Monitoring International Trends

**posted July-Aug 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 6 to 22. Highlights are listed below:

#### **Products and Treatments**

#### **Treating Haemophilia**

* Spark Therapeutics, with reference to its investigational gene therapy *S*PK-8011 for haemophilia A, announced that as of 13 July 2018, preliminary Phase I/ II data showed a 97per cent reduction in annualized bleeding rate and 97 per cent reduction in annualized infusion rate across all 12 participants.
* Sangamo Therapeutics announced positive preliminary data from the Phase I/II clinical trial evaluating SB-525, its gene therapy candidate for haemophilia A.
* UniQure has enrolled the first patient in its registration trial of its gene therapy candidate for haemophilia B, AMT-061. Around 50 subjects will be recruited into the open-label HOPE-B trial.
* A Spark Therapeutics/ Pfizer partnership is in the planning stages for a phase III trial of their [SPK-9001](http://www.pmlive.com/pharma_news/more_encouraging_data_for_spark_and_pfizers_potential_haemophilia_b_cure_1236334) gene therapy for haemophilia B and has reported Phase I/II data showing that it could substantially reduce bleed rates and factor IX replacement use.
* UK start-up, [Freeline Therapeutics](http://www.pmlive.com/pharma_news/freeline_raises_88m_to_accelerate_haemophilia_gene_therapy_1240720), has just raised around $US 112 million to advance its haemophilia B gene therapy candidate which showed promise in early clinical trials.
* Catalyst Biosciences announced updated preliminary data from its open-label Phase II/ III clinical trial evaluating subcutaneously administered prophylactic factor VIIa variant marzeptacog alfa (activated) (MarzAA) for the treatment of haemophilia A or B patients with inhibitors.
* A review study says several genetic and environmental factors can play a role in the development of inhibitors against treatment with factor VIII in [haemophilia A](https://hemophilianewstoday.com/hemophilia-type-a/) patients.
* A study has reported that, although moderate to severe [haemophilia](https://hemophilianewstoday.com/what-is-hemophilia/) patients are generally thought to be protected against the development of cardiovascular disease, cardiovascular-related events can still occur in this patient population. .

#### **Treating beta thalassemia and sickle cell disease**

* Scientists have used gene editing to correct the genetic blood disorder β-thalassemia, in mouse foetuses, *in utero*.
* Celgene Corporation and Acceleron Pharma announced results from a phase III study (BELIEVE) of their drug Luspatercept in adults with transfusion- dependent beta-thalassemia.
* Part A of a Phase III trial of [Global Blood Therapeutics’](https://nam03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.gbt.com%2F&data=02%7C01%7C%7Cf63b7b12d0e74480939308d5e56b9099%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172505464184&sdata=L6cPmdcj98G5feDCYeg%2B%2Ft9gDbtW4RWqzeLw1kPWzNg%3D&reserved=0)  [voxelotor](https://nam03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.gbt.com%2Fpipeline%2Fsickle-cell-disease%2F&data=02%7C01%7C%7Cf63b7b12d0e74480939308d5e56b9099%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172505464184&sdata=ZXRK5xdEjeVxy2AHZvSYDrSOIK%2F423PhnIiSoXxzRmI%3D&reserved=0)  has suggested that once-daily treatment can effectively increase the amount of haemoglobin in about 58 per cent of patients with in just 12 weeks.

#### **Other products**

* Apellis Pharmaceuticals has a new drug under development for the treatment of paroxysmal nocturnal haemoglobinuria.
* Scientists have identified an enzyme that can boost platelet production and may work as a therapeutic for thrombocytopaenia.
* Cytotect CP is a cytomegalovirus (CMV)-specific hyperimmunoglobulin prepared by Biotest with a high antibody titre against CMV. A study has credited it with a strong reduction of maternal-foetal CMV transmission (in pregnant women who are infected with CMV for the first time).

**Safety and Patient Blood Management**

#### **Appropriate Transfusion**

* Researchers have developed a method of maintaining water and water-based solutions in their liquid form for long periods of time and at temperatures far below the usual freezing point, and so without damage from minute shards of ice crystals. They have demonstrated the feasibility of more than doubling the amount of time red blood cells can be stored.
* A study has found that, in the laboratory, enzymes made by bacteria in the human digestive tract can strip the antigens that [determine blood type](https://www.livescience.com/32448-why-do-blood-types-differ.html) from the surface of red blood cells.
* Researchers studying TRALI (Transfusion Related Acute Lung Injury) observed that in mice the composition of the gastrointestinal flora drives the pathogenic immune response in the lungs during TRALI.
* The FDA has revised its policy for testing all donated blood and blood products for Zika virus.

#### **Other**

* Researchers found that prophylactic administration of [tranexamic acid](https://www.empr.com/lysteda/drug/3643/) did not reduce postpartum haemorrhage among women with vaginal delivery receiving prophylactic oxytocin.
* Researchers concluded that in patients undergoing rhinoplasty, preoperative administration of tranexamic acid is safe and might lessen intraoperative bleeding, postoperative eyelid oedema and ecchymosis.
* VarmX is developing PseudoXa to stop or prevent bleeding in patients taking anti-coagulants in the form of synthetic factor Xa inhibitors.  The drug is based on research into the properties of a snake venom and of human factor X.
* A research team has developed a simple and quick method for detecting the impurity in heparin.
* A study found that, despite the move towards non-vitamin K antagonist oral anticoagulants (NOACs) for the prevention of thromboembolic disease, transition is not smooth for some patients and about 5 per cent will revert to warfarin within six months.
* Danish registry data demonstrated a lower risk for myocardial infarction in patients with atrial fibrillation initially treated with a non–vitamin K antagonist oral anticoagulant (NOAC) versus a vitamin K antagonist.
* Researchers reported that in patients with atrial fibrillation the risk for stroke and major bleeding in users of the direct oral anticoagulant rivaroxaban (Xarelto) was similar to or less than that recorded in the pivotal clinical trials.
* A Phase II trial of hepcidin to regulate iron absorption in haemochromatosis patients aims to compare weekly dosing of a synthetic human hepcidin versus placebo on markers of iron metabolism.
* A study has reported that infusions of large doses of intravenous iron may be a safe approach for patients with low oxygen levels in their blood due to [pulmonary hypertension](https://pulmonaryhypertensionnews.com/) and/or [congenital heart disease](https://pulmonaryhypertensionnews.com/?s=congenital+heart+disease).
* Researchers have studied the role of chronic obstructive pulmonary disease (COPD) as an independent risk factor for complications after total knee and hip arthroplasty. They concluded COPD was associated with an increased length of hospital stay, a higher risk of pneumonia and wound infection, higher general complications, and an increased need for red blood cell transfusion.

**Regulatory matters**

* The US Food and Drug Administration (FDA) approved Shire’s Takhzyro for hereditary angioedema prophylaxis in patients 12 years of age and older.
* The FDA has granted emergency use authorization to the Department of Defense to use freeze-dried plasma manufactured by France’s Armed Forces Blood Transfusion Centre (CTSA).
* Health Canada approved Roche’s Hemlibra (emicizumab) for haemophilia A for patients with factor VIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.
* NHS England has approved the reimbursement of Hemlibra (emicizumab) for the prevention of bleeding episodes in adults and children with haemophilia A who have factor VIII inhibitors.
* The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a positive opinion recommending the granting of marketing authorization in the European Union for Shire’s VEYVONDI [vonicog alfa, recombinant von Willebrand factor] (rVWF), for the treatment of bleeding events and treatment/prevention of surgical bleeding in adults (age 18 and older) with von Willebrand disease (VWD) when desmopressin treatment alone is ineffective or not indicated.

**Company news**

* Roche has sold rights to its monoclonal antibody inclacumab to Global Blood Therapeutics, which intends to develop the treatment for vaso-occlusive crises in patients with sickle cell disease.
* CSL has announced that its full year results saw the company’s net profit increase by 30 per cent.
* Express Scripts has been in talks with Biomarin Pharmaceutical, Spark Therapeutics, and Bluebird Bio in an effort to win exclusive distribution rights to their haemophilia gene therapies if/ when they become available, perhaps in 2019 and 2020.
* For the second quarter of 2018, sales of NovoSeven (NovoNordisk’s recombinant factor VIIa ) were down 14 per cent in comparison with the same quarter in 2017).
* [CytoSorbents](https://www.medicaldesignandoutsourcing.com/could-this-system-make-more-kidneys-livers-usable-for-transplant/) has been awarded further funding from the US government to commercialize its HemoDefend red blood cell transfusion filter.

**Country news**

* In Australia, researchers have said that the proportion of northern indigenous infants suffering from inadequate red blood cells and stunted growth is "unexpectedly high."
* The UAE will host the seventh International Genetic Disorders Conference, which will discuss the latest advances in detection and management of genetic diseases.
* An analysis found that expanding testing in emergency departments for hepatitis C virus beyond typical high-risk populations was an effective measure to screen undiagnosed patients who may have otherwise gone without treatment.
* The FDA announced the addition of Lassa fever, chikungunya virus disease, rabies and cryptococcal meningitis to its list of tropical diseases.

**Research not included elsewhere**

* The Wellcome Trust announced a $US 332 million Leap Fund, to finance "bold ideas" considered too risky for traditional funding streams.
* The [Icahn School of Medicine](https://icahn.mssm.edu/)at Mount Sinai Hospital in New York City is to test a new approach for treating [sickle cell disease](https://sicklecellanemianews.com/what-is-sickle-cell-anemia/). Inhaled corticosteroids mean anti-inflammatory medication can be delivered directly to the patient’s lungs.
* A study reports that infarcted hearts in monkeys experienced some recovery after being treated with human embryonic stem cells.
* Scientists plan to conduct a clinical test using platelets grown from induced pluripotent stem cells to treat aplastic anaemia.
* Researchers report that children with [sickle cell disease](http://sicklecellanemianews.com/) who experience obstructive sleep apnea are at risk of developing additional health problems.

**Infectious diseases**

*Mosquito-borne diseases*

* SMK Diagnostics is developing a device to improve the speed, specificity, sensitivity, and portability of testing techniques for a range of mosquito-borne viruses.
* Hong Kong is concerned about an outbreak of dengue fever.
* A study has shown how one lineage of the dengue virus comes to prevail over another, an important understanding in vaccine design.
* A report by scientists at six different primate research centres suggests that Zika-related miscarriage or stillbirth may be more common than previously thought in women infected in early pregnancy.
* A report from the US Centers for Disease Control and Prevention said about 1 in 7 babies exposed to Zika in the womb appear to have significant, ongoing health issues.
* Researchers recommend that before engaging in unprotected sex, men with possible Zika virus exposure who are planning to conceive with their partner wait for three months or more after onset of symptoms (if symptomatic) or their last possible exposure to Zika virus (if asymptomatic).
* Vaccinations have started in a first-in-human trial of an experimental live, attenuated Zika virus vaccine developed by scientists at the US National Institute of Allergy and Infectious Diseases (NIAID).
* The FDA approved a new drug for the prevention of malaria: Arakoda (tafenoquine) tablets for patients aged 18 years and older.

