Attachment C

Monitoring International Trends

Posted May 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 Report, May

Safety and Patient Blood Management (begins page 7 in the detailed report below)

Appropriate transfusion; bleeding risk

- A study found that bleeding risk, which is elevated among patients with cancer receiving anticoagulant therapy, may correlate with metastatic disease, chronic kidney disease, and thrombocytopenia, among other risk factors.
- Researchers found that for patients with intracerebral haemorrhage, those who start antiplatelet therapy do not have an increased risk for recurrence.
- A review concluded that ibuprofen may increase the risk for severe bleeding after tonsillectomy regardless of whether the patient's adenoids were removed.

Preventing and treating anaemia

- Novartis recalled three lots of the 12.5 mg oral suspension of its anaemia treatment Promacta because of a risk of contamination.
- A single-centre study has found that preoperative treatment of iron deficiency reduced blood transfusion requirements after cardiac surgery.

Other

- The US Food and Drug Administration (FDA) issued a final guidance document recommending protocols for reducing the risk of transfusion transmitted babesiosis.

Products and Treatments (begins page 8 in the detailed report below)

Treating haemophilia

- The Hemostasis and Thrombosis Research Society 2019 Scientific Symposium included the presentation of follow-up data on the three patients in the Phase IIb trial of uniQure's AMT-061 in severe or moderately severe haemophilia. After a single administration of AMT-061, average factor IX (FIX) activity six months after treatment for the three subjects had increased.

- A new collaboration between St. Jude Children's Research Hospital and the World Federation of Hemophilia (WFH) will lead to a gene therapy clinical trial (in low- and middle-income nations) for treatment of severe cases of haemophilia B.
- On 28 May, BioMarin said that a single dose of its therapy, valoctocogene roxaparvovec—ValRox—should stop the spontaneous bleeding of people with haemophilia A for at least eight years. The estimate depends heavily on a small group of patients (seven) who have been on the therapy for no more than three years, and the evidence may not be of sufficient significance to gain market approval in the short term.

Treating beta thalassemia and sickle cell disease

- The California Institute for Regenerative Medicine (CIRM) and the US National Heart, Lung and Blood Institute (NHLBI) have begun collaboration to co-fund and help speed the development of cell and gene therapies to cure sickle cell disease.
- Bluebird bio presented new data from clinical studies of LentiGlobin gene therapy for transfusion-dependent β-thalassemia and LentiGlobin gene therapy for sickle cell disease at the 24th European Haematology Association (EHA) Congress.
- Bluebird bio said it expected European approval for its β-thalassemia gene therapy Zynteglo in the second quarter of this year and hopes to launch the drug in Germany before the end of 2019, with launches in Italy, France and the UK in 2020. The company is considering an outcomes-based pricing scheme.
- The FDA has granted Fast Track status to Imara's IMR-687, its investigational treatment for sickle cell disease.
- A study has found that in patients with sickle cell disease severity of disease and location of incident thromboembolic events may be associated with recurrent venous thromboembolism.
- Cyclerion Therapeutics is developing Olinciguat for sickle cell disease. This is an oral once-daily therapy to stimulate an enzyme known to affect the production of nitric oxide.
- Sigilon Therapeutics delivered data on its haemophilia A program (SIG-001) to the American Society of Gene and Cell Therapy (ASGCT) Annual Meeting.

Other products and treatments

- A Phase III trial has shown that prophylactic treatment with Cinryze reduced the number and severity of attacks in young children with hereditary angioedema, without significant adverse events.
- A meta-analysis of nine studies in patients receiving either rituximab or conventional treatment for thrombotic thrombocytopenic purpura (TTP) found that treatment of acquired TTP with rituximab may result in lower rates of relapse and decreased mortality compared with the standard of care.

Regulatory matters (begins page 12 in the detailed report below)

- The European Commission granted conditional Marketing Authorization for Ondexxya (andexanet alfa) for adult patients treated with the factor Xa inhibitors apixaban or rivaroxaban when anticoagulation must be reversed because of uncontrolled bleeding.
- The Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) offered a positive opinion recommending the European Commission give marketing approval for Dova Pharmaceuticals' Doptelet (avatrombopag) for the treatment

of severe thrombocytopenia in adults with chronic liver disease who are scheduled to undergo an invasive procedure.
- Celgene Corporation and Acceleron Pharma announced that Celgene had submitted a Marketing Authorization application to the EMA for luspatercept. This is an agent that regulates late-stage red blood cell maturation.
- The EMA's advisory committee CHMP adopted a negative opinion recommending the refusal of a Marketing Authorization for Emmaus's sickle cell disease drug Xyndari (glutamine).
- The FDA has approved ADMA Biologics' Prior Approval Supplement (PAS) for immune globulin intravenous (human), 10 per cent liquid (Bivigam), indicated for patients with primary humoral immunodeficiency disease, common variable immunodeficiency, Wiskott-Aldrich syndrome, and severe combined immunodeficiency.

Market structure and company news (begins page 13 in the detailed report below)

- Takeda Pharmaceutical announced the opening of a new US research facility in San Diego, California.
- Takeda has agreed to sell TachoSil, a surgical patch designed for bleeding control, to Ethicon, a subsidiary of Johnson & Johnson.
- In the first quarter of 2019, the Biotest Group reported revenue of EUR 77.5 million, a decrease of 11.9 per cent on the EUR 88.0 million in sales during the same period last year.

Specific country events (begins p 15 in the detailed report below)

- In Australia, this year's flu season is expected to cause 4000 deaths across the country. Australians who are obese, and/or diabetic are a growing at-risk sector.
- An Italian study found that sickle cell disease is common among refugees in southern Europe and concluded that screening efforts should be increased.
- From 3 June 2019 the period for which gay and bisexual men in Canada must abstain from sex before donating blood is set to decrease to three months.
- The Canadian Haemophilia Society called on the provinces and territories to make Hemlibra (emicizumab) immediately available to all Canadians with haemophilia A and an inhibitor to factor VIII.
- The US Centers for Disease Control and Prevention (CDC) released a list of the top eight illnesses spread from animals—zoonotic diseases—in the US.
- In the US, officials from the New Mexico Department of Health said two people may have been infected with HIV by the needles used to perform their "vampire facials" at a health spa in Albuquerque.
- The Washington State Health Care Authority chose AbbVie to supply hepatitis C medication. The state will pay a fixed dollar amount for an unlimited supply.
- In the US, reported hepatitis A cases during 2016–2018 increased by almost 300 per cent compared with 2013–2015.
- The first medical drone delivery program to be approved by the US Federal Aviation Administration took flight at a North Carolina hospital.
- The South African National Blood Service is preparing to use unmanned aerial vehicles to transport blood products to rural clinics.

Research not included elsewhere (begins page 16 in the detailed report below)

- AbCellera announced the addition of researchers from the Vaccine Research Center at the US National Institute of Allergy and Infectious Diseases (NIAID), and Ichor Medical Systems to its Pandemic Prevention Platform (P3) team.
- Researchers reported that low-dose radiation given to two mouse models of pulmonary hypertension depleted disease-causing cells, halting and reversing the development of the condition.
- Data presented at the 2019 American Urological Association annual meeting suggest that patients who have elevated platelet counts prior to surgery for high-risk nonmetastatic renal cell carcinoma are at increased risk of cancer recurrence.
- A study has demonstrated that very high levels of neurogranin in the cerebrospinal fluid can be detected in human patients who suffer from prion diseases.
- Researchers at Queen's University Belfast and King's College London have developed technology that can quickly produce large quantities of stem cells from a small blood sample.
- The American Heart Association reported that an experimental antiplatelet compound for acute stroke shows promise.

