw=5&rank=4](https://www.globenewswire.com/Tracker?data=eDmlQZSR4FRYnGEBBPY6rBo4_G5lpQUV_ZpYi66DaBjCef7N9LqLP8xdtM3vxUI1qqwbpczxLDGKM7w_43M4mcL17iQHkPY7n-g7OY0ZpOHkS2VWoKSVTqCrtw5h0eYSPaqCTa2cR3DgPLOZ_WqowcrsLFSvMTNymJiELfiRqDQg_0GpZHA8sGNTuOa94szlu9vPbWeXQZGQhJKMUSCWvGa5nCKePavt6bwiTyQ9L2IDddAuo82vD_wkKJgrFvqGlS1bR3K5xSMQOP3RBBma65ueBz_GL4RzDqXZxCot3-lH8VK1OQNtaWugxMgJep1-oQbc3LEc-H099un4s6BEfbT99kdK3HVddMqt-wwB3-w=) [↑](#footnote-ref-43)
44. There was strong growth across the portfolio, for new haemophilia drugs Eloctate and Alprolix in particular. [↑](#footnote-ref-44)
45. Oxford BioMedica developed its vector manufacturing capacity to its current scale through £7.7 million ($US 10.8 million) in funding, awarded partly as a grant and partly as a loan by the UK government’s Advanced Manufacturing Supply Chain Initiative. Bioverativ is to pay Oxford BioMedica $US 5 million upfront, up to $100 million in payments tied to milestones, and additional royalties on net sales of Bioverativ lentiviral haemophilia products. Bioverativ will fund process development and scale-up activities for its lentiviral vector haemophilia products at Oxford BioMedica. [↑](#footnote-ref-45)
46. In August 2017 Kymriah became the [first CAR-T treatment to win FDA approval](https://genengnews.com/gen-news-highlights/novartis-kymriah-wins-fda-approval-as-first-car-t-cancer-therapy/81254875). [↑](#footnote-ref-46)
47. To download the full Octapharma Group 2017 Annual Report visit the Octapharma Annual Report website: [www.annualreport.octapharma.com](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.annualreport.octapharma.com&esheet=51765223&newsitemid=20180301005561&lan=en-US&anchor=www.annualreport.octapharma.com&index=1&md5=42a5be5090d27801ec7db8f93c82a370) [↑](#footnote-ref-47)
48. Institutional support was also forthcoming. At the University of Rochester, for instance, bleeding-control kits were added to nearly 150 automated external defibrillator cabinets across the campus, and a week of education and training on the kits was offered. The kits contain supplies such as gauze and tourniquets. The gauze can be used to pack wounds and apply pressure to stop bleeding. Tourniquets are used to control heavy bleeding from an arm or a leg. [↑](#footnote-ref-48)
49. commander of the US Army Institute of Surgical Research, or USAISR, at Joint Base San Antonio, Texas. [↑](#footnote-ref-49)
50. [Louisa G. Gordon](https://obgyn.onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=Gordon%2C+Louisa+G), [Catherine A. Hyland](https://obgyn.onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=Hyland%2C+Catherine+A), [Jonathan A. Hyett](https://obgyn.onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=Hyett%2C+Jonathan+A), [Helen O'Brien](https://obgyn.onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=O%27Brien%2C+Helen), [Glenda Millard](https://obgyn.onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=Millard%2C+Glenda), [Robert L. Flower](https://obgyn.onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=Flower%2C+Robert+L), [Glenn J. Gardener](https://obgyn.onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=Gardener%2C+Glenn+J), “Noninvasive fetal *RHD* genotyping of RhD negative pregnant women for targeted anti‐D therapy in Australia: A cost‐effectiveness analysis”, *Prenatal Diagnosis*, [**Volume37, Issue12**](https://obgyn.onlinelibrary.wiley.com/toc/10970223/37/12)**,** December 2017 Pages 1245-1253 [**https://doi.org/10.1002/pd.5176**](https://doi.org/10.1002/pd.5176) [↑](#footnote-ref-50)
