

Monitoring International Trends

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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 potentially put financial or other pressures on the Australian sector.

A selection of recent matters of interest appears below. Highlights include:

Haemophilia Treatment

- Pfizer has made a deal with Sangamo on a new gene therapy for haemophilia A.
- Dimension Therapeutics discontinued its development of an investigational gene therapy for haemophilia B
- uniQure's investigational gene therapy for patients with haemophilia B has been awarded PRIME status by European regulators, setting the treatment on a faster path to possible approval.
- Australia's Therapeutic Goods Administration (TGA) approved CSL Behring's Afstyla, a recombinant single chain coagulation factor VIII, for patients with haemophilia A.
- Aptevo presented data on Ixinity, its recombinant factor IX product.
- Octapharma USA presented study on the development of inhibitors in haemophilia patients, and on the need for frequent venous access for FVIII injection.
- The European Union (EU) Committee for Medicinal Products for Human Use (CHMP) recommended marketing authorisation for Novo Nordisk's long-acting Factor IX, nonacog beta pegol (Refixia).

Patient Blood Management and Patient Safety

- The US FDA, accepting that near the end of their shelf life platelets are at a greater risk of bacterial growth, has suggested that platelets need to be retested.
- In the first confirmed case in Australia of transfusion-transmitted hepatitis E, a boy aged six was infected by a donation from a man who ate pork in France.
- The US Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA) exercised additional options under its contract with Cerus for the development of Intercept red blood cells.
- A study has suggested, without determining the optimal storage time, that liquid plasma may be satisfactory up to a point and may be more quickly available for severe trauma patients than frozen plasma.
- Researchers have recommended that physicians in hospitals should be alert to the signs of platelet refractoriness, and know how to manage bleeding effectively.
- A study has found that prophylactic platelet transfusions were not superior to supportive care for adult dengue patients with thrombocytopenia.
- A clinical trial has indicated that whole blood treated with the Mirasol pathogen reduction technology system may be acceptable for transfusion after storage.
- A Scandinavian retrospective cohort study has suggested donor age and sex were not associated with mortality amongst recipients of red blood cell transfusions.
- The Canadian Blood Services has examined the feasibility of large-scale ferritin testing.

- The American College of Emergency Physicians says emergency medical services personnel must ask about a patient's use of blood thinners.
- The WOMAN—World Maternal Antifibrinolytic—trial concluded: “Tranexamic acid reduces death due to bleeding in women with post-partum haemorrhage with no adverse effects”.

Artificial Blood and Bone

- Plasticell has secured UK government funding to create a safe, effective red blood cell substitute for human clinical transfusion in collaboration with the University of Edinburgh. Plasticell has also partnered with Kings College, London to progress preclinical trials of its artificial blood platelet product.
- Researchers have engineered an implant that resembles real bone, with working marrow capable of producing healthy blood.

Legal challenges

- Liability claims against Pfizer and Bristol-Myers Squibb over bleeding risks for their anticoagulant Eliquis were dismissed.
- Baxalta alleged patent infringement by Genentech and Chugai with their emicizumab product for haemophilia (ACE910).
- Shire Viropharma alleged infringement by CSL of a newly granted US patent in connection with a method of treating hereditary angioedema.

Research

- Scientists have identified new cell subtypes in the human immune system. They fall into the white blood cell class.

The threat from the Zika virus, and other mosquito-borne infections

- Transmission of dengue, chikungunya and Zika is highest around 84 degrees F.
- If mice have antibodies from dengue or West Nile virus, it sets them up for more severe disease from Zika.
- A number of Zika vaccines have reached the stage of human testing.
- Researchers can rapidly generate RNA vaccines, including for Zika.
- In rhesus monkeys, after the immune system has removed traces of Zika virus from the blood, low-level infection may continue at other sites.
- The US National Institutes of Health-backed dengue vaccine was tested in humans.
- Takeda's tetravalent dengue vaccine is based on a live-attenuated dengue serotype 2 virus, which provides the genetic 'backbone' for all four attenuated dengue virus serotypes present in the vaccine.
- The World Health Organization (WHO) said 3.5 million doses of yellow fever vaccine have been shipped to Brazil to help deal with its worst outbreak in years.
- A new study has shown that malaria parasites can shuffle genes, leading to questioning of the efficacy of GlaxoSmithKline's vaccine Mosquirix, and others.
- Researchers at Griffith University have tested their whole blood-stage malaria parasite vaccine PlasProtect in humans.

Influenza, MERS, Ebola, CMV and TB

- This H7N9 flu season in China has been marked by a shift to a highly pathogenic form of the virus in poultry and a wider distribution of human cases beyond the poultry production areas of the south-eastern provinces.
- As of 24 May, there had been a total of 1612 laboratory-confirmed cases of MERS-CoV infection in Saudi Arabia, including 662 deaths.
- WHO confirmed an Ebola outbreak in a remote area of the Congo.
- Hookipa Biotech and VBI Vaccines are trialling vaccines against cytomegalovirus.
- Multidrug resistant tuberculosis is worsening in four of the countries with the largest number of TB cases.

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1. Products

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

Products for treating bleeding disorders

- Pfizer, with one gene therapy for haemophilia B already in the clinic at Spark Therapeutics, has made a deal with Sangamo on a new gene therapy for haemophilia A. Pfizer gains exclusive worldwide licensing on four programs including SB-525, which is ready to undergo a clinical trial. Sangamo is to start a Phase I/II clinical trial to evaluate safety and to measure blood levels of Factor VIII protein, along with other efficacy endpoints. Pfizer's R&D chief Mikael Dolsten said: "We are building an industry-leading expertise in recombinant adeno-associated virus (rAAV) vector design and manufacturing." Pfizer is paying Sangamo \$US 70 million upfront and \$US 475 million in milestones, \$US 300 million related to SB-525. Pfizer is behind BioMarin, which announced last year that its gene therapy for haemophilia A had demonstrated a high chance of restoring patients' natural clotting abilities, reducing or eliminating bleeding episodes. The company initiated a Phase IIb study of BMN 270, hoping to win accelerated approval.
- Dimension Therapeutics, in reporting its first quarter 2017 financial results (loss per share \$US 0.54) announced its decision to discontinue development of DTX101, an investigational adeno-associated gene therapy for the treatment of haemophilia B. It said that data would not meet the company's minimum target product profile for continued development¹. Dimension Therapeutics' research and development expenses for the quarter were approximately \$US 13.7 million compared with \$US 8.8 million for first quarter 2016.

