Monitoring International Trends

**Posted September 2019**

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.

Summary

Some recent matters of interest appear on pages 6 to 15. They are summarised below:

**Safety and Patient Blood Management (begins page 6)**

Appropriate transfusion; bleeding risk (p6)

* + Studies found:
		1. that “common hospital policies that mandate the administration of packed red blood cells through a dedicated IV catheter may be overly cautious”.
		2. that transfusion of red blood cells stored in the absence of oxygen is a technique worth investigating to improve resuscitation from haemorrhagic shock.
		3. that rabbit and mouse papillomaviruses could be transferred by blood to their hosts which raised the possibility that human papillomavirus (HPV) may also be transferable by blood in humans; and
		4. that administering low-dose arginine vasopressin to patients with trauma and haemorrhagic shock cuts by half the volume of blood products required to stabilize.
	+ Scientists have developed a blood incubator using laser technology which could improve pre-transfusion testing for patients undergoing blood transfusions.
	+ Researchers reported on a positive experience using cold‐stored low‐titre type O whole blood in a case of massive postpartum haemorrhage.
	+ Researchers have examined whether fresh frozen plasma and platelet concentrate storage duration is associated with increased in -hospital mortality risk across cardiac surgery, acute medicine, ICU and orthopaedic surgery patients.
	+ Geoff Simon, from the University of the Sunshine Coast, says “the restrictive, or lower, haemoglobin thresholds that guide blood use for people under 65 don’t work as well as they could for older patients…..Our research suggests that we could be managing things differently for better outcomes in older adults.”

Other (p7)

* + A review concluded that findings from the PIVOTAL trial should allay concerns about the use of intravenous iron therapy in patients with end-stage renal disease suffering from anaemia.
	+ Real-world data showed that the oral anticoagulant apixaban was associated with lower rates of major bleeding than its in-class competitors.
	+ Researchers report that a low-intensity regimen of the blood thinner warfarin does not appear to be as effective as conventional dosing at preventing clots or death after joint-replacement surgery.
	+ Hospital ‘lockout rules’ have been suggested for inpatient blood testing to prevent medical staff unnecessarily ordering repeat tests.

**Products and Treatments (begins page 8)**

Treating haemophilia (p8)

* + A review study suggests that problematic thrombotic events are fairly rare in people using NovoSeven, among all types of bleeding disorders for which it is approved,
	+ New analysis suggests simultaneous use of NovoSeven and Hemlibra in patients with haemophilia A is not associated with higher risk of thrombosis.
	+ A new study found haemophilia may be more common than previously thought.
	+ A study concluded that combining immune tolerance induction with Hemlibra is a feasible and safe way of treating children with severe haemophilia A.
	+ Freeline has presented further data on its AAV gene therapy programme for haemophilia B, for the first cohort of two patients.
	+ uniQure announced the enrolment of 56 patients had been achieved in the HOPE-B pivotal trial of its investigational AAV5-based gene therapy

Treating other conditions (p10)

* + Apellis Pharmaceuticals dosed the first patient in the Phase III clinical study of APL-2 for treatment-naïve patients with paroxysmal nocturnal haemoglobinuria.
	+ Biotest completed a Phase III study investigating IgG Next Generation in patients diagnosed with chronic primary immune thrombocytopenia,
	+ Inhibrx enrolled the first patient in a Phase I clinical trial of INBRX-101. This is a modified recombinant version of human alpha-1 antitrypsin for the treatment of patients with alpha-1 antitrypsin deficiency.
	+ Rocket Pharmaceuticals announced the US Phase II clinical development plan for its lentiviral vector -based gene therapy for the treatment of Fanconi Anemia.
	+ A long-term follow-up found that eltrombopag not only increases platelet counts and reduces bleeding and bruising in patients with chronic immune thrombocytopenia, but also significantly improves health-related quality of life.
	+ Findings in patients with persistent immune thrombocytopenia indicate that second-line treatment with eltrombopag and romiplostim provides high efficacy and safety, particularly in comparison with treatment with rituximab.

**Regulatory matters (begins page 11)**

* + Mustang Bio announced that the FDA has designated its lentiviral gene therapy a Regenerative Medicine Advanced Therapy for the treatment of “bubble boy disease”.
	+ The FDA has approved a new whole blood test for donor screening for Babesia.
	+ England’s health technology assessment body has conditionally recommended the use of lanadelumab in some patients with hereditary angioedema.
	+ The FDA is giving priority review to voxelotor as a treatment for sickle cell disease.

**Market structure and company news (begins page 12)**

* + Roche extended for the sixth time the deadline for its share tender offer to purchase all of the outstanding shares of common stock of Spark Therapeutics.
	+ Dutch company Pharvaris has raised funds for the clinical development of an oral treatment for hereditary angioedema.
	+ On 22 August, in the US ADMA announced “the commercial relaunch and its first commercial sales of BIVIGAM,” its IVIG product.

**Specific country events (begins page 12)**

* + SK Plasma from South Korea has signed an agreement with Indonesia’s state-run PT Bio Farma and the Red Cross Society.
	+ The Western Victoria Primary Health Network launched a rural health resource.
	+ In the US, the Minnesota Center for Prion Research and Outreach is hoping to develop real-time diagnostic tests to identify chronic wasting disease in deer, moose, caribou and reindeer.
	+ A report of the first five years of babesiosis surveillance from the US Centers for Disease Control and Prevention shows a significant increase in incidence.
	+ The Irish Blood Transfusion Service has cancelled a 15-year-long donor deferral policy for people who have lived in Britain because the transfusion transmission risk of “Mad Cow Disease" is now regarded as remote.

**Research not included elsewhere (begins page 13)**

* + Researchers found:
		1. that in patients with severe sepsis, the sensitivity of blood cultures decreased after initiation of empirical antimicrobial therapy.
		2. that platelet-rich plasma appears to facilitate healing in ulcers
		3. that “functionalized silver nanoparticles can be used as an antiplatelet agent or in design and manufacturing of blood-facing medical devices, such as vascular grafts, stents, heart valves, and catheters”; and
		4. that supercooling human livers to -4C triples the time they can be kept before transplant, compared with keeping them on ice.

**Infectious diseases** **(begins page 14)**

Mosquito-borne diseases (p14)

* + Researchers say mosquitoes are more prone to acquire the dengue virus when they feed on blood with low levels of iron.
	+ Batavia Biosciences will use a cell line expression system from Horizon Discovery for the production of a potent Zika virus-neutralizing antibody.

Influenza (p14)

* + A research team has identified the structure of a flu virus protein vital to its survival.
	+ The American Academy of Pediatrics confirmed having no preference between the live-attenuated influenza vaccine or inactivated influenza vaccines for children.
	+ Seqirus presented new data that demonstrated circulating influenza B/Victoria viruses are a closer match to cell-based B/Vic vaccine viruses compared with egg-based B/Vic vaccine viruses.

