

# Monitoring International Trends

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## posted November-December 2018

The NBA monitors international developments that may influence the management of blood and blood products in Australia. Our focus is on:

- Potential new product developments and applications;
- Global regulatory and blood practice trends;
- Events that may have an impact on global supply, demand and pricing, such as changes in company structure, capacity, organisation and ownership; and
- Other emerging risks that could put financial or other pressures on the Australian sector.

Recent matters of interest appear on pages 4 to 20. Some highlights are listed below:

### Products and Treatments

- Product developments and clinical trial data of interest were reported at the 60<sup>th</sup> Annual Meeting of the American Society of Hematology (ASH). Abstracts may be found here: <http://www.bloodjournal.org/page/ash-annual-meeting-abstracts?sso-checked=true>
  1. Amongst companies reporting on their haemophilia interests were Bioverativ and Sobi, Spark Therapeutics, Roche and Bayer.
  2. Shire, The Royal College of Surgeons in Ireland, and Science Foundation Ireland, in collaboration with the Irish Haemophilia Society, presented new data, from the clinical study called *The Irish Personalised Approach to the Treatment of Haemophilia* (iPATH), illustrating key drivers to implementing personalised care for people with haemophilia.
  3. Another group of researchers discussed the fact that “While novel non-factor therapies significantly reduce bleeding symptoms in patients with hemophilia A and inhibitors, the absence of [factor] VIII tolerance remains unchanged”.
  4. Amongst companies reporting on their interests in beta thalassemia and sickle cell disease were bluebird bio, Aruvant Sciences, Bioverativ, Celgene and Acceleron Pharma, Global Blood Therapeutics and Ionis Pharmaceuticals.
  5. Other presentations related to immune thrombocytopenia (ITP) and paroxysmal nocturnal hemoglobinuria (PNH).

### Safety and Patient Blood Management

- A study found that fish oil (which contains the omega-3s EPA and DHA) did not increase perioperative bleeding.
- A trial showed that low-dose prophylactic apixaban (Eliquis) reduced the risk of venous thromboembolism (VTE) for patients starting cancer chemotherapy.
- Another trial showed that administering higher doses of intravenous (IV) iron to manage anaemia in patients on haemodialysis significantly reduces dose requirements of erythropoiesis-stimulating agents without increasing the risk of death or hospitalization for infection or any other cause.
- Scientists found that higher iron levels may lead to an elevated risk of cardioembolic stroke.
- Researchers discovered that childhood cancer survivors face a much greater risk of VTE in the first 5 years after diagnosis.

### Regulatory matters

- Cerus Corporation filed for CE Mark registration for the Company's INTERCEPT red blood cell system in Europe.
- Janssen Pharmaceutical is seeking approval from the US Food and Drug Administration (FDA) to use blood thinner Xarelto (rivaroxaban) for the prevention of blood clots in medically ill patients.

- The FDA has approved a label update for Novo Nordisk's Novoeight. It is now approved for control of bleeding episodes and for use as an on-demand therapy in adult and paediatric patients with haemophilia A. The previous label indicated "control and prevention of bleeding episodes."
- Cerus has received the FDA's breakthrough device designation for its pathogen-reduced cryoprecipitate. The basis of the designation is improved treatment of massive haemorrhage.

#### **Company news**

- The takeover of Shire by Takeda was approved by shareholders of both companies, with an arrangement that the deal would complete on 8 January 2019.
- Bayer is to concentrate all haemophilia factor VIII protein production at its plant in Berkeley, California.

#### **Country news**

- The US National Institutes of Health launched an initiative to coordinate and accelerate research into a cure for sickle cell disease.

#### **Research not included elsewhere**

- A research team led from the University of California at Berkeley was granted a patent for unique RNA guides that work with the Cas9 protein to target and cut genes via the gene-editing tool, CRISPR.
- A study has found that patients with both sickle-cell trait and type 2 diabetes experience more frequent diabetes-related complications.
- The incidence of hospitalization for upper gastrointestinal tract bleeding for patients taking an anticoagulant was found to be lower among patients who were also taking a proton pump inhibitor (PPI).

#### **Infectious diseases**

##### *Mosquito-borne diseases*

- Researchers found that sexual partners of known cases of Zika virus infection were 2.2 times more likely to develop Zika than other members of the households.
- A study found that severe thrombocytopaenia is a rare but potentially fatal outcome in patients infected with the Zika virus, and that treating such cases for idiopathic thrombocytopaenic purpura (including administration of IVIg or corticosteroids) may be more effective than platelet transfusion.
- A peptide has been developed which, in laboratory mice infected with Zika, has reduced disease symptoms and the number of deaths.
- Themis says it has had positive results from its Phase II trial of its chikungunya vaccine.

##### *Influenza*

- Llama antibodies, synthesized into a "four-in-one" mega-protein and administered to mice through a nasal spray, protected the mice from 59 strains of influenza A and B.
- Researchers have developed multidomain antibodies which, administered intranasally to mice, gave durable and continuous protection from a significant number of influenza strains.
- Seqirus is expanding its cell-based flu vaccine franchise, unveiling a \$US 140 million expansion to its Holly Springs, North Carolina, plant.
- Japanese research has confirmed that the avian H7N9 virus can be transmitted through respiratory droplets.
- Visterra announced that a Phase IIa study of its monoclonal antibody VIS410 showed safety, tolerability and positive clinical activity trends in non-hospitalized patients with influenza A.

##### *Ebola virus disease*

- In the second-largest Ebola outbreak in history (in the Democratic Republic of Congo) health experts have found themselves attempting control through "ring vaccination" against a background of deadly attacks by rebel groups and amidst concern about the adequacy of stocks of the experimental vaccine.

- The FDA approved emergency use of an Ebola rapid antigen fingerstick test for detecting Ebola and the Alliance for International Medical action has been operating the randomized, controlled trial of several investigational drugs to treat it.
- *Other diseases*
- Prion proteins that cause sporadic Creutzfeldt-Jakob disease (sCJD) have been found to enter the body via the eyes.
- Researchers have identified compounds that block the reactivation of latent HIV-1 in a human cell line containing the latent virus.
- The FDA has authorized the marketing of a new diagnostic test to detect cytomegalovirus (CMV) in newborns less than 21 days of age.
- Victorians had an increase in case numbers for legionnaires' disease.
- Many Queensland hospitals and aged care centres tested positive for legionella bacteria.
- Anthrax was found in a sheep on a property near Swan Hill in late November.

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### 1. Products and treatments

*Here the NBA follows the progress in research and clinical trials that may, within a reasonable timeframe, either make new products and treatments available or may lead to new uses or changes in use for existing products. Many product developments of interest to the NBA are reported at the Annual Meeting of the American Society of Hematology (ASH). Abstracts for the December 2018 meeting may be found here:*

<http://www.bloodjournal.org/page/ash-annual-meeting-abstracts?sso-checked=true>

## Treating haemophilia

- At the [60th Annual Meeting of the American Society of Hematology](#) in San Diego, December 2018:
  - i) Bioverativ and Sobi<sup>1</sup> announced<sup>2</sup> the results of two extension studies showing that treatment of severe haemophilia A with Eloctate and haemophilia B with Alprolix was safe and improved the patients' annualized bleed rates (ABRs) over four years. The two extension studies — ASPIRE ([NCT01454739](#)), and B-YOND ([NCT01425723](#)) — evaluated long-term preventive treatment with the two therapies in previously treated adult, adolescent, and paediatric patients. The lower ABRs included joint bleeds and were observed across all patient populations and at extended dosing intervals. The two therapies had previously shown efficacy in all treatment situations, such as acute, surgical, and emergency situations. ASPIRE included participants who had completed the pivotal, Phase III A-LONG ([NCT01181128](#)) or Kids A-LONG ([NCT01458106](#)) studies. It enrolled 211 male patients, 150 from A-LONG and 61 from Kids A-LONG. B-YOND included, amongst others, patients who completed the Phase III B-LONG ([NCT01027364](#)).
  - ii) An oral presentation reported on the ongoing Phase I/IIa trial of Bioverativ's BIVV001 (rFVIII-Fc-VWF-XTEN), an investigational factor VIII therapy with the potential to provide extended protection from bleeds with prophylactic dosing of once weekly or longer. Data reported at the US National Hemophilia Foundation Bleeding Disorders Conference in October had shown that a single low dose (25 IU/kg) of BIVV001 extended the half-life of factor VIII to 37 hours, while achieving high factor activity levels (>5 per cent at seven days). BIVV001 was generally well tolerated with no development of inhibitors. Now the ASH presentation included preliminary results from the high-dose cohort of the study.
  - iii) Bioverativ provided a number of poster presentations relating to haemophilia treatment<sup>3</sup>.
  - iv) Spark Therapeutics announced updated preliminary data on the first 12 participants in the ongoing Phase I/II clinical trial of *SPK-8011* in haemophilia A<sup>4</sup>. Data showed reductions in bleeds and infusions for the first 12 participants with an encouraging safety profile. The five participants in the first two dose cohorts

