

Monitoring International Trends

Posted November/ December 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 7 to 22. Highlights are listed below:

Safety and Patient Blood Management (begins page 6)

Appropriate transfusion; bleeding risk (p6)

- Researchers reported that transfusions using red blood cells that have spent seven days or less in storage are no more beneficial than older red blood cells in reducing the risk of organ failure or death in critically ill children.

Other (p6)

- Johnson & Johnson's Ethicon unit has launched a biologic protein spray, designed to seal off and control excessive bleeding.

Products and Treatments (begins page 6)

Treating haemophilia (p6)

- The 61st American Society of Hematology (ASH) Annual Meeting was held 7-10 December in Orlando, Florida. Presentations relevant to treatment of haemophilia included research and development outcomes for Takeda, Roche, and Freeline.
- Enzyre is collaborating with Takeda to develop a diagnostic device that will allow haemophilia patients to determine their coagulation status at home.

Treating beta thalassemia and sickle cell disease (p8)

- On 6 December The American Society of Hematology released recommendations aimed at establishing uniformity and global standards for clinical trial endpoints used to evaluate new therapies for sickle cell disease.
- At the ASH Annual Meeting, presentations relevant to treatment of thalassemia and sickle cell disease included research and development outcomes for Global Blood Therapeutics, Sangamo Therapeutics, bluebird bio, Forma Therapeutics, Editas, and Beam Therapeutics.

- Agios Pharmaceuticals announced that clinical proof-of-concept has been established based on a preliminary analysis of a small Phase II trial of mitapivat (AG-348) in patients with non-transfusion-dependent thalassemia.
- A study has suggested that treatment with delta-aminolevulinate, a precursor of heme — the part of haemoglobin that carries oxygen — could be a therapeutic option for people with sickle cell anaemia and β -thalassemia.

Treating other conditions (p11)

- At the ASH meeting, conditions whose treatment was discussed included primary immune thrombocytopenia (ITP), and paroxysmal nocturnal haemoglobinuria (PNH).
- BioCryst Pharmaceuticals presented two abstracts (relevant to treating hereditary angioedema) at the Annual Scientific Meeting of the American College of Allergy, Asthma & Immunology.

Regulatory matters (begins page 12)

- BioMarin Pharmaceuticals is seeking marketing approval in Europe for its investigational gene therapy, valoctocogene roxaparvovec, for the treatment of adults with severe haemophilia A.
- Global Blood Therapeutics announced that the FDA had granted accelerated approval for Oxbryta (voxelotor) tablets for the treatment of sickle cell disease in adults and children 12 years of age and older.
- The Canadian Drug Expert Committee (CDEC) has recommended that Takhzyro (lanadelumb) be reimbursed by public drug plans when used as a preventive treatment for hereditary angioedema (HAE) attacks in patients 12 and older.
- The FDA approved Novartis' Adakveo (crizanlizumab) for sickle cell patients 16 and older.
- Octapharma's human fibrinogen concentrate Fibryga has received approval for use in treatment of acquired fibrinogen deficiency in 15 European countries.

Market structure and company news (begins page 14)

- The US Federal Trade Commission cleared Roche's \$US 4.8 billion buyout of Spark Therapeutics, after a 10-month investigation.
- Syros Pharmaceuticals and Global Blood Therapeutics announced that they have entered into a collaboration to discover, develop and commercialize novel therapies for sickle cell disease and beta thalassemia.
- Grifols announced the launch of Xembify (immune globulin subcutaneous human-klhw), the company's first 20 per cent subcutaneous immunoglobulin therapy for the treatment of patients 2 years of age and older with primary immunodeficiency (PI).

Specific country events (begins page 14)

- Heparin, currently derived from pig intestines, is widely used to treat heart attacks and prevent potentially lethal blood clots. China has been the primary source of the drug, and with the crisis there posed by African swine fever the world needs to develop alternate supplies.

Research not included elsewhere (begins page14)

- A prospective trial in the Netherlands suggested that two biomarkers may assist in creating a prediction model for haemorrhage risk in patients with thrombocytopaenia due to haematologic malignancy.
- Grifols announced that recent results from a clinical trial of its Alzheimer's treatment showed a reduction of the disease's progression in patients with mild and moderate conditions.
- An editorial in *The BMJ* has given voice to international researchers, clinicians, regulators, and advocates to suggest building “an evidence base for healthcare that is free of commercial influences”.
- An international research team has concluded that treating high blood pressure reduced dementia risk by 12 per cent and the risk of developing Alzheimer's disease by 16 per cent.

Infectious diseases (begins page 15)

Mosquito-borne diseases (p15)

- Roche launched its *in vitro* diagnostic test for the Zika virus in countries accepting the CE mark, to screen the donated blood supply. The test is for use on the company's cobas 6800/8800 automated molecular testing systems.
- The FDA approved the cobas test to detect Zika virus in blood donations.
- Emergex Vaccines Holding Limited announced the successful completion of preclinical testing of its lead vaccine candidate for dengue.
- A new study suggests that an autoimmune attack on uninfected red blood cells contributes to anaemia in people with malaria.

Influenza (p16)

- The US National Institute of Allergy and Infectious Disease awarded the Emory Institute of Drug Development a \$US 15.89 million contract to develop and test its influenza drug candidate, EIDD-2801, in humans.
- Vaccitech Ltd reported it is progressing the clinical development of its universal influenza A vaccine.
- Osivax has signed an agreement with the US National Institute of Allergy and Infectious Diseases to continue development of the company's universal flu vaccine candidate.

Ebola virus disease (p17)

- The World Health Organization (WHO) announced that it had prequalified Merck's Ebola vaccine so United Nations agencies and Gavi, the Vaccine Alliance, can buy the vaccine for use in at-risk countries.

MERS-CoV (p17)

- Of the 15 cases of MERS-CoV reported to the World Health Organization in October, four involved healthcare-related clusters.

Other diseases (p17)

- Samoa has suffered a severe measles outbreak with continuing fatalities.
- Minal K. Patel, from WHO in Geneva, and colleagues found that estimated measles-containing vaccine coverage increased globally from 72 to 86 per cent during 2000 to 2018; annual reported measles incidence decreased from 145 to 49 cases per 1 million population (66 percent decrease); and annual estimated measles deaths decreased from 535,600 to 142,300 (73 percent decrease).
- Dr Marion Kainer, the head of infectious diseases at Western Health in Victoria, described the *Candida auris* fungus as 'really unusual', and called for Australia as a matter of urgency to add the fungus to the National Notifiable Diseases List. Victoria will list the fungus as a notifiable disease early in 2020.
- For the calendar year 2019, up to 30 November, more than 1,500 Queenslanders were diagnosed with whooping cough (pertussis).
- The Nipah virus carried by bats and pigs was identified in 1999 in Malaysia and Singapore and has since spread as far as India and Bangladesh. Mortality rates from outbreaks have been between 40 and 90 per cent. The virus is regarded as having "serious epidemic potential".