Ebola virus disease (p15)

* + Scientists say that creating mutations in a key protein that helps Ebola avoid the body’s defences can prevent the virus from making its hosts sick and activate protective immunity.
	+ For the first twelve months of the Ebola outbreak in the Democratic Republic of Congo, Merck’s vaccine has been administered. Now a second vaccine, from Johnson &Johnson, is being introduced.
	+ The US Agency for International Development announced an additional $US21 million humanitarian aid for the eastern Democratic Republic of the Congo.
	+ A new study suggests that Ebola survivors are at an increased risk of death within the first year of hospital discharge.

Other diseases (p15)

* + The World Health Organization’s Global Preparedness Monitoring Board reported a heightened risk for a global pandemic that could kill up to 80 million people.
	+ Moderna announced positive interim results from its Phase I cytomegalovirus vaccine.
	+ A study has concluded that nondaily pre-exposure prophylaxis for HIV (PrEP) was less effective than daily PrEP, especially among MSM in the US.
	+ Queenslanders have been warned to avoid heat-stressed bats which have fallen out of trees. Australian bat lyssavirus is a rabies-like virus that can be transmitted to humans, causing illness which can lead to paralysis, delirium, convulsions and death.
	+ The first case in Australia of extensively drug-resistant typhoid has been reported in a girl aged 20 months returning after three months in Pakistan. Doctors have warned Australia is not immune to this "emerging threat".

Detailed Report

Contents

[1. Safety and patient blood management 6](#_Toc22721274)

[Appropriate Transfusion; Bleeding Risk 6](#_Toc22721275)

[Other 7](#_Toc22721276)

[2. Products and treatments 8](#_Toc22721277)

[Treating haemophilia 8](#_Toc22721278)

[Treating other conditions 10](#_Toc22721279)

[3. Regulatory 11](#_Toc22721280)

[4. Market structure and company news 12](#_Toc22721281)

[5. Specific country events 12](#_Toc22721282)

[6. Research not included elsewhere 13](#_Toc22721283)

[7. Infectious diseases 14](#_Toc22721284)

[Mosquito-borne diseases 14](#_Toc22721285)

[Influenza 14](#_Toc22721286)

[Ebola virus disease 15](#_Toc22721287)

[Other diseases 15](#_Toc22721288)

1. Safety and patient blood management

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

Appropriate Transfusion; Bleeding Risk

* + [*Anesthesiology*](https://www.anesthesiologynews.com/Section/Clinical-Anesthesiology/1) *News* on 4 September reported that a study[[1]](#footnote-1) had found that “common hospital policies that mandate the administration of packed red blood cells (PRBCs) through a dedicated IV catheter may be overly cautious”. The policies “assume detrimental effects on erythrocyte integrity when crystalloids and certain medications are co-administered.” However, achieving additional IV access is painful for the patient, expensive, and another vehicle for infection. Researchers at the University of Alabama at Birmingham and Johns Hopkins University found that “five minutes of incubation of PRBCs with isotonic crystalloids or catecholamines does not deleteriously alter PRBC hemolysis, membrane deformability, or aggregation. Co‐incubation with D5W[[2]](#footnote-2) likely increases hemolysis. Propofol may promote hemolysis.”
	+ Animal studies suggest[[3]](#footnote-3) that transfusion of red blood cells stored anaerobically – in the absence of oxygen – is a technique worth investigating to improve resuscitation from haemorrhagic shock. Researchers reported that “resuscitation from haemorrhagic shock via transfusion of anaerobically stored RBCs recovered cardiac function, restored hemodynamic stability, and improved outcomes*.*”
	+ Scientists[[4]](#footnote-4) have developed a blood incubator using laser technology which could improve pre-transfusion testing for patients undergoing blood transfusions[[5]](#footnote-5).
	+ Papillomavirus has until recently been regarded as solely a sexually transmitted disease, but a recent study[[6]](#footnote-6) found that rabbit and mouse papillomaviruses could be transferred by blood to their hosts. This raised the possibility that human papillomavirus (HPV) may also be transferable by blood in humans. HPV can sometimes progress to cervical or oral cancer. One of the researchers, Jiafen Hu[[7]](#footnote-7), said more research is needed to determine whether HPV can be spread through blood transfusions: "People who are receiving blood transfusions typically have immune systems that aren't working optimally, so their systems are more vulnerable. We might want to think about adding HPV to the list of viruses for which blood donations are screened, as well as researching whether the typical viral load of HPV in human blood would be sufficient to cause infection."
	+ A study[[8]](#footnote-8) showed that administering low-dose arginine vasopressin (AVP) to patients with trauma and haemorrhagic shock cuts the volume of blood products required to stabilize them by half.
	+ Researchers, noting that in the US military cold‐stored low‐titre type O whole blood (LTOWB) has become the preferred product for resuscitation of severe bleeding in deployed surgical units, have noted thatLTOWB use in civilian trauma is becoming more frequent. They report on a positive experience using LTOWB in a case of massive postpartum haemorrhage and speculates that “this approach could have a role in massive obstetric hemorrhage[[9]](#footnote-9)”.
	+ Researchers have examined[[10]](#footnote-10) whether fresh frozen plasma (FFP) and platelet concentrate (PC) storage duration is associated with increased in -hospital mortality risk across cardiac surgery, acute medicine, ICU and orthopaedic surgery patients. They concluded that “there is insufficient evidence to support shortening FFP or PC shelf life based on in hospital mortality”.
	+ Geoff Simon, from the University of the Sunshine Coast, believes blood management in older patients with anaemia and blood loss is a concern, as most seniors are subjected to “one-size-fits-all” medical care. He found that the current adult medical guidelines for blood transfusions are based on data from people under the age of 65[[11]](#footnote-11). He commented: “Often this means that the restrictive, or lower, haemoglobin thresholds that guide blood use for people under 65 don’t work as well as they could for older patients…..Our research suggests that we could be managing things differently for better outcomes in older adults.”  Researchers analysed the blood use in older patients based on international trials, finding that older patients with haemoglobin levels around 100g per litre had lower mortality rates and few cardiac issues compared with older people with haemoglobin levels around 70 to 80g per litre. The team concluded that “older adults require a haemoglobin of 100g per litre to achieve the same oxygen delivery potential as a younger patient with haemoglobin of 70g per litre” and that “this indicates the need for patient blood management guidance to be much more specific to older adults, and distinct from younger adults.”