¹ Dimension said it did not believe the outcome of the DTX101 program would affect ongoing phase I/II clinical development of DTX301 for the treatment of Ornithine Transcarbamylase (OTC) Deficiency.

- At the [Hemostasis and Thrombosis Research Society 2017 Scientific Symposium](#) April 6-8 in Scottsdale, Arizona, [Aptevco Therapeutics](#) presented data on Ixinity (its recombinant factor IX product, IB1001). The company said it was found to be safe and effective in previously treated children under 12 with haemophilia B. Scott Stromatt, senior vice president and chief medical officer, said: “The key efficacy outcomes from this study are comparable to what has previously been demonstrated in our pivotal study of Ixinity, which formed the basis for our licensure in the United States in patients age 12 or older.”
- Also at the Hemostasis and Thrombosis Research Society Symposium, Octapharma USA presented interim clinical research results on the company’s studies investigating two major challenges facing haemophilia patients: the development of inhibitors and the need for frequent venous access for FVIII injection.
 - i) The research team for Octapharma’s Phase III study, GENA-05 (NuProtect)², reported interim data on the rate of inhibitor development in previously untreated patients (PUPs) treated with Octapharma’s human cell line recombinant FVIII (Human-cl rhFVIII)³. Final data are expected in 2019.
 - ii) Octapharma has also been conducting clinical studies of the dosing process (Gena-21⁴ and GENA-21b⁵) to investigate the frequency of dosing with personalized prophylaxis. In the GENA-21 (NuPreviq) study, adult haemophilia A patients were originally started on infusions three times per week or every other day. Subsequent dosing intervals were then determined based on individual pharmacokinetic (PK) data, which resulted in a median dosing interval of 3.5 days and with 58 per cent of patients on a twice a week, or fewer, infusion schedule⁶.
 - iii) Octapharma’s third research presentation at the HTRS symposium introduced WIL-27⁷, investigating the pharmacokinetics, efficacy, safety, and immunogenicity of Wilate in previously treated patients with severe haemophilia A. This prospective, international, multi-centre Phase III study seeks 55 male participants at sites in the US and Europe. Participants must have severe haemophilia A and be aged 12 or more⁸.
- Novo Nordisk’s long-acting Factor IX, nonacog beta pegol (Refixia), received a positive opinion from the European Union (EU) Committee for Medicinal Products for Human Use (CHMP) on 23 March, recommending marketing authorisation for the treatment of adolescents and adults with haemophilia B. The recommendation is based on the results from the Paradigm clinical trial programme, where 115

² <https://clinicaltrials.gov/ct2/show/NCT01712438?term=GENA-05&rank=2>

³ Human-cl rhFVIII sells in the US as Nuwiq, Antihæmophilic Factor (Recombinant) Lyophilized Powder for Solution for Intravenous Injection. It is indicated in adults and children with haemophilia A for on-demand treatment and control of bleeding episodes; perioperative management of bleeding; and routine prophylaxis to reduce the frequency of bleeding episodes.

⁴ <https://clinicaltrials.gov/ct2/show/NCT02256917?term=GENA-21&rank=2>

⁵ <https://clinicaltrials.gov/ct2/results?term=GENA-21b&Search=Search>

⁶ GENA-21b is an ongoing global, prospective, open-label, multi-centre Phase IIIb study undertaken to confirm the data of GENA-21 and assess the benefit of PK-guided individualized prophylaxis in previously treated patients predominantly on routine prophylaxis. During the HTRS symposium, researchers reported snapshot data for GENA 21b, regarding the investigation of PK-guided dosing that may result in longer recommended treatment intervals and lower FVIII consumption than during regular prophylaxis. The median treatment interval during regular prophylaxis is 2.3 days, or three times per week. During individualized prophylaxis in the study, 58.6 per cent of patients were treated twice per week or less with a recommended median treatment interval of 3.5 days at an average single dose of 44 IU/kg. The median annual bleed rate (ABR) for patients in this trial was zero. The preliminary data suggest that patients may potentially experience a 21 per cent decrease reduction in FVIII use through personalized prophylaxis compared with regular prophylaxis with NUWIQ.

⁷ <https://clinicaltrials.gov/ct2/show/NCT02954575?term=WILATE&rank=2>

⁸ The complete study protocol is available at www.ClinicalTrials.gov; ClinicalTrials.gov Identifier: NCT02954575.

previously treated children and adults with haemophilia B were treated with Refixia. The US Food and Drug Administration (FDA) and its Blood Products Advisory Committee (BPAC), have taken longer to consider the new drug. There has been concern that the amount of neurologic monitoring may have been insufficient in the three Phase III trials to detect adverse events that would be associated with PEG⁹ accumulation in the brain¹⁰.

Other products

- Prometic Life Sciences presented new data at the 2017 American Thoracic Society (ATS) International Conference in Washington, D.C. showing the benefits of plasminogen administration in reducing lung injury in a gold standard animal model of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) associated with acute pancreatitis. Both are life-threatening conditions resulting in respiratory failure in the critically ill patient¹¹.
- Sanguinate is [Prolong Pharmaceuticals](#)' investigational drug for treatment of sickle cell disease (SCD)-associated complications. It is reported to have yielded promising results in patients experiencing vaso-occlusive crisis (VOC). A research study, [SANGUINATE Returns RBCs To More Normal Morphology In Patients With VOC](#), was presented at the 2017 Annual Symposium of the [Foundation for Sickle Cell Disease Research](#) in Fort Lauderdale, Florida, reporting this new treatment was able to restore the shape of red blood cells, improving the VOC symptoms in SCD patients.