Detailed Report

Contents

1. SAFETY AND PATIENT BLOOD MANAGEMENT	6
Appropriate Transfusion; Bleeding Risk	6
Other	6
2. PRODUCTS AND TREATMENTS	6
Treating haemophilia	6
Treating beta thalassaemia and sickle cell disease	8
Treating other conditions	11
3. REGULATORY.....	12
4. MARKET STRUCTURE AND COMPANY NEWS.....	14
5. SPECIFIC COUNTRY EVENTS.....	14
6. RESEARCH NOT INCLUDED ELSEWHERE	14
7. INFECTIOUS DISEASES	15
Mosquito-borne diseases	15
Influenza	16
Ebola virus disease	17
MERS-CoV	17
Other diseases	17

1. Safety and patient blood management

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

Appropriate Transfusion; Bleeding Risk

- Researchers reported¹ that transfusions using red blood cells that have spent seven days or less in storage are no more beneficial than older red blood cells in reducing the risk of organ failure or death in critically ill children. The researchers noted some caveats. They did not test whether the use of the oldest red cells permitted (35-42 days old) affected outcomes, or if fresh red cells might improve outcomes for children requiring large-volume red cell transfusions. In this study the children received low-volume red cell transfusions. The study was part-funded by the US National Heart, Lung, and Blood Institute (NHLBI).

Other

- Johnson & Johnson's Ethicon unit has launched a biologic protein spray, designed to seal off and control excessive bleeding during open surgeries or minimally invasive procedures. Vistaseal results from collaboration with Grifols and combines human fibrinogen and thrombin. The spray is delivered from a pre-filled syringe. It quickly adheres and forms a clot over the bleed. It has demonstrated clinical success in high-risk patients—those with multiple morbidities including bleeding disorders, diabetes or organ failure, or those taking blood thinners or antiplatelet therapies.

2. 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

- The [61st American Society of Hematology \(ASH\) Annual Meeting](#) was held 7-10 December in Orlando, Florida.
 - i. Takeda delivered haematology poster presentations which it claimed underscored its “commitment to advancing treatments for rare bleeding disorders by incorporating real-world data and developing innovative adeno-associated virus (AAV) gene therapies”².

¹ Philip C Spinella et al., “Effect of Fresh vs. Standard-issue Red Blood Cell Transfusions on Multiple Organ Dysfunction Syndrome in Critically Ill Pediatric Patients: A Randomized Clinical Trial”, published online 10 December 2019 in the *Journal of the American Medical Association*.

DOI: [10.1001/jama.2019.17478](https://doi.org/10.1001/jama.2019.17478)
[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01977547), ID: [NCT01977547](https://clinicaltrials.gov/ct2/show/study/NCT01977547)

² **ADYNOVATE [Antihemophilic Factor (Recombinant), PEGylated]**: In the poster *Real-World Age-Stratified FVIII Consumption and Bleed Outcomes Before and After Switching to Rurioctocog Alfa Pegol in a Retrospective, Observational Study Using US Specialty Pharmacy Data*, ([abstract 2411](#)) outcomes found those who switched experienced a significant 40-50 per cent decrease in their annualized bleed rate.

Hemophilia A: In the poster *Cost-Effectiveness Model of Recombinant FVIII Versus Emicizumab Treatment of Patients With Severe Hemophilia A Without Inhibitors*, ([abstract 2102](#)) results found that prophylaxis with rFVIII was estimated to be less costly and more effective over an estimated 70-year lifespan of a patient with severe hemophilia A.

- ii. New analyses were presented from the Phase III HAVEN 3 study of Hemlibra (emicizumab) in haemophilia A patients without factor VIII inhibitors. They encompass data on the positive effect of Hemlibra on joint health.
- iii. Freeline presented preclinical data on its gene therapy programme for haemophilia A³. This leverages the company's platform technology, including its proprietary AAV capsid, known as AAVS3.
- Enzyre⁴ has entered into a research collaboration agreement with Takeda to develop a diagnostic device that will allow haemophilia patients to determine their coagulation status at home. Enzyre will be funded by Takeda to develop its existing technology, which will not only permit automatic determination of coagulation status, but also

FEIBA® [Anti-Inhibitor Coagulant Complex]: The poster *Real-World Clinical Management of Patients with Hemophilia and Inhibitors: Effectiveness and Safety of aPCC in Patients with >18 Months' Follow-up in the FEIBA Global Outcome Study (FEIBA GO)* ([abstract 2418](#)) describes the long-term, real-world safety and efficacy of FEIBA in patients with congenital hemophilia A or B with inhibitors across different clinical settings.

Von Willebrand Disease: Data from two studies that aim to advance scientific knowledge and understanding of von Willebrand disease (VWD), including the following retrospective analyses:

- The poster *Analysis of Bleeding and Treatment Patterns in Children and Adolescents before and after von Willebrand Disease Diagnosis Using Data from a US Medical Claims Database* ([abstract 2117](#)) highlights U.S. medical claims data that characterizes the diagnosis, bleeding and treatment patterns in children and adolescents with VWD and points to the need for improved treatment and care of this patient population.
- Additionally, the poster *Estimation of the Economic Burden Associated with Major Surgery Due to von Willebrand Disease Based on Claims Data from the USA* ([abstract 4692](#)) assesses the economic burden associated with major surgeries in patients with VWD and found that these patients incur significantly higher costs for health care resources compared to patients without VWD who had similar types of surgery.

Preclinical Studies Addressing Challenges of Current AAV Gene Therapies

These studies inform Takeda's approach to its investigational AAV gene therapy programs; TAK-754 for haemophilia A is currently in Phase 1 clinical study, to be followed by other potential gene therapies including TAK-748, an investigational gene therapy for haemophilia B. [Evaluation of the Human Factor IX Gene Therapy Vector TAK-748 in Hemophilia: Results from Non-Clinical Studies in Factor IX Knockout Mice and Rhesus Monkeys](#). Poster abstract # 4633. To understand the prevalence of pre-existing immunity against commonly used AAV2, AAV5 and AAV8 capsid in adult patients with hemophilia, Takeda conducted an international prospective and ongoing epidemiological study, *"Co-Prevalence of Pre-Existing Immunity to Different Serotypes of Adeno-Associated Virus (AAV) in Adults with Hemophilia"* ([abstract 3349](#)) that found 50 per cent of patients with haemophilia have neutralizing antibodies to AAV2, AAV5 or AAV8 capsid with 40 per cent demonstrating co-prevalence to all three evaluated serotypes. These patients are not likely to respond to gene therapies based on AAV vectors. The poster *AAV8-Specific Immune Adsorption Column: A Treatment Option for Patients with Pre-Existing Anti-AAV8 Neutralizing Antibodies*, ([abstract 5922](#)) reported pre-clinical data on one potential approach to overcoming pre-existing AAV immunity. An AAV8-specific immune adsorption column (IAC) was used to mimic the processing of patients' plasma in an *in vitro* setting by applying different treatment cycles to plasma reservoirs which shows anti-AAV8 titers could be depleted. Insights from this study will be applied to Takeda's research to determine if an IAC could enable the administration of AAV8 gene therapies to patients with pre-existing immunity and potentially facilitate the re-administration of gene therapy. See also [The Factor VIII Variant X5 Enhances Hemophilia A Gene Therapy Efficiency by Its Improved Secretion](#). Poster abstract 3356.