#### **Influenza**

* BiondVax Pharmaceuticals initiated a pivotal clinical efficacy Phase III trial of the M-001 universal flu vaccine candidate.
* BioNTech AG has partnered with Pfizer to develop mRNA-based flu vaccines.
* A study involving data from nine countries determined that, apart from elevated narcolepsy levels after 2009-10 pandemic flu vaccination campaigns in Sweden, there was no association between narcolepsy and AS03- or MF59-adjuvanted 2009 H1N1 (pH1N1) flu vaccines in children or adults.
* On 20 August China confirmed its twentieth human case of H5N6 avian flu, this time in Guangxi province.

#### **Middle East respiratory syndrome coronavirus (MERS-CoV)**

* By the end of June 2018, a total of 2229 laboratory-conﬁrmed cases of MERS-CoV, including 791 deaths had been reported globally; the majority were from Saudi Arabia.
* A new study suggests that more than half of primary cases of MERS-CoV occur in people who have direct contact with dromedary camels.
* Mid-year, Inovio announced positive Phase I results of its [vaccine study](https://nam05.safelinks.protection.outlook.com/?url=https%3A%2F%2Fglobenewswire.com%2Fnews-release%2F2018%2F06%2F27%2F1530265%2F0%2Fen%2FInovio-s-MERS-Vaccine-Generates-High-Levels-of-Antibodies-and-Induces-Broad-based-T-Cell-Responses-in-Phase-1-Study.html&data=02%7C01%7C%7C195301a2f4b74d78a95908d5e56b7a3c%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172137871112&sdata=V%2BS3a4OdaKgyc3EW7OXp2voh6UElx4bKfdMAbGJc7lw%3D&reserved=0) with INO-4700 against MERS.
* The Coalition for Epidemic Preparedness Innovations (CEPI) awarded up to $US 36 million to IDT Biologika to develop a vaccine against MERS.
* Researchers from the US National Institute of Allergy and Infectious Diseases (NIAID) showed how MERS-CoV adapts to infect cells of a new species, which suggests that other coronaviruses might also be able to do so.

*Ebola*

* By 20 August as the Ebola crisis worsened in the Congo at least 90 people had been infected in the north of the country. Forty-nine people had died, including at least one health-care worker. A WHO spokesman said it was proving difficult to roll out vaccine in a conflict zone. Health teams have started using the experimental monoclonal antibody treatment mAb114.
* SAB Biotherapeutics announced that its anti-Ebola immunotherapy (SAB-139) provided “100 per cent protection against a lethal dose of the Ebola virus” in a recent animal study.

*Other diseases*

* WHO reported that more than 41,000 people in Europe were infected with measles in the first half of this year, already exceeding 12-month totals for any other year this decade.
* In the last decade more than 1,100 cases of syphilis have been recorded in Queensland’s north.
* Papua New Guinea recorded the fourth case of polio in an ongoing vaccine-derived poliovirus type 1 outbreak.

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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

* + Spark Therapeutics, with reference to itsinvestigational gene therapy SPK-8011 for haemophilia A, announced that as of 13 July 2018, preliminary Phase I/ II data showed a 97per cent reduction in annualized bleeding rate (ABR) and 97 per cent reduction in annualized infusion rate (AIR) across all 12 participants in the study[[1]](#footnote-1)*.* Spark intends to take SPK-8011[[2]](#footnote-2)into Phase III clinical trials, beginning with a run-in study in the fourth quarter of 2018.
	+ In terms of gene therapy for haemophilia, Spark's timeline places it behind BioMarin, and slightly ahead of Sangamo. The therapy that proves safest may turn out to be the most successful.
	+ Sangamo Therapeutics announced positive preliminary data from the Phase I/ II clinical trial evaluating SB-525, its gene therapy candidate for haemophilia A[[3]](#footnote-3). The Alta study is an open-label, dose-ranging clinical trial designed to assess the safety and tolerability of SB-525 in up to 20 adult subjects with severe haemophilia A. Up to 8 August, five patients had been treated at three dose levels with a sixth patient scheduled for treatment before the end of the month. Sangamo said that so far SB-525 has been generally well tolerated with no treatment-related serious adverse events and no use of tapering courses of oral steroids. The company also said that a dose dependent effect had been observed in the study, with patients in the second dose cohort reporting reduced use of factor replacement. The first patient in the third dose cohort had attained therapeutic factor VIII activity levels. Sangamo and Pfizer expect to present detailed data from the Alta study at a haematology conference in the fourth quarter of 2018.
	+ **Netherlands biotech UniQure has enrolled the first patient in its registration trial of its gene therapy candidate for haemophilia B, AMT-061**[[4]](#footnote-4)**. A**round 50 subjects will be recruited into the open-label HOPE-B trial. AMT-061 is an adeno-associated virus (AAV) based gene therapy designed to deliver a gene sequence for clotting factor IX. After a six-month run-in period to form a baseline picture of bleeding rates, the therapy is delivered by a single intravenous infusion. If successful, it could free haemophilia B patients from lifelong treatment with factor IX replacement drugs. The primary outcome measure in the study will be administration of AMT-061, with secondary endpoints including the need for factor IX replacement drugs and the annualised bleed rate. The study is expected to yield preliminary results in 2020, with interim data being released in 2019.
	+ UniQure is just ahead of its main rival (a Spark Therapeutics/ Pfizer partnership) in the haemophilia B gene therapy race. That partnership is in the planning stages for a phase III trial of their [SPK-9001](http://www.pmlive.com/pharma_news/more_encouraging_data_for_spark_and_pfizers_potential_haemophilia_b_cure_1236334) therapy and has reported Phase I/ II data showing that it could substantially reduce bleed rates and factor IX replacement use.
	+ UK start-up [Freeline Therapeutics](http://www.pmlive.com/pharma_news/freeline_raises_88m_to_accelerate_haemophilia_gene_therapy_1240720), has just raised around $US 112 million to advance its haemophilia B gene therapy candidate which showed promise in early clinical trials.
	+ Catalyst Biosciences issued an [announcement](https://seekingalpha.com/pr/17245740-catalyst-biosciences-announces-updated-positive-interim-data-2018-hemophilia-drug-development)  containing updated preliminary data from its open-label Phase II/ III clinical trial evaluating subcutaneously administered prophylactic factor VIIa variant marzeptacog alfa (activated) (MarzAA) for the treatment of haemophilia A or B patients with inhibitors. The results were presented at the Hemophilia Drug Development Summit in Boston in August[[5]](#footnote-5).
	+ A review study[[6]](#footnote-6) says several genetic and environmental factors can play a role in the development of inhibitors against treatment with factor VIII in [haemophilia A](https://hemophilianewstoday.com/hemophilia-type-a/) patients. They stressed the need to develop predictive algorithms to determine which patients are at the highest risk for inhibitors so their management may be improved.
	+ A study[[7]](#footnote-7) has reported that, although moderate to severe [haemophilia](https://hemophilianewstoday.com/what-is-hemophilia/) patients are generally thought to be protected against the development of cardiovascular disease[[8]](#footnote-8), cardiovascular-related events can still occur in this patient population. Haemophilia patients can suffer from [atherosclerosis](http://heart.org/HEARTORG/Conditions/Cholesterol/AboutCholesterol/Atherosclerosis_UCM_305564_Article.jsp), or plaques in the arteries, at a similar rate to the general population, and [hypertension](https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/symptoms-causes/syc-20373410), or high blood pressure, is frequently present in men with severe haemophilia.

## Treating beta thalassemia and sickle cell disease

* + Scientists at Yale University and Carnegie Mellon University have used gene editing to correct the genetic blood disorder β-thalassemia, in mouse foetuses, *in utero*.  The approach was based on peptide nucleic acid (PNA) technology[[9]](#footnote-9), with no evidence of off-target effects that can occur with techniques, such as [CRISPR](http://www.genengnews.com/search?q=crispr). Compared with untreated controls, the mice treated *in utero* showed significant reductions in β-thalassemia symptoms, higher haemoglobin levels and increased long-term survival[[10]](#footnote-10).
	+ US-based companies Celgene Corporation and Acceleron Pharma announced results from a phase III, randomized, double-blind, multi-centre clinical study (BELIEVE) of their drug Luspatercept[[11]](#footnote-11) in adults with transfusion- dependent beta-thalassemia. They said Luspatercept achieved primary and all key secondary endpoints[[12]](#footnote-12). The companies plan to submit regulatory applications for luspatercept in the US and Europe in the first half of 2019[[13]](#footnote-13).
	+ In January 2018, the US Food and Drug Administration (FDA) granted [Global Blood Therapeutics’](https://nam03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.gbt.com%2F&data=02%7C01%7C%7Cf63b7b12d0e74480939308d5e56b9099%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172505464184&sdata=L6cPmdcj98G5feDCYeg%2B%2Ft9gDbtW4RWqzeLw1kPWzNg%3D&reserved=0)  [voxelotor](https://nam03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.gbt.com%2Fpipeline%2Fsickle-cell-disease%2F&data=02%7C01%7C%7Cf63b7b12d0e74480939308d5e56b9099%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172505464184&sdata=ZXRK5xdEjeVxy2AHZvSYDrSOIK%2F423PhnIiSoXxzRmI%3D&reserved=0)  [breakthrough therapy designation](https://nam03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fsicklecellanemianews.com%2F2018%2F01%2F16%2Fvoxelotor-fda-breakthrough-therapy-designation-sickle-cell-anemia%2F&data=02%7C01%7C%7Cf63b7b12d0e74480939308d5e56b9099%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172505620449&sdata=4437tpBHQGI2EYAvjkEyl8037CHyNC8Li8kMiJdQbsE%3D&reserved=0), in addition to the previously granted fast track, orphan drug, and rare paediatric disease designations given to voxelotor as a potential [sickle cell disease](https://nam03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fsicklecellanemianews.com%2Fwhat-is-sickle-cell-anemia%2F&data=02%7C01%7C%7Cf63b7b12d0e74480939308d5e56b9099%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172505620449&sdata=BSwWLAiDcSPlz%2FJbeR5GejrevomyaULHlaGebXc817s%3D&reserved=0) (SCD) treatment. The [European Medicines Agency](https://nam03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.ema.europa.eu%2Fema%2F&data=02%7C01%7C%7Cf63b7b12d0e74480939308d5e56b9099%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172505620449&sdata=sUIYvlbzdhxzUSQv6y6ELz1r0w%2BV9dUrZeTvFGQ0ViA%3D&reserved=0) also included volexotor[[14]](#footnote-14) in its [Priority Medicines (PRIME)](https://nam03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.ema.europa.eu%2Fema%2Findex.jsp%3Fcurl%3Dpages%2Fregulation%2Fgeneral%2Fgeneral_content_000660.jsp&data=02%7C01%7C%7Cf63b7b12d0e74480939308d5e56b9099%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172505620449&sdata=y%2BuI81s20S%2BClrvRAyYKukDmcG9G4phdaBiH3YcBF0Q%3D&reserved=0) program[[15]](#footnote-15). Now Part A of a Phase III trial has suggested that once-daily treatment can effectively increase the amount of haemoglobin in about 58 per cent of patients with in just 12 weeks[[16]](#footnote-16). Under its [accelerated approval](https://nam03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.fda.gov%2FDrugs%2FResourcesForYou%2FHealthProfessionals%2Fucm313768.htm&data=02%7C01%7C%7Cf63b7b12d0e74480939308d5e56b9099%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172505620449&sdata=%2BMqv5Dduf%2BvMpsczAnuLG5dvOw3BDEBTBP3d1BI1IZg%3D&reserved=0) program, the FDA can grant early approval to therapies that show high potential to provide a clinical benefit for patients with serious or life-threatening diseases over existing therapeutic options. The company is still required to complete additional clinical studies to prove the anticipated benefits of the therapy. Ted W. Love, president and CEO of GBT, said in a [press release](https://nam03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fglobenewswire.com%2Fnews-release%2F2018%2F06%2F27%2F1530205%2F0%2Fen%2FGBT-Announces-Positive-Top-line-Data-from-Part-A-of-the-Phase-3-HOPE-Study-of-Voxelotor-in-Sickle-Cell-Disease.html&data=02%7C01%7C%7Cf63b7b12d0e74480939308d5e56b9099%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172505620449&sdata=nHTDFzMx%2F%2B5RqGnIv%2BdEldjAYz5yDsazjN82DTmJ8j0%3D&reserved=0), “Based upon voxelotor’s robust impact on hemolytic anemia, we believe it meets the standard for accelerated approval, and we look forward to providing further updates on our regulatory discussions as soon as possible, but no later than year-end”.