2. Safety and patient blood management

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

Appropriate Transfusion

- According to the US Centers for Disease Control and Prevention (CDC) bacterial contamination of platelets has been the greatest transfusion-based infectious risk in the US. It says one in 1,000 to 3,000 platelet units may be contaminated, and that transfusion-transmitted sepsis has been confirmed in at least one in 100,000 recipients¹². Platelets are stored for five days at room temperature after a blood culture to detect for bacteria. The FDA has accepted that near the end of their shelf life (at day 4 or 5) platelets are at a greater risk of bacterial growth, and suggested guidance that platelets need to be retested because of bacteria that could go undetected by the first test. The American Hospital Association, the American Red Cross and AABB all sought a delay in the recommendation because of its operational and economic implications¹³. Options for retesting platelets include a rapid test and pathogen reduction technology.

⁹ Refixia (nonacog beta pegol, N9-GP) is an extended half-life factor IX molecule for replacement therapy in patients with haemophilia B. Glycopegylation is the prolongation technology used for the half-life extension, and is a novel approach in haemophilia B. Pegylated products have been approved in haemophilia A and other therapeutic areas.

¹⁰ There was particular concern that paediatric patients may be at the greatest risk because they could be taking Refixia for the longest period of time, presumably resulting in greater accumulation and eventual problems later in life.

¹¹ "Plasminogen Reduces Acute Lung Injury in an Acute Pancreatitis Model", poster presentation

¹² The CDC believes transfusion-transmitted infections are under-reported and that physicians need to be trained to recognise and manage them.

¹³ AABB, America's Blood Centers (ABC) and the American Red Cross (ARC) submitted [joint comments](#) to the Food and Drug Administration concerning the agency's March 2016 draft guidance, [Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services To](#)

- In the first confirmed case of the hepatitis E virus being transferred through blood donated in Australia, a boy aged six was infected by a donation from a man who ate pork in France¹⁴.
- The US Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA) [exercised additional options](#) under its contract with Cerus for the development of Intercept red blood cells (RBCs). The funds will support a Phase III study to assess the RBCs for the treatment of anaemia in cardiovascular surgery patients and a UK-based study in patients undergoing exchange transfusion for sickle cell disease. Another Phase III study, called RedeS, is comparing Intercept RBCs with conventional RBCs in areas at risk for the Zika virus.
- For severe trauma patients at risk of bleeding to death, the speedy transfusion of plasma, platelets and red blood cells in a 1:1:1 ratio may be required. Thawing plasma causes delays, so a recent study¹⁵ has compared the haemostatic properties of thawed and liquid plasma over several days of storage. At initial processing after donation 17 pooled ABO-matched plasma units were split into a liquid plasma unit and a frozen unit (subsequently thawed and stored for up to five days), and multiple haemostasis parameters, coagulation factors, and platelet activation assays were undertaken. A further 119 liquid plasma samples were analysed for platelet activation and cellular content. At day seven liquid plasma was comparable with thawed plasma at day five by every assay. However, after 11 days of storage, coagulation factors began to decline in liquid plasma. While this study did not determine the optimal storage time, it did suggest that liquid plasma may be satisfactory up to a point and may be more quickly available for severe trauma patients.
- Researchers have previously reported improved survival for trauma patients transfused with higher ratios of fresh frozen plasma (FFP) compared with red blood cells (RBCs), but there is less evidence for the same experience among non-trauma patients needing massive transfusions¹⁶. Now researchers in Boston¹⁷ have completed a retrospective study of 865 patients requiring massive transfusions at the Massachusetts General Hospital. They found the transfusion ratios of FFP:RBCs were similar between patients who survived (1:1.5 units) and those who died (1:1.4 units) (P=0.43). Of those cases, 767 were non-trauma patients. For 544 the primary reason for transfusion was intraoperative bleeding. For non-trauma patients, survival was similar between patients receiving high transfusion ratios of FFP:RBCs compared with low transfusion ratios of FFP:RBC. However, lower transfusion ratios of FFP:RBCs were associated with increased survival for medical and general surgery patients, while the patients undergoing vascular surgery had a better chance of survival with higher FFP:RBC ratios. The researchers concluded that additional studies are needed to determine the optimal ratio of FFP:RBCs in massive transfusion for subgroups of non-trauma patients.

[Enhance the Safety and Availability of Platelets for Transfusion.](#) The comments, which were drafted by members of the AABB FDA Liaison Committee, identify critical concerns involving blood collection establishments and transfusion services. The groups strongly encourage FDA to consider the guidance's unintended adverse impact on the blood supply and patient safety.

¹⁴ Veronica C Hoad, et al., "First confirmed case of transfusion-transmitted hepatitis E in Australia", *Med J Aust* 2017; 206 (7): 289-290. doi: 10.5694/mja16.01090

¹⁵ Backholer L, et al, "A paired comparison of thawed and liquid plasma", *Transfusion*, 2016 Volume 57, Issue 4, April 2017 Pages 881–889 DOI: 10.1111/trf.13915

¹⁶ Defined as at least 10 units of RBCs in 24 hours.

¹⁷ Mesar T, "Association Between Ratio of Fresh Frozen Plasma to Red Blood Cells During Massive Transfusion and Survival Among Patients Without Traumatic Injury". *JAMA Surg* Published online March 8, 2017. doi:10.1001/jamasurg.2017.0098.