Infectious diseases (begins page 17 in the detailed report below)

Mosquito-borne diseases

- CSIRO scientist Dr Brendan Trewin has warned that a dengue fever outbreak would once again be possible in Brisbane, as the *Aedes aegypti* mosquito can survive Brisbane winters, with non-compliant (unsealed) rainwater tanks providing an ideal habitat.
- Queensland researchers have tested two local mosquito species for their ability to spread the Zika virus. *Aedes aegypti* mosquito, which is found on the Australian mainland from the tip of Cape York to south-east Queensland, is a very effective carrier. However Asian Tiger mosquitoes, found mainly in the Torres Strait at present, are much less effective as carriers.
- The Democratic Republic of Congo on 1 May declared a chikungunya outbreak
- *Results from a* preclinical trial of Vaxart's chikungunya vaccine have demonstrated that the vaccine induced significant neutralizing antibodies and protective efficacy against virus-induced pathologic changes.
- Researchers have identified multiple clinical and laboratory predictors of mortality in patients with yellow fever.
- A retrospective study has demonstrated that prior yellow fever immunization did not increase the risk of subsequent severe dengue infections in a dengue-endemic region of Brazil.
- The FDA has designated an investigational treatment for severe malaria a Breakthrough Therapy.
- Malaysia's Health Ministry has said it is on track to meet its 2020 zero malaria target.

Influenza

- Producing the A(H3N2) flu strain is a challenge in vaccine manufacturing, but an alternative cell line, produced using a new gene editing tool, offers hope of a better match and improved efficacy.
- GlaxoSmithKline has discontinued development of its universal flu vaccine candidate GSK3816302A after seeing interim data from its Phase I trial.

- Scientists from the University of Adelaide's Research Centre for Infectious Diseases have developed a single vaccination approach to prevent influenza and pneumococcal infections and say this enhances protection against both.
- Moderna announced the publication of results from two Phase I clinical trials showing that mRNA vaccines against H10N8 and H7N9 influenza viruses were well-tolerated and resulted in robust immune responses.
- A report on 28 May said Western Australia's horror early start to the flu season had resulted in an urgent call for blood donors. The call for healthy blood donors was being repeated by the Red Cross Blood Service across Australia, as regular blood donors dropped out temporarily because of illness.
- The world's first confirmed human H5N1 avian flu patient since 2017 died in Nepal.
- Oman reported a case of H9N2 avian flu in a 13 month-old baby.

Ebola virus disease

- The current outbreak of Ebola in the Democratic Republic of Congo is the tenth there in four decades, and the worst so far documented in that country. By 22 May 2019 there had been 1789 confirmed cases with 1160 confirmed deaths, together with 88 probable cases and associated deaths. Over thirty healthcare workers had died. The outbreak has been particularly difficult to control because of its location in a war zone. Ebola treatment centres are not immune from attack, and vaccination and treatment staff have been attacked/ murdered while engaged in their professional activities.

MERS-CoV

- From 2012 when this virus was first detected in humans, to early May 2019, the World Health Organisation (WHO) has been notified of 2,419 MERS-CoV cases, at least 836 of them fatal. Most are from Saudi Arabia.

Other diseases

- A new study suggests that Q fever may be infecting and killing more Americans than once believed.
- Inovio Pharmaceuticals and the Coalition for Epidemic Preparedness Innovations (CEPI) have dosed subjects in a Phase I clinical trial of Inovio's DNA candidate vaccine, INO-4500, to prevent infection from the Lassa virus.
- The US is having its worst outbreak of measles since 1994. Officials said most people who had fallen ill were unvaccinated.
- On 7 May, WHO provided an update on measles activity in the Western Pacific region, noting a resurgence in all regions but spotlighting an unusually high number of cases in several Western Pacific countries where measles had previously been eliminated. Australia was reporting higher numbers of cases in 2019 compared with the same periods over the last 4 years.
- A recent review has found that up to 5 per cent of infants born in the US to mothers infected with Chagas disease become congenitally infected. Untreated, they can develop chronic infection at a young age, and be at risk for serious heart and gastrointestinal complications.
- Singapore managed its first case of monkeypox, in a visitor from Nigeria.
- A number of animals on a deer farm in Minnesota have died of chronic wasting disease (CWD), and there appears to be cross-infection with wild deer.

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Detailed Report

Contents

1. Safety and patient blood management

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

Appropriate Transfusion; Bleeding Risk

- A study[1] published in the *American Journal of Hematology* found that bleeding risk, which is elevated among patients with cancer receiving anticoagulant therapy, may correlate with metastatic disease, chronic kidney disease, and thrombocytopenia, among other risk factors.
  i) Researchers examined patient records for the US from 1999 to 2018 to compare bleeding incidences between patients with or without cancer, grouped by anticoagulant therapy and by possible bleeding risk factors. Bleeding risk factors that were considered included thrombocytopenia, body mass index (BMI) of 40 or higher, stage III or higher chronic kidney disease (CKD), type of cancer, and existence of metastasis.
  ii) For all anticoagulants examined, patients with cancer had higher bleeding incidence rates than patients without cancer. For patients taking warfarin, bleeding incidence was 20.2 per cent for those with cancer and 12.6 per cent for those without cancer. With rivaroxaban, corresponding figures were 16.7 per cent and 12.1 per cent. With apixaban, rates were 14.5 per cent and 9.3 per cent, and with low-molecular-weight heparin, 13.2 per cent and 9.7 per cent.
  iii) Platelet counts of 100 x 10^9/L or lower and stage III or higher CKD were associated with greater bleeding risk for patients with cancer for each anticoagulant. Metastatic disease was associated with greater bleeding risk for all anticoagulants except warfarin. Primary gastrointestinal cancer showed a significantly greater association with bleeding risk compared with other cancer types, and this was true across anticoagulants.
  iv) The study authors concluded that anticoagulation strategies need to be tailored to a patient's overall condition in order to minimize bleeding risk.
- According to two recent studies[2]: for patients with intracerebral haemorrhage, those who start antiplatelet therapy do not have an increased risk for recurrence, including those with cerebral microbleeds.
- Ibuprofen may increase the risk for severe bleeding after tonsillectomy regardless of whether the patient's adenoids were removed, according to recent findings[3]. Gillian R. Diercks[4] and colleagues wrote: "Ibuprofen is an effective analgesic after tonsillectomy alone or tonsillectomy with adenoidectomy, but concerns remain about whether it increases postoperative haemorrhage."

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[1] Angelini DE, Radivoyevitch T, McCrae KR, Khorana AA. Bleeding incidence and risk factors among cancer patients treated with anticoagulation [published online April 21, 2019]. *Am J Hematol*. doi:10.1002/ajh.25494

[2] RESTART Collaboration, "Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial", *The Lancet*, 22 May 2019 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)30840-2/fulltext#
Prof Rustam Al-Shahi Salman et al., "Effects of antiplatelet therapy on stroke risk by brain imaging features of intracerebral haemorrhage and cerebral small vessel diseases: subgroup analyses of the RESTART randomised, open-label trial", *The Lancet Neurology*, 22 May 2019 https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(19)30184-X/fulltext

[3] Gillian R Diercks et al., "Comparison of Ibuprofen vs Acetaminophen and Severe Bleeding Risk After Pediatric Tonsillectomy; A Noninferiority Randomized Clinical Trial", *JAMA Otolaryngology Head and Neck Surgery*, online 4 April 2019. https://jamanetwork.com/journals/jamaotolaryngology/article-abstract/2729845

[4] of the department of otolaryngology at Massachusetts Eye and Ear Infirmary at Harvard Medical School

Preventing and treating anaemia

- Novartis announced in mid-May that it was recalling three lots of the 12.5 mg oral suspension of its anaemia treatment Promacta because there was a risk of peanut flour contamination that occurred at a third-party contract manufacturing site. It said the tablet forms of the drug were unaffected by the recall. The oral suspension is indicated for the treatment of paediatric and adult patients with chronic immune thrombocytopenia, certain adult patients with hepatitis C-associated thrombocytopenia, and certain adult and paediatric patients with severe aplastic anaemia who have not received prior immunosuppressive therapy or had an insufficient response to immunosuppressive therapy.
- A single-centre study[5] has found that preoperative treatment of iron deficiency reduced blood transfusion requirements after cardiac surgery[6].
- Rockwell Medical commenced commercial sales of Dialysate Triferic in the US. Triferic is a novel therapeutic platform for the treatment of anaemia that replaces ongoing iron losses by a process similar to that of normal iron metabolism. It offers a new alternative in the treatment of anaemia in haemodialysis-dependent chronic kidney disease patients.

