

# 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:

- Bayer has begun enrolling children in an international Phase III trial to evaluate BAY 94-9027 for prophylaxis and acute treatment of haemophilia A (page 2).
- Intravenous immunoglobulin products are ceding some of their market share to subcutaneous immunoglobulin (page 2).
- The US Food and Drug Administration (FDA) has approved Baxter's recombinant factor IX, Rixubis, for routine prophylaxis, for the control and prevention of bleeding episodes, and for perioperative use (page 4).
- The US National Institutes of Health (NIH) is funding the Transfusion of Prematures trial, which randomly assigns half the babies in the trial to receive transfusions at a low haemoglobin level, with half of them at a high haemoglobin level (page 7).
- In Japan, the Ministry of Health, Labour and Welfare confirmed its first blood donor case of Chagas disease (page 7).
- Washington University School of Medicine (St. Louis) is studying whether the length of storage time of red blood cells affects organ failure in critically ill children who are transfused (page 9).
- Research suggests that cardiac surgical patients who receive red blood cells have a higher infection risk and that the risk rises with each unit transfused (page 9). Other research suggests that cardiac surgical patients given red blood cells stored for more than three weeks were more than twice as likely as those who received fresher red cells to experience delirium (page 9).
- Patients treated with the newer oral anticoagulants have been found to have a higher risk of gastrointestinal bleeding than those who receive standard care (page 11).
- The World Health Organization (WHO) continues to monitor the possible pandemic potential of avian flu H7N9 which arose in China (page 12) and MERS- CoV, the Middle East Respiratory Syndrome Coronavirus (page 13).

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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.*

### Clotting factors

- a) Bayer, having completed enrolment of adult haemophilia A patients in the PROTECT VIII trial<sup>1</sup>, has begun enrolling children in an international Phase III trial to evaluate its investigational compound BAY 94-9027 for prophylaxis and acute treatment of haemophilia A. The drug is designed to increase the circulating half-life of rFVIII activity through site specific attachment of a polyethylene glycol (PEG) polymer to the light chain of the rFVIII molecule, without compromising its full biologic activity.

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<sup>1</sup> PROphylaxis in haemophilia A patientS via directly pEgylated long-aCTing rFVIII.

## Immunoglobulin

- a) In June, GBI Research reported that “intravenous immunoglobulin products are beginning to lose market shares to subcutaneous immunoglobulin (SCIg). In Europe the subcutaneous product accounts for over one- quarter of the market. It reduces the risk of infection through catheterization, lessens patient suffering, and may permit self- administration.”
- b) In May, Baxter announced that its intravenous immunoglobulin (IVIg) product, Gammagard, had failed to meet the primary endpoints in a large trial for Alzheimer’s disease. Norman Relkin of Weill Cornell Medical College at the Alzheimer’s Association International Conference in July said that secondary analyses demonstrated that the 266 trial participants with the epsilon-4 *APOE* gene variant given high-dose IVIg showed smaller declines in Modified Mini-Mental State Examination (3MS) scores than those given either a lower IVIg dose or placebo. *APOE4* carriers on high-dose IVIg also had better performance on three specific neuropsychological tests<sup>2</sup>.
- c) Biotest announced the first liver transplant patient has been treated with its 10 per cent hepatitis C hyperimmune globulin Civacir in a Phase III clinical trial.

## Anaemia treatments

- d) Rockwell Medical announced that a Phase III trial of its drug soluble ferric pyrophosphate (SFP) has met the primary endpoint of improving haemoglobin levels in dialysis patients.
- e) Vifor Pharma published results of a major study which suggests its intravenous treatment Ferinject significantly extends the period before other anaemia treatment is required. The FIND-CKD study, in 600 patients with non-dialysis-dependent chronic kidney disease (ND-CKD)<sup>3</sup> assessed over 56 weeks the efficacy and safety of IV iron for the treatment of iron deficiency anaemia (IDA). Ferinject (ferric carboxymaltose) was compared with oral iron treatment. The study showed that the Vifor product, at an initial dose of 1,000mg and subsequent dosing as required decreases the need for treatment with erythropoiesis-stimulating agents (ESAs) or blood transfusion in this population. Detailed results will be presented at the American Society of Nephrology meeting in Atlanta in November.
- f) Xenetic Biosciences has Australian and New Zealand approval to conduct Phase II trials of ErepoXen (polysialylated human erythropoietin), to test efficacy and safety of multiple doses in chronic kidney disease (CKD) sufferers who are not receiving dialysis nor receiving erythropoiesis-stimulating agents (ESA). Phase III trials will be conducted in the US and Europe.

## Devices and Services

- g) The US Defense Advanced Research Projects Agency (DARPA) in July granted a \$US 23 million contract to Battelle, NxStage and Aethlon to collaborate on a sepsis treatment mobile medical device to treat sepsis in soldiers. The expectation is that the device will remove blood, treating it, and re-infuse it.
- h) Timestrip has made a small, finger pressure activated labels that can be applied to blood bags the moment they are taken out of refrigeration units. Thus activated they show if and when the core temperature of individual blood bags has breached the critical temperature abuse point, after which that blood cannot be returned to the blood bank for future use.