- Patients with platelet function disorders (PFDs) may present with severe bleeding episodes or excessive surgical bleeding. Standard treatment consists of platelet transfusions, but repeated transfusions may lead to the development of antiplatelet antibodies (APA) or clinical refractoriness. An approved treatment option for patients with one of the well-known PFDs, Glanzmann's thrombasthenia (GT), is recombinant activated coagulation factor VII (rFVIIa). Efficacy of rFVIIa in patients with GT and platelet refractoriness can be gauged from a patient registry, an international survey, and multiple case reports. A recent journal article¹⁸ reviews the rFVIIa clinical data in patients with GT and platelet refractoriness and considers clinical implications relevant to the hospital-based physician. The authors, aware that uncontrolled bleeding is life-threatening, recommend that physicians in hospitals should be alert to the signs of platelet refractoriness, be able to recognize continued internal or external bleeding, and know how to manage bleeding effectively. They emphasise that the management of patients who receive rFVIIa should be in consultation with a haematologist with experience in PFDs, and patients with suspected platelet refractoriness should be referred to a haematologist as early as possible. They say a critical unmet need is the development of a definition of an adequate response to platelet transfusion, which would facilitate early recognition of platelet refractoriness in patients with PFDs who exhibit a normal platelet count.
- A study¹⁹ has found that prophylactic platelet transfusions were not superior to supportive care²⁰ for adult dengue patients with thrombocytopenia. Authors said further research is needed to confirm the results of this trial in other populations, including children.
- A clinical trial has suggested that whole blood treated with the Mirasol pathogen reduction technology system may be acceptable for transfusion after storage²¹.
- A Scandinavian retrospective cohort study²² has suggested donor age and sex were not associated with mortality amongst recipients of red blood cell transfusions.

Treating anaemia

- The Canadian Blood Services, wishing to identify donors at highest risk of iron deficiency, examined the feasibility of large-scale ferritin testing²³. Over a period of eighteen months, they performed ferritin testing on 12,595 blood donors who had passed the haemoglobin screen. This group constituted 2.6 per cent of all donors. Donors with low ferritin levels (<25 µg/L) were advised to see their health care providers to return their iron stores to normal. They were deferred as blood donors for at least 6 months. Iron deficiency (<25 µg/L ferritin) was identified in 54 per cent of women donors and 33 per cent of male donors. Over 41 per cent of repeat male

¹⁸ Meera Chitlur, et al., "Recognition and management of platelet-refractory bleeding in patients with Glanzmann's thrombasthenia and other severe platelet function disorders", *International Journal of General Medicine*, 3 April 2017 Volume 2017:10 Pages 95—99. DOI <https://doi.org/10.2147/IJGM.S128953>

¹⁹ Lye DC, et al., "Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicentre, open-label, randomised, superiority trial". *The Lancet*, Volume 389, No. 10079, p1611–1618, 22 April 2017. DOI: [http://dx.doi.org/10.1016/S0140-6736\(17\)30269-6](http://dx.doi.org/10.1016/S0140-6736(17)30269-6)

²⁰ bed rest, fluids, and general pain and fever-reducing medications

²¹ Cancelas JA, et al., "Red blood cells derived from whole blood treated with riboflavin and ultraviolet light maintain adequate survival in vivo after 21 days of storage". *Transfusion* 2017. May;57(5):1218-1225. doi: 10.1111/trf.14084. Epub 2017 Mar 31.

²² Edgren G, et al. "Association of Donor Age and Sex With Survival of Patients Receiving Transfusions". *JAMA Intern Med*. Published online April 24, 2017. doi:10.1001/jamainternmed.2017.0890

²³ Goldman M, et al., "A large national study of ferritin testing in Canadian blood donors". *Transfusion* 2017;57: 564-70.

donors and 65 per cent of repeat female donors had low iron levels. Almost 60 per cent of donors deferred for low iron returned to donate within a year, but they donated less often and had a lower return rate compared with donors with normal iron levels. The Canadian Blood Services decided to increase the minimum inter-donation interval for women donors from 56 days to 84 days, with a maximum of four whole blood donations per year.

Other

- the American College of Emergency Physicians suggests requiring emergency medical services personnel to ask about a patient's use of blood thinners could be vital, particularly in elderly patients.
- The findings of the WOMAN—World Maternal Antifibrinolytic—trial, were reported in *The Lancet*²⁵. Over 20 000 women were enrolled. The trial took place in 21 varied geographical settings, including countries with some of the highest rates and absolute numbers of maternal deaths. The trial concluded: “Tranexamic acid reduces death due to bleeding in women with post-partum haemorrhage with no adverse effects. When used as a treatment for post-partum haemorrhage, tranexamic acid should be given as soon as possible after bleeding onset.” The investigators acknowledge that in many settings where most maternal deaths take place—at home or in very poorly resourced facilities—intravenous administration of tranexamic acid may not be possible, and they urged further studies of tranexamic acid given by other routes.

3. Regulatory

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

- CSL Behring announced on 19 April that the Australian Therapeutic Goods Administration (TGA) had approved Afstyla [lonococog alfa] a recombinant single chain coagulation factor VIII (rFVIII SingleChain) in patients with haemophilia A²⁶. Afstyla is indicated in all patients with haemophilia A for routine prophylaxis to prevent or reduce the frequency of bleeding episodes; for control and prevention of bleeding episodes; and for perioperative management (surgical prophylaxis). Afstyla is the first single-chain recombinant factor VIII product to treat haemophilia A. The single chain design provides sustained protection from bleeds with a strong binding affinity to Von Willebrand factor. In clinical trials, patients undergoing prophylaxis enjoyed a median annualised spontaneous bleeding rate of zero with the convenience of dosing twice or thrice weekly. The drug was well tolerated²⁷.
- Emmaus Life Sciences announced that the Oncologic Drug Advisory Committee of the FDA would review the Company's New Drug Application (NDA) for its orally-administered pharmaceutical grade L-glutamine product (Endari™), for the treatment of sickle cell disease. If approved, Endari would be the first FDA-approved treatment for paediatric patients with sickle cell disease, and the first new treatment in nearly 20 years for adult patients. Endari has Orphan Drug designation in the US, Orphan Medicinal Product designation in the EU and Fast Track designation from the FDA.

²⁴ Daniel K Nishijima et al., “Out-of-Hospital Triage of Older Adults With Head Injury: A Retrospective Study of the Effect of Adding “Anticoagulation or Antiplatelet Medication Use” as a Criterion”, *Annals of Emergency Medicine*, DOI: <http://dx.doi.org/10.1016/j.annemergmed.2016.12.018>

²⁵ DOI: [http://dx.doi.org/10.1016/S0140-6736\(17\)31111-X](http://dx.doi.org/10.1016/S0140-6736(17)31111-X)

²⁶ Afstyla is also approved in the US, Canada and the EU.