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<sup>1</sup> Bioverativ and Sobi collaborate on the development and commercialization of Alprolix and Eloctate, which is marketed as Elocta in Europe.

<sup>2</sup> *ASPIRE Final Results Confirm Established Safety and Sustained Efficacy for Up to 4 Years of Treatment with rFVIII-Fc in Previously Treated Subjects with Severe Hemophilia A* (Poster #1192) and *B-YOND Final Results Confirm Established Safety, Sustained Efficacy, and Extended Dosing Interval for Up to 4 Years of Treatment with rFIX-Fc in Previously Treated Subjects with Severe Hemophilia B* (Poster #1214)

<sup>3</sup> *BIVV001: The First Investigational Factor VIII Therapy to Break Through the VWF Ceiling in Hemophilia A, with Potential for Extended Protection for One Week or Longer* (Poster #636); *Real-World Data of Immune Tolerance Induction Using rFVIII-Fc in Subjects with Severe Hemophilia A with Inhibitors at High Risk for ITI Failure* (Poster #2500); *Real-World Data on the Use of rFIX-Fc in Subjects with Hemophilia B for Up to 3.7 Years Demonstrates Improved Bleed Control and Adherence with Reduced Treatment Burden* (Poster #2493); *Changing the Paradigm in Hemophilia Care: Extended Half-Life Products (rFVIII-Fc and rFIX-Fc)* (Poster #3514); *Economic Impact of Immune Tolerance Induction (ITI) with Recombinant Factor VIII Fc Fusion Protein (rFVIII-Fc) Compared to Conventional Recombinant Factor VIII (rFVIII)* (Poster #3520); *A Novel Humanized Hemophilia-A Mouse Model to Facilitate Preclinical In Vivo Studies of Human Specific FVIIIa-mimetic Bispecific Antibodies* (Poster #2458); and *Phospholipid-Independent Activity of FVIIIa Mimetic Bispecific Antibodies in Plasma* (Poster #2461)

<sup>4</sup> The data were presented by Principal Investigator Lindsey A. George, assistant professor of pediatrics, The Perelman School of Medicine, University of Pennsylvania and attending physician in the Division of Hematology at Children's Hospital of Philadelphia. See Dr. George's presentation [here](#).

have shown persistent, stable factor VIII activity levels. Spark said it would initiate a Phase III run-in study.

- v) Shire, The Royal College of Surgeons in Ireland, and Science Foundation Ireland, in collaboration with the Irish Haemophilia Society, presented new data, from the clinical study called *The Irish Personalised Approach to the Treatment of Haemophilia* (iPATH), illustrating key drivers to implementing personalised care for people with haemophilia. Where standard prophylaxis with recombinant factor VIII (rFVIII) uses a weight-based dosing strategy, some patients are insufficiently protected from bleeds earlier than others because the half-life of factor VIII may vary between individual patients. Treatment can be improved by integrating FVIII pharmacokinetics (PK) to produce an individualized treatment regimen. In a poster presented at ASH<sup>5</sup>, researchers described important biomarkers that influence bleeding risk, including a link between type O blood group and shorter half-life, and a link between age and longer half-life. The study also supports the feasibility of using limited, 2-sample PK profiling to capture accurate PK curves that can then be utilized to guide individualized, PK-guided prophylaxis<sup>6</sup>.
- vi) Roche reported data from the primary analysis of the Phase III HAVEN 2 trial of Hemlibra (emicizumab) prophylaxis in children younger than 12 years of age with haemophilia A with factor VIII inhibitors, including longer follow-up for once-weekly dosing and new data for less frequent dosing schedules (every two weeks or every four weeks). Guy Young, Director of the Hemostasis and Thrombosis Center, Children's Hospital Los Angeles<sup>7</sup> said: "These updated data from HAVEN 2 showed that the majority of children with haemophilia A with factor VIII inhibitors treated with emicizumab had zero treated bleeds across three different dosing schedules, reinforcing the ability of this medicine to provide sustained, effective bleed control." Sandra Horning, Roche's Chief Medical Officer<sup>8</sup>, commented: "The updated analysis from the HAVEN 2 study supports the potential of Hemlibra to control bleeds at less frequent subcutaneous dosing, providing parents and their children more flexibility to choose a treatment schedule that is right for them"<sup>9</sup>.
- vii) One group of researchers reported<sup>10</sup> to the conference that "While novel non-factor therapies significantly reduce bleeding symptoms in patients with hemophilia A and inhibitors, the absence of [factor] VIII tolerance remains unchanged. Additionally, there are concerns regarding the hemostatic efficacy and safety of bypassing agents necessary for the management of breakthrough bleeds in patients with inhibitors on these novel therapies. Immune tolerance induction remains the primary method for eradicating inhibitors and restoring the

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<sup>5</sup> Lavin, M et al. *The Irish personalized approach to the treatment of haemophilia (iPATH) - determinants of inter-individual variation in FVIII pharmacokinetics* (Poster #1190)

<sup>6</sup> The 2-sample PK profiling was done using myPKFiT™ for ADVATE [Antihemophilic Factor (Recombinant)], a free web-based, Rx software for use with haemophilia A patients 16 and older weighing at least 45 kilograms and treated with ADVATE.

<sup>7</sup> and Professor of Pediatrics, University of Southern California Keck School of Medicine, Los Angeles

<sup>8</sup> and Head of Global Product Development

<sup>9</sup> Roche provided four presentations on Hemlibra at the meeting - *Emicizumab Prophylaxis Provides Flexible and Effective Bleed Control in Children with Hemophilia A with Inhibitors: Results from the HAVEN 2 Study* (Abstract #632) Oral presentation; *Immunogenicity of Emicizumab in People with Hemophilia A (PwHA): Results from the HAVEN 1-4 Studies* (Abstract #633) Oral presentation; *Preference for Emicizumab Over Prior Factor Treatments: Results From the HAVEN 3 and HAVEN 4 Studies* (Abstract #1187) Poster presentation; and *Every 2 Weeks or Every 4 Weeks Subcutaneous Injection of Emicizumab in Pediatric Patients with Severe Hemophilia A without Inhibitors: A Multi-Center, Open-Label Study in Japan (HOHOEMI Study)* (Abstract #1186) Poster presentation.

<sup>10</sup> Glaivly M. Batsuli, assistant professor in the division of hematology and oncology at Emory University and pediatric hematologist/ oncologist at Aflac Cancer and Blood Disorders Center in Atlanta, and colleagues. Abstract [634](#)

hemostatic response to [factor] VIII.” They found that immune tolerance induction with standard or extended half-life recombinant factor VIII after initial treatment with emicizumab appears safe and effective in paediatric patients with haemophilia A and active inhibitors.

- viii) [Bayer](#) offered seven presentations, five posters highlighting new data for Jivi, antihemophilic factor (recombinant) PEGylated-aucl (Bay 94-9027), one on new data for Kovaltry, Antihemophilic Factor (recombinant), and one poster on Anti-TFPI research from Bayer's hematology pipeline<sup>11</sup>.