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<sup>2</sup> Relkin N, et al "Results of the GAP 160701 study: A phase 3 clinical trial of intravenous immunoglobulin for mild to moderate Alzheimer's disease" *AAIC* 2013; Abstract O3-06-04.

<sup>3</sup> The risk for anaemia increases as renal function deteriorates and it is estimated that as many as 70% of patients with ND-CKD are anaemic by the time they reach dialysis. Vifor notes that iron deficiency is the most common cause of anaemia in patients with ND-CKD.

- i) GE Healthcare has a \$US 9.6 million grant from the US Defense Advanced Research Projects Agency (DARPA) to develop a pocket- sized infectious disease diagnostic device for use in the field. GE is working with a team at the University of Washington.
- j) A group at MIT has developed a microchip that can quickly separate white blood cells from whole blood. Integrated into a portable diagnostic device it could be used to analyse blood samples for signs of inflammatory disease such as sepsis.
- k) The FDA CytoSorbents Corporation announced in July that it would present its HemoDefend blood purification technology at the Military Health System Research Symposium (MHSRS). HemoDefend is designed to reduce a broad range of dangerous contaminants, such as free hemoglobin, and antibodies

### Other

- l) Portola Pharmaceuticals said a Phase II proof-of-concept study of its Factor Xa inhibitor antidote showed greater than a 95 per cent reversal of the anticoagulant activity of Eliquis (apixaban) was achieved within two minutes of intravenously administered high-dose PRT4445PRT4445. The drug has a tentatively approved International nonproprietary name (INN) of andexanet alfa.
- m) Kamada announced positive results from a preclinical study Glassia (human alpha-1 antitrypsin) in inter-species islet graft transplantation<sup>4</sup>. The company says the data support the continued clinical development of its AAT therapeutic for type 1 diabetes.
- n) The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) in July gave a positive opinion on an additional therapeutic indication for the fibrin sealant Evicel (Omxix Pharmaceuticals): for use in suture line sealing in dura mater<sup>5</sup> closure.
- o) BioLineRx announced that its drug BL-8040 has shown positive pre-clinical outcomes in treating thrombocytopenia<sup>6</sup>.
- p) Selexys Pharmaceuticals is enrolling patients in a Phase II trial of a drug to reduce the rate of sickle cell-related pain crises.

## 2. Regulatory

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

### Plasma and recombinant products

- a) The FDA in June approved Baxter's Rixubis for use in people over 16 with haemophilia B. It is indicated for routine prophylaxis, for the control and prevention of bleeding episodes, and for perioperative use. Rixubis is a recombinant coagulation factor IX.
- b) Alnylam has received orphan drug designation<sup>7</sup> from the FDA for ALN-AT3, an RNAi therapeutic for the treatment of haemophilia A and B. ALN-AT3 is subcutaneously administered and targets antithrombin.
- c) The FDA has approved extending the time within which Cangene's VariZIG (varicella zoster immune globulin) is recommended for administration after exposure to the varicella-zoster virus. Previously four days, this has become ten days.
- d) The FDA issued Novo Nordisk with another setback for its recombinant factor XIII therapy, seeking a second complete response, citing unresolved findings at the manufacturing facility

<sup>4</sup> Ashkenazi et al., "Pancreatic Islet Xenograft Survival in Mice Is Extended by a Combination of Alpha-1-Antitrypsin and Single Dose Anti-CD4/CD8 Therapy," *PLOS One*, 2013 May 22;8(5):e63625. doi: 10.1371/journal.pone.0063625

<sup>5</sup> Dura mater is a thick membrane surrounding the brain and spinal cord.

<sup>6</sup> reduced platelet production; for data see the *British Journal of Hematology*

<sup>7</sup>The FDA Office of Orphan Products Development (OOPD) provides incentives for development of drugs for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the US.

- e) The FDA has granted orphan drug status to Pluristem Therapeutics for its PLacental eXpanded (PLX) cells for the treatment of aplastic anaemia.

#### Other

- f) Immunetics has received FDA clearance for its BacTx rapid test for bacteria in apheresis platelets. The BacTx system can detect aerobic, anaerobic, gram-negative and gram-positive bacteria in a single test.
- g) The FDA has approved Vifor's Injectafer (ferric carboxymaltose) for the treatment of iron deficiency anaemia in adults who have had an unsatisfactory response or are intolerant to oral iron. The drug has been sold in Europe as Ferinject since 2007.