³ *Design and Characterization of FLT210, a Potent Next Generation AAV-hFVIII Vector Candidate*, presenter Romuald Corbau, Senior Vice President Research, Freeline <https://ash.confex.com/ash/2019/webprogram/Paper128490.html>

⁴ Enzyre, based in Nijmegen in The Netherlands, is a spin out from Radboud University Medical Centre. www.enzyre.com

transfer the test results to the patients' treating physicians immediately through an app on a mobile phone.

- A study⁵ of children with haemophilia in Thailand showed that a lower dose of regular, preventive therapy with factor VIII concentrates was better at reducing bleeding events and improving joint function than on-demand treatment.

Treating beta thalassemia and sickle cell disease

- On 6 December The American Society of Hematology (ASH) released recommendations aimed at establishing uniformity and global standards for clinical trial endpoints used to evaluate new therapies for sickle cell disease (SCD). The recommendations – published in two companion papers in *Blood Advances*⁶ – were developed by a series of expert and patient-led panels convened by ASH and the US Food and Drug Administration (FDA) to improve the design of clinical trials for new SCD therapies, including promoting broader use of patient reported outcomes and biomarkers as clinical endpoints.
- At the [61st American Society of Hematology \(ASH\) Annual Meeting](#) :
 - i. Global Blood Therapeutics announced that eight abstracts related to its sickle cell disease (SCD) research programs, including multiple abstracts related to the safety and efficacy of voxelotor, had been accepted for presentation. Josh Lehrer, chief medical officer of GBT said: “Our data presentations at ASH 2019, including three post-hoc analyses of the HOPE Study, reinforce the safety and efficacy of voxelotor as a potential disease-modifying treatment for SCD. In addition, the analysis of real-world evidence demonstrating the relationship between increased hemoglobin and decreased risk of stroke, as measured by transcranial Doppler flow velocity, provides further confidence in achieving a favourable result from our planned post-approval confirmatory study, which is designed to demonstrate that an improvement in haemolytic anemia translates into important clinical benefit.” The ASH abstracts⁷ are available at www.hematology.org.

⁵ Ratchaneekorn Songnuy et al., “[Prophylactic vs episodic treatment to prevent bleeds and preserve joint function in Thai children with moderate and severe hemophilia A,](#)” in the journal *Haemophilia*. <https://doi.org/10.1111/hae.13894>

⁶ Volume 3, Issue 23

- [End points for sickle cell disease clinical trials: patient-reported outcomes, pain, and the brain](#)
- [End points for sickle cell disease clinical trials: renal and cardiopulmonary, cure, and low-resource settings](#)

For a media report see <https://www.ptcommunity.com/wire/ash-and-fda-unveil-new-recommendations-guide-clinical-development-sickle-cell-disease-therapies> or

<https://www.mdmag.com/conference-coverage/ash-2019/sickle-cell-disease-therapies-ash>

⁷ Abstract #130767: *Concomitant Hydroxyurea and Voxelotor: Results from the HOPE Study* (Presenter: Russell Ware, Cincinnati Children’s Hospital Medical Center)

Abstract #130802: *Correlation of Voxelotor Exposure with Hemoglobin Response and Measures of Hemolysis in Patients from the HOPE Study* (Presenter: Jo Howard, Guy’s and St. Thomas’ NHS Foundation Trust and King’s College London)

Abstract #131177: *Transcranial Doppler Velocities Conversion Rate Based on Increasing Hemoglobin Concentration: Analysis from the SCCRIP Cohort Study* (Presenter: Jeremie Estep, St. Jude Children’s Research Hospital)

Abstract #124933: *Chronic Kidney Disease is Under-Screened in SCD and Mild Albuminuria is Associated with a Drop in Hemoglobin: A Report from the GRNDaD Sickle Cell Registry* (Presenter: Elizabeth Williams, Johns Hopkins School of Medicine)

Abstract #129026: *Incidence of Vaso-occlusive Crisis Does Not Increase with Achieving Higher Hemoglobin Levels on Voxelotor Treatment or After Discontinuation: Analyses of the HOPE Study* (Presenter: Elliott Vichinsky, UCSF Benioff Children’s Hospital, Oakland)

- ii. Sangamo Therapeutics announced in a poster presentation the preliminary results from the first three patients treated in the Phase I/II THALES study evaluating investigational ST-400 *ex vivo* gene-edited cell therapy in transfusion-dependent beta thalassemia⁸.
- iii. New and updated data from bluebird bio's investigational gene and cell therapy programs for sickle cell disease (SCD), transfusion-dependent β -thalassemia (TDT) and multiple myeloma were presented⁹.

Abstract #129351: *Improvement in Red Blood Cell Physiology in Children with Sickle Cell Anemia Receiving Voxelotor* (Presenter: Satheesh Chonat, Aflac Center & Blood Disorders Center of Children's Healthcare of Atlanta and the Department of Pediatrics, Emory University)

Abstract #127173: *Economic Burden of End Organ Damage Among Patients with Sickle Cell Disease in the US* (Presenter: Xue Song, IBM Watson Health)

In a poster session entitled "Hemoglobinopathies, Excluding Thalassemia—Basic and Translational Science":

Abstract #129282: *Pharmacological Increase of Hb-O₂ Affinity with a Voxelotor Analog Does Not Decrease Brain Tissue pO₂ or Limit O₂ Extraction in Brain Tissues of Sickle Cell Mice* (Presenter: Kobina Dufu, GBT)

⁸ The ST-400 ASH poster is available on Sangamo's website in the Investors and Media section under [Events and Presentations](#).