Other

* + A review[[12]](#footnote-12) concluded that findings from the PIVOTAL trial should allay concerns about the use of intravenous iron therapy in patients with end-stage renal disease suffering from anaemia.
	+ Real-world data released at a conference in Paris[[13]](#footnote-13) showed that the oral anticoagulant Eliquis (apixaban) was associated with lower rates of major bleeding than its in-class competitors. Nevertheless, it delivered comparable protection against strokes and blood clotting events in patients with nonvalvular atrial fibrillation.
	+ Researchers at the Hospital for Special Surgery (HSS), Washington University School of Medicine in St. Louis, and their colleagues report[[14]](#footnote-14) that a low-intensity regimen of the blood thinner warfarin does not appear to be as effective as conventional dosing at preventing clots or death after joint-replacement surgery.
	+ Hospital ‘lockout rules’ have been suggested for inpatient blood testing to prevent medical staff unnecessarily ordering repeat tests[[15]](#footnote-15).
1. 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

* + A review study[[16]](#footnote-16) suggests that problematic thrombotic events are fairly rare in people using [NovoSeven](https://hemophilianewstoday.com/novoseven/), among all types of bleeding disorders for which it is approved, including haemophilia[[17]](#footnote-17). NovoSeven was [approved](https://www.novo-pi.com/novosevenrt.pdf) for use in the US in 1999. Researchers reviewed data from clinical trials and post-marketing surveillance, with 12,288 bleeding and surgical episodes reported. Among these, 21 thrombotic events occurred in 18 patients, representing an overall incidence rate of 0.17 per cent. The biggest risk factor for a thrombotic event was being aged 65 or older. Other risk factors included the use of [activated prothrombin complex concentrates](https://www.drugs.com/mmx/activated-prothrombin-complex-concentrate.html) (aPCC) and the presence of broadly defined heart disease.
	+ New analysis of the Phase III HAVEN program[[18]](#footnote-18) suggests simultaneous use of [NovoSeven](https://www.novosevenrt.com/) (recombinant factor VIIa) and [Hemlibra](https://www.hemlibra.com/) ([emicizumab](https://hemophilianewstoday.com/emicizumab-ace910-for-hemophilia-a/)) in patients with haemophilia A is not associated with higher risk of [thrombosis](https://natfonline.org/patients/what-is-thrombosis/)[[19]](#footnote-19).
	+ A new study[[20]](#footnote-20) suggests that haemophilia may be more common than previously thought. Researchers from Britain, Canada, France, and the US estimate haemophilia may actually affect more than 1,125,000 men[[21]](#footnote-21) worldwide and that around 418,000 of them may have a more severe form of the disorder[[22]](#footnote-22). The researchers were not surprised to find that haemophilia was most likely to reduce life expectancy in the developing world, where diagnosis and treatment are restricted.
	+ Freeline has presented[[23]](#footnote-23) further data on FLT180a, its AAV gene therapy programme for haemophilia B, for the first cohort of two patients. **Principal investigator Pratima Chowdary said:** “The data is encouraging, showing durability of clinical results for FLT-180a. We are currently progressing the study to identify a dose level that leads to normalisation of FIX activity levels with minimal or no toxicity.”
	+ uniQure N.V. announced that the planned enrolment of 56 patients had been achieved in the HOPE-B pivotal trial of etranacogene dezaparvovec (AMT-061), an investigational AAV5-based gene therapy incorporating the patent-protected FIX-Padua variant for the treatment of patients with severe and moderately severe haemophilia B[[24]](#footnote-24). Etranacogene dezaparvovec has been granted Breakthrough Therapy Designation by the US Food and Drug Administration (FDA) and access to Priority Medicines (PRIME) regulatory initiative by the European Medicines Agency (EMA). Robert Gut, chief medical officer at uniQure, said: “This multi-center, multinational trial involves 39 clinical sites across nine countries.” The trial’s primary endpoint will be to assess FIX activity 26 weeks after dosing. Secondary endpoints will include assessing patients’ annualized bleeding rate (ABR, number of spontaneous bleeding episodes per year), need for FIX replacement therapy over a period of 52 weeks and the number and nature of adverse events ([NCT03569891](https://clinicaltrials.gov/ct2/show/NCT03569891)).
	+ A study[[25]](#footnote-25) concluded that combining immune tolerance induction, used to prevent the development of anti-factor VIII inhibitors, with [Hemlibra](https://www.hemlibra.com/) ([emicizumab](https://hemophilianewstoday.com/emicizumab-ace910-for-hemophilia-a/)) is a feasible and safe way of treating children with severe haemophilia A[[26]](#footnote-26). The report covers clinical outcomes in the first seven patients to be treated with this combined approach[[27]](#footnote-27), named *The Atlanta Protocol*. One of the study authors[[28]](#footnote-28) said in a [press release](https://news.emory.edu/stories/2019/08/hematology_atlanta_protocol/index.html): “Prospective studies will be necessary to compare treatment outcomes to standard ITI regimens, but we are encouraged by the early success of *The Atlanta Protocol*. Two observational clinical trials will investigate further the safety and effectiveness of *The Atlanta Protocol* in hemophilia A in children and adults: the MOTIVATE study ([NCT04023019](https://clinicaltrials.gov/ct2/show/NCT04023019)) (at two sites; Children Healthcare of Atlanta and a centre in Germany), and the Emicizumab PUP and Nuwiq ITI study ([NCT04030052](https://clinicaltrials.gov/ct2/show/NCT04030052)), taking place at Emory University.

Treating other conditions

* + Apellis Pharmaceuticals announced on 3 September the dosing of the first patient in the Phase III clinical study PRINCE (APL2-308), evaluating the efficacy and safety of APL-2 for treatment-naïve patients with paroxysmal nocturnal haemoglobinuria (PNH). PRINCE is the second Phase III study that Apellis has initiated to evaluate APL-2 in this chronic blood disorder.
	+ Biotest AG announced the completion of a Phase III study[[29]](#footnote-29) investigating IgG Next Generation as immunomodulatory therapy in patients diagnosed with chronic primary immune thrombocytopenia (ITP), an autoimmune disease in which the immune system attacks and destroys the body's own platelets, the cells that prevent bleeding in blood vessels and facilitate clotting. In the trial 34 patients were treated. The evaluation of data is ongoing but initial results confirmed efficacy and safety expectations. "Final results are expected end of Q4/2019", said Jörg Schüttrumpf, Head of Corporate R&D. "This product will be a new generation of our polyvalent immunoglobulin portfolio."
	+ Inhibrx announced the enrolment of the first patient in a Phase I clinical trial of INBRX-101 ([NCT03815396](https://c212.net/c/link/?t=0&l=en&o=2566036-2&h=3329448073&u=https%3A%2F%2Fclinicaltrials.gov%2Fct2%2Fshow%2FNCT03815396&a=NCT03815396)). This is an Fc-fusion protein-based therapeutic candidate, a modified recombinant version of human alpha-1 antitrypsin (AAT) for the treatment of patients with alpha-1 antitrypsin deficiency (AATD). Inhibrx expects to announce preliminary functional pharmacokinetic (PK) data from the single dose escalation portion of this trial in the first half of 2020.
	+ [Rocket Pharmaceuticals, Inc.](https://cts.businesswire.com/ct/CT?id=smartlink&url=http%3A%2F%2Fwww.rocketpharma.com%2F&esheet=52087671&newsitemid=20190904005325&lan=en-US&anchor=Rocket+Pharmaceuticals%2C+Inc.&index=1&md5=b98b98eba86d252ecd42cf7e3b65d513) announced the US Phase II clinical development plan for RP-L102, the company’s lentiviral vector -based gene therapy for the treatment of Fanconi Anaemia. Based on feedback from a recent End-of-Phase I meeting with the US Food and Drug Administration (FDA), Rocket plans to open enrolment for the US Phase II trial of RP-L102 in the fourth quarter of 2019Disease.
	+ A long-term follow-up assessment of the EXTEND study found[[30]](#footnote-30) that eltrombopag not only increases platelet counts and reduces bleeding and bruising in patients with chronic immune thrombocytopenia (ITP), but also significantly improves health-related quality of life.
	+ Findings[[31]](#footnote-31) from a systematic review and network meta-analysis of clinical outcomes in patients with persistent immune thrombocytopenia (ITP) indicate that second-line treatment with the thrombopoietin receptor stimulators eltrombopag and romiplostim provides high efficacy and safety, particularly in comparison with treatment with rituximab.
1. Regulatory