## Treating beta thalassemia and sickle cell disease

- At the [60th Annual Meeting of the American Society of Hematology](#) in San Diego, December 2018:
  - i) Bluebird bio presented new positive results from the ongoing Phase I/ II HGB-206 clinical trial evaluating the effectiveness and safety of investigational gene therapy LentiGlobin in patients with severe [sickle cell anaemia](#). The new results reflect data collected up to 14 September<sup>12</sup>. David Davidson, chief medical officer of bluebird bio, said in a [press release](#): “LentiGlobin gene therapy is designed to address the underlying genetic cause of beta-thalassemia and sickle cell disease. The longer-term data emerging from our clinical trials show that most treated patients are producing sufficient amounts of engineered HbAT87Q to achieve and maintain a therapeutic benefit.” Julie Kanter, from the [Medical University of South Carolina](#), said: “In patients with sickle cell disease who underwent autologous transplant with LentiGlobin, gene therapy-derived HbAT87Q levels have remained stable and we saw decreased rates of vaso-occlusive events with up to three years of follow-up.” Bluebird presented a number of other results<sup>13</sup>, including positive results of the completed Phase I/ II

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<sup>11</sup> *Extended Interval Prophylaxis With BAY 94-9027 For > 4 Years Leads To Median Spontaneous Annualized Bleeding Rate < 1 in the PROTECT VIII Extension* (Abstract #1189) Presenter: Mindy Simpson, RUSH University Medical Center; *Decrease in Overall and Joint Bleeding Rates With Extended-Interval Dosing* (Abstract #1206) Presenter: Mark Reding, University of Minnesota; *Pharmacodynamics, Pharmacokinetics and Safety of BAY 1093884, an Antibody Directed Against Human TFPI, in Patients With Factor VIII or IX Deficiency (With and Without Inhibitors): a Phase 1 Study* (Abstract #1176) Presenter: Pratima Chowdary, Royal Free London NHS Foundation Trust; *Improved Pharmacokinetic Profile for BAY 81-8973 Due to Increased Branching and Sialylation of N-Linked Glycans of Recombinant Factor VIII* (Abstract #1209) Presenter: John Teare, Director, Late Stage Program Management, Biological Development, Bayer Pharmaceuticals; *Characteristics of Bleed-free Patients on Every-5-day Dosing in the PROTECT VIII (BAY 94-9027) Study* (Abstract #2486) Presenter: Elena Santagostino, Centro Emofilia e Trombosi A. Bianchi Bonomi, IRCCS Fondazione Ca' Granda, Ospedale Maggiore Policlinico; *Efficacy and Safety of BAY 94-9027 is Sustained for 5 Years: Outcomes in 33 Patients in the PROTECT VIII Extension Study* (Abstract #2492) Presenter: Mark Reding, University of Minnesota; and *BAY 94-9027 Can Be Accurately Measured Across Regions With Appropriate One-Stage Assay Reagent Use* (Abstract #2481) Presenter: Rajiv Pruthi, Mayo Clinic

<sup>12</sup> abstract *Current Results of LentiGlobin Gene Therapy in Patients with Severe Sickle Cell Disease Treated Under Refined Protocol*. (Abstract #1026) Presenter: John Tisdale, National Heart, Lung and Blood Institute, Bethesda, Maryland. (Abstract #1026).

<sup>13</sup> *Clinical Outcomes of LentiGlobin Gene Therapy for Transfusion-Dependent  $\beta$ -Thalassemia Following Completion of the Northstar HGB-204 Study* (Abstract #167) Presenter: John Rasko, Central Clinical School Centenary Institute of Cancer Medicine & Cell Biology, University of Sydney; *LentiGlobin Gene Therapy for Patients with Transfusion-Dependent  $\beta$ -thalassemia (TDT): Results from the Phase 3 Northstar-2 and Northstar-3 Studies* (Abstract #1025) Presenter: Franco Locatelli, Department of Pediatric Hematology and Oncology, IRCCS Ospedale Pediatrico Bambino Gesù, Rome; and *Flipping the Switch: Initial Results of Genetic Targeting of the Fetal to Adult Globin Switch in Sickle Cell Patients* (Abstract #801) Presenter: Erica Esrick, Pediatric Hematology and Oncology, Boston Children's Hospital, Boston. There were also poster presentations - *Outcomes for Initial*

- Northstar (HGB-204) trial ([NCT01745120](#)) that studied the efficacy and safety of LentiGlobin in patients with [beta-thalassemia](#).
- ii) Aruvant Sciences announced that preliminary safety and efficacy data from an ongoing Phase I/II study of RVT-1801 were delivered in an oral presentation by Dr. Punam Malik<sup>14</sup>. The purpose of the ongoing clinical trial is to investigate the safety, feasibility, and efficacy of RVT-1801 for the treatment of sickle cell disease in conjunction with reduced intensity conditioning. RVT-1801 is designed to deliver the gamma-globin gene for production of foetal haemoglobin. Foetal haemoglobin has strong anti-sickling properties relative to adult haemoglobin. RVT-1801 uses a patented, modified gamma-globulin sequence to further enhance its affinity to form foetal haemoglobin with its anti-sickling capacity. Malik described the data presented as promising.
  - iii) Bioverativ presented preclinical data on BIVV003, a gene-edited cell therapy candidate for the treatment of sickle cell disease. This is being developed in collaboration with Sangamo Therapeutics<sup>15</sup>. BIVV003 is a non-viral cell therapy that involves gene editing of a patient's hematopoietic stem cells using zinc finger nuclease (ZFN) technology. The US Food and Drug Administration (FDA) accepted the Investigational New Drug application for BIVV003, and Bioverativ began a Phase I/II clinical trial to assess the safety, tolerability, and efficacy in adult patients with sickle cell disease<sup>16</sup>. See [NCT03653247](#).
  - iv) Celgene and Acceleron Pharma announced positive results from a phase III trial (BELIEVE) evaluating the safety and efficacy of luspatercept in adults with beta-thalassemia-associated anaemia who require regular red blood cell (RBC) transfusions<sup>17</sup>. Presenting the data, Professor Maria Domenica Cappellini<sup>18</sup> said: "Currently, the standard of care to help patients with beta-thalassemia manage their anaemia is regular, lifelong red blood cell transfusions, which over time can result in iron overload and life-threatening co-morbidities. These findings from the BELIEVE study are exciting because they suggest that luspatercept may help patients reduce their dependence on red blood cell transfusions<sup>19</sup>."

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*Patient Cohorts with Up To 33 Months of Follow-up in the HGB-206 Phase 1 Trial (Abstract #1080)* Presenter: Julie Kanter, Medical University of South Carolina, Charleston; *Analysis of RBC Properties in Patients with SCD Treated with LentiGlobin Gene Therapy (Abstract #2195)* Presenter: Nicolas Hebert, St. Anthony Research Center, Paris, France; and *Characterizing the U.S. Population with Severe Manifestations of Sickle Cell Disease Using Real-World Evidence (Abstract #4811)* Presenter: Clark Paramore, bluebird bio, Cambridge, Massachusetts.

<sup>14</sup> Director of the Cincinnati Comprehensive Sickle Cell Center at Cincinnati Children's Hospital Medical Center

<sup>15</sup> Bioverativ and Sangamo Therapeutics have an exclusive worldwide collaboration to develop and commercialize zinc finger nuclease mediated gene-edited cell therapies for the treatment of beta thalassemia and sickle cell disease.

<sup>16</sup> Poster presentations on sickle cell disease *Ex Vivo Gene-Edited Cell Therapy for Sickle Cell Disease: Disruption of the BCL11A Erythroid Enhancer with Zinc Finger Nucleases Increases Fetal Hemoglobin in Plerixafor Mobilized Human CD34+ Cells* (Poster # 2190) and *LC-MS Analysis of Anti-Sickling Compounds in Cord Blood Derived RBCs Demonstrates Modification of Fetal Hemoglobin and Globin Chain Binding Preferences* (Poster #1074)

<sup>17</sup> Oral presentation, (Abstract #163).