<https://investor.sangamo.com/static-files/a6756cea-677f-4b64-ba70-e8b9eb74cc14>

<https://pipelinereview.com/index.php/2019120973151/DNA-RNA-and-Cells/Sangamo-Announces-Preliminary-Results-From-the-First-Three-Patients-in-a-Phase-1/2-Study-Evaluating-ST-400-Ex-Vivo-Gene-edited-Cell-Therapy-in-Beta-Thalassemia.html>

Sangamo's three presentations were: Abstract #2060: *Updated Follow-up of the Alta Study, a Phase 1/2, Open Label, Adaptive, Dose-Ranging Study to Assess the Safety and Tolerability of SB-525 Gene Therapy in Adult Patients with Severe Hemophilia A*, Presenter Barbara Konkle, Bloodworks Northwest, Professor of Medicine at University of Washington; Abstract #3544: "Preliminary Results of a Phase 1/2 Clinical Study of Zinc Finger Nuclease-Mediated Editing of BCL11A in Autologous Hematopoietic Stem Cells for Transfusion-Dependent Beta Thalassemia", Presenter Angela Smith, Associate Professor in the Division of Pediatric Blood and Marrow Transplantation at the University of Minnesota; and Abstract #974: "Zinc Finger Nuclease-Mediated Disruption of the BCL11A Erythroid Enhancer Results in Enriched Biallelic Editing, Increased Fetal Hemoglobin, and Reduced Sickling in Erythroid Cells Derived from Sickle Cell Disease Patients", Presenter: Samuel Lessard, Scientist, Sanofi

⁹ *The Relationships Between Target Gene Transduction, Engraftment of HSCs and RBC Physiology in Sickle Cell Disease Gene Therapy*, presenter Melissa Bonner, bluebird bio, Cambridge, Mass. Oral #206; and *Exploring the Drivers of Clinical Benefit in Initial Patients Treated in the HGB-206 Study of LentiGlobin for Sickle Cell Disease (SCD) Gene Therapy*, presenter Mark Walters, Benioff Children's Hospital, Oakland, Calif. Poster #2061; and *Resolution of Sickle Cell Disease Manifestations in Patients Treated with LentiGlobin Gene Therapy: Updated Results from the Phase 1/2 HGB-206 Group C Study*, presenter Julie Kanter, University of Alabama at Birmingham, Birmingham, Ala. Poster #990; and *Clinical Outcomes after Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Transfusion-Dependent β -Thalassemia Treated at the Bambino Gesù Children's Hospital, Rome, Italy* presenter Pietro Merli, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy Poster #969; and *Northstar-3: Interim Results from a Phase 3 Study Evaluating LentiGlobin Gene Therapy in Patients with Transfusion-Dependent β -Thalassemia and Either a β 0 or IVS-I-110 Mutation at Both Alleles of the HBB Gene*, presenter Ashutosh Lal, UCSF Benioff Children's Hospital, Oakland, Calif. Oral #815; and *Northstar-2: Updated Safety and Efficacy Analysis of LentiGlobin Gene Therapy in Patients with Transfusion-Dependent β -Thalassemia and Non- β 0/ β 0 Genotypes*, presenter Alexis Thompson, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Ill. Poster #3543; and *Long-Term Clinical Outcomes of LentiGlobin Gene Therapy for Transfusion-Dependent β -Thalassemia in the Northstar (HGB-204) Study* presenter Janet Kwiatkowski, Children's Hospital of Philadelphia, Philadelphia, Pa. Poster #4628; and *Routine Management, Healthcare Resource Use and Patient/Caregiver-Reported Outcomes of Patients with Transfusion-Dependent β -Thalassaemia in the United Kingdom: A Mixed Methods Observational Study*, presenter Farrukh Shah, Whittington Hospital, London, U.K. Poster #3550; and *Results from the Completed HGB-205 Trial of LentiGlobin for β -Thalassemia and LentiGlobin for Sickle Cell Disease Gene Therapy*, presenter Elisa Magrin, Necker Children's Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France Poster #3358; and

- iv. Researchers¹⁰ reported on the correlation of biomarkers that reflect major aspects of the sickle cell disease patho-physiology—haemolysis, anaemia, hypoxia, inflammation, and iron overload—with cardiopulmonary, renal, and liver dysfunction in adult patients. They concluded: “Our study indicated significant correlations of anemia and hypoxia with both left heart enlargement and elevated pulmonary arterial systolic pressure. Our study also underscores a significant impact of iron overload on renal and liver damages.”
 - v. [Forma Therapeutics, Inc.](#) announced positive Phase I results from the healthy volunteer arm of an ongoing study of FT-4202 as a potential disease-modifying therapy for sickle cell disease (SCD). The company said data demonstrated the safety, tolerability and proof of mechanism of FT-4202 in healthy subjects, as well as *in vitro* in SCD red blood cells¹¹.
 - vi. Editas Medicine reported [in vivo proof-of-concept data](#) supporting the development of EDIT-301 as a durable medicine to treat sickle cell disease and beta-thalassemia¹².
 - vii. Jane Hankins, from the Department of Haematology at St Jude’s Children’s Research Hospital discussed the [St. Jude-Methodist Sickle Cell Disease Transition Clinic](#). Patients learn how to handle their own care as they become adults. Patients receive education, transition skill-building and help with planning their care. During their first few adult-care visits, patients are seen by both a paediatric and an adult haematologist. Anjelica Saulsberry presented her work with Hankins and others on how neurocognitive impairment associated with sickle cell disease can predict poor transition outcomes¹³. The researchers are exploring options for how to help patients remain engaged in care as an adult.
 - viii. Beam Therapeutics presented preclinical data for the company’s programs addressing sickle cell disease and beta thalassemia¹⁴.
- Agios Pharmaceuticals announced that clinical proof-of-concept has been established based on a preliminary analysis of a small Phase II trial of mitapivat (AG-348) in patients with non-transfusion-dependent thalassemia. In addition to this study, mitapivat is being trialled in sickle cell disease under a Cooperative Research and Development Agreement (CRADA) with the US National Institutes of Health¹⁵.

Updated Results from an Ongoing Phase 1 Clinical Study of bb21217 Anti-BCMA CAR T Cell Therapy, presenter Jesus G. Berdeja, Sarah Cannon Center for Blood Cancers, Nashville, Tenn. Oral #927; and *Markers of Initial and Long-Term Responses to Idecabtagene Vicleucel (Ide-Cel; bb2121) in the CRB-401 Study in Relapsed/Refractory Multiple Myeloma*, presenter Ethan G. Thompson, Celgene, Seattle, Wash. Poster #4328. Abstracts outlining bluebird bio’s accepted data at ASH have been made available on the ASH conference website.