²⁷ The AFFINITY clinical development program included Phase I through to Phase III open-label, multicentre studies evaluating safety and efficacy in children and adults (ages 1 to 61 years) with severe haemophilia A.

The FDA's target action date under the Prescription Drug User Fee Act is 7 July 2017.

- uniQure's investigational gene therapy for patients with haemophilia B has been awarded PRIME status by European regulators, setting the treatment on a faster path to possible approval.
- The European Medicines Agency (EMA) has granted Apellis Pharmaceuticals Orphan Drug designation²⁸ to APL-2 in the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH). APL-2 is intended to control symptoms and modify the underlying disease.
- Rigel Pharmaceuticals filed a new drug application (NDA) with the FDA, seeking approval for its oral spleen tyrosine kinase inhibitor, fostamatinib for the treatment of patients with chronic and persistent immune thrombocytopenia (ITP). Fostamatinib was previously granted Orphan Drug designation by the FDA for that indication. The NDA was supported by positive data from three phase III studies.
- OncBioMune Pharmaceuticals in mid-April announced the forthcoming submission to COFEPRIS (Mexico's equivalent of the FDA) of the Anti-D immunoglobulin product marketed as KamRho by Kamada and licensed by OncBioMune for the Mexican market.
- The FDA granted Akari Therapeutics "fast track" designation²⁹ for Coversin, its treatment for paroxysmal nocturnal hemoglobinuria³⁰ (PNH) in patients who have polymorphisms conferring eculizumab resistance. Coversin is in Phase II clinical trials.
- Almost one-third of drugs cleared by the FDA have been found to pose safety risks that are identified only after their approval³¹.

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.

- Plasticell, a UK company developing cell therapies including hematopoietic cell replacement therapies, has secured government funding to create a safe, effective red blood cell substitute for human clinical transfusion³². The project will manufacture red blood cells from pluripotent stem cells, in collaboration with the University of Edinburgh. Plasticell has also partnered with Kings College, London to

²⁸ To achieve such orphan status a sponsor must establish that the product is specifically intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating rare disease, and that the product will have significant benefits for patients. The EMA defines rare as affecting fewer than 5 in 10,000 people in the European Union (EU). Amongst incentives offered by the EU to companies developing rare disease treatments are protocol assistance, access to the centralized authorization procedure, and market exclusivity once the product becomes available.

²⁹ Fast track designation is awarded to drugs addressing rare but severe illnesses.

³⁰ In paroxysmal nocturnal hemoglobinuria, a body's immune system attacks its own red blood cells. A significant risk associated with the disease is blood clots.

³¹ The study was reported 9 May in the Journal of the American Medical Association. Nicholas S. Downing et al., "Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010", JAMA. 2017;317(18):1854-1863. doi:10.1001/jama.2017.5150

³² Another UK project is the [NovoSang](#) consortium, which in 2016 started giving stem-cell derived red blood cells to volunteers in trials.

progress preclinical trials of its artificial blood platelet product³³, manufactured from pluripotent stem cells³⁴.

- Shire's Hereditary Angioedema (HAE) product Cinryze, derived from human plasma, is currently being made by Sanquin in the Netherlands, using a series of precipitation, filtration and chromatography steps. Shire CEO Flemming Ornskov told investors his company is now looking to produce approximately 30 per cent of its Cinryze supply from its own manufacturing facilities, as having just one manufacturing source leaves the supply chain at risk. The acquisition of Baxalta gave Shire plasma fractionation capabilities, and technology transfer from Sanquin has begun. Shire is building supply capability at its plants in Vienna and Los Angeles.
- Shire worked with World Federation of Hemophilia (WFH) and other leading haemophilia institutions to develop its findings that the Global Annual Bleed Rate (GABR) showed a bleeding incident occurs every 3 to 15 seconds in haemophilia patients worldwide. The WFH data also showed that of the approximately 180,000 people suffering from haemophilia A and B worldwide, only 25 percent have been diagnosed and receive proper care, and 8 percent are treated to prevent bleeds.
- Wirecard North America, in partnership with CSL Plasma, launched the industry's first cash-back donor prepaid card, providing cash rebates for everyday spending activities. The cash-back option was introduced to support the Platinum level loyalty tier of CSL Plasma's new iGive Rewards Loyalty Program.
- Swedish Orphan Biovitrum announced its results for the first quarter 2017. Total revenues amounted to SEK 1,396 million an increase of 10 per cent compared with Q1 2016. This included Elocta sales of SEK 250million, and Alprolix sales of SEK 50 million. in the Sobi territory.
- bluebird bio, Inc. has entered into a worldwide license agreement concerning its proprietary lentiviral vector platform with GlaxoSmithKline Intellectual Property Development Limited (GSK)³⁵. Bluebird will receive an upfront payment, potential development and regulatory milestone payments, and single digit royalties on net product sales.
- The US government continues to subsidise private investment in vaccine development and manufacturing. Emergent BioSolutions, in partnership with the US government, spent \$US 80 million to double the size of its Baltimore plant³⁶.

³³ Platelets derived from human donors can not only transmit infections but can set off immune reactions that render the therapy ineffective (alloimmune refractoriness). Furthermore, since platelet donations require pathogen testing and cannot be frozen for later use, supply shortages can occur.

³⁴ Plasticell says it has developed robust, cost-effective methods of producing functional platelets from human induced pluripotent stem cells (iPSCs) and has scaled these up to intermediate bioreactor level, allowing manufacture of product for pre-clinical studies. Kings College will contribute world-leading expertise and in vivo models to characterise the dynamics, lifespan, safety and efficacy of transfused platelets.

³⁵ GSK will non-exclusively license specific bluebird patent rights related to lentiviral vector technology to develop and commercialize gene therapies for two rare genetic diseases, Wiscott-Aldrich syndrome and metachromatic leukodystrophy. two rare genetic diseases.