## Other products

* + Apellis Pharmaceuticals has a new drug under development for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), a rare, acquired, life-threatening blood disease. The company says the drug has the potential to improve haemoglobin levels in patients currently being treated with eculizamab (Soliris)[[17]](#footnote-17).
	+ Scientists at the Scripps Research Institute have uncovered a new approach for treating thrombocytopenia. They identified an enzyme that can boost platelet production and may work as a future therapeutic[[18]](#footnote-18).
	+ Cytotect CP is a cytomegalovirus (CMV)-specific hyperimmunoglobulin prepared by Biotest with a high antibody titre against CMV. The product is approved for prophylaxis of clinical manifestations of CMV infection in patients subjected to immunosuppressive therapy, particularly in transplant recipients. Now a study coordinated by the University of Tübingen[[19]](#footnote-19) shows strong reduction of maternal-foetal CMV transmission (in pregnant women who are infected with CMV for the first time) from 35.2 per cent to 2.5 per cent (primary endpoint). Transmission of CMV from pregnant women to the foetus is a major cause of post-natal complications (developmental disorders) in newborns.
	+ A [randomized controlled trial](https://www.thelancet.com/journals/laneur/article/PIIS1474-4422%2818%2930202-3/fulltext) concluded that oral fingolimod is no better than placebo for treating chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)[[20]](#footnote-20). First author Richard Hughes[[21]](#footnote-21) and colleagues wrote: “There is no evidence from randomised controlled trials that any immunomodulatory treatments other than corticosteroids, intravenous or subcutaneous immunoglobulin, and plasma exchange are beneficial in CIDP”.
	+ Kamada has received positive scientific advice from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) related to the development plan for its planned pivotal Phase III study for its Inhaled Alpha-1 Antitrypsin therapy (Inhaled AAT) for the treatment of alpha-1 antitrypsin deficiency (AATD).  The CHMP concurs with the overall design of the proposed study, including its objectives, patient population, proposed endpoints and their clinical importance, and the safety monitoring plan. The Committee had some comments, which Kamada says it will address in the final study protocol.
	+ Severe combined immunodeficiency (SCID), has several variations based on the exact cause for the abnormal functions of T and B cells. St. Jude Children’s Research Hospital in Memphis has a therapy, developed in the lab of its director of experimental haematology Brian Sorrentino, which targets the most common form: X-linked SCID. This therapy genetically modifies a patient’s own blood stem cells and reinfuses them, giving the patients a low dose of the cancer drug busulfan. The aim is not only to help patients live beyond infancy but to do so without regularly receiving intravenous immunoglobulin.

# Safety and patient blood management

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

## Appropriate Transfusion

* + Massachusetts General Hospital researchers have developed a method of maintaining water and water-based solutions in their liquid form for long periods of time and at temperatures far below the usual freezing point, and so without damage from minute shards of ice crystals[[22]](#footnote-22). They have demonstrated the feasibility of more than doubling the amount of time red blood cells can be stored.
	+ In blood collection and transfusion services, [type O blood is in high demand](https://www.livescience.com/36559-common-blood-type-donation.html). It does not have antigens on its cell membranes, so people of any blood type given a type O transfusion will not have an immune reaction to the red blood cells. Type O is known as the “universal” blood donor type. Now a study has found that, in the laboratory, enzymes made by bacteria in the human digestive tract can strip the sugars (antigens) that [determine blood type](https://www.livescience.com/32448-why-do-blood-types-differ.html) from the surface of red blood cells. Enzymes were already known which can convert type B blood to type O, but this recently identified group of enzymes is the first to convert type A to type O. Lead study author Stephen Withers[[23]](#footnote-23) recently[[24]](#footnote-24) presented [study results](https://www.eurekalert.org/pub_releases/2018-08/acs-gbp071218.php) showing that enzymes made with DNA extracted from human-gut microbes could remove type A and B antigens from red blood cells[[25]](#footnote-25). Withers and his colleagues have already begun investigating enzyme safety in collaboration with haematologists and Canadian Blood Services. Cost will also need to be considered as a factor in adoption of the technique[[26]](#footnote-26).
	+ Researchers studying TRALI (Transfusion Related Acute Lung Injury)[[27]](#footnote-27) observed that in mice the composition of the gastrointestinal flora drives the pathogenic immune response in the lungs during TRALI[[28]](#footnote-28). The researchers studied two groups of mice. One group was kept in a sterile environment, with the gastrointestinal flora minimally affected by external factors. The other group was kept in a normal environment. Lead investigator Professor John W. Semple[[29]](#footnote-29) said: "We saw that the mice kept in a more sterile environment were resistant to TRALI development while the less sterile-raised mice developed severe TRALI”. The composition of the gastrointestinal flora was demonstrated to be significantly different between the two groups of mice, as was determined by genetic sequencing of the stool. When the gastrointestinal flora were destroyed with several different types of antibiotics, the mice that suffered from TRALI no longer developed the disease. The researchers transplanted stool from mice that developed TRALI into mice that were resistant to TRALI. The resistant mice were then able to develop TRALI. Researchers say it may be possible eventually to assess human risk for TRALI through analysis of gastrointestinal flora.
	+ The FDA has revised its policy for testing all donated blood and blood products for Zika virus. With the decrease in Zika cases in the US, concerns about cost effectiveness and a desire to make the process less burdensome, the agency released a [revised final guidance document](https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM518213.pdf) explaining the new policy. It said: "in order to comply with applicable testing regulations, blood establishments must continue to test all donated whole blood and blood components for Zika virus using a nucleic acid test." But they added that pooled donation using an FDA-licensed screening test may be sufficient, unless there is a higher risk of local mosquito-borne transmission of the virus in a specific geographic area, which would trigger the need for individual donation testing.

## Other

* + Researchers found[[30]](#footnote-30) that prophylactic administration of [tranexamic acid](https://www.empr.com/lysteda/drug/3643/) did not reduce postpartum haemorrhage among women with vaginal delivery receiving prophylactic oxytocin.
	+ Researchers examined[[31]](#footnote-31) the outcomes of tranexamic acid use in rhinoplasty[[32]](#footnote-32), concluding that in patients undergoing rhinoplasty, preoperative administration of tranexamic acid is safe and might lessen intraoperative bleeding, postoperative eyelid oedema and ecchymosis[[33]](#footnote-33).
	+ Netherlands-based VarmX is developing lead compound PseudoXa to stop or prevent bleeding in patients taking anti-coagulants in the form of synthetic factor Xa inhibitors.  The drug is based on research into the properties of a snake venom and of human factor X. New financing will enable the company to advance PseudoXa as a factor Xa anti-coagulant reversal agent into human clinical studies.
	+ In 2008, a contaminant infiltrated the US supply of heparin, killing about 100 patients. The contaminant, structurally similar to heparin, was traced to a Chinese supplier. Now Jason Dwyer[[34]](#footnote-34) and his team have developed a simple and quick method for detecting the impurity in heparin, along with creating a process that could serve as a quality assurance tool elsewhere in the pharmaceutical industry[[35]](#footnote-35).
	+ A Queensland [study](https://www.ncbi.nlm.nih.gov/pubmed/30076515) of more than 3,000 patients in a warfarin program[[36]](#footnote-36) found that, despite the move towards non-vitamin K antagonist oral anticoagulants (NOACs) for the prevention of thromboembolic disease, transition is not smooth for some patients and about 5 per cent will revert to warfarin within six months[[37]](#footnote-37).
	+ Danish registry data demonstrated a lower risk for myocardial infarction in patients with atrial fibrillation initially treated with a non–vitamin K antagonist oral anticoagulant (NOAC) versus a vitamin K antagonist. Christina Ji-Young Lee[[38]](#footnote-38), and colleagues, also reported that the risk for myocardial infarction was not significantly different between NOACs[[39]](#footnote-39).
	+ Researchers reported[[40]](#footnote-40) that in a study including over 11,000 patients with atrial fibrillation from almost 50 countries, the risk for stroke and major bleeding in users of the direct oral anticoagulant rivaroxaban (Xarelto) was similar to or less than that recorded in the pivotal clinical trials.
	+ An international trial of hepcidin to regulate iron absorption in haemochromatosis patients includes sites in Brisbane, Sydney and Melbourne. The Phase II trial aims to compare weekly dosing of a synthetic human hepcidin versus placebo on markers of iron metabolism.
	+ A study has reported[[41]](#footnote-41) that infusions of large doses of intravenous iron may be a safe [treatment](https://pulmonaryhypertensionnews.com/treat-pulmonary-hypertension/) approach for patients with low oxygen levels in their blood due to [pulmonary hypertension](https://pulmonaryhypertensionnews.com/) and/or [congenital heart disease](https://pulmonaryhypertensionnews.com/?s=congenital+heart+disease)
	+ Researchers have studied the role of chronic obstructive pulmonary disease[[42]](#footnote-42) (COPD) as an independent risk factor for complications after total knee and hip arthroplasty[[43]](#footnote-43). They concluded COPD was associated with an increased length of hospital stay, a higher risk of pneumonia and wound infection, higher general complications, and an increased need for red blood cell transfusion. They recommended strengthening the implementation of pneumonia prevention programs on surgical wards.