<sup>18</sup> Professor of Medicine, University of Milan - Fondazione IRCCS

<sup>19</sup> Luspatercept is a first-in-class erythroid maturation agent that is believed to regulate late-stage red blood cell maturation. Phase III clinical trials continue to evaluate the safety and efficacy of luspatercept in patients with myelodysplastic syndrome or MDS (the MEDALIST trial) and in patients with beta-thalassemia (the BELIEVE trial). A COMMANDS phase III trial in first-line, lower-risk, MDS patients, the BEYOND phase II trial in non-transfusion-dependent beta-thalassemia, and a phase II trial in myelofibrosis are ongoing. For more information, see [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

- v) Researchers reported that children from sub-Saharan Africa with sickle cell anaemia treated with hydroxyurea for six months demonstrated reductions in sickle-related clinical events, transfusions and rates of malaria and mortality<sup>20</sup>.
- vi) Global Blood Therapeutics reported additional Phase III data for GBT440 (Voxelotor) that is being evaluated for treating sickle cell disease in adults; and Phase II data for GBT440, its candidate for sickle cell disease in children ages 6-17<sup>21</sup>.
- vii) Ionis Pharmaceuticals presented Phase I data for IONIS-TMPRSS6-LRx, tested for beta-thalassemia.
- viii) Two papers discussed treatment issues for sickle cell patients.
  - (1) Emergency department visits and inpatient admission are known issues, but use differs among individual patients. Pain is a common reason for ED visits. Susan T Paulukonis, program director, California Rare Disease Surveillance Program, evaluated both high-use and quiescent periods among patients seen in California's non-federal hospitals over 12 years<sup>22</sup>.
  - (2) Another presentation during the same session evaluated the impact of treatment adherence to hydroxyurea (HU) on the quality of life (QOL) in younger patients with SCD. Adherence issues persist. The study<sup>23</sup> was presented by Arlene Smaldone, Columbia University School of Nursing and College of Dental Medicine, New York, and her colleagues.
- Administering the investigational drug (SEG101) reduced pain in patients with [sickle cell disease \(SCD\)](#) who were experiencing vaso-occlusive crisis (VOC), according to posthoc results of the Phase II SUSTAIN trial, published online in *The American Journal of Hematology*<sup>24</sup>. The study found that 35.8 per cent of patients with SCD treated with crizanlizumab did not experience a VOC compared with 16.9 per cent of those treated with placebo.

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<sup>20</sup> Tshilolo et al. (Abstract #3)

<sup>21</sup> *Results from Part A of the Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (HOPE) Trial (GBT440-031) at 24-weeks, a Placebo-Controlled Randomized Study Evaluating Voxelotor (GBT440) in Adults and Adolescents with Sickle Cell Disease* (Abstract #118508). GBT previously reported top-line results from the global Phase III HOPE Study showing the trial achieved its primary endpoint of an improvement in haemoglobin greater than 1 g/dL with Voxelotor 1500 mg compared with placebo at 12 weeks. An updated efficacy and safety analysis of the 154 patients in Part A at 24 weeks was presented in an oral session at ASH 2018. *Efficacy and Safety of 1500mg Voxelotor in a Phase 2a Study (GBT440-007) in Adolescents with Sickle Cell Disease* (Abstract #117510) The HOPE-KIDS 1 Study (GBT440-007), an ongoing open-label, single- and multiple-dose Phase IIa study is evaluating the safety, tolerability, pharmacokinetics and exploratory treatment effect of Voxelotor in adolescents ages 4 to 17. GBT also provided a poster presentation, *Societal Costs of Sickle Cell Disease in the United States*, Abstract #119420, and was associated with an oral presentation by Kenneth Ataga, Director, University of Tennessee Health Science Center's (UTHSC) Center for Sickle Cell Disease, Memphis: *Low Hemoglobin Increases Risk for Stroke, Kidney Disease, Elevated Estimated Pulmonary Artery Systolic Pressure, and Premature Death in Sickle Cell Disease: A Systematic Literature Review and Meta-Analysis* (Abstract #117261). The abstract, "[Low Hemoglobin Increases Risk for Stroke, Kidney Disease, Elevated Estimated Pulmonary Artery Systolic Pressure, and Premature Death in Sickle Cell Disease: A Systematic Literature Review and Meta-Analysis](#)," was published online.

<sup>22</sup> Paulukonis ST, Roberts E, Brathwaite R, Wun T, Hulihan MM. Episodes of high emergency department utilization among a cohort of persons living with sickle cell disease. (Abstract #159)

<sup>23</sup> Smaldone A, Manwani D, Green NS. Greater barriers to hydroxyurea (HU) associated with poorer health related quality of life (HRQL) in youth with sickle cell disease. (Abstract #160).

<sup>24</sup> Kutlar A, Kanter J, Liles DK, et al. Effect of crizanlizumab on pain crises in subgroups of patients with sickle cell disease: a SUSTAIN study analysis [published online, October 8, 2018]. *Am J Hematol*. doi: 10.1002/ajh.25308.

## Other products

- At the [60th Annual Meeting of the American Society of Hematology](#) in San Diego, December 2018:
  - i) Novartis announced results of a retrospective, real-world evidence study in patients with immune thrombocytopaenia (ITP) treated with Revolade (eltrombopag), compared with other second-line therapies. The company said data demonstrated that patients experienced better clinical outcomes with Revolade, in terms of fewer bleeding episodes.
  - ii) Apellis Pharmaceuticals updated Phase Ib data for APL-2 for treating paroxysmal nocturnal hemoglobinuria (PNH) and reported Phase II monotherapy data for APL-2 subcutaneous formulation to treat auto-immune haemolytic anemia, or AIAHA<sup>25</sup>.
  - iii) Alexion Pharmaceuticals presented data for ALXN1210, its candidate for PNH<sup>26</sup>.
  - iv) bluebird bio and Celgene Corporation provided initial Phase I data for multiple myeloma treatment candidate bb21217.
  - v) Pluristem Therapeutics reported first cohort data from the Phase I trial of PLX-R18 to treat incomplete hematopoietic recovery following hematopoietic cell transplantation.
  - vi) Incyte and Novartis reported data for ruxolitinib, being evaluated for graft versus host disease.
  - vii) Argenx reported full Phase II data for ARGX-113, its treatment candidate for immune thrombocytopaenia.
- Hookipa Pharma is developing a new class of immunotherapies targeting infectious diseases and cancers, based on its arenavirus platform. It has dosed the first patient

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<sup>25</sup> Poster Presentation 1: *Inhibition of C3 with APL-2 Results in Normalization of Markers of Intravascular and Extravascular Hemolysis in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)* and Poster Presentation 2: *Inhibition of C3 with APL-2 Results in Normalization of Markers of Intravascular and Extravascular Hemolysis in Patients with Autoimmune Hemolytic Anemia (AIHA)*. For abstracts see [ASH conference website](#).