51. The [analysis](http://onlinelibrary.wiley.com/wol1/doi/10.1002/pd.5176/full) found that the cost of implementing such a targeted anti-D program would be largely offset by lower use of anti-D products and related resources. With foetal RhD testing 13,938 RhD negative women could avoid anti-D prophylaxis each year at a cost savings of $ 2.1 million. The estimated total cost for foetal testing was $ 2.2 million. [↑](#footnote-ref-51)
52. “[A microengineered vascularized bleeding model that integrates the principal components of hemostasis](https://www.nature.com/articles/s41467-018-02990-x.pdf)”, was published in [Nature Communications](https://www.nature.com/ncomms/). Lead author of this study was Wilbur Lam, assistant professor in the Department of Pediatrics at Emory University School of Medicine and in the Wallace H. Coulter Department of Biomedical Engineering at [Georgia Tech](http://www.gatech.edu) and Emory University. See his [press release](https://www.eurekalert.org/pub_releases/2018-02/ehs-sm020718.php). [↑](#footnote-ref-52)
53. Chuvash polycythemia is a rare, inherited disorder that is endemic to the Chuvash Republic of Russia, although it is also found elsewhere in the world. [↑](#footnote-ref-53)
54. Ghosh, MC, et al. “Translational repression of HIF2α expression in mice with Chuvash polycythemia reverses polycythemia”. The Journal of Clinical Investigation. <https://doi.org/10.1172/JCI97684>. [↑](#footnote-ref-54)
55. Birte S. Steiniger et al., “Capillary networks and follicular marginal zones in human spleens. Three-dimensional models based on immunostained serial sections”, *PLOS ONE* (2018). [DOI: 10.1371/journal.pone.0191019](http://dx.doi.org/10.1371/journal.pone.0191019) [↑](#footnote-ref-55)
56. #  “A Forward Genetic Screen Targeting the Endothelium Reveals a Regulatory Role for the Lipid Kinase Pi4ka in Myelo- and Erythropoiesis”, Safiyyah Ziyad, Jesse D. Riordan, Ann M. Cavanaugh, Trent Su, Gloria E. Hernandez, Georg Hilfenhaus, Marco Morselli, Kristine Huynh, Kevin Wang, Jau-Nian Chen, Adam J. Dupuy, M. Luisa Iruela-Arispe, “A Forward Genetic Screen Targeting the Endothelium Reveals a Regulatory Role for the Lipid Kinase Pi4ka in Myelo- and Erythropoiesis”, *Cell Reports*, Volume 22, Issue 5, pp1211-1224, 30 January 2018. DOI: <https://doi.org/10.1016/j.celrep.2018.01.017>

 [↑](#footnote-ref-56)
57. # Taku Wakabayashi, Hisamichi Naito, Jun-ichi Suehiro, Yang Lin, Hideya Kawaji, Tomohiro Iba, Tsukasa Kouno, Sachi Ishikawa-Kato, Masaaki Furuno, Kazuhiro Takara, Fumitaka Muramatsu, Jia Weizhen, Hiroyasu Kidoya, Katsuhiko Ishihara, Yoshihide Hayashizaki, Kohji Nishida, Mervin C. Yoder, Nobuyuki Takakura. “**CD157 Marks Tissue-Resident Endothelial Stem Cells with Homeostatic and Regenerative Properties”**. Cell Stem Cell, Volume 22, Issue 3, pp384-397.e6,1 March 2018. DOI: [10.1016/j.stem.2018.01.010](http://dx.doi.org/10.1016/j.stem.2018.01.010)

 [↑](#footnote-ref-57)
58. The paper is available online at Heart Lung and Circulation: <http://www.heartlungcirc.org/article/S1443-9506>(18)30037-4/fulltext [↑](#footnote-ref-58)