# Regulatory

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

* + The US Food and Drug Administration (FDA) approved Shire’s Takhzyro for hereditary angioedema (HAE) prophylaxis in patients 12 years of age and older. The drug has IP protection to 2032 and orphan drug status. Approval for Takhzyro was based on Phase III data showing the drug, dosed every two weeks at 300 mg, could cut down the incidence of monthly attacks by 87 per cent. CSL’s Haegarda, which was approved in 2017, showed a median reduction in monthly attacks of between 89 per cent and 95 per cent versus placebo. However, patients receive the Shire drug just once or twice a month, compared with twice a week for Haegarda. Shire still has the drugs Cinryze and Firazyr within its portolio, so it can charge a premium price for Takhzyro and use the older drugs to service the remainder of the market. Takhzyro is the first monoclonal antibody to be approved in the US for HAE. Shire obtained Takhzyro via its 2016 acquisition of Dyax Corporation. Under the terms of the acquisition, Dyax shareholders are eligible to receive a contingent value right (CVR) worth $US 646 million tied to the drug's US approval.
	+ The FDA has granted emergency use authorization to the Department of Defense (DOD) to use freeze-dried plasma manufactured by France’s Armed Forces Blood Transfusion Centre (CTSA). The approval came six months after the FDA and DOD’s Office of Health Affairs announced plans to implement a new framework to prioritize development of medical products for battlefield use, including by treating DOD medical development programs as if they have received FDA’s breakthrough therapy designation.
	+ Health Canada approved Roche’s Hemlibra (emicizumab) for haemophilia A for patients with factor VIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.
	+ NHS England has approved the reimbursement of Hemlibra (emicizumab) for the prevention of bleeding episodes in adults and children with haemophilia A who have factor VIII inhibitors.
	+ The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a positive opinion recommending the granting of marketing authorization in the European Union for Shire’s VEYVONDI [vonicog alfa, recombinant von Willebrand factor] (rVWF), for the treatment of bleeding events and treatment/prevention of surgical bleeding in adults (age 18 and older) with von Willebrand disease (VWD) when desmopressin treatment alone is ineffective or not indicated.
	+ The FDA has [accepted](https://seekingalpha.com/pr/17248521-fda-accepts-priority-review-alxn1210-treatment-patients-paroxysmal-nocturnal-hemoglobinuria) for review a Biologics License Application (BLA) from Alexion Pharmaceuticals for approval of ALXN1210, a long-acting C5 complement inhibitor, for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH). The agency's action date is February 18, 2019. The European Medicines Agency (EMA) is reviewing the submission for the EU, and Alexion is also to seek approval in Japan.

# 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.*

* + Roche has sold rights to its monoclonal antibody inclacumab to Global Blood Therapeutics, which intends to develop the treatment for vaso-occlusive crises (VOC) in patients with sickle cell disease (SCD). GBT will be responsible for all development, manufacturing, and commercialisation. Roche will receive an upfront payment of $US 2.0 million, up to $US 125 million in development and commercialisation milestone payments for the SCD indication, plus sales-based royalties. Inclacumab is a fully human monoclonal antibody designed to inhibit P-selectin, an adhesion molecule found on endothelial cells and platelets that contributes to the cell-cell interactions involved in the development of VOC. Roche was initially developing the drug to treat coronary artery disease, but discontinued development following Phase II trials. However, GBT can rely on the safety data produced from these earlier clinical studies as it advances inclacumab in SCD. Ted Love, GBT’s president and chief executive, said: “Inclacumab is an ideal complement to voxelotor, our lead investigational oral, once-daily therapy, in Phase III clinical development for SCD. Like voxelotor, inclacumab has a strong scientific rationale and has the potential to provide significant clinical benefit for SCD patients.”
	+ CSL has announced that its full year results saw the company’s net profit increase by 30 per cent[[44]](#footnote-44). Its [press release](https://www.csl.com/-/media/shared/documents/results/2018-fy-announcement.pdf?la=en-us&hash=8B265A64FDDE984B104A4B8EF37338A9F8619705)​ announced expected growth of 10-14 per cent for the year to come. CSL Behring was responsible for most of the sales generated by the company ($US 6.6 billion in sales against total sales of $US 7.5 billion). CEO, Paul Perreault, said the launch of products such as Haegarda and Idelvion was part of the reason the company had seen such growth. He noted that it had opened 27 plasma collection centres in the US, as part of an expansion plan to bolster its CSL Plasma division – a subdivision of CSL Behring. The company had announced a 1.8million square-foot expansion on its site in Kanakakee, Illinois.
	+ In the US Express Scripts has been in talks with Biomarin Pharmaceutical, Spark Therapeutics, and Bluebird Bio in an effort to win exclusive distribution rights to their haemophilia gene therapies if/ when they become available, perhaps in 2019 and 2020.
	+ For the second quarter of 2018, sales of NovoSeven (NovoNordisk’s recombinant factor VIIa ) were down 14 per cent in comparison with the same quarter in 2017).
	+ In the first half of 2018, the Biotest Group reported revenue of EUR 200.7 million. This is an increase of 18 per cent in sales over the same period of the previous year, when the product recall of human albumin had a negative effect. Biotest completed the sale of its US companies on 1 August. During the first half of 2018 Biotest further expanded its network of the Group's own plasma collection centres in Europe. There are now 19 of these. The first process system for purification of the polyspecific immunoglobulin IgG Next Generation was successfully qualified in June 2018 and transferred to Biotest. For the 2018 financial year, the Board of Management expects sales of continuing operations to increase by a mid-single-digit percentage.
	+ Rubius Therapeutics intends to raise $US 200 million in a sale of common stock. The company, based in Cambridge, Massachusetts, plans to develop treatments using red blood cells as the delivery mechanism.
	+ Principia Biopharma of San Francisco is raising $US 86.3 million to take its BTK inhibitor[[45]](#footnote-45) into phase III trials. While the drug is currently in Phase II trials for the autoimmune skin disease pemphigus it is also being developed for the bleeding disorder immune thrombocytopenic purpura (ITP).
	+ Avalon GloboCare announced a strategic partnership with Weill Cornell Medical College’s cGMP Cellular Therapy Facility and Laboratory for Advanced Cellular Engineering, to co-develop bio-production and standardization procedures for the procurement, storage, processing, clinical study protocols, and bio-banking of chimeric antigen receptor (CAR)-T therapy.
	+ [CytoSorbents](https://www.medicaldesignandoutsourcing.com/could-this-system-make-more-kidneys-livers-usable-for-transplant/) has been awarded a further round of funding from the US government to commercialize its HemoDefend red blood cell transfusion filter[[46]](#footnote-46).

# Specific country events

* + In Australia, researchers from institutions including the Menzies School of Health Research and Swinburne University of Technology have said that the prevalence of northern indigenous infants suffering from inadequate red blood cells and stunted growth is "unexpectedly high." Their study involved infants and children aged six months to two years and found that 5 percent of them were underweight and 5 percent were overweight. The researchers wrote in the Australian Journal of Rural Health of "the need for continued preventive health programs focussed on ensuring adequate nutrition amongst infants, young children and their mothers" including “greater emphasis on maternal and pre-pregnancy health and nutrition."
	+ The UAE will host the seventh International Genetic Disorders Conference[[47]](#footnote-47), which will discuss the latest advances in detection and management of genetic diseases. The conference is organised by the UAE Genetic Diseases Association. Estimates suggest there are more than 400 genetic disorders in the UAE. The most common are blood disorders such as thalassaemia, sickle cell, anaemia, haemophilia and G6PD deficiency[[48]](#footnote-48). At least 8.5 per cent of UAE's population are classified as thalassaemia minor or carry the gene. The government's mandatory pre-marital screening has been successful in significantly reducing the incidence of new cases. Dr Maryam Mattar, founder and chairwoman of the Emirates Genetic Diseases Association, said: "There is no doubt that early screening is fundamental in our fight against genetic disorders. The cost of genetic screening of thalassaemia is Dh120, and the cost of treating a patient is Dh35,000 per annum……Prevention is key in reducing the impact of genetic disorders, socially and economically, and is a long-term sustainable solution; especially in the UAE where a high per cent of the population is under 30 years of age."
	+ In the US, specialty pharmacy [US Bioservices](https://www.usbioservices.com) is piloting an in-home inventory-management program, with [MedImpact Healthcare Systems](https://pbm.medimpact.com), for monitoring the at-home use of medications by patients with haemophilia. The system, consisting of [passive](/glossary/term?400) [UHF](/glossary/term?163) [RFID](/glossary/term?126)-enabled coolers that track, in real time, which medications are being stored and which are being used, is intended to prevent the overstocking or expiration of medications.
	+ An analysis[[49]](#footnote-49) conducted in the Boston Medical Center found that expanding testing in emergency departments for hepatitis C virus beyond typical high-risk populations was an effective measure to screen undiagnosed patients who may have otherwise gone without treatment.
	+ The FDA announced the addition of Lassa fever, chikungunya virus disease, rabies and cryptococcal meningitis to its list of tropical diseases. The tropical disease priority review voucher program is designed to encourage the development of new drug and biological products to prevent or treat certain tropical diseases[[50]](#footnote-50).
	+ In Brazil, Green Cross Corporation of South Korea has established a local company to expand its blood product business in the South American market.

# 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.*

* + The Wellcome Trust announced a £250 million ($US 332 million) Leap Fund, intended to finance "bold ideas" that may be considered too risky for traditional funding streams. It will support research that is not a sure enough bet for more traditional funding bodies, Wellcome’s director, Dr. Jeremy Farrar, said in an interview. Established funding bodies — like the US National Institutes of Health or Britain’s Medical Research Council — are “a little bit conservative, because funding is tight and people want to fund things that they really think are going to work,” he said. The Leap Fund aims to deliver breakthroughs on a 5- to 10-year timetable. It will begin in 2020 on an initial 5-year run, during which it will account for 5 per cent of Wellcome's funds. Leap funding will not replace or duplicate any of Wellcome's current research funding schemes.
	+ The US [National Institutes of Health](https://www.nih.gov/)(NIH)  has awarded $US 4 million to the departments of emergency medicine and haematology at the [Icahn School of Medicine](https://icahn.mssm.edu/)at Mount Sinai Hospital in New York City to test a new approach for treating [sickle cell disease](https://sicklecellanemianews.com/what-is-sickle-cell-anemia/) (SCD). Inhaled corticosteroids mean anti-inflammatory medication can be delivered directly to the patient’s lungs[[51]](#footnote-51).
	+ A study**[[52]](#footnote-52)** reports that infarcted hearts in monkeys experienced some recovery after being treated with human embryonic stem cells.
	+ Researchers at Kyoto University plan to conduct a clinical test using platelets grown from induced pluripotent stem cells to treat aplastic anaemia. The team led by professor Koji Eto has established a method to produce high-quality platelets in large numbers through the use of iPS cells.
	+ Researchers report[[53]](#footnote-53) that children with [sickle cell disease](http://sicklecellanemianews.com/) who experience obstructive sleep apnea, a breathing disorder during sleep, are at risk of developing additional health problems.