Other

- On 14 May, Cerus Corporation announced that the US Food and Drug Administration (FDA) had issued a final guidance document recommending protocols for reducing the risk of transfusion transmitted babesiosis[7]. In 15 states where babesiosis is endemic[8], treating donated blood components with the INTERCEPT Blood System is a recognized alternative to year-round babesia testing using a DNA-based test. Dr. Richard Benjamin, Cerus' chief medical officer, said: "Our broad spectrum of pathogen reduction from known and emerging pathogens provides a proactive approach for reducing the risk of transfusion transmitted infections in platelets and plasma."

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

- At the Hemostasis and Thrombosis Research Society 2019 Scientific Symposium[9], Adam Giermasz[10] presented 26 weeks of follow-up data on the three patients in the Phase IIb trial

[5] ClinicalTrials.gov identifier: NCT02031289
[6] Spahn DR, Schoenrath F, Spahn GH, et al. Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial [published online April 26, 2019]. *Lancet*.
[7] The FDA Guidance Document can be viewed here: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-reducing-risk-transfusion-transmitted-babesiosis Babesiosis is caused by a parasite that infects red blood cells, is transmitted by ticks, and can be transmitted through blood donations even when carriers are asymptomatic. It can also lead to haemolytic anaemia and can result in death.
[8] Currently defined as Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, Wisconsin and Washington D.C.
[9] Held 9 – 11 May in New Orleans
[10] From The University of California at Davis

of uniQure's AMT-061[11] in severe or moderately severe haemophilia B[12]. The patients had improved since the previous data readout in February. After a single administration of AMT-061, average factor IX (FIX) activity six months after treatment for the three subjects had increased (57 per cent, 51 per cent and 33per cent of normal, respectively). None of the three experienced serious adverse events or thrombotic events or had developed FIX antibodies. A Phase III study, HOPE-B, is currently recruiting patients with an estimated primary completion date of March 2020. AMT-061 has Breakthrough Therapy Designation from the FDA and access to the Priority Medicine (PRIME) regulatory initiative from the European Medicines Agency (EMA).

- A new collaboration between St. Jude Children's Research Hospital and the World Federation of Hemophilia (WFH) will lead to a gene therapy clinical trial (in low- and middle-income nations) for treatment of severe cases of haemophilia B. Sponsored by St. Jude, the Phase II trial in adult and older-adolescent patients will use a new gene therapy produced jointly by St. Jude and University College London. The therapy uses a re-engineered virus (adeno-associated virus) as a vector to carry the F9 gene into liver cells.
- On 28 May, BioMarin said that a single dose of its therapy, valoctocogene roxaparvovec—ValRox—should stop the spontaneous bleeding of people with haemophilia A for at least eight years. The estimate depends heavily on a small group of patients (seven) who have been on the therapy for no more than three years, and the evidence may not be of sufficient significance to gain market approval in the short term[13]. In that long-term Phase I/II study[14], ValRox's power to produce the blood-clotting protein factor VIII starts to decline after peaking around the four-month mark. But in the third year, it "appears to be approaching a plateau," President of Worldwide Research & Development Hank Fuchs said. Reports assert that, even at the lowest levels in the third year, most patients on ValRox still produced much more factor VIII than the level that is regarded as the border between moderate and mild haemophilia (five international units per decilitre). Reports also suggest that even as factor VIII wanes, bleed rates remain stable. However, Stifel analyst Paul Matteis said: "We do not think the durability debate for ValRox is over".

Treating beta thalassemia and sickle cell disease

- The California Institute for Regenerative Medicine (CIRM) and the US National Heart, Lung and Blood Institute (NHLBI) have begun collaboration[15] to co-fund and help speed the development of cell and gene therapies to cure sickle cell disease (SCD).
  i) One of the eligible projects is led by Mark Walters, a paediatric haematologist and oncologist at UCSF Benioff Children's Hospital in Oakland, California. CIRM granted $US 4.46 million to Walters in April for a therapeutic translational project to achieve a cure based on the autologous transplant of CRISPR/Cas9 gene-edited stem cells. This uses a patient's own stem cells, skipping donor requirements and eliminating the possibility of graft-versus-host disease and rejection. Walters and his team will extract patients' own haematopoietic (blood-forming) stem cells (HSCs) from the bone marrow into laboratory cultures. There they will be genetically edited by CRISPR-Cas9 to correct the HBB mutation

[11] *A Single Infusion of AMT-061 (AAV5-Padua hFIX) is Safe and Effective in Adults with Hemophilia B: Interim Results from Dose-Confirmation Phase 2b Trial* (Poster #44, 10 May)
[12] See updated results and Phase 2b clinical trial
[13] The three-year data come from seven patients. BioMarin estimated valrox's effectiveness at a minimum of eight years by combining those data with two years of results from a lower dose given to six more patients, as well as short-term results from the 20-patient Phase 3 study, dubbed GENEr8-1.
[14] https://investors.biomarin.com/2019-05-28-BioMarin-Provides-3-Years-of-Clinical-Data-from-Ongoing-Phase-1-2-Study-of-Valoctocogene-Roxaparvovec-Gene-Therapy-for-Severe-Hemophilia-A
[15] see press release.

responsible for sickle cell disease. The corrected HSCs will then be re-introduced into the patient to produce healthy red blood cells.

ii) So far, CIRM has granted more than $US 38 million to several different preclinical and clinical-stage projects targeting SCD. Two other cell and gene therapy approaches funded by the agency are already being explored in a Phase I trial (NCT03249831) at City of Hope Medical Center and a Phase I/II trial (NCT02247843) at the University of California Los Angeles.

- bluebird bio presented new data from clinical studies of LentiGlobin gene therapy for transfusion-dependent β-thalassemia (TDT) and LentiGlobin gene therapy for sickle cell disease (SCD) at the 24th European Haematology Association (EHA) Congress[16].

  i) Data was presented from clinical studies of LentiGlobin gene therapy for TDT including updated results up to 54 months from the long-term follow-up period of the completed Phase I/II Northstar (HGB-204) study[17]. New data was presented from the ongoing Phase III Northstar-2 (HGB-207) study in patients who do not have a β^0/β^0 genotype[18] and from the ongoing Phase III Northstar-3 (HGB-212) study in patients who have β^0/β^0 genotype or an IVS-I-110 mutation[19].

  ii) New data from the company's Phase I/II HGB-206 study of LentiGlobin gene therapy for SCD included additional patients treated in the study and updated data for those previously reported[20]. Abstracts were made available on the EHA conference website.

- bluebird bio said it expected European approval for its β-thalassemia gene therapy Zynteglo[21] in the second quarter of this year. This followed the March recommendation to the EMA by its Committee for Medicinal Products for Human Use (CHMP) of conditional approval of the drug to treat transfusion-dependent β-thalassemia in patients aged at least 12 who do not have a β-0/β-0 genotype, and for whom haematopoietic stem cell transplantation (HSCT) is appropriate but a matched donor is unavailable. bluebird hopes to launch the drug in Germany before the end of 2019, with launches in Italy, France and the UK in 2020. bluebird says it will set up 13 qualified treatment centres in those four countries. The therapy will be manufactured in Munich. The company also hopes to submit a Biological License Application to the FDA this year for the therapy. The company is considering an outcomes-based pricing scheme[22].

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[16] Amsterdam, 13-16June.

[17] *Clinical Outcomes of LentiGlobin Gene Therapy for Transfusion-Dependent β-Thalassaemia (TDT) Following Completion of the Northstar (HGB-204) Study*. Presenting Author: Mark Walters, Benioff Children's Hospital, Oakland, California. 14 June (oral presentation).

[18] *Safety and Efficacy of LentiGlobin Gene Therapy in Patients with Transfusion-Dependent β-Thalassaemia and Non-β^0/β^0 Genotypes in the Phase 3 Northstar-2 Study (HGB-207)*. Presenting Author: Franco Locatelli, University of Pavia, Lombardy, Italy 16 June (oral presentation).

[19] *Results from the Phase 3 Northstar-3 Study Evaluating LentiGlobin Gene Therapy in Patients with Transfusion-Dependent β-Thalassaemia and a β^0 or IVS-I-110 Mutation at Both Alleles of the HBB Gene (HGB-212)*. Presenting Author: Andreas Kulozik, University Hospital Heidelberg, Heidelberg, Germany. 14 June (oral presentation).