### 3. 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.*

- a) CSL net profit in 2012/13 increased 19 per cent over the previous year. The CEO said "the company's core products of immunoglobulin and albumin have performed very well". CSL has flagged another \$US 500 million share buyback but remains open to appropriate acquisitions.
- b) US private equity firm Bain Capital is to acquire an 80 per cent stake in Plasma Resources UK (PRUK) in a £230 million deal. The remaining 20 per cent will remain in the hands of the UK government. PRUK is a major blood plasma supplier to the NHS. It operates Bio Products Laboratory which makes plasma products from US plasma, usually collected from donors at 32 centres operated in the US by PRUK-owned DCI Biological. The company has more than 1,200 employees and annual sales are around £110 million. Bain is reported to have faced competition from Germany's Biotest and South Korea's Green Cross Corporation. *The Independent* reported Bain is a co-owner of the Hospital Corporation of America (HCA), which already services half the private patients in London and has three joint ventures with the NHS, renting building space from public hospitals for exclusively private treatment. HCA is also a significant purchaser of plasma-derived products.
- c) Haemonetics is building a facility for manufacturing whole blood and apheresis devices in Penang. The US company said Malaysia offers proximity to customers in its fastest growing markets. The company's vice president of global engineering said: "Penang offers good infrastructure, well-established supply chain and a highly skilled workforce."
- d) For the second quarter of 2013, Baxter reported net income of \$US 590 million compared with net income of \$US 661 million in the same period last year. Worldwide sales were \$US 3.7 billion an increase of 3 per cent from the previous year. Excluding the impact of foreign currency, worldwide sales rose 4 per cent. BioScience revenues of \$US 1.6 billion increased 5 per cent from the prior-year period. Excluding the impact of foreign currency, BioScience sales rose 6 per cent driven primarily by improved demand for the company's haemophilia therapies, including Advate and FEIBA<sup>8</sup>.
- e) Baxter share prices fell more than 3 per cent after the company's Chair and CEO sold 128,000 shares (at \$US72.67).
- f) Grifols net profit in the first half of 2013 rose 37 per cent from the first half of 2013, with increased sales in the US.

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<sup>8</sup> During the quarter Baxter received marketing authorization in all EU member states for the use of HyQvia (solution for subcutaneous use) as replacement therapy for adult patients with primary and secondary immunodeficiencies. Baxter also received FDA approval of RIXUBIS [Coagulation Factor IX (Recombinant)] for routine prophylactic treatment, control of bleeding episodes, and perioperative management in adults with haemophilia B.

- g) AstraZeneca has made a deal with FibroGen potentially worth more than \$US 815 million for rights to an experimental anaemia drug. FG-4592, is given orally. It increases production of red blood cells by making the body believe it is at high altitude. Astellas Pharma already has rights to the medicine in Japan, Europe, the Commonwealth of Independent States, the Middle East and South Africa. FG-4592 has shown promising results in mid-stage Phase II clinical trials and AstraZeneca said it anticipated regulatory filings in the US once final Phase III tests are completed. GlaxoSmithKline and Akebia Therapeutics have similar drugs in Phase II<sup>9</sup>.
- h) The Medicines Company is finalising its deal to buy ProFibrin following a successful Phase III trial of Fibrocaps. The dry powder formulation of fibrinogen and thrombin, which is used to stop bleeding, met primary and secondary endpoints in four classes of surgery: spinal surgery, hepatic resection, soft tissue dissection and vascular surgery.
  - a) Grifols has increased its financial contribution to the Chronic Liver Failure European Consortium, whose research focuses on therapeutic strategies.
  - b) Bayer HealthCare announced the 2013 recipients of the Bayer Hemophilia Awards Program. The \$US 2 million in funding will go to projects such as overcoming immunological barriers to AAV gene therapy, and stem cell transplantation therapy for haemophilia.
  - c) Combat Medical Systems will distribute iTraumaCare's iTClamp Haemorrhage Control System to the US Department of Defense and to the US government. The device creates a stable clot until a wound can be surgically repaired. It is approved for sale in the US, European Union and Canada.

#### 4. Country- specific events

*The NBA is interested in relevant safety issues which arise in particular countries, and also instances of good practice. We monitor health issues in countries from which Australia's visitors and immigrants come.*

##### United States

- a) *US News and World Report* has published its annual rankings of the best hospitals nationally. Those that rank near the top in at least six specialties are included on an honour roll. Eighteen hospitals made the list this year headed by Johns Hopkins (Baltimore), Massachusetts General (Boston) and the Mayo Clinic (Rochester).
- b) The 29th edition of the AABB *Standards for Blood Banks and Transfusion Services* includes the following requirement for TRALI risk reduction: "high plasma volume components for allogeneic transfusion (i.e. plasma, high plasma volume platelet components, and whole blood) shall be from males, females who have not been pregnant, or females who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies". This standard will be implemented from October 1, 2014.
- c) A peaceful demonstration called for otherwise eligible blood donors in the men who have sex with men (MSM) category to attempt to give blood, tendering a paper copy of their negative HIV status. The participants were turned away but hoped the increase in rejected donors would give the FDA an indication of how much blood the gay community could provide.
- d) The Secretary of Health and Human Services added severe combined immune deficiency (SCID) to the Recommended Uniform Screening Panel in May 2010. Now over 50 per cent of babies born in the US. Ohio is the latest state to screen all newborns for the disease.
- e) The Centers for Disease Control (CDC) announced that in 2012 routine screening of a blood donation did not pick up trace amounts of West Nile virus. The ensuing transfusion of a cancer patient in Denver was fatal.

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<sup>9</sup> The drugs mimic the body's response to low oxygen levels, or hypoxia, by increasing the natural production of erythropoietin (EPO) through inhibiting a protein called hypoxia-inducible factor (HIF).