# 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 research team at Purdue University has created a startup company — SMK Diagnostics — that is developing a device to improve the speed, specificity, sensitivity, and portability of testing techniques for a range of mosquito-borne viruses[[54]](#footnote-54). Lia Stanciu, a material scientist on the project, said: “Our device responds within 30 minutes and doesn’t require trained people,” said. “It’s fast and portable.”

### Dengue and chikungunya

* + Hong Kong is concerned about an outbreak of dengue fever.
	+ A study has shown how one lineage of the dengue virus comes to prevail over another, an important understanding in vaccine design[[55]](#footnote-55).

### Zika

* + Researchers believe that differentiating Zika and dengue infections early is important for treatment, and say diagnostic indicators including conjunctivitis, platelet count, and monocyte count can be used to distinguish between the two[[56]](#footnote-56).
	+ A report[[57]](#footnote-57) by scientists at six different primate research centres suggests that Zika-related miscarriage or stillbirth may be more common than previously thought in women infected in early pregnancy. The researchers monitored experimentally infected pregnant monkeys.
	+ A report from the US Centers for Disease Control and Prevention (CDC) said about 1 in 7 babies exposed to Zika in the womb appear to have significant, ongoing health issues[[58]](#footnote-58).
	+ Researchers writing in the CDC’s *Morbidity and Mortality Weekly Report[[59]](#footnote-59)* recommend that before engaging in unprotected sex, men with possible Zika virus exposure who are planning to conceive with their partner wait for three months or more after onset of symptoms (if symptomatic) or their last possible exposure to Zika virus (if asymptomatic).
	+ Vaccinations have started in a first-in-human trial of an experimental live, attenuated Zika virus vaccine developed by scientists at the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health[[60]](#footnote-60). Stephen Whitehead, of NIAID’s Laboratory of Viral Diseases, led the development of rZIKV/D4Δ30-713[[61]](#footnote-61). Dr. Whitehead also has developed a live, attenuated dengue vaccine candidate (TV003) designed to elicit antibodies against all four dengue virus serotypes[[62]](#footnote-62). He plans to develop a single vaccine that would protect against both Zika and dengue viruses. Once the Zika vaccine candidate proves safe in Phase 1 clinical testing, the Zika component can be added to the tetravalent dengue vaccine candidate and the new pentavalent candidate can be evaluated in a Phase I clinical trial.

### Malaria

* + For the first time in more than eighteen years, the FDA approved a new drug for the prevention of malaria: Arakoda (tafenoquine) tablets for patients aged 18 years and older.

## 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.*

### Seasonal influenza

* + BiondVax Pharmaceuticals reported the first participant's initial visit in a pivotal clinical efficacy Phase III trial of the M-001 universal flu vaccine candidate. The primary endpoints of the trial are to demonstrate protection from influenza and safety of M-001. A secondary endpoint will assess reduction in flu illness severity among those receiving M-001 versus placebo. In six completed clinical trials in Israel and Europe[[63]](#footnote-63), M-001 has been shown to be safe, well-tolerated, and immunogenic to a broad range of influenza strains. An additional Phase II trial in the US, sponsored and conducted by the US National Institutes of Health (NIH), is ongoing[[64]](#footnote-64).
	+ BioNTech AG has entered into a multi-year research and development collaboration with Pfizer to develop mRNA-based vaccines for prevention of influenza. The deal is reportedly worth $US 425 million.
	+ A study involving data from nine countries[[65]](#footnote-65) determined that, apart from elevated narcolepsy levels after 2009-10 pandemic flu vaccination campaigns in Sweden, there was no association between narcolepsy and AS03- or MF59-adjuvanted 2009 H1N1 (pH1N1) flu vaccines in children or adults.

### Avian influenza

* + On 20 August China confirmed its twentieth human case of H5N6 avian flu, this time in Guangxi province.

## MERS-CoV (Middle Eastern respiratory syndrome coronavirus)

* + MERS was detected in a patient in England, the first case since 2013. The patient entered the UK aboard a Saudi Arabian Airlines flight.
	+ By the end of June 2018, a total of 2229 laboratory-conﬁrmed cases of MERS-CoV, including 791 deaths, had been reported globally; the majority were from Saudi Arabia (1853 cases, including 717 deaths). With improved infection prevention and control practices in hospitals, the number of hospital-acquired cases of MERS has dropped signiﬁcantly since 2015. Household clusters are still occurring[[66]](#footnote-66). The age group 50–59 years continues to be at highest risk of acquiring infection as primary cases. The age group 30–39 years is most at risk of becoming secondary cases. The number of deaths is higher in the age group 50–59 years for primary cases and 70–79 years for secondary cases.
	+ Researchers from the US National Institute of Allergy and Infectious Diseases (NIAID) showed how MERS-CoV adapts to infect cells of a new species[[67]](#footnote-67), which suggests that other coronaviruses might also be able to do so[[68]](#footnote-68).
	+ A new study**[[69]](#footnote-69)** suggests that more than half of primary cases of MERS-CoV occur in people who have direct contact with dromedary camels.
	+ In April 2018, Inovio was awarded $US 56 million by The Coalition for Epidemic Preparedness Innovations (CEPI) to develop (through Phase II) vaccines against MERS and the Lassa virus respectively. Mid-year, Inovio announced positive Phase I results of its [collaborative vaccine study](https://nam05.safelinks.protection.outlook.com/?url=https%3A%2F%2Fglobenewswire.com%2Fnews-release%2F2018%2F06%2F27%2F1530265%2F0%2Fen%2FInovio-s-MERS-Vaccine-Generates-High-Levels-of-Antibodies-and-Induces-Broad-based-T-Cell-Responses-in-Phase-1-Study.html&data=02%7C01%7C%7C195301a2f4b74d78a95908d5e56b7a3c%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172137871112&sdata=V%2BS3a4OdaKgyc3EW7OXp2voh6UElx4bKfdMAbGJc7lw%3D&reserved=0) of INO-4700 (GLS-5300) against MERS. The study, in partnership with the US Walter Reed Army Institute, showed that the vaccine was well-tolerated and demonstrated overall high levels of antibody responses in around 95 per cent of participants. It generated broad-based T cell responses in almost 90 per cent of trial subjects[[70]](#footnote-70). In collaboration with GeneOne Life Science, Inovio is beginning a Phase I/II study in the third quarter of 2018[[71]](#footnote-71). CEPI’s goal is for the MERS vaccine to be available for stockpile as soon as possible for emergency use.
	+ The Coalition for Epidemic Preparedness Innovations (CEPI) awarded up to $US 36 million to IDT Biologika to develop a vaccine against MERS. The initial tranche for IDT is worth $1US 5.7 million.

## Ebola virus disease (EVD)

* + By 20 August as the Ebola crisis worsened in the Congoat least 90 people had been infected in several regions of North Kivu province and neighbouring Ituri province. Forty-nine people had died, including one of the 10 health-care workers who had been infected. A WHO spokesman said that because of [the uncertain security situation](http://thehill.com/policy/healthcare/400302-health-authorities-face-fight-against-ebola-in-a-war-zone) contact tracers could not access where they needed to go, it was difficult to roll out vaccine in a conflict zone, and "blind spots" could give the virus a chance to spread. The vaccine being used for some health workers has been VSV-EBOV which was used in the last outbreak. Health teams have started using the experimental monoclonal antibody treatment mAb114, based on antibodies of a patient who survived Ebola in the DRC city of Kikwit in 1995. ZMapp has been approved for use but availability is restricted because it must be stored at -20°C. Other treatments approved for use in the DRC are Remdesivir, Favipiravir and Regn3450 - 3471 – 3479.
	+ Scientists reported[[72]](#footnote-72) that therapeutic antibodies may be the best way to stop the Ebola virus. They suggested new therapies should disable the Ebola virus's capacity to infect and kick-start the patient's immune system to fight the virus.
	+ [SAB Biotherapeutics, Inc. (SAB)](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.sabbiotherapeutics.com%2F&esheet=51853274&newsitemid=20180815005602&lan=en-US&anchor=SAB+Biotherapeutics%2C+Inc.+%28SAB%29&index=1&md5=247698e1f23c73ee4417f48d537a01b8), of South Dakota, announced that its anti-Ebola immunotherapy (SAB-139) provided “100% protection against a lethal dose of the Ebola virus” in a recent animal study[[73]](#footnote-73). The study was conducted at the [Integrated Research Facility, National Institute of Allergy and Infectious Diseases, National Institutes of Health](http://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.niaid.nih.gov%2Fabout%2Fintegrated-research-facility&esheet=51853274&newsitemid=20180815005602&lan=en-US&anchor=Integrated+Research+Facility%2C+National+Institute+of+Allergy+and+Infectious+Diseases%2C+National+Institutes+of+Health&index=3&md5=b128886119f353c19e37299384c91510), [United States Army Medical Research Institute of Infectious Diseases (USAMRIID](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.usamriid.army.mil%2F&esheet=51853274&newsitemid=20180815005602&lan=en-US&anchor=United+States+Army+Medical+Research+Institute+of+Infectious+Diseases+%28USAMRIID&index=4&md5=0deefe1e850a09a9ad26f506f7e3165d)), [Naval Medical Research Center (NMRC)](http://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.med.navy.mil%2Fsites%2Fnmrc%2FPages%2FNMRD.aspx&esheet=51853274&newsitemid=20180815005602&lan=en-US&anchor=Naval+Medical+Research+Center+%28NMRC%29&index=5&md5=13983665b2d414247fc799a8640991a1) and others. SAB-139 was produced from SAB’s proprietary DiversitAb platform utilizing transgenic cattle to produce large amounts of natural human, rather than bovine, antibodies in response to an antigen—in this case EVD. “Polyclonal antibodies are a powerful tool against emerging infectious diseases,” said Eddie J. Sullivan, SAB Biotherapeutics president and CEO. “They are our body’s natural defense to combat pathogens. With our platform, we can rapidly produce large amounts of targeted human antibodies without using humans—the limiting factor in current convalescent therapies in responding to a widespread outbreak.”
	+ Ology Bioservices of Florida was awarded an OTA (Other Transaction Agreement) to support the Joint Project Manager Medical Countermeasure Systems (JPM-MCS), a component of the Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO CBRND) for advanced biologics manufacturing services—specifically, to manufacture an anti-Ebola monoclonal antibody (mAb)[[74]](#footnote-74).
	+ A study[[75]](#footnote-75) has found that people who survive the Ebola virus can continue to suffer severe psychiatric and neurological conditions such as depression, migraines, nerve pain and stroke.
	+ [GeoVax Labs, Inc](https://www.globenewswire.com/Tracker?data=zGQeZiw8rRoscukzLtEMugpiHTmcRB8cpM2iLVF-8d2WXmEz0aNJIyM4HAfg9xbbrE5TUf26HPEvSxqZcxPrBQ==). has commented on a recent paper[[76]](#footnote-76) concerning new findings on how the Ebola virus (EBOV) disables the host immune system and spreads infection.
		1. Those authors had concluded that the very high levels of EBOV glycoprotein (GP) shed by EBOV and live Ebola vaccines may play a role in pathogenesis and associated vaccine-related adverse effects[[77]](#footnote-77) (e.g. oligoarthritis, maculopapular dermatitis, vesicular dermatitis, and dermal vasculitis)1.
		2. GeoVax's Chief Scientific Officer, Farshad Guirakhoo, said "This could be an important safety issue that requires post-marketing surveillance when certain vaccines under development are potentially administered in millions of doses, especially in countries across sub-Saharan Africa where widespread HIV infection can compromise the immune systems of people being vaccinated. The Ebola vaccine constructs used in this *in vitro* study (human parainfluenza type 3, HPIV3 and vesicular stomatitis virus, VSV) are chimeric viruses made in the laboratory by swapping the GP genes of the vectors with the GP genes of the vaccine viruses. These chimeras replicate very efficiently in their vaccinated hosts. In contrast to live vaccines, all of the GeoVax vaccine candidates (e.g. Ebola, Lassa, Marburg, Sudan, Zika, etc.) are not considered chimeric (not swapping the GP genes), are replication-deficient in mammalian hosts, and therefore are not capable of undergoing multiple rounds of replication necessary to produce high amounts of shed GP in the circulation of vaccinees. But based on the findings of this study, we are planning to test our vaccines to assure that the GP production does not induce death of monocytes. Despite the replication deficiency of our vaccines in humans, they offer full protection, similar to replicating vectors, without compromising the safety (e.g. adverse events)[[78]](#footnote-78) after a single dose. Another unique benefit of our vaccines is that we use two antigens for construction of VLPs which not only enhances the immunogenicity of the vaccine but could also broaden the immune response to protect against more viral strains[[79]](#footnote-79)."