[20] *Updated Results from the HGB-206 Study in Patients with Severe Sickle Cell Disease Treated Under a Revised Protocol with LentiGlobin Gene Therapy Using Plerixafor-Mobilised Haematopoietic Stem Cells (HGB-206)* Presenting Author: Julie Kanter, Division of Hematology and Oncology, University of Alabama at Birmingham. 16 June (oral presentation).

[21] The LentiGlobin-based therapy consists of autologous CD34+ stem cells transduced *ex vivo* with a lentiviral vector delivering the human β globin gene. If approved, Zynteglo will be the first commercially available product to treat TDT.

[22] see bluebird's Five-Year Pricing Model for LentiGlobin Could Resonate with Payers The company is looking at an annuity-based payment model over five years, with the possibility of subsequent adjustments depending on how patients respond to treatment. In January at the J.P. Morgan healthcare conference, the company said it was considering tying as much as 80 per cent of Zynteglo's price to how well it works. It said Zynteglo offers a "lifetime intrinsic value" of more than $US 2 million, but it did not disclose a proposed price.

- The FDA has granted Fast Track status to Imara's IMR-687 its investigational treatment for sickle cell disease. The drug also has Orphan Drug and Rare Pediatric designations. It is an orally-delivered, once-daily, highly selective inhibitor of phosphodiesterase 9 (PDE9) designed to decrease red blood cell sickling and the adherence of white blood cells to the walls of blood vessels[23]. It is the subject of a Phase IIb placebo-controlled clinical trial[24] involving 54 patients with sickle cell anaemia; a Phase I trial in healthy volunteers found IMR-687 to be well tolerated.
- A study[25] has found that in patients with sickle cell disease severity of disease and location of incident thromboembolic events may be associated with recurrent venous thromboembolism (VTE). Researchers found that patients with severe SCD were more than twice as likely to experience recurrent thromboembolism compared with patients with less severe disease. The authors suggested that patients with SCD who experienced VTE may benefit from continuous anticoagulation, though this must be considered against the high risk of bleeding in this patient population. They concluded that: "a prospective, multicenter, randomized trial may be warranted and feasible given the frequency of VTE in this population".
- Nitric oxide, a free radical produced by several types of cells, is used as a signalling molecule that promotes blood flow; so it is possible symptoms of sickle cell disease may be associated with nitric oxide deficiency in the blood. Cyclerion Therapeutics is developing Olinciguat, an oral once-daily therapy to stimulate an enzyme known to affect the production of nitric oxide. Olinciguat is being tested in the Phase II STRONG-SCD clinical trial (NCT03285178), enrolling 88 patients, age 16 to 70, at 26 US sites. Participants will be randomized to four ascending doses of Olinciguat or a placebo for 12 weeks. Top-line results from the STRONG-SCD trial are expected by mid 2020. Olinciguat received Orphan Drug status from the FDA in June 2018.
- Sigilon Therapeutics on 1 May delivered an oral presentation[26] featuring data on its haemophilia A program (SIG-001) at the American Society of Gene and Cell Therapy (ASGCT) Annual Meeting in Washington, D.C. The company plans regulatory filing of SIG-001 later this year so it can begin clinical trials.

Other products and treatments

- A Phase III trial[27] has shown that prophylactic treatment with Cinryze reduced the number and severity of attacks in young children with hereditary angioedema (HAE)[28], without significant adverse events[29].

[23] See Imaratx.com.
[24] https://clinicaltrials.gov/ct2/show/NCT03401112
[25] Brunson A, Keegan T, Mahajan A, White R, Wun T. High incidence of venous thromboembolism recurrence in patients with sickle cell disease [published online May 9, 2019]. *Am J Hematol*. doi:10.1002/ajh.25508
[26] *Correcting Bleeding Disorders Using Blood Clotting Factors Produced by Shielded Engineered Allogenic Cells*
[27] Emel Aygören-Pürsün et al., "A Randomized Trial of human C1 inhibitor prophylaxis in children with hereditary angioedema," in *Pediatric Allergy and Immunology*. 9 April 2019 https://doi.org/10.1111/pai.13060
[28] HAE is a genetic disorder marked by sudden and recurrent episodes of swelling in the deeper layers of the skin, the upper airway, and the gastrointestinal tract. The disease results from mutations in the *SERPING1* gene, leading to lower levels of C1-inhibitor (C1-INH), in the case of HAE type 1, or to a dysfunctional C1-INH whose levels remain normal or elevated in the case of HAE type 2.
[29] Cinryze was approved by the US Food and Drug Administration (FDA) in 2008 for the long-term prophylactic treatment of adults and teenagers with HAE. A decade later, the FDA extended the approval to children age 6 and older, largely based on promising findings from a multi-centre, randomized, single-blind, crossover Phase III clinical trial (NCT02052141) designed to assess the

- A meta-analysis of nine studies in patients receiving either rituximab or conventional treatment for thrombotic thrombocytopenic purpura (TTP) found that treatment of acquired TTP with rituximab may result in lower rates of relapse and decreased mortality compared with the standard of care[30].

3. Regulatory

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

- The European Commission (EC) granted conditional Marketing Authorization for Ondexxya (andexanet alfa)[31]. Ondexxya is the first antidote to be approved in Europe for adult patients treated with the factor Xa inhibitors apixaban or rivaroxaban when anticoagulation must be reversed because of uncontrolled bleeding. Jan Beyer-Westendorf, of University Hospital Dresden commented: "As the number of European patients prescribed these factor Xa inhibitors continues to increase, so too does the incidence of hospital admissions related to bleeding. The approval of Ondexxya represents a significant step forward in the treatment of these patients, who previously had no approved treatment option." Scott Garland, Portola's president and chief executive officer, said: "Our initial launch efforts will be focused on a select group of countries where factor Xa use is among the highest". As part of the conditional approval, Portola will provide further study results[32]. Ondexxya was approved by the FDA in May 2018 and is marketed in the US by Portola under the trade name Andexxa [coagulation factor Xa (recombinant), inactivated-zhzo][33].

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safety and efficacy of Cinryze in young children with HAE. After reporting the first interim results of the trial, researchers now described the complete findings of the study involving 12 children with HAE ages 6–11.

[30] Owattanapanich W, Wongprasert C, Rotchanapanya W, Owattanapanich N, Ruchutrakool T. Comparison of the long-term remission of rituximab and conventional treatment for acquired thrombotic thrombocytopenic purpura: a systematic review and meta-analysis [published online January 29, 2019]. *Clin Appl Thromb Hemost.* doi:10.1177/1076029618825309

[31] The conditional approval relied on data from two Phase III ANNEXA studies (ANNEXA-R and ANNEXA-A) that evaluated the safety and efficacy of Ondexxya in reversing the anticoagulant activity of the factor Xa inhibitors rivaroxaban or apixaban in healthy subjects, and data from the Phase IIIb/IV ANNEXA-4 study that evaluated efficacy and safety data from 352 bleeding patients. For further information:

Deborah M Siegal et al., "Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity" December 17, 2015, *N Engl J Med* 2015; 373:2413-2424 DOI: 10.1056/NEJMoa1510991 https://www.nejm.org/doi/full/10.1056/NEJMoa1510991;

Stuart J Connolly et al. "Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors" September 22, 2016 *N Engl J Med* 2016; 375:1131-1141 DOI: 10.1056/NEJMoa1607887 https://www.nejm.org/doi/full/10.1056/NEJMoa1607887;

Stuart J Connolly et al., "Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors", April 4, 2019, *N Engl J Med* 2019; 380:1326-1335 DOI: 10.1056/NEJMoa1814051 https://www.nejm.org/doi/full/10.1056/NEJMoa1814051

[32] the final study reports for both the ANNEXA-4 trial and the randomized controlled clinical trial requested by the US Food and Drug Administration (FDA), as well as additional pharmacokinetic data.

[33] Portola has another FDA-approved drug, Bevyxxa (betrixaban), an oral, once-daily factor Xa inhibitor for the prevention of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness.