³⁶ This arose from a 2012 partnership between Emergent and the US Department of Health and Human Services that named the facility as one of three Centers for Innovation in Advanced Development and Manufacturing. The agreement called for the US government and Emergent to invest together \$US 220 million over eight years to develop responses to emerging public health threats and to ensure the company could produce 50 million doses of flu vaccine in four months in the event of a pandemic. The agreement could be extended for seventeen further years, on an annual basis. Since the initial agreement, Emergent has received add-on government contracts to work on treatments for Ebola, Marburg and a Zika vaccine.

5. Legal Matters

The NBA is interested in the implications for Australia of any proceedings against companies, governments and professional practitioners in relation to blood and blood products; or of relevant public enquiries.

- US District Judge Denise Cote in New York dismissed liability claims against Pfizer and Bristol-Myers Squibb over bleeding risks for their anticoagulant Eliquis, ruling that the drug makers and US drug regulators clearly presented Eliquis' risks to patients and doctors in the approved labelling for the drug.
- Baxalta, a wholly-owned subsidiary of Shire, filed a complaint against Genentech and Tokyo-based Chugai Pharmaceutical in the US District Court for the District of Delaware. Baxalta alleges infringement of its US Patent No. 7,033,590, which it alleges covers the defendants' emicizumab product for haemophilia(ACE910), which is still under development. Baxalta seeks monetary damages, and an injunction enjoining both Genentech and Chugai from selling emicizumab in the US.
- CSL was made aware that Shire Viropharma had filed a complaint in the US District Court for the District of Delaware. The complaint alleged infringement of a newly granted US patent in connection with a method of treating hereditary angioedema. CSL said it remained highly confident that CSI830 does not infringe any valid claim of the Shire Viropharma patent and that it would vigorously defend against the claims.

6. Research (not elsewhere included)

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.

- On 12 May in *Science*³⁷ researchers described a compound known as Hinokitiol which can correct iron-delivery defects in preclinical models. Hinokitiol is found in the wood of trees. It was originally isolated from the Taiwanese hinoki tree, but is also found in cedar wood.
- Shyni Varghese at the University of California, San Diego, and her colleagues have engineered an implant that resembles real bone. Its working marrow is capable of producing healthy blood. Scientists hope the implant, initially placed beneath the skin in mice, may eventually help treat various blood and immune disorders in humans without the side effects of current treatments³⁸.
- Researchers have developed a technique that uses modified insulin and red blood cells to create a glucose-responsive "smart" insulin delivery system³⁹. This technique effectively reduced blood sugar levels for 48 hours in a strain of mice that had Type 1 diabetes.
- Scientists have identified new cell subtypes in the human immune system. Called monocytes and dendritic they fall into the white blood cell class⁴⁰.

³⁷ Anthony S. Grillo et al., "Restored iron transport by a small molecule promotes absorption and hemoglobinization in animals". *Science*, 2017; 356 (6338): 608 DOI: [10.1126/science.aah3862](https://doi.org/10.1126/science.aah3862)

³⁸ Reported in *Proceedings of the National Academy of Sciences*. DOI: 10.1073/pnas.1702576114

³⁹ Chao Wang et al, "Red Blood Cells for Glucose-Responsive Insulin Delivery", *Advanced Materials* (2017). DOI: [10.1002/adma.201606617](https://doi.org/10.1002/adma.201606617)

⁴⁰ The findings were published in the journal *Science* on Friday, 21 April.

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

- A study⁴¹ has found that transmission of dengue, chikungunya and Zika is highest at around 84 degrees Fahrenheit. Scientists had long considered 90 degrees to be the peak-transmission temperature. As climate change causes rising temperatures, future transmission becomes more likely to occur in subtropical and even temperate areas. Temperature affects how often mosquitoes bite, the amount of time it takes for them to ingest a virus from one human and inject it into another, and their life cycle. The research team found that mosquitos posed the greatest risk to humans at 84 degrees and risk declined in cooler and warmer temperatures.
- A study has shown⁴² that if mice have antibodies from dengue or West Nile virus, it sets them up for more severe disease from their close cousin, Zika virus. Such "antibody-dependent enhancement", if it occurs in humans, could challenge the development of vaccines for West Nile, dengue, and Zika.
- The US National Institutes of Health (NIH) announced the development of a platform (SHERLOCK) capable of detecting small amounts of nucleic acid (DNA and RNA) sequences, which will help when it comes to detecting viral or bacterial infections within a population during infectious disease outbreaks.

Zika

- CDC researchers warned that the Zika virus may trigger cases of epilepsy in infants⁴³.
- A number of Zika vaccines have reached the stage of human testing. Austrian biotech Themis is the latest, with its live attenuated recombinant candidate⁴⁴, following Inovio, the US National Institutes of Health NIH⁴⁵, and a partnership between the US Walter Reed Army Institute of Research and Sanofi.
- Researchers at the Massachusetts Institute of Technology have used a new strategy that can rapidly generate customized RNA vaccines, producing a new vaccine

⁴¹ Erin A. Mordecai et al. "Detecting the impact of temperature on transmission of Zika, dengue, and chikungunya using mechanistic models", *PLOS Neglected Tropical Diseases* (2017). [DOI: 10.1371/journal.pntd.0005568](https://doi.org/10.1371/journal.pntd.0005568)

⁴² "Dengue may bring out the worst in Zika", DOI: 10.1126/science.aal0982

⁴³ Dr. Daniel Pastula, Dr. Marshelyn Yeargin-Allsopp and Rosemarie Kobau reported in the online 17 April issue of *JAMA Neurology*.

⁴⁴ Themis licensed the measles virus vaccine vector platform from Institut Pasteur. Selected antigens of Zika can be inserted to trigger an immune response against the virus.