<sup>26</sup> Alexion's accepted abstracts are listed below and are available on the ASH website - *A Phase 3 Study of Ravulizumab (ALXN1210) versus Eculizumab in Adults with Paroxysmal Nocturnal Hemoglobinuria Naive to Complement Inhibitors: Results of a Subgroup Analysis with Patients Stratified by Baseline Hemolysis Level, Transfusion History, and Demographics*. (Abstract #110623) Oral Presentation; *Results from a Phase 3, Multicenter, Non-Inferiority Study of Ravulizumab (ALXN1210) Versus Eculizumab in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria Currently Treated with Eculizumab*. (Abstract #119147) Oral Presentation; *Ravulizumab (ALXN1210) versus Eculizumab in Adults with Paroxysmal Nocturnal Hemoglobinuria: Pharmacokinetics and Pharmacodynamics Observed in Two Phase 3 Randomized, Multicenter Studies*. (Abstract #110858) Oral Presentation; *A Prospective Analysis of Breakthrough Hemolysis in 2 Phase 3 Randomized Studies of Ravulizumab (ALXN1210) versus Eculizumab in Adults with Paroxysmal Nocturnal Hemoglobinuria*. (Abstract #110874) Poster Presentation; *Efficacy of Eculizumab in Pediatric Patients with Paroxysmal Nocturnal Hemoglobinuria in the International PNH Registry*. (Abstract #111306) Poster Presentation; *Economic Benefit of Early In-hospital Diagnosis and Treatment Initiation of Eculizumab in aHUS*. (Abstract #112893) Poster Presentation; *Prognostic Value of Clone Size in Paroxysmal Nocturnal Hemoglobinuria (PNH) for Thrombotic Events in Untreated Patients in the International PNH Registry*. (Abstract #111324) Poster Presentation; *Baseline Characteristics of Patients with Paroxysmal Nocturnal Hemoglobinuria Identified in the Department of Defense Database*. (Abstract #113478) – online; and *The Value of Population Based Data to Study Rare Diseases: An Example Using the Department of Defense Healthcare System*. (Abstract #113497) online.

in its randomized, placebo-controlled, Phase II clinical trial to evaluate the safety and efficacy of HB-101, a bivalent prophylactic vaccine for cytomegalovirus (CMV), in CMV-negative patients waiting for kidney transplantation from living CMV-positive donors.

- A study<sup>27</sup> found platelet-rich plasma therapy (using a person's own blood) to be effective for facial rejuvenation, specifically for improving the texture and colour of photodamaged facial skin. Researchers<sup>28</sup> found that a single treatment improved the fine and coarse texture of the photoaged facial skin, compared with normal saline. Those treated with PRP had a significantly less rough and wrinkled skin at six months.
- [GigaGen Inc.](#) presented data<sup>29</sup> at the 18th Biennial Meeting of the European Society for Immunodeficiencies<sup>30</sup> concerning the company's recombinant hyperimmune gammaglobulin program. David Johnson, chief executive officer, said: "Our data being presented at ESID validates the therapeutic potential of our novel recombinant hyperimmune gammaglobulin, generated by our Surge platform, to deliver increased potency and antigen specificity relative to existing plasma-derived products. We are now in the process of evaluating efficacy in additional studies and look forward to moving this program toward the clinic to help immune deficient patients fight harmful pathogens, including bacterial infections."
- [Humacyte](#) launched a Phase II trial of its Humacyl human acellular vessel evaluating its use for vascular replacement or reconstruction in patients with life or limb-threatening vascular trauma. In June 2018 [Fresenius Medical Care](#) signed a \$US 150 million deal with Humacyte through which Fresenius will have exclusive rights to commercialize Humacyl bioengineered blood vessel technology.

## 2. Safety and patient blood management

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

### Appropriate Transfusion

- Haemolytic transfusion reactions can be mis-diagnosed in patients with sickle cell disease<sup>31</sup> and even be misinterpreted as severe vaso-occlusive crisis. A report<sup>32</sup> in [Transfusion](#) underlines the need for correct and speedy diagnosis of complications in sickle cell disease to avoid inappropriate and even life-threatening treatment.

### Other

- A smartphone app can diagnose anaemia by analysing the colour of a person's fingernails in a photograph<sup>33</sup>.

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<sup>27</sup> published in the *JAMA Dermatology*: [10.1001/jamadermatol.2018.3977](https://doi.org/10.1001/jamadermatol.2018.3977)

<sup>28</sup> Murad Alam, Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, and colleagues

<sup>29</sup> *Recombinant Hyperimmune Gammaglobulin for Recurrent Bacterial Infections in Primary Immune Deficiency* (Abstract #288)

<sup>30</sup> October 24-27, 2018, at the Centro de Congressos de Lisboa in Lisbon,

<sup>31</sup> Patients with sickle cell disease may be given long-term red blood cell transfusions to help manage their disease, but they face an increased risk of developing antibodies that can recognize and destroy the transfused cells.

<sup>32</sup> The case was reported by researchers at [Emory University School of Medicine](#) in a study titled "[Multiple hemolytic transfusion reactions misinterpreted as severe vaso-occlusive crisis in a patient with sickle cell disease.](#)"

<sup>33</sup> Journal reference: *Nature Communications*, DOI: [10.1038/s41467-018-07262-2](https://doi.org/10.1038/s41467-018-07262-2)

- A study reported in [Circulation](#) found that fish oil (which contains the omega-3s EPA and DHA) did not increase perioperative bleeding. Instead, higher blood omega-3 levels were associated with lower risk of bleeding.
- The AVERT trial showed that low-dose prophylactic apixaban (Eliquis) reduced the risk of venous thromboembolism (VTE) for patients starting cancer chemotherapy<sup>34</sup>.
- Administering higher doses of intravenous (IV) iron to manage anaemia in patients on hemodialysis significantly reduces dose requirements of erythropoiesis-stimulating agents without increasing the risk of death or hospitalization for infection or any other cause, according to findings from a randomized controlled trial<sup>35</sup>.
- Scientists found that higher iron levels may lead to an elevated risk of cardioembolic stroke. This usually occurs due to a travelling blood clot blocking oxygen supply to the brain<sup>36</sup>.
- At Kidney Week in San Diego in October, FibroGen<sup>37</sup> presented the results from two Phase III clinical trials conducted in China evaluating roxadustat for the treatment of anaemia associated with chronic kidney disease (CKD). The results, supporting a marketing application under review by the National Medical Products Administration in China, suggested that roxadustat corrected and maintained haemoglobin levels in both dialysis-dependent and non-dialysis-dependent CKD patients.
- Researchers found that childhood cancer survivors face a much greater risk of VTE in the first 5 years after diagnosis<sup>38</sup>.

### 3. Regulatory

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

- Cerus Corporation filed for CE Mark registration for the Company's INTERCEPT red blood cell (RBC) system<sup>39</sup>. The CE Mark submission included a robust clinical

<sup>34</sup> Philip Wells, of the Ottawa Hospital in Ontario, and colleagues reported in the *New England Journal of Medicine*. (For an infographic on the study results, [click here.](#))

<sup>35</sup> Macdougall IC, White C, Anker SD, et al. *High-dose versus low-dose intravenous iron therapy in hemodialysis: The PIVOTAL Trial*. Presented at the American Society of Nephrology's Kidney Week 2018 conference in San Diego, Oct. 23-28. (Abstract FR-OR143). Published online concurrently in the *New England Journal of Medicine*. Macdougall IC, White C, Anker SD, et al, for the PIVOTAL Investigators and Committees. [Intravenous iron in patients undergoing maintenance hemodialysis](#). *N Engl J Med*. 2018; published online ahead of print.

<sup>36</sup> Dipender Gill et al., "Iron Status and Risk of Stroke: A Mendelian Randomization Study", *Stroke*, volume 49, no. 12. <https://doi.org/10.1161/STROKEAHA.118.022701>

<sup>37</sup> FibroGen is partnering with AstraZeneca to commercialise roxadustat for anaemia in the US, other markets in the Americas, Australia/New Zealand, China and Southeast Asia. It is partnering with Astellas in Japan, Europe, the Middle East and South Africa.

<sup>38</sup> Madenci AL, Weil BR, Liu Q, et al. [Long-term risk of venous thromboembolism in survivors of childhood cancer: a report from the childhood cancer survivor study](#). *J Clin Oncol*. 2018;36(31):3144-3150

<sup>39</sup> William 'Obi' Greenman, the Company's president and chief executive officer, said: "The INTERCEPT RBC CE Mark submission is a major milestone in the Company's history and represents the culmination of years of effort to complete the full INTERCEPT portfolio of products to help ensure that patients have access to safe blood transfusions. Red blood cell transfusions are one of the most common hospital procedures globally, and there are more than 25 million red blood cell units transfused in Europe, Middle East and Africa (EMEA) annually. The INTERCEPT red blood cell system is designed to reduce the risk of transfusion transmitted infections and other potential complications such as transfusion-associated graft-versus host disease." Carol Moore, Cerus' senior vice president of regulatory affairs and quality, said: "We anticipate the regulatory review process could exceed 15 months given the breadth of the submission, which covers both device and biologic elements".

dossier developed from Cerus' two European Phase III clinical studies, STARS<sup>40</sup> and SPARC<sup>41</sup>.