- f) Since West Nile virus (WNV) appeared in New York City 1999 it has been responsible for 16 196 cases of neuroinvasive disease -- which develops in fewer than 1 per cent of infected people -- and 1549 deaths<sup>10</sup>. The 2012 WNV outbreak—with 286 deaths, the deadliest since the virus emerged in the US- affected all 48 contiguous states, although Texas (and Dallas County in particular) had the heaviest disease burden. In Dallas county, in the period June to December 2012, there were 173 cases of neuroinvasive disease from WNV, 225 less-severe cases, and 19 deaths reported through the National Electronic Disease Surveillance System. There were 17 virus-positive blood donors. Nearly all the patients with neuroinvasive disease, required hospitalization, 35 per cent received intensive care, and 18 percent needed assisted ventilation. The case-fatality rate was 10 percent. The rate of neuroinvasive disease was 7.3 per 100 000 residents, compared with 2.91 per 100 000 in 2006, which was the largest West Nile virus outbreak in Dallas County before last year. A rapid rise in human disease cases followed shortly behind increased infection detected among mosquitoes, primarily the southern house mosquito, *Culex quinquefasciatus*. Considering data from 2002 underlined weather factors associated with WNV disease burden, including total rainfall in the winter and early spring, and summer heat. However, the number of days in the winter with a hard freeze was the strongest predictor of disease; the fewer such days the more disease<sup>11</sup>.
- g) The US National Institutes of Health (NIH) is funding the Transfusion of Prematures trial, which randomly assigns half the babies in the trial to receive transfusions at a low haemoglobin level, with half of them at a high haemoglobin level. Advocacy group Public Citizen has protested that the restrictive transfusion strategy is more likely to cause neurologic or other harm, and that 900 infants will be exposed to this.
- h) The CDC says about 300,000 Americans are diagnosed each year with Lyme disease, which is about ten times higher than the number reported to the CDC.

#### United Kingdom

- i) The sixteenth annual SHOT (serious hazards of transfusion) report shows an increase in reported adverse events/ reactions, over half of them being preventable errors<sup>12</sup>.
- j) The Welsh assembly has passed a “presumed consent” rule that assumes people are organ donors unless they, or their families, specify they are not.
- k) Public Health England has warned that waning immunity to mumps in those given at least one dose of the two-dose MMR (measles, mumps and rubella) vaccine may be contributing to transmission.

#### Canada

- l) Health Canada has completed its public consultation process on whether Canadian Plasma resources should be licensed to collect plasma from remunerated donors. Dr. Graham Sher, CEO of Canadian Blood Services supports the plan to pay plasma donors. He said Canadian Blood Services separate red blood cells from plasma and send the plasma to the US, but this voluntary system doesn't meet national needs for plasma protein therapies. “We today send about 260,000 litres of plasma for fractionation and .... if we were to be self-sufficient in this country, we would need about 800,000 or 900,000 litres.” The Canadian Nurses Association, Canadian Doctors for Medicare and the Canadian Federation of Nurses Unions are amongst those who have written to the Health Minister raising concern about the proposed changes. Canadian Blood Services and the Canadian Hemophilia Society have written in support.

<sup>10</sup> Lyle R. Petersen, Aaron C. Brault, Roger S. Nasci, “West Nile Virus: Review of the Literature”. 2013. *JAMA* 310:308-315.

<sup>11</sup> “Wendy M. Chung, Christen M. Buseman, ; Sibeso N. Joyner, Sonya M. Hughes,; Thomas B. Fomby, James P. Luby, Robert W. Haley, “The 2012 West Nile Encephalitis Epidemic in Dallas, Texas”. *JAMA*. 2013;310(3):297-307. doi:10.1001/jama.2013.8267.

<sup>12</sup> *BMJ* 2013; 347 doi: <http://dx.doi.org/10.1136/bmj.f4400> (Published 10 July 2013)

- m) Canadian Blood Services and HemaQuebec are now able to accept blood from gay men who have not had homosexual sex in the previous five years.

#### India

- n) The Weekly Iron Folic Acid Supplementation (WIFS) programme was launched on July 17. WIFS covers people in the age group of 10 to 19 years across the country: girls and boys enrolled in class VI-XII of government and government aided schools and out-of-school girls in rural and urban areas. A number of children were said to have been taken ill after the first dose.
- o) In the last year 1,504 cases of HIV from blood transfusions have been reported.