¹⁰ led by Xu Zhang, Department of Medicine, University of Illinois at Chicago,

¹¹ <https://pipelinereview.com/index.php/2019120973161/Small-Molecules/FORMA-Therapeutics-Announces-Clinical-Data-for-Sickle-Cell-Disease-Candidate-FT-4202-Demonstrating-Multi-modal-Activity-of-PKR-Activation-Increases-Oxygen-Affinity-and-De.html>

¹² <https://pipelinereview.com/index.php/2019121073183/DNA-RNA-and-Cells/Editas-Medicine-Announces-In-Vivo-Proof-of-Concept-Data-for-EDIT-301-in-Development-for-the-Treatment-of-Sickle-Cell-Disease-and-Beta-Thalassemia.html>

¹³ <https://ash.confex.com/ash/2019/webprogram/Paper121617.html>

¹⁴ *Complementary base editing approaches for the treatment of sickle cell disease and Beta-thalassemia*, poster presented by Ling Lin, senior scientist II, Beam

¹⁵ <https://pipelinereview.com/index.php/2019120973147/Small-Molecules/Agios-Establishes-Proof-of-Concept-for-Mitapivat-in-Non-transfusion-dependent-Thalassemia-Based-on-Preliminary-Phase-2-Results.html>

- A study¹⁶ has suggested that treatment with [delta-aminolevulinatate](#) (ALA), a precursor of heme — the part of haemoglobin that carries oxygen — could be a therapeutic option for people with sickle cell anaemia and β -thalassemia.

Treating other conditions

- At the ASH meeting:
 - i. Treatment with avatrombopag¹⁷ was reported to be cost-effective, compared with other options, for the treatment of thrombocytopaenia in patients with chronic liver disease (CLD). The study¹⁸ compared the drug with platelet transfusion and with lusutrombopag¹⁹.
 - ii. In an oral presentation [UCB](#) announced positive results from a Phase II study (TP0001; NCT02718716) of its novel, first-in-class subcutaneous monoclonal antibody, rozanolixizumab, in patients with primary immune thrombocytopenia (ITP)²⁰.
 - iii. Achillion Pharmaceuticals reported in a poster presentation top-line data from a dose-finding Phase II trial assessing the safety and effectiveness of its oral small molecule factor D inhibitor danicopan (ACH-4471) in combination with intravenous eculizumab in paroxysmal nocturnal haemoglobinuria (PNH) patients who have an inadequate response to C5 monotherapy²¹.
 - iv. [bluebird bio, Inc.](#) and [Bristol-Myers Squibb](#) announced updated safety and efficacy results from the ongoing Phase I study (CRB-402) of bb21217, an investigational BCMA²²-targeted chimeric antigen receptor (CAR) T cell therapy being studied in patients with relapsed/refractory multiple myeloma (R/RMM)²³.

¹⁶ Li Liu et al., “ [\$\delta\$ -Aminolevulinatate induces fetal hemoglobin expression by enhancing cellular heme biosynthesis](#),” in the journal *Experimental Biology and Medicine*. <https://doi.org/10.1177/1535370219872995>

¹⁷ Doptelet from Dova Pharmaceuticals is an oral thrombopoietin receptor agonist [approved by both the FDA](#) and the European Medicines Agency (EMA) for treatment of thrombocytopenia in adults with CLD who are scheduled to undergo a procedure

¹⁸ Allen LF, et al. Abstract 3454. Presented at: ASH Annual Meeting and Exposition; Dec. 7-10, 2019; Orlando. Lee F Allen is from Dova Pharmaceuticals.

¹⁹ Mulpleta from Shinogi

²⁰ Phase II data reportedly demonstrated that rozanolixizumab was well tolerated by patients with primary ITP across all dose groups. Clinically relevant improvements in platelet count and decrease in immunoglobulin G (IgG) levels were observed in all dose groups. Safety, tolerability and efficacy data supported Phase III development of rozanolixizumab for primary ITP. Rozanolixizumab's subcutaneous route of administration could provide a new treatment option for patients with primary ITP. <https://pipelinereview.com/index.php/2019121073163/Antibodies/UCB-Presents-Final-Results-from-Phase-II-Study-of-Rozanolixizumab-in-Primary-Immune-Thrombocytopenia-ITP-at-2019-ASH-Annual-Meeting.html>

²¹ <https://pipelinereview.com/index.php/2019121073185/Small-Molecules/Achillion-Reports-Positive-Data-from-Phase-2-Study-of-Danicopan-ACH-4471-in-Combination-with-Eculizumab-in-PNH-Patients-who-Have-an-Inadequate-Response-to-Eculizumab-Mono.html> Achillion's poster presentations were: *A Phase 2 Open-Label Study of Danicopan (ACH-0144471) in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Who Have an Inadequate Response to Eculizumab Monotherapy* Abstract # 3514 and *Mechanistic Evaluation of Efficacy Using Biomarkers of the Oral, Small Molecule Factor D Inhibitor, Danicopan (ACH-4471), in Untreated Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)* Abstract 2226

²² B-cell maturation antigen

²³ <https://pipelinereview.com/index.php/2019121073169/DNA-RNA-and-Cells/bluebird-bio-and-Bristol-Myers-Squibb-Present-Updated-Data-from-Ongoing-Phase-1-Study-of-BCMA-Targeted-CAR-T-Cell-Therapy-bb21217-in-Relapsed/Refractory-Multiple-Myelom.html>

- v. There were several data presentations²⁴ concerning the complement program of [Alexion Pharmaceuticals, Inc.](#)
 - vi. Data was presented²⁵ concerning Rigel Pharmaceuticals treatment for immune thrombocytopaenia, Tavalisse tablets (fostamatinib disodium hexahydrate).
 - vii. Roche reported Phase I/ II data from the COMPOSER study, which assessed the investigational treatment crovalimab in patients with paroxysmal nocturnal haemoglobinuria (PNH), where red blood cells are destroyed by the body's immune system. Crovalimab is a novel humanised anti-C5 monoclonal antibody designed to block the complement system (which plays a key role in this disease). The antibody was created by Chugai Pharmaceutical and is being co-developed by Roche.
- [BioCryst Pharmaceuticals, Inc.](#) presented two abstracts²⁶ (relevant to treating hereditary angioedema) at the Annual Scientific Meeting of the American College of Allergy, Asthma & Immunology (ACAAI)²⁷.

3. Regulatory

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

- [BioMarin Pharmaceuticals](#) is seeking marketing approval in Europe for its investigational gene therapy, [valoctocogene roxaparvovec](#), for the treatment of adults with severe haemophilia A²⁸. The therapy is administered as a single infusion. It uses [adeno-associated virus \(AAV\) vectors](#) to deliver a functional copy of the missing protein, [clotting factor VIII](#). An ongoing Phase III trial, GENE8-1 ([NCT03370913](#)), is investigating the treatment's safety and efficacy, and is still recruiting adult patients. BioMarin's MAA submission was based on updated three-year data from a Phase I/II study ([NCT02576795](#)) and on an interim analysis of the ongoing Phase III GENE8-1

²⁴ **Paroxysmal Nocturnal Hemoglobinuria (PNH) Abstracts:** [Breakthrough Hemolysis in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria Treated with Ravulizumab: Results of a 52-Week Extension from Two Phase 3 Studies](#). Abstract ID#: 952 – Poster Presentation; [One-Year Efficacy and Safety from A Phase 3 Trial of Ravulizumab in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria Receiving Prior Eculizumab Treatment](#). Abstract ID#: 2231 – Poster Presentation; and Adrian R Levy et al., “Comparison of Lost Productivity Due to Eculizumab and Ravulizumab Treatments for Paroxysmal Nocturnal Hemoglobinuria in France, Germany, Italy, Russia, Spain, the United Kingdom, and the United States.” *Blood*, <https://doi.org/10.1182/blood-2019-127443>. Also **Atypical Haemolytic Uremic Syndrome (aHUS) Abstract:** [Discordance between Free C5 and CH50 Complement Assays in Measuring Complement C5 Inhibition in Patients with aHUS Treated with Ravulizumab](#). Abstract ID#: 1099 – Poster Presentation. Note: ravulizumab-cwvz is also known as Ultomiris, and eculizumab is also known as Soliris.