- Johnson & Johnson's Janssen Pharmaceutical is seeking approval from the FDA to use blood thinner Xarelto (rivaroxaban) for the prevention of blood clots in medically ill patients. The company says hospital-associated blood clotting (thromboembolism) events are the leading cause of premature death and disability in Americans hospitalized for acute medical illnesses. Xarelto is already approved in the US for five blood clotting indications.
- Chugai Pharmaceutical has approval from the Taiwan Food and Drug Administration for its bispecific monoclonal antibody Hemlibra for routine prophylaxis in patients with haemophilia A with factor VIII inhibitors by once weekly subcutaneous injection. Approval is based on data from two trials in people with haemophilia A with factor VIII inhibitors: results of the HAVEN 1 study in adolescents and adults, and the interim analysis of the HAVEN 2 paediatric trial.
- The FDA has approved a label update for Novo Nordisk's Novoeight. It is now approved for control of bleeding episodes and for use as an on-demand therapy in adult and paediatric patients with haemophilia A. The previous label indicated "control and prevention of bleeding episodes." The Warnings and Precautions section also has been updated to include additional data on neutralizing antibodies that can occur with Novoeight use.
- China is the first country to approve AZ, FibroGen's anaemia drug.
- Cerus has received the FDA's breakthrough device designation for its pathogen-reduced cryoprecipitate. The basis of the designation is improved treatment of massive haemorrhage.
- The FDA expanded the use of the Novartis low platelets drug Promacta<sup>42</sup> to treat patients two years and older suffering from treatment-resistant severe aplastic anaemia (SAA)<sup>43</sup>. It is to be used in combination with standard immunosuppressive therapy. The FDA also designated Promacta as a breakthrough therapy for decreasing the risk of haemorrhage in patients with radiation sickness.
- Rocket Pharmaceuticals issued an [announcement](#) that the FDA had signed off on its Investigational New Drug application for gene therapy RP-L102 for the treatment of [Fanconi anemia](#), a rare inherited form of anaemia that leads to bone marrow failure.

#### 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*

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<sup>40</sup> The STARS trial was randomized, double-blinded and multicentred. It evaluated the efficacy and safety of INTERCEPT RBC in acute anaemia patients. Red blood cell components were transfused to cardiovascular surgery patients at two German sites. The trial met the primary endpoint, which demonstrated that the mean haemoglobin content of INTERCEPT-treated RBCs was equivalent to conventional RBCs.

<sup>41</sup> The SPARC trial was a randomized, double blinded cross-over study. It evaluated the efficacy and safety of INTERCEPT RBC in chronic anaemia patients. It enrolled 86 thalassemia patients at three international sites. Subjects were randomly assigned to a sequential treatment period of either INTERCEPT-treated RBCs or conventional RBCs with cross over to the other treatment arm at the end of the first period. Each period comprised 6 transfusion episodes. The study met the primary endpoint, which was designed to assess up to a 15 per cent relative difference in mean consumption of haemoglobin, a measure of red blood cell efficacy and iron burden.

<sup>42</sup> Promacta has been approved in more than 90 countries as a treatment for low platelet count in patients with chronic immune thrombocytopenic purpura.

<sup>43</sup> SAA is a blood disorder in which a patient's bone marrow fails to produce enough red blood cells, white blood cells and platelets. Novartis said European regulators are expected to decide on the drug's use in SAA in 2019.

*and/or development, contracts for supply of manufacturing inputs, and marketing agreements. Companies considered include suppliers, potential suppliers and developers of products which may be of interest.*

- The takeover of Shire by Takeda was approved by shareholders of both companies, with an arrangement that the deal would complete on 8 January 2019. Takeda will be one of the world's top 10 drug makers after the takeover and also one of the most indebted as, in addition to issuing new shares, the company has secured US\$30.9bn in bank loans to complete the deal. The company plans to turn the deal profitable by cutting costs, with annual savings of at least US\$1.4bn predicted three years after completion. Takeda also has plans to sell up to US\$10bn worth of non-core assets to pay back debt. Takeda will maintain its headquarters in Japan and its primary listing on the Tokyo Stock Exchange as well as its current listings on local Japanese stock exchanges. The listing and trading of its American Depositary Shares began on 24 December 2018.
- Takeda received clearance from the European Commission for the proposed acquisition on condition it sell Shire's investigational inflammatory bowel disease drug SHP647, so as not to lessen potential competition (with potential rival Entyvio).
- Bayer is to concentrate all haemophilia factor VIII protein production at its plant in Berkeley, California.

## 5. Specific country events

- The US National Institutes of Health launched an initiative to coordinate and accelerate research into a cure for sickle cell disease. W. Keith Hoots, director of the blood diseases and resources division at the National Heart, Lung and Blood Institute, said the Cure Sickle Cell Initiative would make use of the most advanced basic science and genetic research from around the world, supporting both industry and academic research into cell and genetic therapies, clinical trials, comparisons of treatment methods, and data accrual.
- The US Centers for Disease Control and Prevention (CDC) describes the Asian longhorned tick, *Haemaphysalis longicornis*, as "a tick indigenous to Asia, where it is an important vector of human and animal disease agents". The tick species has been identified in Arkansas, Connecticut, Maryland, New Jersey, New York, North Carolina, Pennsylvania, Virginia and West Virginia, on domestic animals, wildlife, and people. In the US no cases of human disease have yet been attributed to the tick, but it's a known vector for haemorrhagic fever in humans<sup>44</sup>. Americans already contract a number of diseases from endemic ticks, including Lyme disease, babesiosis, Powassan encephalitis, Rocky Mountain spotted fever and other infections.

## 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*

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<sup>44</sup> The species carries "severe fever with thrombocytopenia syndrome virus" (SFTSV) which brings on serious haemorrhagic fever. It emerged in China and has since been found in South Korea and Japan. Described by Chinese researchers in the *New England Journal of Medicine* in 2011, symptoms include fever, vomiting, diarrhoea and anaemia. Multiple organ failure can result, and 12 per cent of cases prove fatal. The tick can also spread a virus known to cause Japanese spotted fever in humans.

particular projects varies, and even research which achieves its desired scientific outcomes may not lead to scaled-up production, clinical trials, regulatory approval and market development.

- A research team led from the University of California - Berkeley was [awarded a patent](#) for unique RNA guides that work with the Cas9 protein to target and cut genes via the gene-editing tool, CRISPR.
- Researchers at Yale have developed a new way to study the parasite *Babesia duncani* that causes human babesiosis and can be transmitted through blood transfusion. They transferred the parasites from hamster red blood cells to human red blood cells cultured *in vitro*. This allowed them to examine the parasite in human red blood cells over time and study its biology. They confirmed that *Babesia duncani* can replicate rapidly in human red blood cells, doubling in less than 24 hours. They tested four current treatments and found that the parasite has low susceptibility to these therapies<sup>45</sup>.
- A study has found that patients with both sickle-cell trait and type 2 diabetes experience more frequent diabetes-related complications, including hypertension, [diabetic retinopathy](#), and decreased renal function, compared with patients with type 2 diabetes alone<sup>46</sup>.
- Researchers from [Duke University](#) say<sup>47</sup> they have created [microRNA](#)-based tests that could be used to monitor blood doping in athletes.
- According to research published in *JAMA*<sup>48</sup>, the incidence of hospitalization for upper [gastrointestinal tract bleeding](#) for patients taking an anticoagulant was lower among patients who were also taking a proton pump inhibitor (PPI).
- A study in *Blood Advances*<sup>49</sup> found that among older patients with [polycythemia vera \(PV\)](#), therapeutic phlebotomy and hydroxyurea are associated with improved overall survival and decreased risk for thrombosis but are underused.
- Development of a safe and effective drug for postpartum haemorrhaging is the goal of research by the Bridge Institute at the USC Michelson Center for Convergent Bioscience and the US Department of Energy's SLAC National Accelerator Laboratory based at Stanford University. The work is reported in [Nature Chemical Biology](#).
- In a study reported 13 December in [Nature](#), researchers injected mouse brains with a growth hormone tainted with amyloid- $\beta$ , a protein implicated in Alzheimer's disease, and saw it accumulate. The results reinforced the hypothesis that amyloid- $\beta$  may be spread between people under rare conditions from contamination<sup>50</sup>, but does not show the protein to be contagious. Surgeons are being urged to ensure tools used for brain surgery are thoroughly decontaminated.