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

* + Emergent BioSolutions of Maryland announced that it had entered into an agreement to acquire PaxVax. It will acquire typhoid vaccine Vivotif, cholera vaccine Vaxchora, and an Adenovirus vaccine candidate being developed for military personnel under contract with the US Department of Defense (DoD) and additional clinical-stage vaccine candidates targeting chikungunya and other emerging infectious diseases.
	+ The World Health Organization (WHO) through its Regional Office for Europe reported[[80]](#footnote-80) that more than 41,000 people in the region were infected with measles in the first half of this year, already exceeding 12-month totals for any other year this decade[[81]](#footnote-81). At least 37 people had died from the disease.
	+ In the last decade more than 1,100 cases of syphilis have been recorded in Queensland’s north. In the last six years six babies have died in the state from syphilis, and for those babies that do survive the infection, there is the potential for blindness and deafness. Penicillin is a cheap and effective cure, but reportedly sufferers do not want to face the stigma of being tested.
	+ Papua New Guinea recorded the fourth case of polio in an ongoing vaccine-derived poliovirus type 1 outbreak that marks the first return of the disease to the country since 2000.
	+ An American Heart Association scientific statement[[82]](#footnote-82) says early detection and monitoring of patients with [Chagas disease](https://www.healio.com/cardiac-vascular-intervention/imaging/news/online/%7B7c36e65b-7775-4854-bbd2-05e319e5789f%7D/screening-for-chagas-disease-in-latin-american-migrants-identifies-heart-abnormalities-low-mortality-risk)[[83]](#footnote-83) may aid in treating these patients if they develop cardiac complications later in life, but more research is needed.
1. The data also showed evidence of stable, durable expression, with no decline in plateau FVIII levels, in both participants in the 5x1011 vg/kg cohort who had been followed for over a year; and a dose response as demonstrated by FVIII expression ranging from 16 to 49 per cent, with a mean of 30 per cent after 12 weeks in five of the participants in the 2x1012 vg/kg cohort.Spark’s share price fell in response to the news that two patients receiving the 2x1012 vg/kg dose suffered an immune response that caused their factor VIII levels to drop below 5 per cent, requiring them to shift to on-demand factor VIII treatment. [↑](#footnote-ref-1)
2. at a dose of 2x1012 vg/kg [↑](#footnote-ref-2)
3. SB-525 is being developed as part of a global collaboration between Sangamo and Pfizer for the development and commercialization of potential gene therapy programs for haemophilia A. [↑](#footnote-ref-3)
4. This is an improved version of UniQure’s AMT-060 candidate, which has been through a Phase I/II trial where it showed some signs of efficacy. The company says AMT-061 has an eight- to nine-fold increase in factor IX activity. [↑](#footnote-ref-4)
5. In two additional patients who have completed dosing of 30 µg/kg MarzAA and one who completed dosing after a previous report, no bleeds or anti-drug antibodies had been observed. No injection site reactions had been observed after more than 200 administrations. Previously: [Catalyst Bio's marzeptacog alfa shows positive action in hemophilia study; shares up 25% premarket](https://seekingalpha.com/news/3370972-catalyst-bios-marzeptacog-alfa-shows-positive-action-hemophilia-study-shares-25-percent) (July 18) [↑](#footnote-ref-5)
6. ##  Isabella Garagiola et al, “[Risk factors for inhibitor development in severe hemophilia A](https://www.sciencedirect.com/science/article/pii/S0049384818303682),” in [*Thrombosis Research*](https://www.sciencedirect.com/journal/thrombosis-research). [Volume 168](https://www.sciencedirect.com/science/journal/00493848/168/supp/C), August 2018, Pages 20-27 <https://doi.org/10.1016/j.thromres.2018.05.027>