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

* + Mustang Bio ([MBIO](https://seekingalpha.com/symbol/MBIO)) released an [announcement](https://seekingalpha.com/pr/17610692-mustang-bio-st-jude-children-s-research-hospital-announce-mbminus-107-lentiviral-gene-therapy) that the FDA has designated MB-107, its lentiviral gene therapy, a Regenerative Medicine Advanced Therapy (RMAT)[[32]](#footnote-32) for the treatment of the rare inherited disorder X-linked severe combined immunodeficiency, popularly known as “bubble boy disease”. The company is developing MB-07 with St. Jude Children's Research Hospital in Tennessee.
	+ The US Food and Drug Administration (FDA) has approved a new [whole blood test](https://www.mdmag.com/specialty/cardiology) for donor screening for Babesia[[33]](#footnote-33).
	+ England’s health technology assessment body (NICE[[34]](#footnote-34)) has recommended the use of Takhzyro (lanadelumab) in patients with hereditary angioedema, but only in specific circumstances and provided it is supplied at the agreed discounted price.
	+ The FDA is giving [priority review](https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review) to [Global Blood Therapeutics](https://www.gbt.com/)‘ application for approval of [voxelotor](https://www.gbt.com/programs/scd/voxelotor/) as a treatment for sickle cell disease[[35]](#footnote-35). This oral and once daily therapy is designed to increase the affinity of sickled haemoglobin molecules for oxygen. This prevents red blood cells from sticking to each other and forming clumps[[36]](#footnote-36). An FDA decision is expected on or before 26 February 2020.
1. 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.*

* + On 3 September Roche extended for the sixth time the deadline for its share tender offer to purchase all of the outstanding shares of common stock of Spark Therapeutics. The companies said in a joint statement: “The offer was extended to provide additional time for the US Federal Trade Commission (FTC) and the UK Competition and Markets Authority (CMA) to complete their previously disclosed reviews of Roche’s pending acquisition of Spark. The parties remain committed to the transaction and are working cooperatively and expeditiously with the FTC and the CMA.”
	+ Dutch company Pharvaris has raised funds for the clinical development of an oral treatment for hereditary angioedema. They will be applied tothe clinical progress of Pharvaris’ oral small molecule treatment. The drug has begun a Phase I trial, with a phase II trial expected to begin early next year.
	+ On August 22, in the US ADMA [announced](https://ir.admabiologics.com/press-releases/detail/446/adma-biologics-announces-commercial-relaunch-and-its-first) “the commercial relaunch and its first commercial sales of BIVIGAM,” their IVIG product. Given the nationwide shortage of immunoglobulin the timing was opportune. The company also said it expected to launch ASCENIV before the end of the year. **ASCENIV** is a plasma-derived, polyclonal, immune globulin intravenous (human) 10% liquid.
1. Specific country events
	* SK Plasma from South Korea has signed an agreement with Indonesia’s state-run PT Bio Farma and the Red Cross Society. The agreement focusses on registering SK’s finished products and exporting them to Indonesia; collecting local plasma in Indonesia and contract manufacturing at its plant in Andong, in South Korea’s North Gyeongsang Province; and transferring technology and establishing a fractionation plant run by PT Bio Farma in Indonesia. SK Plasma said it is planning to advance into other parts of Southeast Asia and the Middle East. It expects its new plant in Andong Bio Industrial Complex with fractionation capacity of 600,000 litres of plasma per year will underpin its global expansion.
	* The Western Victoria Primary Health Network launched a rural health resource in Horsham. The Rural Health chapter of the online Health Pathways resource will provide information that will allow rural-based health professionals to be better equipped to deal with agriculture-related medical issues.
	* In the US, the newly established Minnesota Center for Prion Research and Outreach (MNPRO) within the University of Minnesota College of Veterinary Medicine, is hoping to develop real-time diagnostic tests to identify CWD, or chronic wasting disease, in deer, moose, caribou and reindeer. It is a contagious, fatal neurological disorder. CWD is not known to transition to humans, but the fact that bovine spongiform encephalopathy, “mad cow” disease, another prion-type contagion, did transfer to humans, is a matter for concern.
	* A report[[37]](#footnote-37) of the first five years of babesiosis surveillance from the US Centers for Disease Control and Prevention (CDC) shows a significant increase in incidence. The report also refers to Lyme disease.
	* The Irish Blood Transfusion Service has cancelled a 15-year-long donor deferral policy for people who have lived in Britain because the transfusion transmission risk of “mad cow disease" is now regarded as remote.
2. 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.*