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<sup>45</sup> [published in the Journal of Biological Chemistry](#) Choukri Ben Mamoun et al., "Establishment of a continuous in vitro culture of *Babesia duncani* in human erythrocytes reveals unusually high tolerance to recommended therapies." *J Biol Chem*. 2018 Dec 28;293(52):19974-19981. doi: 10.1074/jbc.AC118.005771. Epub 2018 Nov 21.

<sup>46</sup> Skinner SC, Diaw M, Pialoux V, et al. [Increased prevalence of type 2 diabetes-related complications in combined type 2 diabetes and sickle cell trait](#) [published online October 16, 2018]. *Diabetes Care*. doi:10.2337/dc18-1289

<sup>47</sup> [news release](#). The researchers published their findings in the [British Journal of Haematology](#).

<sup>48</sup> By Wayne A. Ray, of the department of health policy at Vanderbilt University School of Medicine, and colleagues

<sup>49</sup> Nikolai A. Podoltsev, from Yale University, and colleagues. [Abstract/Full Text](#)

<sup>50</sup> A 2015 study found unusually large deposits of amyloid- $\beta$  in the autopsied brains of four people who had received injections of growth hormone as children in the UK. [The Guardian](#) reports thousands of children received growth hormone derived from cadavers to treat stunted growth between 1958 and 1985. Some growth hormone at that time was contaminated with amyloid- $\beta$ . These days synthetic growth hormone is used.

- Results of a new study<sup>51</sup> suggest that the presence of thrombocytopaenia is associated with an increased risk of all-cause mortality and cardiovascular-related mortalities in patients with severe hepatic steatosis.

## 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 study published in *The Journal of Infectious Diseases* looked at the risk of sexual and other transmission within households in Zika-endemic areas, based on experience in Puerto Rico in 2016 and 2017. Sexual partners of known cases were 2.2 times more likely to develop Zika infection compared with household partners who did not have sexual relations with the index case. Researchers also found household environments contained risk factors for Zika transmission and infection. Household members were 2.5 times more likely to become infected if their homes contained open and unscreened doors and windows or 2.1 time more likely if their homes had open windows and doors with screens.
- Another report in the same journal was from researchers who modelled the value of developing a Zika vaccine<sup>52</sup>. They found the most cost-effective strategy would be to vaccinate women of childbearing age and young adults, as the cost of the vaccine would be less than the medical costs of dealing with congenital Zika syndrome. They reported that the vaccination model that would be most economically valuable was one that took place five years before a Zika outbreak.
- A study found that severe thrombocytopaenia is a rare but potentially fatal outcome in patients infected with the Zika virus, and that treating such cases for idiopathic thrombocytopaenic purpura may be more effective than platelet transfusion. Researchers from the CDC and Puerto Rico Department of Health reviewed the medical records of [patients diagnosed with Zika virus infection](#) in 2016 in Puerto Rico. Tyler M. Sharp, a US Public Health Service commander and epidemiologist for the CDC's Dengue Branch told *Infectious Disease News*: "Patients with severe thrombocytopenia associated with Zika virus infection should be managed for ITP, including administration of IVIg or corticosteroids, but not platelet transfusion."<sup>53</sup>

<sup>51</sup> The abstract, "[The Impact of Thrombocytopenia on the Risk of Mortality Amongst Adult Patients with Severe Hepatic Steatosis: A Population Based Study United States Adults](#)," was presented at the 2018 American Association for the Study of Liver Diseases ([AASLD](#)) Liver Meeting, November 9-13, 2018, in San Francisco, California.

<sup>52</sup> During the 2015-2016 epidemic, 18 groups of scientists were actively working on a Zika vaccine. The World Health Organization estimates that is now 7.

<sup>53</sup> Elizabeth A Van Dyne et al., "Incidence and Outcome of Severe and Non-severe Thrombocytopenia Associated with Zika Virus Infection — Puerto Rico, 2016" *Open Forum Infectious Diseases*, ofy325, <https://doi.org/10.1093/ofid/ofy325> Published: 03 December 2018

- Researchers have generated six Zika virus antibodies that could be used to test for and possibly treat a mosquito-borne disease<sup>54</sup>.
- A peptide developed by scientists based at Nanyang Technological University (NTU), Singapore, in collaboration with colleagues at the Federal University of Minas Gerais, Brazil, and Ghent University, Belgium has been found to attack the Zika virus. In laboratory mice infected with Zika it has reduced disease symptoms and the number of deaths<sup>55</sup>.
- Emergent BioSolutions and Valneva announced positive interim results from the Phase I study evaluating VLA1601, their vaccine candidate against the Zika virus.
- Themis says it has had positive results from its Phase II trial of its chikungunya vaccine. It plans to start a Phase III trial early in 2020.

## Influenza

- A [recent study](#) by researchers at the Scripps Research Institute in La Jolla, in collaboration with Janssen Pharmaceutical Companies (Johnson & Johnson), found that llama antibodies, synthesized into a “four-in-one” mega-protein and administered to mice through a nasal spray, protected the mice from 59 strains of influenza A and B<sup>56</sup>. Senior co-author Ian Wilson said that because llama antibodies are so tiny, they can bind to the surface of the flu virus to keep it from replicating. He explained the use of a nasal spray for delivery: “You’re delivering it to the upper respiratory tract, exactly where you’re getting infected, so you’re getting a higher concentration of antibodies in the site that you want”.
- Investigation of the impact of prior flu vaccination on current-season effectiveness in Canadian patients hospitalized for lab-confirmed flu over four consecutive flu seasons mainly found no significant impact<sup>57</sup>.
- Researchers seeking universal protection against flu say they have developed multidomain antibodies with breadth and strength. Administered intranasally to mice with an adeno-associated virus vector, the antibodies gave durable and continuous protection from a significant number of influenza strains<sup>58</sup>.
- InVax<sup>59</sup>, in collaboration with Trudeau Institute Contract Research Organization and Hong Kong University, says its universal flu vaccine candidate has demonstrated preclinical success. The company is now developing the vaccine for human clinical trials.
- BiondVax currently has a potential universal flu vaccine, M-001, in Phase III clinical trials.
- Seqirus is expanding its cell-based flu vaccine franchise. Having scaled up to make 20 million doses in the last year, it has now [unveiled](#) a \$US 140 million expansion to its Holly Springs, North Carolina, plant.
- Favipiravir, a broad-spectrum antiviral developed in Japan, has appeared to hold promise for treating both avian and seasonal flu, but in a new study<sup>60</sup> researchers

<sup>54</sup> Adinarayana Kunamneni, Chunyan Ye, Steven B. Bradfute, Ravi Durvasula. “Ribosome display for the rapid generation of high-affinity Zika-neutralizing single-chain antibodies”. *PLOS ONE*, 2018; 13 (11): e0205743 DOI: [10.1371/journal.pone.0205743](https://doi.org/10.1371/journal.pone.0205743)

<sup>55</sup> Joshua A. Jackman et al. “Therapeutic treatment of Zika virus infection using a brain-penetrating antiviral peptide”, *Nature Materials* (2018). DOI: [10.1038/s41563-018-0194-2](https://doi.org/10.1038/s41563-018-0194-2)

<sup>56</sup> The only strain that llama antibodies could not control was an avian flu not currently known to infect humans.