#### Other

- m) In Japan, the Ministry of Health, Labour and Welfare confirmed its first blood donor case of Chagas disease. The man from South America had donated blood ten times from 2006 to June 2013; ten people had received his blood. Since 15 October 2012, Japan's Red Cross has required a voluntary declaration of living in or travel to Latin American countries; so the declaration was obtained in June 2013, but not for earlier donations. The infection can be asymptomatic for decades.
- n) Researchers say that by 2050 more than 400,000 babies with sickle cell disease will be born annually round the world, compared with around 306,000 in 2010. In that year India, Nigeria and the Democratic Republic of Congo accounted for 57 per cent of these, and that proportion is expected to increase by 2050<sup>13</sup>.
- o) A study of silent hepatitis E infection amongst blood donors in the Netherlands<sup>14</sup> found 17 HEV RNA-positive donations among 45 415 donations, equivalent to one HEV-positive blood donation per day in the Netherlands. For 16 of the donors, genotyping revealed HEV genotype 3, which is circulating in Dutch pigs. Hepatitis E can be transmitted by transfusion<sup>15</sup> but the authors suggest that as transfusion is only a minor source of infection "the routine screening of blood donations for the presence of HEV does not yet seem warranted". Immunosuppressed recipients of blood are at particular risk, but they say "fortunately, it appears that chronic HEV infection in immunosuppressed patients can be cured by a temporary reduction of immunosuppression, or by antiviral treatment using ribavirin".
- p) Malaysia's plasma fractionator-to-be, Strovi Tel Sdn Bhd, expects to produce plasma anti-haemophilia factor VIII, prothrombin complex concentrate, human albumin and intravenous human immunoglobulin (IVIg). Currently Malaysia purchases plasma products via three methods namely, toll fractionation with CSL (Australia), , which meets 20% of the country's needs, central tender by Ministry of Health and PhamaNiaga's Approved Pharmaceutical Product List vendors and local purchase orders based on requirements. Products purchased via local purchase order and central tender are sourced from global commercial fractionators. The Malaysian plant is expected to be operational within four years and will have a capacity of 300,000 litres. Technical expertise is being provided by French-government linked biopharmaceutical group LFB under a royalty arrangement. The plant will be a European Medicines Agency-compliant processing facility.
- q) In Australia a telephone survey<sup>16</sup> concluded that "despite the common perception that other people would be motivated to donate blood with the introduction of a financial incentive, remuneration may provide minimal incentive in Australia and is unlikely to increase donor participation for the time being."

<sup>13</sup> Fottrell E, Osrin D (2013) Sickle Cell Anaemia in a Changing World. *PLoS Med* 10(7): e1001483. doi:10.1371/journal.pmed.1001483. Published: July 16, 2013.

<sup>14</sup> Slot E, Hogema BM, Riezebos-Brilman A, Kok TM, Molier M, Zaaijer HL. "Silent hepatitis E virus infection in Dutch blood donors, 2011 to 2012". *Euro Surveill*. 2013;18(31):pii=20550. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20550>

<sup>15</sup> And has been reported in Saudi Arabia, Japan, France and the United Kingdom.

<sup>16</sup> Bambrick, H. and Gallego, G. (2013), Community attitudes to remunerated blood donation in Australia: results from a national telephone survey. *Transfusion Medicine*. doi: 10.1111/tme.12062

- r) US firm Ortho-Clinical Diagnostics – owned by Johnson & Johnson – supplied five Irish hospitals with mislabelled test kits, which led to 220 mothers being given an anti-D blood product in error; 30 mothers who may have required it were not given it; 12 babies may have received red blood cells when they did not need them; and 278 babies' blood groups may have been recorded incorrectly.
- s) In China, a number of Western pharmaceutical companies are caught up in government investigations of alleged bribery.
- t) In Greece, nine new WNV cases were recorded in a week. Greece is now regarded as a country where WNV is endemic. The proportion of patients with symptoms involving the central nervous system has doubled this year.
- u) The total hip replacement market is growing rapidly in the US, France, Germany, Italy, Spain, the UK, Japan, Brazil, China and India<sup>17</sup>. The three major factors in this (varying between countries) are aging populations, more young people facing arthritis, and a developing middle class seeking quality care.

## 5. Safety and patient blood management

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

### Transfusion

- a) Washington University School of Medicine (St. Louis) is being funded by the US National Heart, Lung and Blood Institute of the NIH and the Canadian Institutes of Health Research to identify whether the length of storage time of red blood cells affects organ failure in critically ill children who are transfused.
- b) Research published in the June issue of *The Annals of Thoracic Surgery* says that patients who undergo cardiac surgery and receive red blood cell transfusions have a higher infection risk than those not transfused; the risk rises with each unit transfused.
- c) The US Army Medical Research and Materiel Command, Combat Casualty Care Research Program is funding three academic medical centres to evaluate early intervention using plasma in trauma patients. Studies on soldiers in Iraq and Afghanistan and in patients in trauma centres have suggested that early replacement of clotting factors improves survival from massive injuries. The study will evaluate whether patients who receive plasma quickly after suffering a non-head related trauma (in the field or in the ambulance) have reduced bleeding/transfusion and pain, better clinical outcomes and improved survival rates.
- d) At the 2013 annual meeting of the Society of Cardiovascular Anesthesiologists<sup>18</sup> Charles Brown from Johns Hopkins University School of Medicine and his colleagues discussed the possible correlation between age of blood transfused and delirium. They found cardiac surgical patients given red blood cells that had been stored for more than three weeks were more than twice as likely as those who received fresher red cells to experience delirium. The researchers controlled for other risk factors such as patient age, cerebrovascular disease, cardiopulmonary bypass time. They also controlled for units of red cells transfused, mindful of an earlier study that hinted that patients who receive more units might be at greater risk for postoperative delirium<sup>19</sup>.