- The EMA's advisory committee CHMP adopted a positive opinion for the use of Novo Nordisk's Esperoct[34] (turoctocog alfa pegol, N8-GP) recommending marketing authorisation for the treatment of adolescents and adults with haemophilia A: for prophylaxis, on-demand treatment of bleeding and for surgical procedures.
- CHMP also offered a positive opinion recommending the European Commission give marketing approval for Dova Pharmaceuticals' Doptelet (avatrombopag) for the treatment of severe thrombocytopenia in adults with chronic liver disease who are scheduled to undergo an invasive procedure.
- Celgene Corporation and Acceleron Pharma announced that Celgene had submitted a Marketing Authorization application to the EMA for luspatercept. This is an investigational erythroid maturation agent that regulates late-stage red blood cell maturation. It is designed for the treatment of (i) adult patients with beta-thalassemia-associated anaemia who require red blood cell transfusions and (ii) adult patients with very low to intermediate-risk myelodysplastic syndromes associated anaemia who have ring sideroblasts, require red blood cell transfusions and have received or are not eligible for erythropoiesis-stimulating agents. The safety and efficacy results included in the application are from the Phase III studies MEDALIST and BELIEVE.
- The EMA's advisory committee CHMP adopted a negative opinion recommending the refusal of a Marketing Authorization for Emmaus's sickle cell disease drug Xyndari (glutamine).
  i) The FDA had approved the drug (branded as Endari in the US) in July 2017[35], noting it was the first new treatment for the disorder in two decades.
  ii) The FDA had said the approval was based on a trial showing that patients treated with Endari experienced fewer hospital visits for sickle cell crises, on average, when compared with placebo. CHMP, however, said it "considered that the main study did not show that Xyndari was effective at reducing the number of sickle cell crises or hospital visits."
  iii) CHMP emphasised that more patients in the study who were taking Xyndari than taking placebo dropped out of the study before it was finished, "and information on how the medicine worked for those patients was not available. The CHMP considered that the way data from these patients were dealt with was not appropriate."
- The FDA has approved ADMA Biologics' Prior Approval Supplement (PAS) for immune globulin intravenous (human), 10 per cent liquid (Bivigam), previously known as RI-002. Bivigam is indicated for patients with primary humoral immunodeficiency disease (PIDD), which includes X-linked and congenital agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and severe combined immunodeficiency. The FDA had approved the therapy in December 2012, but manufacturing and compliance issues led to voluntary suspension of commercial production in 2016. The PAS approval permits the company to commence sales of the product.

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.

[34] Esperoct is an extended half-life factor VIII molecule for replacement therapy in patients with haemophilia A, which provides a 1.6-fold half-life prolongation in adults/adolescents compared with standard half-life factor VIII products.

[35] https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-sickle-cell-disease

Companies considered include suppliers, potential suppliers and developers of products which may be of interest.

- Takeda Pharmaceutical announced the opening of a new US research facility in San Diego, California. This complements Takeda's two other research facilities, in Cambridge, Massachusetts and in Shonan, Japan.
- Takeda has agreed to sell TachoSil, a surgical patch designed for safe, fast and reliable bleeding control, to Ethicon, a subsidiary of Johnson & Johnson, for $US 400 million.
- In the first quarter of 2019, the Biotest Group reported revenue of EUR 77.5 million, a decrease of 11.9 per cent on the EUR 88.0 million in sales during the same period last year[36].
  i) There was a 17.6 per cent increase in research and development costs, due to the production of clinical material for the development projects IgG Next Generation and Trimodulin[37].
  ii) The Group has expanded its network of plasma collection stations in Europe to 21 to secure the long-term supply of plasma. Plasma Service Europe GmbH, Dreieich, Germany, a 100 per cent subsidiary of Biotest AG, acquired a plasmapheresis centre in Hanover in January 2019. Another centre was opened in Budapest in April 2019.
  iii) In January 2019 Biotest received the extension of the approved indications of Intratect in 22 European countries to include the neurological indications chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN), as well as an extension in the area of secondary immunodeficiencies (SID).
- CSL has appointed Paul McKenzie as chief operating officer. He was previously executive vice president of Biogen.
- On 7 May, Cerus Corporation announced financial results for the quarter ended March 31, 2019. Total first quarter revenue was $US 22.0 million, including record quarterly product revenue of $US 17.5 million (a 29 per cent increase on the first quarter 2018) and government contract revenue of $US 4.5 million[38]. Globally, disposable kit demand increased 35 per cent from the first quarter last year. The company said it had a $US 90 million new debt facility consisting of a staged $US70 million term loan and a $US 5 million revolving line of credit, expandable up to $US 20 million.

[36] The quarterly statement is available on the company's website at http://www.biotest.com/de/en/investor_relations/news_and_publications/public

[37] Biotest is developing Trimodulin, for the treatment of patients with severe community acquired pneumonia. Trimodulin is a human plasma-derived native polyclonal antibody preparation for intravenous administration. It contains immunoglobulins IgM (~23%), IgA (~ 21%) and IgG (~56%). The drug has three mechanisms: opsonization of causal pathogens, neutralizing of microbial pathogens and their virulence factors (endo and exo toxins) and targeting the host inflammatory response.

[38] This contract revenue is from an agreement with the Biomedical Advanced Research and Development Authority (BARDA), which is part of the Office of the Assistant Secretary for Preparedness and Response within the U.S. Department of Health and Human Services. This revenue was $US3.5 million during the same period in 2018. The increase was as a result of increasing INTERCEPT red blood cell clinical and development activities. The total potential value of the current BARDA agreement is $US 201 million with $US 29 million recognized as revenue to 31 March 2019.

5. Specific country events

- In Australia, reports on 7 May said this year's flu season is expected to cause 4000 deaths across the country. By then, there had been almost 40,000 confirmed influenza cases nationally this year, compared with 58,500 recorded for the entire 2018 calendar year.
  i) Immunisation Coalition chairman Professor Robert Booy explained it is a unique season in that there were two types of influenza A – H1 and H3 strains – when usually it is only one. He said: "[This year] has been really strange … There has been a sustained and rising summer and autumn surge that began at the end of last year and is continuing to increase."
  ii) University of Queensland influenza virologist Dr Kirsty Short said Australians who were obese, and/or had diabetes are a growing at-risk sector: "In the 2009 so-called 'swine flu' epidemic, what we saw was that both obesity and diabetes for the first time emerged as susceptibility factors for severe influenza. (They) were significantly more likely to be hospitalised with the flu, they were significantly more likely to be admitted to the ICU and were significantly more likely to die from the virus."
- An Italian study[39] found that sickle cell disease is common among refugees in southern Europe and concluded that screening efforts should be increased.
- From 3 June 2019 the period for which gay and bisexual men in Canada must abstain from sex before donating blood is set to drop from one year to three months.
- On 7 May, the Canadian Haemophilia Society (CHS) called on the provinces and territories to make Hemlibra (emicizumab) immediately available to all Canadians with haemophilia A and an inhibitor to factor VIII. Hemlibra was approved for patients with haemophilia A and inhibitors by Health Canada on 2 August 2018.
- In the US, the Centers for Disease Control and Prevention (CDC) on 6 May released a list of the top eight illnesses spread from animals — zoonotic diseases — in the US. The list includes some strains of the flu, *Salmonella* infection, West Nile virus, the plague, emerging coronaviruses such as Middle East respiratory syndrome, rabies, brucellosis (a bacterial infection) and Lyme disease. The eight illnesses were chosen based on the potential for the disease to cause an epidemic or pandemic, the severity of the disease, the economic impact, the potential for the introduction or spread of the disease in the US, and the potential for bioterrorism.
- In the US, officials from the New Mexico Department of Health said two people may have been infected with HIV by the needles used to perform their "vampire facials" at a health spa in Albuquerque. In the anti-ageing procedure (alleged) blood is drawn from the patient and centrifuged, then platelet rich plasma is reinjected into the face. The spa was closed down last September.
- In the US, the Washington State Health Care Authority chose AbbVie to supply hepatitis C medication under a subscription-based payment model. The state will pay a fixed dollar amount to AbbVie for an unlimited supply of hepatitis C drugs, as it chases its goal of eliminating hepatitis C in the state by 2030. This follows a similar deal made by the state of Louisiana with a Gilead Sciences subsidiary.
- In the US, reported hepatitis A cases during 2016–2018 increased by almost 300 per cent compared with 2013–2015, with outbreaks associated with contaminated food, among men who have sex with men, and primarily, among persons reporting drug use or homelessness[40].