* + A study[[38]](#footnote-38) has confirmed that in patients with severe sepsis, the sensitivity of blood cultures decreased after initiation of empirical antimicrobial therapy. In a press release, one of the contributors to the study[[39]](#footnote-39) said: “This is a constant debate in the medical field. Emergency medicine physicians want to administer antibiotics as soon as possible because it prevents mortality, whereas internal medicine physicians want two sets of blood cultures before antibiotics are administered so they can more reliably diagnose the organism.” Akhter concluded: “Although administering antibiotics to septic patients is important, it is imperative to get at least one blood culture before providing treatment.
	+ Researchers in dermatology say**[[40]](#footnote-40)** that platelet-rich plasma, or PRP, appears to facilitate healing in ulcers as it changes the matrix metalloproteinase and cytokine expression shortly after topical application. Michael J Hesseler**[[41]](#footnote-41)** and colleagues wrote: “topical activated PRP or autologous leukocyte- and platelet-rich fibrin applied once to twice a week for 3 to 6 weeks improves wound healing and support a standardized treatment regimen for PRP in chronic ulcers.”
	+ Researchers studied[[42]](#footnote-42) the effect of silver nanoparticles (AgNPs) on human blood platelet function. They found “all tested functionalized AgNPs inhibited platelet aggregation at nontoxic concentrations” and concluded that “functionalized AgNPs can be used as an antiplatelet agent or in design and manufacturing of blood-facing medical devices, such as vascular grafts, stents, heart valves, and catheters.
	+ Scientists report**[[43]](#footnote-43)** that supercooling human livers to -4C triples the time they can be kept before transplant, compared with keeping them on ice.
1. 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

* + Researchers say[[44]](#footnote-44) mosquitoes are more prone to acquire the dengue virus when they feed on blood with low levels of iron.
	+ An antibody which neutralizes the Zika virus was discovered three years ago by collaborating researchers at Vanderbilt University Medical Center (VUMC) and at Washington University School of Medicine in St Louis. This antibody (ZIKV-117) binds to part of the Zika virus. Now Batavia Biosciences, a clinical research company, has signed a licence agreement to use a cell line expression system from Horizon Discovery for the production of a potent Zika virus-neutralizing antibody. It will collaborate with VUMC and IDBiologics, a company which develops human antibodies to infectious diseases.

Influenza

* + A team led by Professor Ervin Fodor[[45]](#footnote-45) has identified the structure of a flu virus protein vital to its survival; this could potentially facilitate development of new flu treatments[[46]](#footnote-46).
	+ The American Academy of Pediatrics (AAP) confirmed having no preference between the live-attenuated influenza vaccine (LAIV) or inactivated influenza vaccines (IIV) for children, but it said both types will be quadrivalent (four-strain) and widely available. All children 6 months and older are encouraged to be vaccinated.
	+ At the Options for the Control of Influenza (OPTIONS X) Conference in Singapore, Seqirus presented new data that demonstrated circulating influenza B/Victoria viruses are a closer match to cell-based B/Vic vaccine viruses compared with egg-based B/Vic vaccine viruses[[47]](#footnote-47). This built on an earlier analysis that evaluated the degree of matching between circulating influenza A (H3N2) viruses and corresponding H3N2 cell and egg-based vaccine viruses, underlining the potential role of egg-adaptation in variable vaccine effectiveness[[48]](#footnote-48). Cultivating influenza viruses in eggs can cause changes in the vaccine strain that may lead to the body's immune system producing antibodies that are less closely matched to the circulating influenza viruses. Cell grown candidate vaccine viruses (CVVs) may yield vaccine virus strains that better match the circulating influenza virus strains[[49]](#footnote-49).Seqirus is the largest cell-based influenza vaccine manufacturer in the US.  Its facility in Holly Springs, North Carolina that uses cell-based technology was built in partnership with the US Biomedical Advanced Research and Development Authority (BARDA) to support pandemic preparedness.

Ebola virus disease

* + Scientists say[[50]](#footnote-50) that creating mutations in a key protein that helps Ebola avoid the body’s defences can prevent the virus from making its hosts sick and activate protective immunity.
	+ For the first twelve months of the Ebola outbreak in the Democratic Republic of Congo, Merck’s vaccine has been administered. Now a second vaccine, from Johnson &Johnson, is being introduced. Unlike the Merck vaccine, which is delivered in a single dose, the Johnson &Johnson vaccine requires two shots eight weeks apart.
	+ The US Agency for International Development (USAID), announced an additional $US21 million humanitarian aid for the eastern Democratic Republic of the Congo (DRC). This brings USAID's total funding for the DRC's Ebola outbreak to almost $US 158 million. The agency said in a press statement: "With this funding, the United States is working with partners to provide life-saving assistance, including measures to prevent and control infections in health facilities, enhanced disease surveillance, training for health care workers, communities, promotion of safe and dignified burials, and food to support people and efforts to engage communities affected by Ebola."
	+ A new study[[51]](#footnote-51) suggests that Ebola survivors are at an increased risk of death within the first year of hospital discharge.

Other diseases

* + The [World Health Organization’s Global Preparedness Monitoring Board](https://apps.who.int/gpmb/annual_report.html) reported that the world is at a heightened risk for a deadly global pandemic that could kill up to 80 million people. Recommendations include investing in preparedness, conducting exercises, ensuring resources are in place to develop and distribute counter- measures, and making adequate funding available for poorer nations to grow their own health systems.
	+ Moderna announced positive interim results from its Phase I cytomegalovirus (CMV) vaccine (mRNA-1647) study and progress toward Phase II and pivotal trials. The company’s investigational Zika vaccine (mRNA-1893), currently in a Phase 1 study, was [recently granted FDA Fast Track designation](https://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Finvestors.modernatx.com%2Fnews-releases%2Fnews-release-details%2Fmoderna-receives-fda-fast-track-designation-zika-vaccine-mrna&esheet=52092063&newsitemid=20190912005220&lan=en-US&anchor=recently+granted+FDA+Fast+Track+designation&index=3&md5=8f307b8b0c9c6b35bd40582015f8e945). Moderna has so far demonstrated positive Phase I data readouts for six prophylactic vaccines (H10N8, H7N9, RSV, chikungunya virus, hMPV+PIV3 and CMV).
	+ A study[[52]](#footnote-52) has concluded that nondaily pre-exposure prophylaxis for HIV (PrEP) was less effective than daily PrEP, especially among MSM in the United States where the sex act coverage associated with daily use was substantially higher.
	+ Queenslanders have been warned to avoid heat-stressed bats which have fallen out of trees. Australian bat lyssavirus (ABLV) is a rabies-like virus that can be transmitted from bats to humans, causing serious illness which can lead to paralysis, delirium, convulsions and death.
	+ The first case in Australia of extensively drug-resistant typhoid has been reported in a girl aged 20 months returning after three months in Pakistan[[53]](#footnote-53). Doctors have warned Australia is not immune to this "emerging threat".
1. Domagoj Mladinov et al., ”Effect of incubation with crystalloid solutions or medications on packed red blood cells”, *Transfusion*, first published 28 May 2019<https://doi.org/10.1111/trf.15353> [↑](#footnote-ref-1)
2. D5W (dextrose 5 per cent water) IV fluid [↑](#footnote-ref-2)
3. Williams, A.T *et al*. (2019) “Transfusion of Anaerobically or Conventionally Stored Blood After Hemorrhagic Shock”. *Shock*. 30 August 2019 [doi.org/10.1097/SHK.0000000000001386](http://doi.org/10.1097/SHK.0000000000001386). [↑](#footnote-ref-3)
4. from [BioPRIA](http://www.biopria.com.au/), based at Australia’s Monash University, together with industry partner Haemokinesis, a company involved in developing and distributing laboratory systems in the field of immunohaematology [↑](#footnote-ref-4)
5. Clare A Manderson et al., “Photothermal incubation of red blood cells by laser for rapid pre-transfusion blood group typing”, published 2 August 2019 in [Nature’s Scientific Reports](https://www.nature.com/articles/s41598-019-47646-y) **9**, Article number: 11221 (2019). [↑](#footnote-ref-5)
6. Nancy M. Cladel, at al., “**Papillomavirus can be transmitted through the blood and produce infections in blood recipients: Evidence from two animal models”.** Emerging Microbes & Infections, 2019; 8 (1): 1108 DOI: [10.1080/22221751.2019.1637072](http://dx.doi.org/10.1080/22221751.2019.1637072) [↑](#footnote-ref-6)
7. assistant professor of pathology and laboratory medicine at Pennsylvania State University College of Medicine [↑](#footnote-ref-7)
8. Carrie A Sims, “Effect of Low-Dose Supplementation of Arginine Vasopressin on Need for Blood Product Transfusions in Patients With Trauma and Hemorrhagic Shock; A Randomized Clinical Trial”, 28 August 2019 in *JAMA Surgery*. doi:10.1001/jamasurg.2019.2884 <https://jamanetwork.com/journals/jamasurgery/article-abstract/2749069> [↑](#footnote-ref-8)
9. #  Timothy M Bahr et al., “First report of using low‐titer cold‐stored type O whole blood in massive postpartum hemorrhage”, 30 August 2019,*Transfusion*, <https://doi.org/10.1111/trf.15492>