²⁵ *Enhanced Responses to Fostamatinib as Second-Line Therapy and in Persistent Immune Thrombocytopenia (ITP) Patients*, presenter Ralph Boccia, poster abstract #1069 and *Fostamatinib, a Spleen Tyrosine Kinase (SYK) Inhibitor, for the Treatment of Warm Antibody Autoimmune Hemolytic Anemia (wAIHA): Final Results of the Phase 2, Multicenter, Open-Label Study*, presenter Kerry Rogers, poster abstract #3518. The conference abstracts can be accessed [here](#).

²⁶ *Oral Prophylaxis with BCX7353 Reduces HAE Attack Rates and is Well-Tolerated: APeX-2 Study Results*, Poster P150, and *Safety and Tolerability of Once-Daily Oral Kallikrein Inhibitor BCX7353 in Phase 3 APeX-2 HAE Study*, Poster P154.

²⁷ 7-11 November in Houston, Texas

²⁸ BioMarin submitted a [marketing authorization](#) application (MAA) to the [European Medicines Agency](#) (EMA) for the experimental [gene therapy](#), formerly known as [BMN 270](#). The EMA designated valoctocogene roxaparvovec as priority medicine, or [PRIME](#), in 2017. Now, it has been granted [accelerated assessment](#), which may potentially shorten its MAA review process from 210 to 150 days.

trial ([NCT03370913](#)) already mentioned. BioMarin is expecting the EMA to start reviewing its application in January 2020. The company is planning to submit a [biologics license application](#) for valoctocogene roxaparvovec to the [U.S. Food and Drug Administration](#) (FDA). The investigational treatment has been given a [breakthrough therapy](#) designation by the FDA, as well as [orphan drug status](#) from both the FDA and EMA.

- Global Blood Therapeutics announced that the FDA had granted accelerated approval for Oxbryta (voxelotor) tablets for the treatment of sickle cell disease (SCD) in adults and children 12 years of age and older. Oxbryta, taken once daily, is a new therapy that directly inhibits sickle haemoglobin polymerization²⁹. The accelerated approval of Oxbryta is based on clinical trial results - meaningful and statistically significant improvements in haemoglobin levels, accompanied by reductions in red blood cell destruction (haemolysis)³⁰. Oxbryta will continue to be tested in a post-approval confirmatory study in children as young as two years of age.
- The [Canadian Drug Expert Committee](#)³¹ (CDEC) has recommended that [Takhzyro](#)³² ([lanadelumab](#)) be reimbursed by public drug plans when used as a preventive treatment for [hereditary angioedema](#) (HAE) attacks in patients 12 and older. After giving Takhzyro priority review, [Health Canada approved the medication in September 2018 as a routine preventive treatment for HAE attacks](#) in people 12 and older. That decision was based on results from the HELP Phase III trial ([NCT02586805](#)). That has now been further supplemented by results from the trial's open-label extension study ([NCT02741596](#)). The new findings were recently presented in three posters ([P156](#), [P158](#), and [P159](#)) at the [2019 American College of Allergy, Asthma and Immunology Annual Meeting](#) in Houston, Texas. New data from the trial's open-label extension study has also been published in the [Annals of Allergy, Asthma & Immunology](#).
- The FDA approved Novartis' Adakveo (crizanlizumab) for patients 16 and older. The monthly infusion is said to halve occurrences of sickle cell pain episodes³³.
- Octapharma's human fibrinogen concentrate Fibryga has received approval for use in treatment of acquired fibrinogen deficiency in 15 European countries. The approval extends the market authorisation for Fibryga which is already approved for use in patients with congenital fibrinogen deficiency.

²⁹ People with SCD form abnormal haemoglobin. Through a process called haemoglobin polymerization, red blood cells become sickled – deoxygenated, crescent-shaped and rigid. This leads to haemolytic anemia (low hemoglobin due to red blood cell destruction) and blockages in capillaries and small blood vessels, which restricts the flow of blood and oxygen. The reduced oxygen delivery to tissues and organs can result in life-threatening complications, including stroke and irreversible organ damage.

³⁰ Elliott Vichinsky et al., "A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease", [The New England Journal of Medicine](#) August 8, 2019 N Engl J Med 2019; 381:509-519
DOI: 0.1056/NEJMoa1903212

³¹ CDEC is an arm of the [Canadian Agency for Drugs and Technologies in Health](#) (CADTH), an independent, not-for-profit organization responsible for providing healthcare decision-makers with evidence to make informed decisions.

³² Takeda's Takhzyro is a human antibody that inhibits the activity of the enzyme [kallikrein](#) and prevents the overproduction of [bradykinin](#), a peptide that normally regulates blood pressure and inflammation by dilating blood vessels, and, in HAE, leads to bouts of swelling.

³³ <https://pipelinereview.com/index.php/2019111672920/Antibodies/New-Novartis-medicine-Adakveo-crizanlizumab-approved-by-FDA-to-reduce-frequency-of-pain-crisis-in-individuals-living-with-sickle-cell-disease.html>

4. 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.

- The US Federal Trade Commission cleared Roche's \$US 4.8 billion buyout of Spark Therapeutics, after a 10-month investigation. The UK Competition and Markets Authority had given Roche the green light after its own [investigation](#). Spark has been one of three companies advancing a one-time treatment for haemophilia A through late-stage testing. A gene therapy candidate for haemophilia B is licensed to Pfizer.
- Syros Pharmaceuticals and Global Blood Therapeutics announced in December that they have entered into a collaboration to discover, develop and commercialize novel therapies for sickle cell disease (SCD) and beta thalassemia. They said that this will combine GBT's knowledge of the therapeutic area with the power of Syros' gene control platform. They want to develop drugs to induce the production of foetal haemoglobin, which has protective effects on the red blood cells of patients with SCD and beta thalassemia and mitigates the clinical manifestation of these diseases.
- Grifols announced the launch of Xembify (immune globulin subcutaneous human-klhw), the company's first 20 per cent subcutaneous immunoglobulin therapy for the treatment of patients 2 years of age and older with primary immunodeficiency (PI). The company says the product is suitable for PI patients with diabetes or cardiac impairment. Xembify was approved by the FDA in July 2019. Grifols says it is now working to obtain additional approvals in Canada, Europe and other countries³⁴.