### Treating iron deficiency

- e) Andreea Seicean<sup>20</sup> from the Case Western Reserve University, and colleagues used data from the American College of Surgeons National Surgical Quality Improvement Program Database (for 24,473 adults who underwent elective spine surgery) to examine the correlation between preoperative anaemia with adverse perioperative

<sup>17</sup> estimates from GlobalData.

<sup>18</sup> abstract 86

<sup>19</sup> *Am J Med* 1998;105:380-384

<sup>20</sup> "Pre-operative Anemia and Peri-operative Outcomes in Patients Who Undergo Elective Spine Surgery", *Spine*, July 1 2013.

outcomes. They found that patients with mild or moderate anaemia were more likely to have a prolonged hospital stay, complications or death within 30 days of surgery. were increased for patients with moderate and mild anemia vs. patients without anemia. The correlation between anaemia and adverse outcomes was independent of intra- or postoperative transfusion. Poor outcomes were not more likely in patients with preoperative cardiovascular comorbidities.

- f) A clinical trial showed that prophylactic erythropoietin mitigates anaemia during aggressive chemotherapy for breast cancer and more than halves transfusion rates<sup>21</sup>; but thrombotic events occurred in 7% of the epoetin alfa-treated patients compared with 3% among controls. Erythropoiesis-stimulating agents are FDA approved only for treatment of chemotherapy-induced anaemia, not for prophylaxis.
- g) A study in the online issue of *Neurology*<sup>22</sup> suggests that anaemia may increase the risk of dementia.

#### Other

- h) A paper published in The Cochrane Database of Systematic Reviews<sup>23</sup> suggests that delaying clamping for at least a minute after birth, which allows more time for blood to move from the placenta, significantly improves iron stores and haemoglobin levels in newborns and does not increase the risks to mothers.
- i) A study at Massachusetts General Hospital showed that for patients who have had a heart attack on the right side (which affects the heart's ability to pump blood to the lungs) inhaling nitric oxide improves blood supply.

## 6. Research

*A wide range of scientific research has some potential to affect the use of blood and blood products. However, research projects have time horizons which vary from "useful tomorrow" to "at least ten years away". Likelihood of success of particular projects varies, and even research which achieves its desired scientific outcomes may not lead to scaled-up production, clinical trials, regulatory approval and market development.*

- a) At Oxford University, research led by the Medical Research Council Weatherall Institute of Molecular Medicine has discovered a new type of bone marrow stem cell in mice that is primed to produce substantial numbers of platelets. They hope this will lead to new treatments to restore platelets in chemotherapy and bone marrow transplant patients. The study was reported in *Nature*.
- b) A new study from Imperial College, London,<sup>24</sup> reports around one quarter of operating room errors are due to technology and equipment problems, but a pre-operative surgical checklist could cut the error rate in half<sup>25</sup>.
- c) A child in the UK, born with severe combined immunodeficiency syndrome, is being treated at Great Ormond Street Hospital by re-engineering her bone marrow to add a vital missing gene. Doctors hope this will allow her to develop her own immune system

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<sup>21</sup> Volker Moebus and colleagues reported in the July 17 issue of the *Journal of the National Cancer Institute*.

<sup>22</sup> Published July 31, 2013. 2,552 older adults were studied over 11 years. Subjects who had anaemia at the beginning had around 41 per cent higher risk of developing dementia than those who were not anaemic. The association remained after taking into account age, race, sex and education. Authors: Kristine Yaffe, professor of psychiatry, neurology and epidemiology, University of California, San Francisco; and Sam Gandy, director, Mount Sinai Center for Cognitive Health, New York City.

<sup>23</sup> Susan J McDonald, Philippa Middleton, Therese Dowswell, Peter S Morris," Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes", Published Online: 11 JUL 2013. DOI: 10.1002/14651858.CD004074.pub3

<sup>24</sup> published online July 25 in the journal *BMJ Quality & Safety*.

<sup>25</sup> Colin D. Bicknell et al., "Surgical technology and operating-room safety failures: a systematic review of quantitative studies", published online 25 July 2013, *BMJ Qual Saf* doi:10.1136/bmjqs-2012-001778

- d) Researchers at the Massachusetts Institute of Technology have used gold nanoparticles controlled by infrared laser light to turn blood clotting on and off<sup>26</sup>.
- e) Fibrinogen is a significant determinant of thrombosis, and hence a significant risk factor for coronary heart disease. Data from 2,520 people in the Coronary Artery Risk Development in Young Adults Study (CARDIA) related reported alcohol intake and measured levels of fibrinogen on two occasions thirteen years apart. In comparison with subjects who did not consume alcohol, those who became or remained drinkers had lesser increases in fibrinogen, while those who gave up alcohol had the highest increase in fibrinogen over the 13 years.
- f) Patients treated for venous thrombosis or acute coronary syndrome with the newer oral anticoagulants have been found to have a higher risk of gastrointestinal bleeding than those who receive standard care<sup>27</sup>.
- g) Researchers associated with Massachusetts General Hospital have generated in an animal model blood vessels that functioned for up to nine months. They used vascular precursor cells derive from human induced pluripotent stem cells (iPSCs)<sup>28</sup>.
- h) Researchers at Kyoto University have identified a protein important in generating red blood cells in humans<sup>29</sup>. Shinji Hirata, of the University's Centre for iPS Cell Research and Application said the discovery "could help develop an effective method for producing blood cells".
- i) At the Charité Medical University in Berlin, a team led by Hans Bäuml and Yu Xiong, says it has made some progress with a new haemoglobin-based oxygen carrier<sup>30</sup>. It is about to start studies in live animals.