 [↑](#footnote-ref-9)
10. Monica Suet Ying Ng et al., “Fresh frozen plasma and platelet concentrate storage duration not associated with in hospital mortality risk”, 27 August 2019, *Vox Sanguinis,* <https://doi.org/10.1111/vox.12838> [↑](#footnote-ref-10)
11. Geoff Simon et al., “Impacts of Ageing on Anaemia Tolerance, Transfusion Thresholds and Patient Blood Management”, in [*Transfusion Medicine Reviews*](https://www.researchgate.net/journal/0887-7963_Transfusion_Medicine_Reviews)· [10.1016/j.tmrv.2019.03.001](http://dx.doi.org/10.1016/j.tmrv.2019.03.001) [↑](#footnote-ref-11)
12. Kshirsagar AV, Li X. “Long-term risks of intravenous iron in end-stage renal disease patients.” Adv Chronic Kidney Dis. 2019;26:292-297. <https://doi.org/10.1053/j.ackd.2019.05.001> [↑](#footnote-ref-12)
13. Steg PG. *Apixaban in the prevention of stroke and systemic embolism in patients with atrial fibrillation in real-life setting in France SNIIRAM study.* Presented at the European Study of Cardiology 2019 Congress, September 1, 2019; Abstract 1362. [↑](#footnote-ref-13)
14. Brian f Gage et al., “Effect of Low-Intensity vs Standard-Intensity Warfarin Prophylaxis on Venous Thromboembolism or Death Among Patients Undergoing Hip or Knee Arthroplasty: A Randomized Clinical Trial”, 3 September 2019, *Journal of the American Medical Association*  *JAMA*. 2019;322(9):834-842. doi:10.1001/jama.2019.12085 <https://jamanetwork.com/journals/jama/article-abstract/2749215> [↑](#footnote-ref-14)
15. Alexis Hure et al., “Identifying low value pathology test ordering in hospitalised patients: a retrospective cohort study across two hospitals”, *Pathology*[Volume 51, Issue 6](https://www.sciencedirect.com/science/journal/00313025/51/6), October 2019, Pages 621-627 <https://doi.org/10.1016/j.pathol.2019.06.003> [↑](#footnote-ref-15)
16. Madhvi Rajpurkar et al., “[Thrombotic events with recombinant activated factor VII (rFVIIa) in approved indications are rare and associated with older age, cardiovascular disease, and concomitant use of activated prothrombin complex concentrates (aPCC)](https://www.dovepress.com/thrombotic-events-with-recombinant-activated-factor-vii-rfviia-in-appr-peer-reviewed-fulltext-article-JBM)” , 18 September 2019, [*Journal of Blood Medicine.*](https://www.dovepress.com/journal-of-blood-medicine-journal) Volume 2019:10 Pages 335—340. **DOI** <https://doi.org/10.2147/JBM.S219573>