⁴⁵ Texas, Florida, Puerto Rico and five at-risk countries: Brazil, Mexico, Panama, Costa Rica and Peru. This vaccine is made with a circular piece of DNA carrying genes from the Zika virus that, once in the body, make particles that resemble Zika sufficiently to alert the immune system but cannot cause infection. For more information about the trial, visit [Questions and Answers: VRC 705: Phase 2/2b Trial Testing the NIAID Zika Virus Investigational DNA Vaccine](#).

candidate for the Zika virus⁴⁶. It consists of strands of genetic material (messenger RNA) packaged into a nanoparticle that delivers the RNA into cells. The RNA is then translated into proteins that call forth an immune response from the host. It is seen as potentially safer than a DNA vaccine because the RNA does not incorporate itself into the host genome.

- Researchers found that in rhesus monkeys, after the body's immune system has removed the last traces of Zika virus from the blood, low-level infection may continue at other sites. Their study⁴⁷ revealed that the cerebrospinal fluid (CSF) is one such sanctuary, which, if also true for infected humans, may have implications for long-term neurological health. Researchers found the virus remained in the monkeys' CSF for up to 42 days and in the lymph nodes and colorectal mucosa for up to 72 days. "There is clear evidence from humans that Zika virus does persist in certain anatomic sanctuaries," said Harvard Medical School's Dan Barouch who with colleagues pinpointed some of these hideouts in monkeys.

Dengue

- The NIH-backed dengue vaccine TV003 was tested in a small group of volunteers in Baltimore and Burlington, Vermont. It is a live-attenuated tetravalent (four-strain) vaccine. It has been shown to be safe and immunogenic in healthy adults who had prior flavivirus exposure⁴⁸. The study addressed one of the feared outcomes of dengue vaccinations: antibody-dependent enhancement (ADE)⁴⁹. Researchers studying TV003, which is currently in phase III trials in Brazil, have said it could be used as a framework for a Zika vaccine.
- Takeda's experimental tetravalent dengue vaccine (TAK-003) is based on a live-attenuated dengue serotype 2 virus (DENV-2), which provides the genetic 'backbone' for all four attenuated dengue virus serotypes present in the vaccine. Takeda's Phase I and Phase II clinical trials includes 8 studies to date that assess the safety and/or immunogenicity of the vaccine⁵⁰. As reported in *The Lancet Infectious Diseases*⁵¹, an interim analysis of DEN-204 data indicated that TAK-003 caused antibody responses to all four dengue serotypes, irrespective of previous dengue exposure. A second dose improved antibody responses against DENV-3 and DENV-4 in children who were seronegative before vaccination. Takeda's largest clinical trial of the vaccine is its global, pivotal TIDES Phase III trial, designed to assess whether two doses of the vaccine candidate can safely protect against all four strains of dengue in children and

⁴⁶ Jasdave S. Chahal et al., "An RNA nanoparticle vaccine against Zika virus elicits antibody and CD8+ T cell responses in a mouse model", *Scientific Reports* (2017). DOI: 10.1038/s41598-017-00193-w

⁴⁷ M. Aid et al., "Zika virus persistence in the central nervous system and lymph nodes of rhesus monkeys," *Cell*, 169: 1–11, 2017.

⁴⁸ Phase II trials have already shown TV003 to be safe and immune-producing but the new data published yesterday *PLoS Neglected Tropical Diseases* showed the results of using the vaccine in 58 healthy adults aged 18 to 50 who had previously been exposed to a flavivirus such as dengue, yellow fever, West Nile Virus, or St. Louis or Japanese encephalitis. Prior infection was determined by neutralizing antibodies in serology testing.

⁴⁹ Dengue virus has four strains, and previous infection with one strain can make subsequent infections with other strains worse. In post-licensure trials, Sanofi-Pasteur's Dengvaxia was associated with higher rates of hospitalization in children due to dengue. The vaccine was assumed to be acting as the recipients' "first exposure" to the virus and producing ADE. Dengvaxia is not recommended for use in patients under the age of 9.

⁵⁰ The ongoing Phase II DEN-204 study is designed to assess the safety and immunogenicity of one- and two-dose schedules of TAK-003 in 1,794 healthy children and adolescents ages two through 17 who are resident in dengue-endemic countries in Latin America and Asia.

⁵¹ Sáez-Llorens, Xavier et al., "[Safety and immunogenicity of one versus two doses of Takeda's tetravalent dengue vaccine in children in Asia and Latin America: interim results from a phase 2, randomised, placebo-controlled study](https://doi.org/10.1016/S1473-3099(17)30166-4)", *The Lancet Infectious Diseases*, March 2017. [http://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(17\)30166-4/abstract](http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(17)30166-4/abstract)

adolescents 4-16 years old, regardless of previous dengue exposure. Evaluation of the trial's primary endpoint is expected in 2018.

- Chugai Pharmaceutical of Tokyo and the Agency for Science, Technology and Research, Singapore (A*STAR) announced that a joint research project between Chugai and A*STAR for an anti-dengue virus antibody has been selected as a grant recipient by the Global Health Innovative Technology Fund (GHIT Fund). Chugai and A*STAR have been engaged in the joint research since 2015.

Yellow fever

- The [World Health Organization](#) said it and its partners have shipped 3.5 million doses of yellow fever vaccine to Brazil to help the country deal with its worst outbreak in years. In 2016, WHO and its partners are alleged to have lost track of at least 1 million doses of yellow fever vaccine sent to Angola. Meanwhile the CDC said that national supplies of yellow fever vaccine had been expected to run out in mid-2017. The FDA agreed to the import by Sanofi Pasteur of an alternative yellow fever vaccine it manufactured in France.

Malaria

- Researchers at Griffith University have tested their whole blood-stage malaria parasite vaccine PlasProtect in humans and say it is safe and induces an immune response. Their next trial will immunise volunteers and challenge them with the malaria parasite.
- A new study⁵² has shown that malaria parasites can shuffle genes, leading to different strains in different people and the ability to elude the immune system. This leads to questioning of the efficacy of GlaxoSmithKline's vaccine Mosquirix, and others.