5. Specific country events

- Heparin, currently derived from pig intestines, is widely used to treat heart attacks and prevent potentially lethal blood clots. China has been the primary source of the drug, and with the crisis there posed by African swine fever the world needs to develop alternate supplies.

6. 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 prospective trial³⁵ in the Netherlands suggested that two biomarkers may assist in creating a prediction model for haemorrhage risk in patients with thrombocytopenia due to haematologic malignancy³⁶.

³⁴ <https://pipelinereview.com/index.php/2019121373232/Antibodies/Grifols-launches-XEMBIFY-immune-globulin-subcutaneous-human-klhw-20-a-new-Primary-Immunodeficiency-treatment.html>

³⁵ [ClinicalTrials.gov](https://clinicaltrials.gov) identifier: [NCT02783313](https://clinicaltrials.gov/ct2/show/study/NCT02783313)

³⁶ Ypma PF, van Geloven N, Kerkhoffs JL, et al. [The association between haemorrhage and markers of endothelial insufficiency and inflammation in patients with hypoproliferative thrombocytopenia: a cohort study](#) [published online November 15, 2019]. *Br J Haematol*. doi: 10.1111/bjh.16291

- Grifols announced that recent results from a clinical trial of its Alzheimer's treatment showed a reduction of the disease's progression in patients with mild and moderate conditions. The AMBAR study is evaluating whether the progression of Alzheimer's disease can be stabilized through therapeutic plasma exchange, where plasma is periodically replaced by an albumin solution with or without immunoglobulin³⁷.
- An editorial in *The BMJ* – [Pathways to independence: Towards producing and using trustworthy evidence](#) – gives voice to international researchers, clinicians, regulators, and advocates to suggest building “an evidence base for healthcare that is free of commercial influences”. Dr Ray Moynihan, lead author of the editorial and assistant professor at Bond University, said: “If we want to produce trustworthy evidence and tackle the epidemic of medical excess, decision-makers at all levels within healthcare need to disentangle themselves from those profiting from that excess.” The authors say that “the financial dependence of industry-funded research distorts results and leads to a [situation in which](#) company-sponsored studies overstate product benefits while downplaying harms”³⁸.
- An international research team has cross-referenced data from six longitudinal studies that tracked the health of over 31,000 adults over age 55 across several years. They concluded that treating high blood pressure — regardless of the specific antihypertensive drug selected — reduced dementia risk by 12 per cent and the risk of developing Alzheimer's disease by 16 per cent³⁹.

7. Infectious diseases

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

Mosquito-borne diseases

- Roche launched its *in vitro* diagnostic test for the Zika virus in countries accepting the CE mark, to screen the donated blood supply. The test is for use on the company's cobas 6800/8800 automated molecular testing systems. It detects RNA strands that can be traced back to the Zika virus in human plasma samples. In launching the test Roche drew attention to [a report](#) from the World Health Organization detailing three local Zika cases on the south coast of France during the summer, thought to be the first cases of mosquito-based transmission in Europe.
- The FDA approved the cobas test to detect Zika virus in blood donations. Peter Marks, director of the FDA's Center for Biologics Evaluation and Research, said:

³⁷ <https://www.grifols.com/en/the-ambar-study> ; <https://www.clinicaltrialsarena.com/news/grifols-data-alzheimers-trial-ambar/> ; <https://clinicaltrials.gov/ct2/show/NCT01561053>

³⁸ <https://www1.racgp.org.au/newsgp/professional/company-sponsored-trials-tainting-medical-research>

³⁹ Ding J, et al. [Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies](#). *Lancet Neurology*. 2019;pii: S1474-4422(19)30393-X. doi: 10.1016/S1474-4422(19)30393-X. <https://www.ncbi.nlm.nih.gov/pubmed/31706889>

"Screening blood donations for the Zika virus is critical to preventing infected donations from entering the U.S. blood supply. Today's approval is the result of a commitment by the manufacturer to work rapidly and collaboratively with the FDA and the blood collection industry to respond to a public health crisis and ensure the safety of blood in the U.S. and its territories."

- Emergex Vaccines Holding Limited announced the successful completion of preclinical testing of its lead vaccine candidate for dengue. The vaccine consists of gene-chip peptides bound to a quantum cluster gold nanoparticle delivery system. The company said it was shown to have an excellent safety profile in a repeat dose Good Laboratory Practice (GLP) grade toxicology study using a standard industry model⁴⁰. It reported no adverse reactions at any dose level. Emergex will now move its vaccine candidate into the clinical phases of development.
- A new study⁴¹ suggests that an autoimmune attack on uninfected red blood cells contributes to anaemia in people with malaria.

Influenza

- The US National Institute of Allergy and Infectious Disease (NIAID) awarded the Emory Institute of Drug Development (EIDD) a \$US 15.89 million contract to develop and test its influenza drug candidate, EIDD-2801, in humans. The contract includes Phase I safety studies and Phase II challenge studies in healthy volunteers who will be infected with the flu. The drug has been shown to blunt disease severity and suppress viral spread in animal models, when tested against seasonal and avian flu⁴².
- [Vaccitech Ltd](#) reported it is progressing the clinical development of Universal Influenza A Vaccine (VTP-100) in Belgium and Australia and expects top-line data early in 2020.
- French firm Osivax has signed an agreement with the US National Institute of Allergy and Infectious Diseases (NIAID) to continue development of the company's universal flu vaccine candidate OVX836⁴³.
- Anthony S. Fauci, director of the National Institute for Allergy and Infectious Diseases at the US National Institutes of Health testified in December before the US House Energy and Commerce Subcommittee on Oversight and Investigations hearing, *Flu Season: US Public Health Preparedness and Response*. He told the committee that "we are not going to get a universal flu vaccine next month or next year." However, he said: "We are certainly better off this year than we were last year in our quest for a universal flu vaccine. Last year we didn't even have a candidate. This year we're now eight months into Phase 1. And by early 2020 we'll know whether our candidate will induce the kind of response that you would predict would be protective". Robert P. Kadlec, Assistant Secretary for Preparedness and Response, US Department of Health and Human Services told the Committee: "There is no singular threat that could devastate our country, our health and our economy, and our social institutions more than pandemic influenza."