 [↑](#footnote-ref-6)
7. Suman L Sood et al., “[A cross-sectional analysis of cardiovascular disease in the hemophilia population](http://www.bloodadvances.org/content/2/11/1325?sso-checked=true),” in [*Blood Advances*](http://www.bloodadvances.org/?sso-checked=true). 2018 2:1325-1333; doi: https://doi.org/10.1182/bloodadvances.2018018226 [↑](#footnote-ref-7)
8. Because of low levels of clotting factors VIII or IX [↑](#footnote-ref-8)
9. Developed at Carnegie Mellon’s Center for Nucleic Acids Science and Technology (CNAST) [↑](#footnote-ref-9)
10. Adele S. Ricciardi, “[In utero nanoparticle delivery for site-specific genome editing.](https://www.nature.com/articles/s41467-018-04894-2)” *Nature Communications* volume 9, Article number: 2481 (2018)*,* 26 June 2018. [↑](#footnote-ref-10)
11. Luspatercept is a first-in-class erythroid maturation agent (EMA) that is thought to regulate late-stage red blood cell maturation. [↑](#footnote-ref-11)
12. It achieved a statistically significant improvement in the primary endpoint of erythroid response, which was defined as at least a 33 percent reduction from baseline in red blood cell (RBC) transfusion burden with a reduction of at least 2 units during the protocol-defined period of 12 consecutive weeks, from week 13 to week 24, compared with placebo. [↑](#footnote-ref-12)
13. Phase III clinical trials continue to evaluate the safety and efficacy of luspatercept in patients with MDS (the MEDALIST trial) and in patients with beta-thalassemia (the BELIEVE trial). A Phase III trial is being planned in first-line, lower-risk, MDS patients (the COMMANDS trial). The BEYOND Phase II trial in non-transfusion-dependent beta-thalassemia and a Phase II trial in myelofibrosis are ongoing. See [www.clinicaltrials.gov](http://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.clinicaltrials.gov&esheet=51833996&newsitemid=20180709005856&lan=en-US&anchor=www.clinicaltrials.gov&index=1&md5=ee8c4fbbfe07a9302e1084617c2cadbc). [↑](#footnote-ref-13)
14. Voxelotor, previously designated [GBT440](https://nam03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fsicklecellanemianews.com%2Fgbt440-for-sickle-cell-anemia%2F&data=02%7C01%7C%7Cf63b7b12d0e74480939308d5e56b9099%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172505620449&sdata=cGUW14%2FOae76%2BHgU%2BEGcLYts6FSLph9KiJkuG4j8ZAM%3D&reserved=0), is an oral, once-daily therapy for SCD. It is intended to increase haemoglobins’ affinity for oxygen, which, when bound, will prevent the aggregation of haemoglobins and the resulting sickling of red blood cells. [↑](#footnote-ref-14)
15. These designations are granted to therapies that have demonstrated promising results to treat rare diseases. They provide support for faster development and review. [↑](#footnote-ref-15)
16. The ongoing, randomized, double-blind Phase 3 HOPE trial ([NCT03036813](https://nam03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fclinicaltrials.gov%2Fct2%2Fshow%2FNCT03036813&data=02%7C01%7C%7Cf63b7b12d0e74480939308d5e56b9099%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172505620449&sdata=Eeua8POh%2Fd6CDcQ74%2FDfQ1hrpou4MWatSQh8y%2Bgci1U%3D&reserved=0)) is a two-part study designed to evaluate the effectiveness and safety of voxelotor in sickle cell patients ages 12 to 65. In part A, researchers compared the effects of 900 or 1,500 mg per day of voxelotor with a placebo in 154 patients treated for at least 12 weeks. [↑](#footnote-ref-16)
17. In the PHAROAH trial, which is assessing the ability of APL-2 to benefit PNH patients on treatment with eculizumab who are severely anaemic and transfusion-dependent, participants are being treated with APL-2 in addition to eculizumab. After at least one year of co-treatment, several patients have been switched to APL-2 monotherapy.   In the PADDOCK trial, APL-2 is being evaluated for safety and efficacy in PNH patients who have not been previously treated with eculizumab. [↑](#footnote-ref-17)
18. Zaverio M. Ruggeri, Paul Schimmel, et al. “**Tyrosyl-tRNA synthetase stimulates thrombopoietin-independent hematopoiesis accelerating recovery from thrombocytopenia”.** Proceedings of the National Academy of Sciences, 2018; 201807000 DOI: [10.1073/pnas.1807000115](http://dx.doi.org/10.1073/pnas.1807000115) [↑](#footnote-ref-18)
19. Karl Oliver Kagan et al., [Prevention of maternal‐fetal transmission of CMV by hyperimmunoglobulin (HIG) administered after a primary maternal CMV infectionin early gestation](https://obgyn.onlinelibrary.wiley.com/doi/10.1002/uog.19164) in *Ultrasound in Obstetrics and* *Gynecology,* June 2018 doi:10.1002/uog.19164 [↑](#footnote-ref-19)
20. Richard Hughes et al., in *The Lancet Neurology,* **s**| [Volume 17, ISSUE 8](https://www.thelancet.com/journals/laneur/issue/vol17no8/PIIS1474-4422%2818%29X0008-8),, pp 689-698 1 August 2018. [↑](#footnote-ref-20)
21. National Hospital for Neurology and Neurosurgery, London [↑](#footnote-ref-21)
22. [published in Nature Communications](https://www.nature.com/articles/s41467-018-05636-0), Haishui Huang, “Long-term deep-supercooling of large-volume water and red cell suspensions via surface sealing with immiscible liquids”, *Nature Communications* volume 9, Article number: 3201 (2018). [↑](#footnote-ref-22)
23. a biochemist at the University of British Columbia [↑](#footnote-ref-23)
24. 20 August at a meeting of the American Chemical Society (ACS) in Boston. [↑](#footnote-ref-24)
25. The findings have not yet been published in a peer-reviewed journal. [↑](#footnote-ref-25)
26. In [a small study in humans published in the journal Transfusion in 2000](https://www.ncbi.nlm.nih.gov/pubmed/11099655) people received transfusions of either type O blood or enzyme-altered type B blood. A 2008 review in the [British Journal of Haematology](https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2141.2007.06839.x) said the method was too expensive and inefficient for real-world use. [↑](#footnote-ref-26)
27. a pulmonary complication that can occur after a blood transfusion and the leading cause of transfusion-related fatalities. [↑](#footnote-ref-27)
28. Rick Kapur et al. “Gastrointestinal microbiota contributes to the development of murine transfusion-related acute lung injury”, *Blood Advances* (2018). [DOI: 10.1182/bloodadvances.2018018903](http://dx.doi.org/10.1182/bloodadvances.2018018903) [↑](#footnote-ref-28)
29. Lund University, Sweden [↑](#footnote-ref-29)
30. Loïc Sentilhes, “Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery”, [August 23, 2018](https://www.nejm.org/toc/nejm/379/8?query=article_issue_link) N Engl J Med 2018; 379:731-742 DOI: 10.1056/NEJMoa1800942 [↑](#footnote-ref-30)
31. Sara Juliana de A. de Vasconcellos, “Preoperative tranexamic acid for treatment of bleeding, edema, and ecchymosis in patients undergoing rhinoplasty: A systematic review and meta-analysis”, JAMA Otolaryngol Head Neck Surg. 2018; doi: 10.1001/jamaoto.2018.1381 [↑](#footnote-ref-31)
32. plastic surgery to correct/ reconstruct the nose, to restoring function or improve appearance. [↑](#footnote-ref-32)
33. subcutaneous spot of bleeding with a diameter exceeding 1 cm [↑](#footnote-ref-33)
34. associate professor of chemistry at the University of Rhode Island [↑](#footnote-ref-34)
35. Buddini Iroshika Karawdeniya et al. "Surveying silicon nitride nanopores for glycomics and heparin quality assurance." *Nature Communications,* volume 9, Article number: 3278 (2018). <https://doi.org/10.1038/s41467-018-05751-y> [↑](#footnote-ref-35)
36. [Bernaitis N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bernaitis%20N%5BAuthor%5D&cauthor=true&cauthor_uid=30076515) et al., “Warfarin control in patients transitioning to warfarin after non-vitamin K oral anticoagulant (NOAC) therapy”. Journal of Thrombosis and Thrombolysis, 2018 Aug 3. doi: 10.1007/s11239-018-1719-x. [Epub ahead of print] [↑](#footnote-ref-36)
37. More than half did so on the recommendation of their GP but the rationale for the advice was not available to the researchers. Reasons given for reverting to warfarin included intolerance (23 per cent), bleeding (9 per cent), hospitalisation (6 per cent), thromboembolic events (3 per cent) and renal function (2 per cent). [↑](#footnote-ref-37)
38. Aalborg University, Denmark [↑](#footnote-ref-38)
39. The study was [published online](http://www.onlinejacc.org/content/72/1/17) 25 June in the Journal of the American College of Cardiology. J Am Coll Cardiol. 2018;72: 17-26, 27-28. [Abstract](http://www.onlinejacc.org/content/72/1/17), [Editorial](http://www.onlinejacc.org/content/72/1/27) [↑](#footnote-ref-39)
40. Paulus Kirchhof, of the University of Birmingham in England, and colleagues in the [*Journal of the American College of Cardiology*](http://www.onlinejacc.org), published online 2 July. [↑](#footnote-ref-40)
41. Coralie Blanche et al., “[Use of intravenous iron in cyanotic patients with congenital heart disease and/or pulmonary hypertension](https://www.internationaljournalofcardiology.com/article/S0167-5273%2818%2930363-2/fulltext),” [*International Journal of Cardiology*](https://www.journals.elsevier.com/international-journal-of-cardiology). September 15, 2018 volume 287,pp 79-83. DOI: <https://doi.org/10.1016/j.ijcard.2018.05.062> [↑](#footnote-ref-41)
42. a chronic inflammatory lung disease that causes obstructed airflow from the lungs. [↑](#footnote-ref-42)
43. #  Antonio Klasan et al., “COPD as a risk factor of the complications in lower limb arthroplasty: a patient-matched study”, [International Journal of Chronic Obstructive Pulmonary Disease](https://www.dovepress.com/international-journal-of-chronic-obstructive-pulmonary-disease-journal), 21 August 2018 [Volume 2018:13](https://www.dovepress.com/international-journal-of-chronic-obstructive-pulmonary-disease-archive6-v1253) Pages 2495—2499 **DOI**:<https://doi.org/10.2147/COPD.S161577>

 [↑](#footnote-ref-43)
44. CSL achieved a post-tax net profit of $US 1.7bn ($2.34bn AUD). [↑](#footnote-ref-44)
45. PRN1008 is a small-molecule inhibitor of Bruton’s Tyrosine Kinase (BTK), a protein important to immune function. The company says damping it down limits cellular processes activated in autoimmune and inflammatory diseases. [↑](#footnote-ref-45)
46. The National Heart, Lung, and Blood Institute (NHLBI), a division of the US National Institutes of Health, granted the three-year, Phase IIB Bridge Small Business Innovation Research award of up to $US 3 million. [↑](#footnote-ref-46)
47. on November 9 and 10 in Dubai. [↑](#footnote-ref-47)
48. An error of metabolism that causes red blood cells to break down [↑](#footnote-ref-48)
49. Elissa M. Schechter‐Perkins et al, “Implementation and Preliminary Results of an Emergency Department Nontargeted, Opt‐out Hepatitis C Virus Screening Program,” *Academic Emergency Medicine* (2018). [DOI: 10.1111/acem.13484](http://dx.doi.org/10.1111/acem.13484) [↑](#footnote-ref-49)
50. <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm534162.htm> [↑](#footnote-ref-50)
51. Jeffrey Glassberg et al., “[Inhaled steroids reduce pain and sVCAM levels in individuals with sickle cell disease: A triple‐blind, randomized trial](https://onlinelibrary.wiley.com/doi/full/10.1002/ajh.24742),” published 28 March 2017, [*American Journal of Hematology*](https://onlinelibrary.wiley.com/journal/10968652) <https://doi.org/10.1002/ajh.24742> [↑](#footnote-ref-51)
52. ###  Yen-Wen Liu et al., “Human embryonic stem cell–derived cardiomyocytes restore function in infarcted hearts of non-human primates” *Nature Biotechnology* volume 36, pages 597–605 (2018). Published 2 July 2018. [Nature Biotechnology.](http://dx.doi.org/10.1038/nbt.4162)