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61. [Harmke A. Polinder-Bos](http://jasn.asnjournals.org/search?author1=Harmke+A.+Polinder-Bos&sortspec=date&submit=Submit), David Vállez García, [Johanna Kuipers](http://jasn.asnjournals.org/search?author1=Johanna+Kuipers&sortspec=date&submit=Submit), [Jan Willem J. Elting](http://jasn.asnjournals.org/search?author1=Jan+Willem+J.+Elting&sortspec=date&submit=Submit),[Marcel J.H. Aries](http://jasn.asnjournals.org/search?author1=Marcel+J.H.+Aries&sortspec=date&submit=Submit),[Wim P. Krijnen](http://jasn.asnjournals.org/search?author1=Wim+P.+Krijnen&sortspec=date&submit=Submit), [Henk Groen](http://jasn.asnjournals.org/search?author1=Henk+Groen&sortspec=date&submit=Submit), [Antoon T.M. Willemsen](http://jasn.asnjournals.org/search?author1=Antoon+T.M.+Willemsen&sortspec=date&submit=Submit), [Peter J. van Laar](http://jasn.asnjournals.org/search?author1=Peter+J.+van+Laar&sortspec=date&submit=Submit), [Fijanne Strijkert](http://jasn.asnjournals.org/search?author1=Fijanne+Strijkert&sortspec=date&submit=Submit), [Gert Luurtsema](http://jasn.asnjournals.org/search?author1=Gert+Luurtsema&sortspec=date&submit=Submit), [Riemer H.J.A. Slart](http://jasn.asnjournals.org/search?author1=Riemer+H.J.A.+Slart&sortspec=date&submit=Submit), [Ralf Westerhuis](http://jasn.asnjournals.org/search?author1=Ralf+Westerhuis&sortspec=date&submit=Submit), [Ron T. Gansevoort](http://jasn.asnjournals.org/search?author1=Ron+T.+Gansevoort&sortspec=date&submit=Submit), [Carlo A.J.M. Gaillard](http://jasn.asnjournals.org/search?author1=Carlo+A.J.M.+Gaillard&sortspec=date&submit=Submit) and [Casper F.M. Franssen](http://jasn.asnjournals.org/search?author1=Casper+F.M.+Franssen&sortspec=date&submit=Submit) , “Hemodialysis Induces an Acute Decline in Cerebral Blood Flow in Elderly Patients”, *Journal of the American Society of Nephrology*.Published online before print March 1, 2018, doi: 10.1681/ASN.2017101088 [↑](#footnote-ref-61)
62. See *New England Journal of Medicine*, March 2018. Bruno Hoen, et al., “Pregnancy outcomes after ZIKV Infection in French Territories in the Americas”, [March 15, 2018](http://www.nejm.org/toc/nejm/378/11?query=article_issue_link) *N Engl J Med* 2018; 378:985-994 DOI: 10.1056/NEJMoa1709481 [↑](#footnote-ref-62)
63. Lead researcher was Dr. Bruno Hoen, head of infectious and tropical diseases at Pointe-a-Pitre Hospital in Guadeloupe. Between March 2016 and November 2016, the research team followed the pregnancies of 546 women with confirmed Zika infection in the French Caribbean territories of French Guiana, Guadeloupe and Martinique. Birth defects appeared in 39 foetuses and infants. Microcephaly was the most common. This is characterised by unusually small brains and skulls. Seventeen babies also showed signs of congenital Zika syndrome, whch includes microcephaly, decreased brain tissue, eye damage, frozen or disabled joints, and rigid limbs. The risk of birth defects was highest early in pregnancy but still significant at any point, researchers found. [↑](#footnote-ref-63)
64. Dong, Y., Simões, M. L., Marois, E., & Dimopoulos, G. (2018). “CRISPR/Cas9 -mediated gene knockout of Anopheles gambiae FREP1 suppresses malaria parasite infection”. *PLOS Pathogens*, 14(3), e1006898. <https://doi.org/10.1371/journal.ppat.1006898> [↑](#footnote-ref-64)
65. MMWR Morb Mortal Wkly Rep. 2018:67;180-185. [Full text](https://www.cdc.gov/mmwr/volumes/67/wr/mm6706a2.htm?s_cid=mm6706a2_w) [↑](#footnote-ref-65)