[39] Lucia De Franceschi et al., "Access to emergency departments for acute events and identification of sickle cell disease in refugees", Blood 2019 133:2100-2103; doi: https://doi.org/10.1182/blood-2018-09-876508

[40] Centers for Disease Control, *Morbidity and Mortality Weekly Report*.

- The first medical drone delivery program to be approved by the US Federal Aviation Administration took flight at a North Carolina hospital.
- The South African National Blood Service (SANBS) hopes to make a big investment in an unmanned aerial vehicles (UAV) network to transport blood products to rural clinics. It has sought Civil Aviation Authority (CAA) approval to begin a test service.
- The Indian Council of Medical Research (ICMR) has developed an affordable test kit for diagnosis of common blood disorders such as severe haemophilia A and von Willebrand disease (VWD). According to the ICMR scientists, the diagnosis can be done within 30 minutes of blood sample collection.

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.

- AbCellera announced in Vancouver the addition of researchers from the Vaccine Research Center at the US National Institute of Allergy and Infectious Diseases (NIAID), and Ichor Medical Systems (Ichor) to its Pandemic Prevention Platform (P3) team. This initiative sparked by the US Defense Advanced Research Projects Agency (DARPA) is to enable rapid response to pandemic viral outbreaks. As part of the four-year, USD $30 million project, the additional researchers will contribute expertise in virology, vaccinology, nucleic acid antibody vectorization and delivery to complement AbCellera's capabilities. The goal is to build an end-to-end platform able to develop field-ready medical countermeasures within 60 days of a viral outbreak.
- Researchers reported[41] that low-dose radiation given to two mouse models of pulmonary hypertension depleted disease-causing cells, halting and reversing the development of the condition.
- New data presented at the 2019 American Urological Association annual meeting[42] suggest that patients who have elevated platelet counts prior to surgery for high-risk nonmetastatic renal cell carcinoma are at increased risk of cancer recurrence. Emily L Davidson, of the University of Wisconsin in Madison, and colleagues reported that preoperative platelet counts above 250,000/µL of blood are independently associated with a significant 50 per cent increased risk of recurrence compared with lower platelet counts. The team concluded that: "Integration of platelet count into risk stratification models may help identify patients who benefit from adjuvant therapy or clinical trial enrolment."
- A recently published study[43] demonstrates that very high levels of neurogranin in the cerebrospinal fluid can be detected in human patients that suffer from prion diseases. Neurogranin is a protein found naturally in neurons. Its role is to participate in the process of the synapse and can be detected by analysing cerebrospinal fluid. In this study it has been found that the levels of neurogranin are associated with the duration of the disease.

[41] Pamela C Egan et al., "Low dose 100 cGy irradiation as a potential therapy for pulmonary hypertension," published 22 April 2019in the *Journal of Cellular Physiology*. https://doi.org/10.1002/jcp.28723

[42] Davidson EL, Master VA, Raman JD, et al. *Platelet count is an independent predictor of post-surgical recurrence in high risk non-metastatic renal cell carcinoma.* Presented at the 2019 American Urological Association annual meeting held May 3-6 in Chicago. Abstract PD46-06.

[43] Kaj Blennow et al, "CSF neurogranin as a neuronal damage marker in CJD: a comparative study with AD", *Journal of Neurology, Neurosurgery & Psychiatry* (2019). DOI: 10.1136/jnnp-2018-320155

"Neurogranin is a marker of neuronal damage. When we find it in high quantities, it is indicating that neurons are harmed, therefore the disease will move faster, it will have a short duration," explained one commentator.

- Researchers at Queen's University Belfast and King's College London have developed technology that can quickly produce large quantities of stem cells from a small blood sample[44]. They found these stem cells can generate and replace damaged cells within blood vessels. They suggest this treatment could prevent a variety of vascular-related complications including heart attacks, kidney disease, blindness, and amputations in people with diabetes.
- The American Heart Association reported that an experimental antiplatelet compound for acute stroke shows promise[45].
- Jason Karnes**,** assistant professor in the UA College of Pharmacy, received a five-year, $US 769,000 K01 career development award from the US National Institutes of Health to identify predictive and early diagnostic biomarkers for heparin-induced thrombocytopenia. This research also will help develop effective, personalized preventive and therapeutic interventions.

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

- CSIRO scientist Dr Brendan Trewin has warned that a dengue fever outbreak would once again be possible in Brisbane, as the *Aedes aegypti* mosquito can survive Brisbane winters, with non-compliant (unsealed) rainwater tanks providing an ideal habitat: 70 per cent of the mosquito species survives to adulthood in rainwater tanks, while 50 per cent can survive in buckets of water. Associate Professor Greg Devine (of the QIMR Berghofer Medical Research Institute) said each year many people arrived in Australia infected with dengue fever and other infectious diseases which could be transmitted by *Aedes aegypti*, and that "non-compliant tanks pose a real risk of becoming *Aedes aegypti* habitats and breeding sites, which could lead to outbreaks of dengue, chikungunya and Zika, to a population that has no immunity to these diseases."

[44] Marta Vilà-González et al. “Enhanced Function of Induced Pluripotent Stem Cell-Derived Endothelial Cells Through ESM1 Signaling”, *Stem Cells* (2018). DOI: 10.1002/stem.2936

[45] Christine Voors-Pette, Kristell Lebozec, Peter Dogterom, Laurie Jullien, Philippe Billiald, Pauline Ferlan, Lionel Renaud, Olivier Favre-Bulle, Gilles Avenard, Matthias Machacek, Yannick Plétan, Martine Jandrot-Perrus. “Safety and Tolerability, Pharmacokinetics, and Pharmacodynamics of ACT017, an Antiplatelet GPVI (Glycoprotein VI) Fab”. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 2019; DOI: 10.1161/ATVBAHA.118.312314 or https://www.ahajournals.org/doi/pdf/10.1161/ATVBAHA.118.312314

- Queensland researchers[46] have tested two local mosquito species for their ability to spread the Zika virus. They found that the *Aedes aegypti* mosquito, which is found on the Australian mainland from the tip of Cape York to south-east Queensland, is a very effective carrier[47]. However Asian Tiger mosquitoes, found mainly in the Torres Strait at present, are much less effective as carriers[48]. The researchers found Zika virus in the ovaries of the *Aedes aegypti* mosquitoes, which might mean they could transmit it to their young without an external source of the virus.
- The FDA has approved the ZIKV Detect 2.0 IgM Capture ELISA (from InBios International Inc) for routine use in detecting Zika virus immunoglobulin (IgM) antibodies in human blood[49] (most importantly, the FDA says this test should not be used to test blood or plasma donors for Zika). Until now, tests for detecting Zika virus IgM antibodies — including this test— had been authorized only for emergency use[50].
- Chembio Diagnostics says its test for dengue has been approved by Brazil's health regulatory agency. The test was developed with another Brazilian government agency, Bio-Manguinhos.
- The Democratic Republic of Congo on 1 May declared a chikungunya outbreak, with over 6000 cases reported since 1 January, and the likelihood of underestimation.
- Results from a preclinical trial of Vaxart's chikungunya vaccine have been published[51]. Sean Tucker, founder and chief scientific officer of Vaxart, said: "These preclinical results demonstrate that our vaccine candidate induced significant neutralizing antibodies against chikungunya virus as well as protective efficacy against virus-induced pathologic changes. Importantly, we saw reduced footpad swelling, a model for arthritis induction in humans caused by chikungunya infection".
- Researchers have identified multiple clinical and laboratory predictors of mortality in patients with yellow fever[52]. Risk factors associated with higher mortality included older age; male sex; higher leukocyte and neutrophil counts; higher alanine aminotransferase, aspartate transaminase, bilirubin and creatinine; prolonged prothrombin time; and higher yellow fever virus RNA plasma viral load.

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[46] from the Queensland University of Technology (QUT) in association with QIMR Berghofer

[47] Leon E Hugo, Francesca D Frentiu et al., "Vector competence of Australian *Aedes aegypti* and *Aedes albopictus* for an epidemic strain of Zika virus", *PLOS Neglected Tropical Diseases*. Published: April 4, 2019 https://doi.org/10.1371/journal.pntd.0007281

[48] Dr Francesca Frentiu (QUT's Institute of Health and Biomedical Innovation) reported that around 10 per cent of Asian Tiger mosquitoes could effectively transmit the virus through their saliva 14 days after becoming infected, while for *Aedes aegypti* mosquitoes the figure was 50 to 60 per cent.