Note: One of the four authors is identified as an employee of Novo Nordisk [↑](#footnote-ref-16)
17. NovoSeven initiates a molecular cascade that will allow for blood to clot. It is an effective way to prevent bleeding in people with haemophilia; however, it carries the risk of causing blood clots that can block blood flow. [↑](#footnote-ref-17)
18. The new analysis used clinical data collected from three pivotal Phase III trials — HAVEN 1 ([NCT02622321](https://clinicaltrials.gov/ct2/show/NCT02622321)), HAVEN 2 ([NCT02795767](https://clinicaltrials.gov/ct2/show/NCT02795767)), and HAVEN 4 ([NCT03020160](https://clinicaltrials.gov/ct2/show/NCT03020160)). The analysis was the result of a collaboration between Novo Nordisk and Roche. Recommendations included that further studies be conducted with larger groups of patients to examine further the safety of simultaneous clinical use of NovoSeven and Hemlibra. [↑](#footnote-ref-18)
19. Gallia G Levy, et al., “[Safety analysis of rFVIIa with emicizumab dosing in congenital hemophilia A with inhibitors: Experience from the HAVEN clinical program](https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.14491),” in [The Journal of Thrombosis and Haemostasis](https://onlinelibrary.wiley.com/journal/15387836)first published 24 May 2019 <https://doi.org/10.1111/jth.14491> [↑](#footnote-ref-19)
20. [published on September 10 in the journal Annals of Internal Medicine](https://annals.org/aim/article-abstract/2749729/establishing-prevalence-prevalence-birth-hemophilia-males-meta-analytic-approach-using) [↑](#footnote-ref-20)
21. The previous estimate was no more than 500,000 [↑](#footnote-ref-21)
22. The researchers’ estimates were based on patient registries in Australia, Britain, Canada, France, Italy, and New Zealand as the basis of their analysis, focusing on male babies born in each nation. They sorted the patients in the registries by year of birth and compared them with statistics on total male newborns for each year. They estimated that for every 100,000 males globally 21 have haemophilia A or B (7 of whom have a more severe form of the condition). Among newborns, per 100,000 male babies, 29 have inherited the defect in the F8 (haemophilia A) or F9 (haemophilia B) gene, and 12 will have a severe form. [↑](#footnote-ref-22)
23. at the Joint 10th BIC and the 3rd Inhibitor International Conferences (Italy), 6 – 8 September 2019. **Abstract title: *B-AMAZE, a Phase 1/2 trial of a novel investigational adeno associated virus (AAV) gene therapy (FLT180a) in subjects with severe or moderately severe haemophilia B (HB)*** [↑](#footnote-ref-23)
24. HOPE-B builds on data generated by the company’s ongoing Phase IIb trial ([NCT03489291](https://clinicaltrials.gov/ct2/show/NCT03489291)) of AMT-061, which showed that a single infusion of the therapy is able to increase the activity of FIX up to 54 per cent of its normal levels (average of 45 per cent of its normal levels considering all participants), up to six months after dosing. None of the patients had any spontaneous bleeding during the trial, had to resort to FIX replacement therapy to control bleeds or experienced a significant loss of FIX activity. In an ongoing Phase I/II trial ([NCT02396342](https://clinicaltrials.gov/ct2/show/NCT02396342?term=NCT02396342&rank=1)) of [AMT-060](http://www.uniqure.com/gene-therapy/hemophilia.php), uniQure’s first-generation gene therapy to treat hemophilia B, the company demonstrated that all 10 patients enrolled had achieved stable and sustained increases in FIX activity levels, which were reflected in long-term benefits to their health over the course of 3.5 years. [↑](#footnote-ref-24)
25. Glaivy Batsuli et al., “Immune tolerance induction in paediatric patients with haemophilia A and inhibitors receiving emicizumab prophylaxis”, [*Haemophilia*](https://onlinelibrary.wiley.com/journal/13652516), 2 August 2019, <https://doi.org/10.1111/hae.13819> [↑](#footnote-ref-25)
26. Roche’s Hemlibra is a non-factor replacement therapy to treat haemophilia A patients with or without inhibitors. It functions as a [bypassing agent](https://hemophilianewstoday.com/bypassing-agents/) to mimic the activity of FVIII. While effective in preventing bleeding, Hemlibra does not eradicate FVIII inhibitors. Immune tolerance induction (ITI) —where FVIII is administered over a period until the body recognizes the product without reacting against it — is the only strategy known to remove inhibitors and re-establish a normal response to FVIII replacement therapy. [↑](#footnote-ref-26)
27. Researchers at [Emory University School of Medicine](https://www.med.emory.edu), working with the [Aflac Cancer and Blood Disorders Center of Children’s Healthcare of Atlanta](https://www.choa.org/medical-services/cancer-and-blood-disorders), reviewed seven children between 21 months and 12 years old. They were given a combination of ITI with FVIII infusions three times a week plus Hemlibra. They were followed for a median time of 35 weeks. Three of the seven experienced either a complete clearing of inhibitors or a drop to unmeasurable levels. Three of the seven patients had no bleeding events; nine bleeding events were experienced among the other four during the follow-up period. No blood clots or other adverse events were recorded. Six children had surgery during the study period, without major complications or excess bleeding. Length of hospital stays averaged one to two days, rather than three to seven days. [↑](#footnote-ref-27)
28. Robert Sidonio, an associate director of the Hemostasis and Thrombosis Program at Children’s Healthcare of Atlanta, and an assistant professor of paediatrics at Emory. [↑](#footnote-ref-28)
29. Study no. 992 is a phase III, open label, prospective, multicentre trial investigating the clinical efficacy and safety of IgG Next Generation as immunomodulatory therapy in adult patients diagnosed with chronic primary immune thrombocytopenia (ITP) at high risk of bleeding or before surgery to correct the platelet count. Patients are randomized in a 1:1 ratio to receive either 1 g/kg bodyweight per day for 2 consecutive days or 0.4 g/kg bodyweight per day on 5 consecutive days. The primary objective of this study is to determine the percentage of patients who achieve response. A response is defined as a platelet count of >=30×109/L and at least a 2-fold increase of the baseline count and the absence of bleeding. More information about the study design can be found at [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu) (EudraCT Number: 2015-003653-17) [↑](#footnote-ref-29)
30. Abderrahim Khelif, at al.,“Changes in health‐related quality of life with long‐term eltrombopag treatment in adults with persistent/chronic immune thrombocytopenia: Findings from the EXTEND study”, *American Journal of Haematology*, Volume 94, Issue 2, pp 200-208

<https://doi.org/10.1002/ajh.25348> [↑](#footnote-ref-30)
31. Puavilai T, Thadanipon K, Rattanasiri S, et al. [Treatment efficacy for adult persistent immune thrombocytopenia: a systematic review and network meta-analysis](https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.16161). British Journal of Haematology doi:10.1111/bjh.16161 First published: 18 August 2019 <https://doi.org/10.1111/bjh.16161> [↑](#footnote-ref-31)
32. RMAT is similar to Breakthrough Therapy status for drugs/biologics. It provides for the accelerated review of the marketing application and more intensive guidance on development. [↑](#footnote-ref-32)
33. Babesia parasite is usually transmitted to humans via infected tick bites but may also be transmitted via blood transfusion or from mother to foetus in pregnancy. The parasite destroys red blood cells. [↑](#footnote-ref-33)
34. The National Institute for Health and Care Excellence [↑](#footnote-ref-34)
35. The FDA previously gave voxelotor [Fast Track](https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track) status and awarded it [Orphan Drug](https://www.fda.gov/industry/developing-products-rare-diseases-conditions/designating-orphan-product-drugs-and-biological-products), [Rare Pediatric Disease](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-pediatric-disease-priority-review-vouchers) and [Breakthrough Therapy](https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy) designations. The [European Medicines Agency](http://www.ema.europa.eu/ema/) (EMA) included voxelotor in its [Priority Medicines (PRIME)](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp) program. [↑](#footnote-ref-35)
36. The application is backed by findings from the ongoing Phase III HOPE trial ([NCT03036813](https://clinicaltrials.gov/ct2/show/NCT03036813)), assessing safety and efficacy in patients aged 12 to 65. The trial enrolled 274 patients at 60 institutions across 12 countries, who were randomly assigned to voxelotor at a daily dose of either 900 mg or 1500 mg, or to a non-active placebo, for at least 24 weeks. [Trial findings](https://sicklecellanemianews.com/2019/06/20/voxelotor-increases-hemoglobin-reduces-anemia-adults-adolescents-scd-hope-trial/), were [published](https://www.nejm.org/doi/10.1056/NEJMoa1903212) in [The New England Journal of Medicine](https://www.nejm.org/). At the highest dose, voxelotor reduced the levels of two established biomarkers of red blood cell damage: reticulocytes (by 19.9%) and bilirubin (by 29.1%). Voxelotor at either dose raised haemoglobin levels in almost half of all treated patients (48.4%), compared with 9% in those dosed with a placebo. Treatment had a positive effect on preventing a [vaso-occlusive crisis](https://sicklecellanemianews.com/vaso-occlusive-crisis/) over time compared to placebo. The incidence of adverse events was similar in both treated and untreated groups, and most were found to be unrelated to voxelotor or placebo. Voxelotor use considered to be safe and was well-tolerated by [↑](#footnote-ref-36)
37. Gray EB, Herwaldt BL. MMWR Surveill Summ. 2019;68(No. SS-6):1-11, <http://dx.doi.org/10.15585/mmwr.ss6806a1>. [↑](#footnote-ref-37)
38. Matthew P Cheng et al., “Blood Culture Results Before and After Antimicrobial Administration in Patients With Severe Manifestations of Sepsis: A Diagnostic Study”, Annals of Internal Medicine, 2019;171(8):547-554. **DOI:** 10.7326/M19-1696 <https://annals.org/aim/article-abstract/2751453/blood-culture-results-before-after-antimicrobial-administration-patients-severe-manifestations> [↑](#footnote-ref-38)
39. **Murtaza Akhter,**  assistant professor in the department of emergency medicine at the University of Arizona College of Medicine – Phoenix [↑](#footnote-ref-39)
40. Michael J Hesseler et al., “Platelet-rich plasma and its utility in medical dermatology: A systematic review”, Journal of the American Academy of Dermatology, DOI: <https://doi.org/10.1016/j.jaad.2019.04.037> [↑](#footnote-ref-40)
41. Department of Dermatology, University of Michigan [↑](#footnote-ref-41)
42. #  Justyna Hajtuch et al., “Effects of functionalized silver nanoparticles on aggregation of human blood platelets”, *Dovepress* 11 September 2019 Volume 2019:14 Pages 7399—7417 **DOI** <https://doi.org/10.2147/IJN.S213499>