 [↑](#footnote-ref-52)
53. “[Comorbid obstructive sleep apnea and increased risk for sickle cell disease morbidity,](https://doi.org/10.1007/s11325-018-1630-x)” was published in [Sleep and Breathing](https://link.springer.com/journal/11325). [↑](#footnote-ref-53)
54. The researchers took advantage of the fact that many mosquito-borne viruses are composed of single-stranded ribonucleic acids, or RNAs. They created new biomolecule “probes” composed of specific sequences that will match and bind only to a given target RNA virus. [↑](#footnote-ref-54)
55. Tauyne Menegaldo Pinheiro et al, “Viral immunogenicity determines epidemiological fitness in a cohort of DENV-1 infection in Brazil”, *PLOS Neglected Tropical Diseases* (2018). [DOI: 10.1371/journal.pntd.0006525](http://dx.doi.org/10.1371/journal.pntd.0006525) [↑](#footnote-ref-55)
56. Yan G, Pang L, Cook AR, et al. [Distinguishing Zika and dengue viruses through simple clinical assessment, Singapore.](https://www.nc.cdc.gov/eid/article/24/8/17-1883_article) *Emerg Infect Dis*. 2018;24(8):1565-1568. [↑](#footnote-ref-56)
57. Dawn M Dudley et al. “**Miscarriage and stillbirth following maternal Zika virus infection in nonhuman primates”**. Nature Medicine, 2018; DOI: [10.1038/s41591-018-0088-5](http://dx.doi.org/10.1038/s41591-018-0088-5) [↑](#footnote-ref-57)
58. The data come from a registry of nearly 1500 children in Puerto Rico and the US Virgin Islands whose mothers were confirmed to have been exposed to Zika while pregnant. Six per cent of the babies suffered from birth defects such as small head size and brain and eye damage. Nine per cent had at least one neurodevelopmental issue such as seizures or difficulty swallowing. And 1 per cent suffered both birth defects and nervous system problems. [↑](#footnote-ref-58)
59. [Abstract/Full Text](https://www.cdc.gov/mmwr/volumes/67/wr/mm6731e2.htm?s_cid=mm6731e2_w) “Update: Interim Guidance for Preconception Counseling and Prevention of Sexual Transmission of Zika Virus for Men with Possible Zika Virus Exposure — United States, August 2018” August 10, 2018 / 67(31);868-871 [↑](#footnote-ref-59)
60. The trial will enrol a total of 28 healthy, non-pregnant adults ages 18 to 50 at the Johns Hopkins Bloomberg School of Public Health Center for Immunization Research in Baltimore, Maryland, and at the Vaccine Testing Center at the Larner College of Medicine at the University of Vermont in Burlington. Volunteers who test positive for a prior flavivirus infection (such as Zika, dengue, or yellow fever) will be excluded from the trial to ensure that any antibodies detected in blood samples are related to the experimental vaccine alone. All participants will be randomly assigned to receive a single subcutaneous dose of the experimental vaccine (20 participants) or a placebo (eight participants). NIAID is sponsoring the trial. Charles River Laboratories, in Malvern Pennsylvania, manufactured the vaccine candidate for this Phase 1 clinical trial. The trial will take up to one year to complete. See [ClinicalTrials.gov](http://ClinicalTrials.gov); search identifier [NCT03611946](https://clinicaltrials.gov/ct2/show/NCT03611946?term=live+attenuated+zika&rank=1). [↑](#footnote-ref-60)
61. Genetic engineering allowed the creation of a chimeric virus, made by combining genes from multiple viruses, in this case a dengue virus type 4 backbone that expresses Zika virus surface proteins. The chimeric virus is live but attenuated, too weak to cause disease in recipients. When injected it should prompt an immune response. The Phase I clinical trial will analyze this response and assess the safety of the experimental vaccine, which showed promise in earlier tests in rhesus macaques. [↑](#footnote-ref-61)
62. The experimental vaccine is currently under evaluation in a [Phase 3 clinical trial conducted in Brazil by the Butantan Institute](https://www.niaid.nih.gov/news-events/dengue-vaccine-enters-phase-3-trial-brazil). [↑](#footnote-ref-62)
63. two Phase I/II and four Phase II [↑](#footnote-ref-63)
64. <https://www.niaid.nih.gov/news-events/niaid-sponsored-trial-universal-influenza-vaccine-begins> [↑](#footnote-ref-64)
65. Daniel Weibel, “Narcolepsy and adjuvanted pandemic influenza A (H1N1) 2009 vaccines – Multi-country assessment”, *Vaccine*, 16 August 2018. <https://doi.org/10.1016/j.vaccine.2018.08.008> [↑](#footnote-ref-65)
66. In late May, Saudi officials identified clusters of cases in Najran and Jeddah linked to household outbreaks. [↑](#footnote-ref-66)
67. M Letko et al. “Adaptive evolution of MERS-CoV to species variation in DPP4”. Cell Reports DOI: [10.1016/j.celrep.2018.07.045](http://doi.org/10.1016/j.celrep.2018.07.045) (2018). [↑](#footnote-ref-67)
68. [MERS](https://nam05.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2Fmers%2Findex.html&data=02%7C01%7C%7C195301a2f4b74d78a95908d5e56b7a3c%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172138027339&sdata=CuWNeW0isF22pvWCbYwA3MeoFAgt6nsXkFKNHGT38m8%3D&reserved=0) is caused by a coronavirus that is related to the virus which causes [severe acute respiratory syndrome (SARS)](https://nam05.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.cdc.gov%2Fsars%2Findex.html&data=02%7C01%7C%7C195301a2f4b74d78a95908d5e56b7a3c%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172138027339&sdata=WY6kWx5I644OGN0xaEkjjMUryvDjPdMktDiBqzwKWGA%3D&reserved=0). Between 2002 and 2004, the SARS coronavirus infected more than 8,000 people worldwide, and had a case fatality rate of about 10 per cent. Since the MERS-CoV was identified in Saudi Arabia in 2012, the case fatality rate has been around 36 per cent. [↑](#footnote-ref-68)
69. Romy Conzade et al., “Reported Direct and Indirect Contact with Dromedary Camels among Laboratory-Confirmed MERS-CoV Cases”, *Viruses* **2018**, *10*(8), 425; doi:[10.3390/v10080425](http://dx.doi.org/10.3390/v10080425) [↑](#footnote-ref-69)
70. In [preclinical testing,](https://nam05.safelinks.protection.outlook.com/?url=https%3A%2F%2Fclinicaltrials.gov%2Fct2%2Fshow%2FNCT02670187&data=02%7C01%7C%7C195301a2f4b74d78a95908d5e56b7a3c%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C636667172138027339&sdata=Rrc3T0EEYHPkZM3msNMMDvf5bEohoI5xpyqIotnh%2BOc%3D&reserved=0) INO-4700 induced 100 per cent protection from a live virus challenge in a rhesus macaque, non-human, primate study. [↑](#footnote-ref-70)
71. The study will be conducted by GeneOne Life Science in Korea and fully funded by a $US 34 million grant from the Samsung Foundation through the International Vaccine Institute. In 2015 a business traveller returned to South Korea from Saudi Arabia and was the index case for a South Korean epidemic in 17 hospitals. There were 186 confirmed cases with a 20 per cent fatality rate. [↑](#footnote-ref-71)
72. Erica Ollman Saphiire et al., “[Systematic analysis of monoclonal antibodies against Ebola virus GP defines features that contribute to protection](https://linkinghub.elsevier.com/retrieve/pii/S0092867418309607)”, Cell, [Volume 174, ISSUE 4](https://www.cell.com/cell/issue?pii=S0092-8674(17)X0017-2), P938-952.e13, 9 august, 2018.:<https://doi.org/10.1016/j.cell.2018.07.033> [↑](#footnote-ref-72)
73. published in [The Journal of Infectious Diseases](http://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Facademic.oup.com%2Fjid%2Fadvance-article%2Fdoi%2F10.1093%2Finfdis%2Fjiy377%2F5054139&esheet=51853274&newsitemid=20180815005602&lan=en-US&anchor=The+Journal+of+Infectious+Diseases&index=2&md5=3c4fa580670bdf7eab52b8ce738cf84f). Thomas Luke, et al., “Fully Human Immunoglobulin G From Transchromosomic Bovines Treats Nonhuman Primates Infected With Ebola Virus Makona Isolate”, published 16 July 2018, The Journal of Infectious Diseases, jiy377, <https://doi.org/10.1093/infdis/jiy377> [↑](#footnote-ref-73)
74. The award was made possible through collaborative funding between JPEO CBRND and the (DARPA). The antibody, designated mAb114, was developed at the Vaccine Research Center (VRC), part of the National Institute of Allergy and Infectious Diseases (NIAID) with the National Institutes of Health, in part through funding previously provided by the Defense Advanced Research Projects Agency DARPA. The VRC is a collaborator with JPM-MCS, DARPA, and Ology Bioservices on this program. Including optional work, the agreement has a value of $US 8.4 million. [↑](#footnote-ref-74)
75. #  Patrick J Howlett et al., “Case Series of Severe Neurologic Sequelae of Ebola Virus Disease during Epidemic, Sierra Leone”, *Emerging Infectious Diseases,* Volume 24, number 8, August 2018. DOI: 10.3201/eid2408.171367

 [↑](#footnote-ref-75)
76. #  [Mathieu Iampietro](https://www.researchgate.net/profile/Mathieu_Iampietro), et al., "Ebola Virus Shed Glycoprotein Triggers Differentiation, Infection, and Death of Monocytes Through Toll-Like Receptor 4 Activation",  [The Journal of Infectious Diseases](https://www.researchgate.net/journal/1537-6613_The_Journal_of_Infectious_Diseases) ·published 31 July 2018 [DOI: 10.1093/infdis/jiy406](http://dx.doi.org/10.1093/infdis/jiy406)

 [↑](#footnote-ref-76)
77. Such as oligoarthritis, maculopapular dermatitis, vesicular dermatitis, and dermal vasculitis. See    Huttner A, et al. “The effect of dose on the safety and immunogenicity of the VSV Ebola candidate vaccine: a randomised double-blind, placebo-controlled phase 1/2 trial.” [Lancet Infect Dis.](https://www.globenewswire.com/Tracker?data=Xm_YVBdXo7yyoe9kQQJ9CIJ6v94N7dySitJhL2ES54gXytEWtUMuERd57gG0MbuqbtICzwFOCeXJk-yONrts9tFL6432ahJforOO6AHI3Vbe_3WR0QKG5GF6phNfIfh2hrMx2j2Kxxm8Wns2m4eUgM0me3WvtPsT0haxJkPyE4s66Pj4q0O4pL4aRGuHrs6PNHTyVrgri9T_6guJcVS49DXL_rh2TY34OzBJ29HyAmo=) 2015 Oct;15(10):1156-1166. doi: 10.1016/S1473-3099(15)00154-1. Epub 4 August 2015. [↑](#footnote-ref-77)
78. Goepfert PA, et al.  “Specificity and 6-month durability of immune responses induced by DNA and recombinant modified vaccinia Ankara vaccines expressing HIV-1 virus-like particles”. [J Infect Dis.](https://www.globenewswire.com/Tracker?data=OolwnodvaAAW7sYbhd0T4v8SwhuU1XLH8AyuEbgCkFkmaBgzmoMfAWyOzSPdwii9OO1q4EOB5qd8RXoTso1E7NK1nqjNuKzHsvtFEkGfKmHp0k7LR7DFM1SItLWr5izYgaqShSQDsDPt2dwPy--suxonv0nTu4PVUCqJj_rqaUZKaA_HfcZKbgyP2CBO7IqhWlsAEn2pcHw-NDYHVGTVgw1f7u6gpD70FtMnxIuD-6yP7o0GijpbOr3bxmcae94W22aPnY3dupEA5NTEaTcqW-NAcVUm1B-t2O-59_qZz6o_4niQsQtRmopgORz4lT_ar8DoGkJXZ7tbJ_SRn100JAX2-9JPLVPoU0AbYXsqdrRpGxAg02ducypAZWRDd_Qn) 2014 Jul 1;210(1):99-110. doi: 10.1093/infdis/jiu003. Epub 7 January 2014. [↑](#footnote-ref-78)
79. GeoVax uses a Modified Vaccinia Ankara (MVA) Virus-Like Particle (VLP) platform, which generates noninfectious VLPs in the subject. Gene sequences of target antigens are inserted into the MVA genome which drives their expression in infected cells.Further, GeoVax introduces into the viral genome matrix sequences that incorporate antigens into VLPs and at the same time facilitate their budding from the membranes of host cells. Thus, vaccination induces two pools of antigens as targets for the immune response - host cells and VLPs secreted from host cells. Geovax says its strategy mimics a natural viral infection, triggering the body to produce a robust and durable immune response with involvement of both antibodies and T cells. [↑](#footnote-ref-79)
80. Aug 20 WHO Europe [report](http://www.euro.who.int/en/media-centre/sections/press-releases/2018/measles-cases-hit-record-high-in-the-european-region) [↑](#footnote-ref-80)
81. The previous high was 23,927 for all of 2017. [↑](#footnote-ref-81)
82. Pereira Nunes MC, et al; on behalf of the American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Stroke Council. [Chagas cardiomyopathy: an update of current clinical knowledge and management: a scientific statement from the American Heart Association [published online August 20, 2018]**.**](https://www.ahajournals.org/doi/10.1161/CIR.0000000000000599) *Circulation*. doi:10.1161/CIR.0000000000000599 [↑](#footnote-ref-82)
83. caused by the protozoan Trypanosoma cruzi [↑](#footnote-ref-83)