[49] The FDA considered data from a clinical study of 807 test samples and various analytical studies, demonstrating the ZIKV Detect 2.0 IgM Capture ELISA to be safe and effective. The test is to be used only in patients presenting with clinical symptoms consistent with Zika infection, and/or who meet Centers for Disease Control and Prevention (CDC) Zika epidemiologic criteria (such as living in, or travelling to, a location with active Zika transmission at the time). The FDA advised that test results should be used together with clinical observations, patient history, epidemiologic information and the results of other laboratory tests in arriving at patient management decisions. The FDA advised that negative results may be seen in specimens collected prior to day 4 from the onset of symptoms or after the window of detectable IgM closes, and therefore do not preclude the possibility of Zika virus infection, past or present.

[50] under the FDA's emergency use authorization (EUA). The FDA said this current approval does not affect the availability of the 14 other Zika nucleic acid diagnostics available under EUAs.

[51] Emery G Dora et al. "An adjuvanted adenovirus 5-based vaccine elicits neutralizing antibodies and protects mice against chikungunya virus-induced footpad swelling", *Vaccine,* Volume 37, Issue 24, 27 May 2019, Pages 3146-3150. https://doi.org/10.1016/j.vaccine.2019.04.069

[52] Esper G Kallas et al., "Predictors of mortality in patients with yellow fever: an observational cohort study", *The Lancet Infectious Diseases*, 16 May 2019 https://doi.org/10.1016/S1473-3099(19)30125-2 https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(19)30125-2/fulltext

- A retrospective study[53] has demonstrated that prior yellow fever immunization did not increase the risk of subsequent severe dengue infections in a dengue-endemic region of Brazil.
- The FDA has designated an investigational treatment for severe malaria a Breakthrough Therapy[54]. LJPC-0118, is being developed by La Jolla Pharmaceutical Company[55]. Based on trial results, La Jolla plans to submit a New Drug Application to the FDA in the fourth quarter of 2019.
- Malaysia's Health Ministry has said it is on track to meet its 2020 zero malaria target.

Influenza

- Human flu seasons dominated by A(H3N2) viruses are recognised as severe, and they hit elderly patients the hardest. Producing the A(H3N2) flu strain is a challenge in vaccine manufacturing, but an alternative cell line, produced using a new gene editing tool, offers hope of a better match and improved efficacy[56]. Yoshihiro Kawaoka, of the University of Wisconsin, said that the US National Institutes of Health (NIH) is interested in new cell lines to make H3N2 human challenge strains, since these viruses don't grow well in existing cell lines. The human challenge trials play a key role in identifying preferred vaccine virus candidates.
- GlaxoSmithKline has discontinued development of its universal flu vaccine candidate GSK3816302A after seeing interim data from its Phase I trial. The experimental vaccine combined the Icahn School of Medicine Mount Sinai's chimeric hemagglutinin technology and GSK's AS03 adjuvant. GSK says it will continue to apply its adjuvants and other technologies to the development of further universal flu vaccines.
- Scientists from the University of Adelaide's Research Centre for Infectious Diseases have developed a single vaccination approach to prevent influenza and pneumococcal infections and say this enhances protection against both[57]. The single vaccine is based on a new class of vaccines they are developing.
- Moderna announced the publication[58] of results from two Phase I clinical trials showing that mRNA vaccines against H10N8 and H7N9 influenza viruses were well-tolerated and resulted in robust immune responses. The company said mRNA-based vaccines had the potential to address pandemic influenza strains quickly and effectively.
- A report on 28 May said Western Australia's horror early start to the flu season[59] had resulted in an urgent call for blood donors. Sixty people a day were cancelling their appointments to donate blood. Pharmacies across the state were reporting a shortage of influenza vaccine. The call for healthy blood donors was being repeated by the Red Cross

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[53] Marina Jolli Luppe et al., "Yellow fever (YF) vaccination does not increase dengue severity: A retrospective study based on 11,448 dengue notifications in a YF and dengue endemic region", *Travel Medicine and Infectious Disease*, online 8 May 2019. https://doi.org/10.1016/j.tmaid.2019.05.002

[54] To be awarded Breakthrough status a treatment must demonstrate substantial improvement over current therapeutic options. The FDA recently approved two new therapies for malaria: Arakoda and Krintafel.

[55] See lajollapharmaceutical.com.

[56] Kosuke Takada, Yoshihiro Kawaoka et al., A humanized MDCK cell line for the efficient isolation and propagation of human influenza viruses", *Nature Microbiology*, published 29 April 2019.

[57] Shannon C David, Mohammed Alsharifi et al., "Direct interaction of whole-inactivated influenza A and pneumococcal vaccines enhances influenza-specific immunity", *Nature Microbiology*, 20 May 2019

[58] Robert A Feldman, "mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials", *Vaccine*, Volume 37, Issue 25, 31 May 2019, Pages 3326-3334 https://doi.org/10.1016/j.vaccine.2019.04.074

[59] There had been 3013 reported so far in 2019, compared with 1151 for the same period in 2018.

Blood Service across Australia, as regular blood donors dropped out temporarily because of illness.

- The world's first confirmed human H5N1 avian flu patient since 2017 died in Nepal. Since 2003, the World Health Organization (WHO) has reported 860 human H5N1 cases, 454 of them fatal, many in Egypt, Indonesia, and Vietnam.
- Oman reported a case of H9N2 avian flu in a 13 month-old baby.

Ebola virus disease

- The current outbreak of Ebola in the Democratic Republic of Congo is the tenth there in four decades, and the worst so far documented in that country[60]. The Ministry of Health officially declared the outbreak on 1 August 2018 but it probably began months earlier.
  i) As advised in our April web post, by 25 March 2019 the number of Ebola cases in DCR had passed 1000, with 58 recorded in the previous week. By then 634 deaths had been reported. Over 91,000 people in DRC had been vaccinated with Merck's experimental VSV-EBOV vaccine, introduced in a previous outbreak in West Africa. A preliminary estimate published by WHO suggested that the vaccine had been more than 97 per cent effective in a ring trial where contacts — and contacts of contacts — of confirmed cases had been offered vaccination.
  ii) In April there were 400 new cases, a doubling of the March case count. By 7 May 110,000 people had received the vaccine. There had been a concern about a potential vaccine shortage, but a recent analysis of the vaccine dose needed to protect people found that the amount could be substantially reduced, by more than half for some people[61]. WHO also received advice[62] that a third vaccination ring should be added, everyone in a village or a city neighbourhood where a case occurs, regardless of contact history. Plans were made to use an experimental Johnson and Johnson two-dose vaccine to assist in building community immunity, although the DCR health minister has said he would prefer the use of just the Merck vaccine, to avoid confusing the population.
  iii) By 22 May 2019 there had been 1789 confirmed cases with 1160 confirmed deaths, together with 88 probable cases and associated deaths[63]. Over thirty healthcare workers had died. By 29 May, estimates suggested there had been 1926 confirmed or probable cases, a third of them children, and 80 per cent not identified as contacts of people known to have Ebola.
  iv) The outbreak has been particularly difficult to control because of co- location with a war zone. Ebola treatment centres are not immune from attack, and vaccination and treatment staff have been attacked/ murdered while engaged in their professional activities[64].