<sup>57</sup> Dec 3 *Clin Infect Dis* [abstract](#)

<sup>58</sup> See Nick S Laursen et al., “Universal protection against influenza infection by a multidomain antibody to influenza hemagglutinin”, *Science* 2 Nov 2018: Vol. 362, Issue 6414, pp. 598-602

<sup>59</sup> Of Pasadena, California

<sup>60</sup> The study, “[The mechanism of resistance to favipiravir in influenza](#),” was published in *Proceedings of the National Academy of Sciences*.

said they were able to demonstrate that a mutation in a conserved region of the viral RNA polymerase conferred resistance to favipiravir *in vitro* and in cell culture<sup>61</sup>

- In a new study led by the Human Vaccines Project researchers will be conducting a comprehensive evaluation of the human immune system's response to influenza<sup>62</sup>.
- Japanese research has confirmed that the avian H7N9 virus can be transmitted through respiratory droplets<sup>63</sup>.
- Visterra announced that a Phase IIa study of its monoclonal antibody VIS410 showed safety, tolerability and positive clinical activity trends in non-hospitalized patients with influenza A<sup>64</sup>.

## Ebola virus disease

- The second-largest Ebola outbreak in history<sup>65</sup> (in the Democratic Republic of Congo) has had health experts worried about whether the stock of an experimental vaccine can meet the demands of the continuing epidemic. This has been by far the largest deployment of the promising but still experimental Ebola vaccine, which is owned by Merck<sup>66</sup>. The company keeps a stockpile of 300,000 doses; preparing them takes months. "We are extremely concerned about the size of the vaccine stockpile," WHO's emergencies director, Dr. Peter Salama, said, as 300,000 doses is not sufficient as urban Ebola outbreaks become more common. Health workers, contacts of Ebola victims and their contacts have received the vaccine in a "ring vaccination" approach. There is the need for mass vaccination in major cities. This Ebola outbreak is occurring against a background of deadly attacks by rebel groups, and "ring vaccination" is difficult to implement amongst displaced persons/ fleeing refugees.
- In November, the FDA approved emergency use of an [Ebola rapid antigen fingerstick](#) test for detecting Ebola.
- A synthetic DNA vaccine is demonstrating promising results against the Ebola virus in preclinical animal research. Scientists at The Wistar Institute Vaccine and Immunotherapy Centers targeted a virus surface protein called glycoprotein<sup>67</sup>.
- The [Alliance for International Medical Action](#) has been operating<sup>68</sup> the randomized, controlled trial of several investigational drugs<sup>69</sup> to treat Ebola, accepting patients of any age with a confirmed diagnosis of the Ebola virus.

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<sup>61</sup> "We show evolution of resistance to favipiravir in the pandemic H1N1 influenza A virus in a laboratory setting," they wrote.

<sup>62</sup> The clinical study at Vanderbilt University Medical Center will be led by Dr C. Buddy Creech, who directs the Vanderbilt Vaccine Research Program.

<sup>63</sup> The research team was led by Professor Yoshihiro Kawaoka at the University of Tokyo.  
<http://dx.doi.org/10.1016/j.chom.2017.09.008>

<sup>64</sup> The data (together with *in vitro* data describing the antiviral activity of VIS410 in combination with small molecule antivirals) were presented at the 6<sup>th</sup> International Society for Influenza and other Respiratory Virus Diseases (ISIRV) Advances in Respiratory Virus Therapeutics Conference 13 -15 November 2018 in Washington D.C.

<sup>65</sup> By 31 December well over 300 people had died in the outbreak and many more had been infected.

<sup>66</sup> Merck announced in November it was [starting](#) a rolling submission to the FDA for its vaccine, rVSVΔG-ZEBOV-GP. Besides Merck, GlaxoSmithKline, Johnson & Johnson, and smaller biotechs such as Inovio Pharmaceuticals are developing Ebola vaccines.

<sup>67</sup> Ami Patel et al., "Protective Efficacy and Long-Term Immunogenicity in Cynomolgus Macaques by Ebola Virus Glycoprotein Synthetic DNA Vaccines", published 10 October 2018, *The Journal of Infectious Diseases*, jiy537, <https://doi.org/10.1093/infdis/jiy537>

<sup>68</sup> In association with the US National Institutes of Health. [Anthony S. Fauci](#), director of National Institute of Allergy and Infectious Diseases, said: "Combatting Ebola requires a comprehensive response that draws on the strengths of all areas of public health. Biomedical research can lead to critical new tools, such as potentially life-saving therapies. Through scientifically and ethically sound

- New research<sup>70</sup> shows that human cells possess a protein called RBB6P that mimics a critical Ebola virus protein to fend off a viral attack.
- Grifols announced at the end of December that it would produce for the Liberian Government a plasma-derived treatment for the Ebola virus. Production would occur at its plant in Clayton, North Carolina.

## Other diseases

- A study<sup>71</sup> has found that prion proteins that cause sporadic Creutzfeldt-Jakob disease (sCJD) may enter the body via the eyes. Researchers at the US National Institute of Allergy and Infectious Diseases, the University of California at San Diego and the University of California at San Francisco could also detect prion protein infection by looking at the eyes. The study also showed that prion proteins can be spread via eye surgeries. Single use optical instruments have been suggested to limit disease spread.
- Researchers from the University of Pittsburgh identified compounds that block the reactivation of latent HIV-1 in a human cell line containing the latent virus<sup>72</sup>.
- The FDA has authorized the marketing of a new diagnostic test to aid in detecting cytomegalovirus (CMV) in newborns less than 21 days of age.
- In 25 European countries, annual sentinel surveillance of *Neisseria gonorrhoea* isolates showed decreasing susceptibility to ceftriaxone, according to a report in *BMC Infectious Diseases*<sup>73</sup>. Azithromycin resistance remained stable, with a resistance rate of 7.5 per cent in 2016 compared with 7.1 per cent in 2015. But seven isolates (0.3 per cent) from five countries displayed high-level azithromycin resistance, an increase from five in 2015. Cefixime resistance was detected in 2.1 per cent of isolates in 2016 compared with 1.7 per cent in 2015, and ciprofloxacin resistance was 46.5 per cent (compared with 49.4 per cent in 2015). The research team (from Public Health England, the European Centre for Disease Prevention and Control, and the World Health Organization) say the decreasing ceftriaxone susceptibility and relatively high azithromycin resistance are a major concern, since European guidelines recommend ceftriaxone plus azithromycin as the first-line therapy for gonorrhoea.
- Victorians were warned in November about the risk of using potting mixes, following reports of an increase in case numbers for legionnaires' disease.
- Agriculture officials in Victoria reported responding to positive identification of anthrax in a sheep on a property near Swan Hill in late November. The property concerned was quarantined and biosecurity protections were put in place.
- A report in November 2018 said that over half of Queensland's hospitals and aged care centres have tested positive for potentially deadly legionella bacteria, a year after the State Government launched a crackdown on outbreaks.

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clinical trials, we hope to efficiently and definitively establish the safety and efficacy of these investigational Ebola treatments, offering new ways to save lives."

<sup>69</sup> mAb114, developed by the US government; ZMapp, an intravenous treatment made by Mapp Biopharmaceutical; Remdesivir, made by Gilead Sciences; and Regeneron's REGN-EB3.

<sup>70</sup> By Christopher Basler of Georgia State University and colleagues at Georgia State, Northwestern University, the Gladstone Institutes and the University of California San Francisco. See [Batra, J et al \(2018\) "Protein Interaction Mapping Identifies RBBP6 as a Negative Regulator of Ebola Virus Replication". \*Cell\* 175 \(7\) 1917-1930.](#)

<sup>71</sup> Christina D Orru et al, "Prion Seeds Distribute throughout the Eyes of Sporadic Creutzfeldt-Jakob Disease Patients," in the journal [mBio](#). <https://mbio.asm.org/content/9/6/e02095-18>

<sup>72</sup> See *Antimicrobial Agents and Chemotherapy*, 3 December 2018.

<sup>73</sup> Dec 3 *BMC Infect Dis* [study](#)