## 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, and the tick-borne babesiosis and Lyme disease).*

### Mosquito-borne diseases: including dengue, chikungunya and malaria

- a) Australian researchers and health authorities are concerned by the incidence of Asian tiger mosquitos (*Aedes albopictus*) on Australia's borders, together with the number of travellers returning to Australia with chikungunya. In the US the spread of the Asian tiger mosquito to more than half the states has led to fears of a number of viruses, with chikungunya suggested to be a very real threat<sup>31</sup>.
- b) Restrictions on whole blood donations in Cairns were lifted in August after a nine-month ban because of the local dengue fever outbreak.
- c) NIH has awarded \$US 11.4 million to the University of Rhode Island for an additional five years of research on the dengue virus.

<sup>26</sup> de Puig H, Cifuentes Rius A, Flemister D, Baxamusa SH, Hamad-Schifferli K (2013) "Selective Light-Triggered Release of DNA from Gold Nanorods Switches Blood Clotting On and Off". PLoS ONE 8(7): e68511. doi:10.1371/journal.pone.0068511

<sup>27</sup> Lisanne Holster, Vera E. Valkhoff, Ernst J. Kuipers, "New Oral Anticoagulants Increase Risk for Gastrointestinal Bleeding: A Systematic Review and Meta-analysis", *Gastroenterology*, Volume 145, Issue 1, Pages 105-112.e15, July 2013

<sup>28</sup> see *Proceedings of the National Academy of Sciences*. PNAS/doi/10.1073/pnas.1310675110)

<sup>29</sup> See August 2 online *Journal of Clinical Investigations*

<sup>30</sup> *ACS Nano* 2013, DOI: 10.1021/nn402073n)

<sup>31</sup> See PLoS *Neglected Tropical Diseases*, January 2013. The fact that this mosquito bites during the daytime requires heightened public awareness.

- d) A study from the University of Bristol has shown that there may be significant differences between the properties of the viral proteins in each of the four types of dengue virus, which has implications for the design of anti-viral therapies against all four types<sup>32</sup>.
- e) Meanwhile, Siga Technologies announced in New York that it has selected a lead candidate for its dengue anti-viral program.
- f) Arbovax has applied to the FDA to begin human trials of its dengue vaccine.
- g) Florida Keys has been investigating the use of drones to locate remote mosquito-breeding areas.
- h) Inovio plans to begin testing its malaria vaccine in humans next year. Meanwhile, an intravenous malaria vaccine in a clinical study led by Robert Seder of the US National Institute of Allergy and Infectious Diseases protected well against *Plasmodium falciparum*, probably the most lethal of the four malaria strains. Its route of administration would be a disadvantage for mass vaccinations.

### Influenza: strains, spread, prevention and treatment

- i) As at August 11, China believed it had seen 135 confirmed cases of H7N9 avian influenza, and recent experience suggested it could be transmissible between humans.
- j) CDC researchers who conducted animal studies with the H7N9 virus found amongst other things that the virus could pass through the eyes of mice to infect their respiratory tract. Once in the respiratory tract, the virus replicated very much faster than the human seasonal H3N2 virus<sup>33</sup>.
- k) Scientists have found H7N9 transmissible between ferrets by respiratory droplets.
- l) Some influenza scientists want to do controversial gain-of-function research on the H7N9 virus. Their proposal was notified in a letter published in *Nature* and *Science*. Also published was a letter from officials of the US Department of Health and Human Services notifying it will require prior review of proposals if the work is being done with US funding. Not all the proposed work involves US funding.
- m) Scientists at the Mount Sinai Medical Center in New York have identified a technique for engineering influenza viruses that are harmless to humans but still capable of passing through the air between laboratory ferrets. This could facilitate safer pathogen research.
- n) A recent study in *mBio*<sup>34</sup> found 35 per cent of viruses taken from the first H7N9 patient to be resistant to Tamiflu and Relenza. Since lab testing for the activity of a viral enzyme would not detect resistant strains, and patients might be given either of these treatments, this could lead resistant strains to flourish.
- o) Beijing-based Sinovac Biotech Ltd, which is in charge of H7N9 vaccine development in China, says that three batches of vaccine fluid are ready for rationing and vaccine formulation. To follow will be safety appraisals, stability studies and clinical trials.
- p) Novavax announced a positive preclinical trial for its virus-like particle vaccine candidate against H7N9. The vaccine protected 100 per cent of the mice studied. The study was reported in the journal *Vaccine*.
- q) NanoViricides said in July that it has signed a "confidential disclosure agreement" with Public Health England to develop a proposal for the testing of different candidates against viruses of "mutual interest". The first two viruses will be H7N9,

<sup>32</sup> Andrew Davidson et al., "Serotype-specific Differences in Dengue Virus Non-structural Protein 5 Nuclear Localization", *Journal of Biological Chemistry*, Vol. 288, Issue 31, 22621-22635, August 2, 2013.