[60] and the second-largest Ebola outbreak recorded anywhere. Only the Ebola outbreak in West Africa in 2014 had as at 22 May 2019 recorded more cases and deaths.
[61] The changes were recommended by the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization.
[62] Again from its Strategic Advisory Group of Experts (SAGE) on Immunization
[63] "Probable" deaths refer to deaths that were linked to confirmed Ebola cases but not tested before burial.
[64] MSF had suffered attacks on its Ebola Treatment Centres in Butembo and Katwa and suspended running such centres at least temporarily. It was assisting in existing health care structures in North Kivu and Ituri provinces and managing transit centres, testing patients with suspected Ebola and referring them on to treatment centres if necessary. In the US, the Centers for Disease Control and Prevention (CDC) on 6 May released a list of the top eight illnesses spread from animals — zoonotic diseases — in the US. The list includes some strains of the flu, *Salmonella* infection, West Nile virus,

MERS-CoV

- From 2012 when this virus was first detected in humans, to early May 2019, the WHO has been notified of 2,419 MERS-CoV cases, at least 836 of them fatal. Most are from Saudi Arabia. The Saudi total for 2019 up to 8 May was 137 infections[65].
- Dromedary (one-humped) camels are recognized as being the major source of MERS-CoV transmission, but until now not much has been understood about the susceptibility of Bactrian (double-humped) camels, whose habitat overlaps to some extent with dromedaries. Researchers based at the US National Institute of Allergy and Infectious Diseases (NIAID) Rocky Mountain Laboratories in Hamilton, Montana, experimentally infected two male camels that were housed in an animal biosafety level 3 facility. They reported that the animals were susceptible to MERS-CoV and that "the virus shedding kinetics of MERS-CoV in Bactrian camels was virtually identical to previous experimental studies in dromedary camels". They concluded that if MERS-CoV were introduced to Bactrian camel populations, the animals could act as a reservoir, similar to dromedaries and possibly exposing humans to infection[66].

Other diseases

- A new study[67] suggests that Q fever may be infecting and killing more Americans than once believed. It is found mostly in dry, dusty areas of California and the Southwest[68]. Lead researcher Dr Christine Akamine[69] said: "Q fever is underdiagnosed in the United States. We suspect this is because most patients have only mild symptoms and do not present for medical evaluation." Her research revealed that more patients than expected had severe cases of Q fever and that diagnosis was often delayed.
    i) For the study, Akamine and colleagues collected data on patients hospitalized for Q fever between 2000 and 2016 in a dusty, dry, windy area of Southern California. Of the 20 patients who were diagnosed with Q fever, three developed chronic cases of the disease and two died. Akamine said that Q fever can be cured with antibiotics; but chronic cases can lead to serious heart and blood vessel infections and have poor outcomes. Akamine emphasised that her study covered only hospitalized patients and only one hospital.

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the plague, emerging coronaviruses such as Middle East respiratory syndrome, rabies, brucellosis (a bacterial infection) and Lyme disease. The eight illnesses were chosen based on the potential for the disease to cause an epidemic or pandemic, the severity of the disease, the economic impact, the potential for the introduction or spread of the disease in the U.S., and the potential for bioterrorism.

[65] The WHO provided more details on 36 MERS-CoV cases, 12 of them fatal, reported from Saudi Arabia between Mar 1 and Apr 8 that weren't part of a large outbreak in Wadi ad-Dawasir. WHO provided details on 36 MERS-CoV cases, 12 of them fatal, amongst those reported from Saudi Arabia between 1 March and 8 April. Of the 36, nine patients had a history of exposure to camels or camel milk, and 12 had been exposed to another MERS-CoV patient. Five were healthcare workers. Patient ages ranged from 22 to 80, and all but 8 were male. Three had asymptomatic infections, and 24 had underlying medical conditions.

[66] Danielle R. Adney, Michael Letko, Izabela K. Ragan, Dana Scott, Neeltje van Doremalen, Richard A. Bowen & Vincent J. Munster, “Bactrian camels shed large quantities of Middle East respiratory syndrome coronavirus (MERS-CoV) after experimental infection”, *Emerging Microbes and Infections*, 8;1, 717-723 https://doi.org/10.1080/22221751.2019.1618687

[67] https://www.ajtmh.org/content/journals/10.4269/ajtmh.18-0283
Christine M. Akamine et al., “Q Fever in Southern California, a Case Series of 20 Patients from a VA Medical Center”, published online May 20 in the *American Journal of Tropical Medicine and Hygiene*.

[68] People become infected either by direct contact with livestock that carry the bacteria *Coxiella burnetii*, or by inhaling the spores carried by dust and wind.

[69] assistant professor of medicine at Loma Linda University in California

ii) Dr Marc Siegel[70] commented: "We need much faster diagnosis and early treatment." He said that physicians who treat people in areas where Q fever is more common should be on the lookout for unexplained flu-like symptoms and have patients tested for Q fever and maybe prescribe antibiotics even before test results are in.

- In Australia, recent publicity about the incidence of Q fever in Queensland and New South Wales has led to the Yass Branch of NSW Farmers offering a clinic to save participants money compared with arranging the tests and vaccination on their own.
- Inovio Pharmaceuticals and the Coalition for Epidemic Preparedness Innovations (CEPI) have dosed subjects in a Phase I clinical trial[71] of Inovio's DNA candidate vaccine, INO-4500, to prevent infection from the Lassa virus. About 60 volunteers will participate. The first-in-human, placebo-controlled, blinded, dose-escalation trial, as well as it's the vaccine development program, is funded through CEPI[72]. Melanie Saville, CEPI Vaccine Development director, said: "With marked increases in the number of cases documented in Nigeria over the last two years and outbreaks occurring annually, Lassa fever remains a serious public health threat across West Africa." Inovio expects to advance its Lassa candidate vaccine into a Phase II field trial in endemic countries of West Africa beginning in the second half of 2019. Inovio president and CEO Dr Joseph Kim said: "Inovio's class-leading synthetic nucleic vaccines delivered intradermally with its proprietary Cellectra efficacy enhancing systems are well suited to rapidly produce countermeasures against emerging viral threats, potentially protecting large populations from a pandemic. Inovio has rapidly advanced several global health candidate vaccines, including those against HIV, Ebola, MERS, and Zika, and has reported above 90 per cent immune response rates from multiple clinical studies."
- The US is having its worst outbreak of measles since 1994[73]. Officials said most people who had fallen ill were unvaccinated[74]. By 17 May, 880 confirmed cases had been recorded by the US Centers for Disease Control and Prevention (CDC). By 24 May there had been 60 further cases and the outbreak had reached 26 states. Health officials in a number of states had been discouraging air travel by infected people, citing the federal government's authority to place them on a Do Not Board list managed by the CDC.
- On 7 May, WHO provided an update on measles activity in the Western Pacific region, noting a resurgence in all regions but spotlighting an unusually high number of cases in several Western Pacific countries where measles had previously been eliminated. WHO said the infections had been caused by imported cases. In the Philippines, cases had increased 378 per cent compared with the same period in 2018. Australia was reporting higher numbers of cases in 2019 compared with the same periods over the last 4 years, and Japan is experiencing its largest case load in a decade. Malaysia in 2018 had an increase of almost 900 per cent compared with 2013. Hong Kong reported an airport-linked cluster of 29 cases, and 32 cases in Macao this year include 10 cases in hospital staff. Of 150 cases in South Korea reported since 17 December, eight clusters were linked to imported infections.

[70] a professor of medicine at NYU Langone Medical Center in New York City
[71] Evaluating safety, tolerability and immune responses
[72] In 2018 Inovio received a $56m grant from CEPI to develop vaccine candidates through Phase II against Lassa fever and Middle East Respiratory Syndrome (MERS).
[73] The total that year was 958. In 1992, 2,126 cases were recorded. Measles was declared eliminated from the US in the year 2000. While the disease no longer has a constant presence, outbreaks still happen via travellers from countries where measles is still common, such as Israel, the Philippines and Ukraine.
[74] Public health officials have blamed the measles resurgence on the spread of misinformation about vaccines by organised opponents of vaccination.

- A recent review[75] has found that up to 5 per cent of infants born in the US to mothers infected with Chagas disease become congenitally infected. Untreated, they can develop chronic infection at a young age, and be at risk for serious heart and gastrointestinal complications.
- Singapore managed its first case of monkeypox, in a visiting Nigerian man, who was hospitalised in an isolation ward at the National Centre for Infectious Diseases.
- A number of animals on a deer farm in Minnesota have died of chronic wasting disease (CWD)[76], and there appears to be cross-infection with wild deer. No human cases have been identified but hunters and residents are being advised against eating meat which may be contaminated.

[75] Morven S Edwards et al., "Evaluation and Management of Congenital Chagas Disease in the United States", *The Journal of the Pediatric Infectious Diseases Society*. 24 April 2019. Edwards MS, et al. *J Pediatr Infect Dis Soc.* 2019;doi:10.1093/jpids/piz018.

[76] A fatal prion disease in cervids, known to occur in the US, Canada, Scandinavia and South Korea.