⁴⁰ Nilabh Shastri et al., "Producing Nature's Gene-Chips: The Generation of Peptides for Display by MHC Class 1 Molecules", *Annual Review of Immunology*, Volume 20, 2002 pp 463-493.
<https://www.annualreviews.org/doi/abs/10.1146/annurev.immunol.20.100301.064819>

⁴¹ Rivera-Correa, J. et al. (2019) "Atypical memory B-cells are associated with Plasmodium falciparum anemia through anti-phosphatidylserine antibodies". *eLife*. doi.org/10.7554/eLife.48309

⁴² Mart Toots et al., "Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia", *Science Translational Medicine* 23 Oct 2019: Vol. 11, Issue 515, eaax5866 DOI: 10.1126/scitranslmed.aax5866
<https://stm.sciencemag.org/content/11/515/eaax5866.full>

⁴³ Dec 5 Osivax [press release](#)

Ebola virus disease

- The World Health Organization (WHO) announced that it had prequalified Merck's Ebola vaccine, a move made only one day after the European Commission granted approval for VSV-EBOV, which has been in use on a compassionate basis and under further study in the current Ebola outbreak in the Democratic Republic of the Congo (DRC)⁴⁴. The WHO said prequalification means the vaccine meets the WHO's quality, safety, and efficacy standards, so United Nations agencies and Gavi, the Vaccine Alliance, can buy the vaccine for use in at-risk countries⁴⁵.

MERS-CoV

- Of the 15 cases of MERS-CoV reported to the World Health Organization (WHO) in October, four involved healthcare-related clusters. Five of the 15 patients, all with diabetes, died. Three of the patients reported recent camel contact. All three drank camel milk⁴⁶.

Other diseases

- Samoa has suffered a severe measles outbreak with continuing fatalities. The first case may have arrived from overseas in late August, but in a country with low vaccination rates (about 31 per cent at that time) it had become a raging outbreak by October, and by late November there had been more than 50 deaths, mostly children aged four and under. Mass vaccination programs in children have been conducted with some overseas help.
- Globally, Minal K. Patel, from WHO in Geneva, and colleagues have described progress made toward the World Health Assembly milestones and regional measles elimination during 2000 to 2018. They found that estimated measles-containing vaccine coverage increased globally from 72 to 86 per cent during 2000 to 2018; annual reported measles incidence decreased from 145 to 49 cases per 1 million population (66 percent decrease); and annual estimated measles deaths decreased from 535,600 to 142,300 (73 percent decrease). An estimated 23.2 million deaths were averted by vaccination during 2000 to 2018. However, compared with 2016, in 2018, the number of measles cases increased 167 percent globally; since 2017, estimated global measles mortality has increased. The authors wrote: "The trends of increasing measles incidence and mortality are reversible; however, further progress toward achieving elimination goals will require 1) resource commitments to strengthen routine immunization systems, close historical immunity gaps, and improve surveillance to rapidly detect and respond to cases, and 2) a new perspective to use measles as a stimulus and guide to improving immunization programs."
- *Candida auris* is a persistent, deadly fungus first identified about a decade ago. It has been found to be particularly dangerous when it invades the bloodstream. Patients

⁴⁴ In mid-October, the European Medicines Agency (EMA) conditionally approved the vaccine under the Ervebo brand name for immunization of people 18 years and older.

⁴⁵ Welcoming European Commission approval Seth Berkley, Gavi's chief executive officer, had said the vaccine had "huge potential" and had already been administered to more than 250,000 people in the DRC. It had the potential to make major Ebola outbreaks a thing of the past. He said approval paved the way for a Gavi-supported stockpile and that the Gavi board would also consider, if recommended, future support for preventive vaccination of groups beyond outbreak settings, such as healthcare workers in high-risk countries. On 5 December, GAVI announced it is establishing a stockpile of 500,000 doses of Ebola vaccine for emergency use in outbreaks, beginning with Merck's Ervebo vaccine.

⁴⁶ Dec 5 WHO [update](#)

with weakened immune systems have a [30–60% chance of dying](#) from the infection. Unlike some other fungal infections, it can spread from person to person. It has developed resistance to many common anti-fungal agents, including fluconazole, and even led to temporary closure of an ICU⁴⁷. It may be [often misidentified](#) as a common yeast infection.

- i) Dr Marion Kainer, the head of infectious diseases at Western Health in Victoria, [described](#) the fungus as ‘really unusual’, and called for Australia as a matter of urgency to add the fungus to the National Notifiable Diseases List (NNDL), as has been done in the US. Victoria will list the fungus as a notifiable disease early in 2020. At present, the fungus is being monitored through the [National Alert System for Critical Antimicrobial Resistance](#), which is part of the Australian Commission on Safety and Quality in Health Care. The new National Antimicrobial Resistance Strategy, to be launched in 2020, will consider *Candida auris* as part of a broader focus on resistant fungi.
 - ii) Researchers from Johns Hopkins Bloomberg School of Public Health who studied the fungus concluded that climate change might be playing a role in its rapid emergence in more than 30 countries⁴⁸. They found *Candida auris* was better adapted to growing at higher temperatures than its close relatives. Their paper said: “There is concern that higher ambient temperatures will lead to the selection of fungal lineages to become more thermally tolerant.” Dr Arturo Casadevall, lead author of the paper, said ‘We are very remarkably resistant to fungal diseases. The reason for that is because we have advanced immunity and a high temperature. The combination of the two gives us phenomenal resistance because most fungi cannot grow in mammalian temperatures⁴⁹.
- For the calendar year 2019, up to 30 November, more than 1,500 Queenslanders were diagnosed with whooping cough (pertussis). Of those, 190 presented to the emergency department, up from 124 the same time last year.
 - The Nipah virus carried by bats and pigs was identified in 1999 in Malaysia and Singapore and has since spread as far as India and Bangladesh. Mortality rates from outbreaks have been between 40 and 90 per cent. The virus is regarded as having "serious epidemic potential". Richard Hatchett, chief executive of the CEPI Coalition for Epidemic Preparedness Innovations, who recently co-chaired a Nipah conference in Singapore, said: "Outbreaks of Nipah virus have so far been confined to South and Southeast Asia, but the virus has serious epidemic potential, because *Pteropus* fruit bats that carry the virus are found throughout the tropics and sub-tropics, which are home to more than two billion people." He said that since Nipah can also pass from person to person, it could also spread into densely populated areas. His co-chair, Wang Linfa, a Duke NUS⁵⁰ professor, said: "There are currently no specific drugs or vaccines for Nipah virus infection, even though the World Health Organization has identified (it) as a priority disease."

⁴⁷ <https://www.telegraph.co.uk/news/2016/07/08/intensive-care-unit-closed-as-three-people-die-from-new-superbug/>

⁴⁸ Arturo Casadevall et al., On the Emergence of *Candida auris*: Climate Change, Azoles, Swamps, and Birds, *mBio*. 2019;doi:10.1128/mBio.01397-19.

⁴⁹ [Infectious Diseases News](#).

⁵⁰ National University of Singapore