Other

- Western Australia's Department of Health reminded travellers in the north of the state to avoid mosquito bites after flocks of sentinel chickens in the Kimberley and Pilbara were found to have the Murray Valley encephalitis (MVE) and Kunjin virus.⁵³

Influenza

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

- A compound in mucus of a South Indian frog can latch onto flu virus particles and cause them to burst apart, researchers report in *Immunity*⁵⁴. The peptide is [a potent and precise killer](#), able to demolish a whole class of flu viruses while leaving other viruses and cells unharmed.

Avian influenza

- China is in its fifth and biggest H7N9 wave. From 5 to 11 May a further 23 H7N9 avian flu cases were reported. This season has been marked by a shift to a highly pathogenic form of the virus in poultry and a wider distribution of human cases beyond the poultry production areas of the south-eastern provinces.

⁵²Karen P. Day et al., "Evidence of strain structure in *Plasmodium falciparum* var gene repertoires in children from Gabon, West Africa", *Proceedings of the National Academy of Sciences*, published online before print May 1, 2017, doi: 10.1073/pnas.1613018114 *PNAS May 1, 2017*

⁵³ MVE can be fatal if not treated. Symptoms include fever, drowsiness, headache, a stiff neck, nausea and dizziness. Sufferers may experience fits or lapse into a coma, and if they survive may be left with permanent brain damage. The Kunjin virus usually has milder symptoms, but some sufferers have headaches, neck stiffness, fever, delirium and coma.

⁵⁴ *Immunity*, 2017. DOI: [10.1016/j.immuni.2017.03.018](https://doi.org/10.1016/j.immuni.2017.03.018)

- A 24 May update from the United Nations Food and Agriculture Organization (FAO) reported H7N9 had been detected for the first time in live-bird markets in Inner Mongolia province, part of an ongoing northward spread of the virus.
- The US CDC said in a 23 May update that it has completed work on a new H7N9 candidate vaccine virus that matches the new lineage of the virus that has recently emerged in China⁵⁵.

MERS-CoV (Middle East Respiratory Syndrome–Coronavirus)

- As of 24 May 2017, there had been a total of 1612 laboratory-confirmed cases of MERS-CoV infection in Saudi Arabia, including 665 deaths.

Ebola virus disease

- The World Health Organisation confirmed an Ebola outbreak in a remote area of the Congo.

Other diseases: occurrence, diagnosis, prevention and treatment

- Daiichi Sankyo announced that it has entered into a new joint research agreement with the Drugs for Neglected Diseases *initiative* (DNDi) with regard to a new research program, the Hit-to-Lead Project, with the aim of developing drug treatments for two neglected tropical diseases, leishmaniasis and Chagas disease. In February 2016, Daiichi Sankyo and DNDi launched a High-Throughput Screening project of 40,000 compounds from Daiichi Sankyo with the goal of discovering anti-leishmaniasis and anti-Chagas disease compounds, and subsequently identified three compound series. Daiichi Sankyo signed this agreement to advance a Hit-to-Lead Project to develop derivatives from these series as new leishmaniasis and Chagas disease treatments from April 2017.
- [Hookipa Biotech AG](#) presented un-blinded safety and immunogenicity data from the first four months of the company's Phase I first-in-human trial of HB-101, a vaccine against human cytomegalovirus (CMV). The vaccine is based on Hookipa's proprietary Vaxwave platform. The data was presented at the CMV 2017 Conference (www.cmv2017.nl/home) in Leeuwenhorst, The Netherlands. Further follow-up safety and immunogenicity results of the study are expected in November 2017. Joern Aldag, Hookipa's CEO, said: "These clinical data show that Hookipa's Vaxwave technology and, specifically, the bivalent CMV vaccine candidate HB-101 are safe and immunogenic..... the vaccine elicited potently CMV-neutralizing antibodies and high frequencies of CMV-specific CD8+ T cells with as few as two doses and we are actively gearing up for Phase II efforts."
- VBI Vaccines provided an update on its Phase I clinical study, which is assessing the safety and tolerability of VBI's [vaccine candidate to prevent congenital CMV infection](#) , a leading cause of birth defects. The Phase I study involves approximately 125 healthy CMV-negative adults. The study will also determine the vaccine immunogenicity by measuring levels of vaccine-induced CMV neutralizing antibodies⁵⁶.

⁵⁵ Most recent H7N9 viruses belong to the Yangtze River Delta lineage, which exhibits reduced cross-reactivity to earlier candidate vaccine viruses, suggesting that stockpiled vaccines made with the earlier virus might not protect against the newly circulating viruses. The CDC is now shipping the new candidate vaccine virus to manufacturers. The CDC also reported that an analysis of publicly available genetic data showed that about 10 per cent of viruses from China's fifth wave have markers suggesting resistance to one or more neuraminidase inhibitors. In February, Taiwanese health officials had notified resistance markers had been identified in a sample from a patient who contracted an infection in China.

⁵⁶ A description of the study design, eligibility criteria, and investigator sites, is available at ClinicalTrials.gov using identifier [NCT02826798](https://clinicaltrials.gov/ct2/show/study/NCT02826798).

- A new report⁵⁷ says multidrug resistant tuberculosis is worsening in four of the countries with the largest number of TB cases.
- Outbreaks of Legionnaires' disease have occurred in Melbourne and Adelaide.
- A number of properties in the Swan Hill district of Victoria have had confirmed cases of anthrax in sheep.
- During April, 79 cases of whooping cough were confirmed in the Northern NSW Local Health District. In 2016 it was 77, in 2015 it was eight, with three in 2014 and four in 2013. Greg Bell, Acting Director of The North Coast Public Health Unit, said persistent low vaccination levels in some parts of Northern NSW was worrying.
- Two children- one in northern NSW and one in South Australia- acquired tetanus.

⁵⁷ Aditya Sharma et al., "Estimating the future burden of multidrug-resistant and extensively drug-resistant tuberculosis in India, the Philippines, Russia, and South Africa: a mathematical modelling study", *The Lancet Infectious Diseases*, 9 May 2017. DOI: [http://dx.doi.org/10.1016/S1473-3099\(17\)30247-5](http://dx.doi.org/10.1016/S1473-3099(17)30247-5)