66. See [ClinicalTrials.gov](https://www.clinicaltrials.gov/) using the identifiers [NCT03312231](https://www.clinicaltrials.gov/ct2/show/study/NCT03312231) and [NCT03318315](https://www.clinicaltrials.gov/ct2/show/NCT03318315). [↑](#footnote-ref-66)
67. Some participants will receive the adjuvant AS03 along with the vaccine. The adjuvant is produced by GSK’s vaccines business, headquartered in Belgium, with support from BARDA. [↑](#footnote-ref-67)
68. NIAID funded research on a previous version of the vaccine. The new version uses a form of the virus collected in 2017, to increase the chance that it will generate immunity against the newer strain of H7N9 currently circulating in the wild. [↑](#footnote-ref-68)
69. Kathryn Del Vecchio et al. A cationic, “C-terminal patch and structural rearrangements in Ebola virus matrix VP40 protein control its interactions with phosphatidylserine”, *Journal of Biological Chemistry* (2018). [DOI: 10.1074/jbc.M117.816280](http://dx.doi.org/10.1074/jbc.M117.816280) [↑](#footnote-ref-69)
70. ZMapp combines three humanized antibodies produced in genetically-modified tobacco plants that target three Ebola glycoprotein epitopes. [↑](#footnote-ref-70)
71. ZMapp was given to seven patients. Five patients survived the Ebola infection, while two died. [↑](#footnote-ref-71)
72. Seventy-one patients, from sites in Liberia, Sierra Leone, Guinea, and the US were randomized 1:1 to be given either therapy regimen. The patients receiving ZMapp were administered 50 mg per kilogram of their body weight, once every 3 days. The primary endpoint was mortality at 28 days from baseline. Of the 36 patients to receive ZMapp plus standard care, 8 (22%) died from the virus, while 13 of the 35 (37%) patients to receive lone standard care died. Researchers noted that baseline viral load was a strong predictor for both mortality and hospitalization length in all treatment and age groups. See “A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection”, *New England Journal of Medicine,* 2016; 375:1448-1456 DOI: 10.1056/NEJMoa1604330. [↑](#footnote-ref-72)
73. The study leader is Ricardo Carrion, Associate Scientist and Associate Director of the facility’s Biosafety Level 4 laboratory. [↑](#footnote-ref-73)
74. Details appeared 16 February in the journal Scientific Reports. See “A Multiplex Serologic Platform for Diagnosis of Tick-Borne Diseases.” The TBD-Serochip is reported to be able to discriminate antibody responses to Anaplasma phagocytophilum, Babesia microti, Borrelia burgdorferi, Borrelia miyamotoi, Ehrlichia chaffeensis, Rickettsia rickettsii, Heartland virus, and Powassan virus. [↑](#footnote-ref-74)
75. Each tick can be infected with more than one agent; Ixodes scapularis ticks for instance can pass on at least five human pathogens. In this article, the researchers report finding antibodies to another agent in more than one-quarter of blood specimens from patients with TBD. Evidence of exposure to other tick-borne pathogens in patients with Lyme disease has already been well documented. [↑](#footnote-ref-75)
76. Director of the Center for Infection and Immunity and John Snow Professor of Epidemiology at Columbia University's Mailman School of Public Health. [↑](#footnote-ref-76)
77. The research is available on [the CDC website](https://www.cdc.gov/mmwr/volumes/67/wr/mm6709a3.htm) [↑](#footnote-ref-77)