 [↑](#footnote-ref-42)
43. Reinier J DeVries et al., “Supercooling extends preservation time of human livers”, 9 September 2019, [*Nature Biotechnology*](https://www.nature.com/nbt) volume 37, pages1131–1136 (2019) <https://www.nature.com/articles/s41587-019-0223-y> [↑](#footnote-ref-43)
44. Mos Yibin Zhu, et al., “**Host serum iron modulates dengue virus acquisition by mosquitoes**.” Nature Microbiology, 2019; DOI: [10.1038/s41564-019-0555-x](http://dx.doi.org/10.1038/s41564-019-0555-x) [↑](#footnote-ref-44)
45. Sir William Dunn School of Pathology, University of Oxford [↑](#footnote-ref-45)
46. Ervin Fodor et al., “Structures of influenza A virus RNA polymerase offer insight into viral genome replication”, [*Nature*](https://www.nature.com/nature) volume 573, pages287–290 (2019) <https://www.nature.com/articles/s41586-019-1530-7> [↑](#footnote-ref-46)
47. Rajaram S., P. Suphaphiphat, M. Haag, et al. (2019). *Retrospective evaluation of antigenic similarity between egg-derived Versus cell-derived influenza vaccine reference strains and circulating influenza B-Victoria and Yamagata viruses.* Presented at OPTIONS X, August 2019. [↑](#footnote-ref-47)
48. Rajaram S., Van Boxmeer J., Leav B., et al. (2018). Retrospective evaluation of mismatch from egg-based isolation of influenza strains compared to cell-based isolation and the possible implications for vaccine effectiveness. Presented at IDWeek 2018, October 2018. [↑](#footnote-ref-48)
49. Centers for Disease Control (CDC). (2019). *Cell-Based Flu Vaccines.* [https://www.cdc.gov/flu/prevent/cell-based.htm](https://c212.net/c/link/?t=0&l=en&o=2566747-1&h=172802988&u=https%3A%2F%2Fwww.cdc.gov%2Fflu%2Fprevent%2Fcell-based.htm&a=https%3A%2F%2Fwww.cdc.gov%2Fflu%2Fprevent%2Fcell-based.htm). Accessed August 2019. Also Centers for Disease Control (CDC). (2018). *Selecting Viruses for the Seasonal Influenza Vaccine.* [https://www.cdc.gov/flu/prevent/vaccine-selection.htm](https://c212.net/c/link/?t=0&l=en&o=2566747-1&h=4155688940&u=https%3A%2F%2Fwww.cdc.gov%2Fflu%2Fprevent%2Fvaccine-selection.htm&a=https%3A%2F%2Fwww.cdc.gov%2Fflu%2Fprevent%2Fvaccine-selection.htm). Accessed August 2019. [↑](#footnote-ref-49)
50. Courtney Woolsey et al., “A VP35 Mutant Ebola Virus Lacks Virulence but Can Elicit Protective Immunity to Wild-Type Virus Challenge”, [Cell Reports](https://doi.org/10.1016/j.celrep.2019.08.047). . 17 September 2019. [Volume 28, ISSUE 12](file:///C%3A%5CUsers%5C83556484%5CAppData%5CLocal%5CMicrosoft%5CWindows%5CTemporary%20Internet%20Files%5CContent.Outlook%5CUEM3BXP0%5CVolume%2028%2C%20ISSUE%2012), P3032-3046.e6 <https://doi.org/10.1016/j.celrep.2019.08.047> [↑](#footnote-ref-50)
51. ###  [*Keita M, et al "Subsequent mortality in survivors of Ebola virus disease in Guinea: a nationwide retrospective cohort study" Lancet Infect Dis 2019; DOI: 10.1016/S1473-3099(19)30313-5.*](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2819%2930313-5/fulltext) And the associated comment:  [*Fausther-Bovendo H, Kobinger G "Increased mortality in survivors of Ebola virus disease" Lancet Infect Dis 2019; DOI: 10.1016/S1473-3099(19)30429-3.*](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2819%2930429-3/fulltext)

 [↑](#footnote-ref-51)
52. Dobromir Dimitrov, et al., “Predicted Effectiveness of Daily and Nondaily Preexposure Prophylaxis for Men Who Have Sex With Men Based on Sex and Pill-taking Patterns From the Human Immuno Virus Prevention Trials Network 067/ADAPT Study”, 22 August 2019, Clinical Infectious Diseases, ciz799, <https://doi.org/10.1093/cid/ciz799> [↑](#footnote-ref-52)
53. Philip N Britton et al., **“**First reported case of extensively drug‐resistant typhoid in Australia”,

 Letter published online 16 September 2019, *The Medical Journal of Australia*, Med J Aust 2019; 211 (6): . || doi: 10.5694/mja2.50316 <https://www.mja.com.au/journal/2019/211/6/first-reported-case-extensively-drug-resistant-typhoid-australia> [↑](#footnote-ref-53)