<sup>33</sup> The study, "Pathogenesis and transmission of A (H7N9) avian influenza virus in ferrets and mice," appeared in *Nature* (2013) doi:10.1038/nature12391

(<<http://www.nature.com/nature/journal/vaop/ncurrent/full/nature12391.html>>).

<sup>34</sup> The online open-access journal of the American Society for Microbiology, published July 16, 2013. The study was conducted by Robert Webster of Saint Jude Children's Research Hospital in Memphis, Tennessee and international colleagues.

and the MERS virus (see below). NanoViricides is also arranging independent studies in Mexico of its broad-spectrum injectable and oral FluCide candidates, using multiple unrelated subtypes and strains of influenza A, including the H7N9 strain. It will also have its anti-MERS (Middle East Respiratory Syndrome) drug candidate tested in cell culture and animal models when available.

- r) Inovio Pharmaceuticals released positive preclinical data on the company's H7N9 vaccine candidate. In a mouse study conducted with researchers from the University of Pennsylvania and Canada's National Microbiology Laboratory in Winnipeg, the vaccine achieved immune response levels exceeding protective levels expected in common influenza subtypes.
- s) Medimmune's H7N9 vaccine is the only one to contain live virus. This is weakened, designed to trigger the immune system into antibody production without producing an active infection. However, there is a risk that if someone were vaccinated while infected with seasonal flu gene swapping could yield a hybrid virus with the transmission capacity of seasonal flu.
- t) Vaxart has oral vaccine candidates for H1N1 seasonal flu and H5N1 avian influenza in Phase I trials.
- u) Rather than develop a universal flu vaccine, some scientists are suggesting sequential vaccination with distinct strains isolated from the last century<sup>35</sup>.

#### **Middle East Respiratory Syndrome (MERS-CoV)**

- v) Concern continues about the pandemic potential of MERS-CoV, particularly with sizeable international gatherings of pilgrims to occur soon in the Middle East<sup>36</sup>. By 9 August worldwide there had been 94 confirmed cases and 46 deaths. Of these 67 cases and 38 deaths had occurred in Saudi Arabia. WHO had convened an Emergency Committee concerning the virus<sup>37</sup>. While there is a view that the virus originated in bats<sup>38</sup>, there is no certainty as to which animal is likely to be transmitting it to humans, although as at August 11 a number of reports were suggesting camels might also be involved<sup>39</sup>. The FDA approved a diagnostic test to detect MERS-CoV.

#### **Other diseases: occurrence, prevention and treatment**

- w) The isolation of wild poliovirus type 1 (WPV1) in 30 sewage samples from 10 sampling sites has triggered a major supplementary immunisation response in southern Israel. WHO assesses the risk of further international spread of WPV from Israel as moderate to high. Nations with frequent travel and contacts with polio affected countries have been advised to strengthen surveillance for cases of acute flaccid paralysis (AFP). response. Countries have also been advised to analyse immunization coverage data and arrange catch-up immunization where needed. WHO's International Travel and Health recommends that all travellers to and from polio affected areas be fully vaccinated against polio. Just 3 countries remain endemic for indigenous transmission of WPV: Nigeria, Pakistan and Afghanistan.

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<sup>35</sup> Yang, Li et al., "Immune history shapes specificity of pandemic H1N1 antibody responses" *Journal of Experimental Medicine*, July 15, 2013 vol.210 no 8, pp1493-1500, doi: 10.1084/jem.20130212

<sup>36</sup> July 17, 2013 in *PLOS: Current Outbreaks*. From June to November 2012, 16.8 million passengers departed Saudi Arabia, Jordan, Qatar, and the United Arab Emirates on commercial airlines. Of these, 16.3 per cent were going to India, 10.4 per cent to Egypt, 7.8 per cent to Pakistan and 4.3 per cent to the UK. Only 1.74 million of them were foreign pilgrims who performed the Hajj, but of these over 65 per cent came from low and lower-middle income countries with limited capacity to provide a rapid and effective public health response to a pandemic.

<sup>37</sup> Including Professor Chris Baggeley, Chief Medical Officer, Department of Health and Ageing, Canberra, Australia. The committee was established to advise the WHO about whether MERS poses a public health emergency as defined by International Health Regulations; and to advise the WHO on temporary recommendations to address the outbreak if required.

<sup>38</sup> Ithete NL, Stoffberg S, Corman VM, et al. Close relative of human Middle East respiratory syndrome coronavirus in bat, South Africa. *Emerg Infect Dis* 2013 (published online Jul 23)

<sup>39</sup> *The Lancet Infectious Diseases*, DOI: [10.1016/S1473-3099\(13\)70164-6](https://doi.org/10.1016/S1473-3099(13)70164-6)

Additionally, in 2013, the Horn of Africa is affected by an outbreak of WPV. WHO says polio sufferers have also been located in Somalia and Kenya in 2013. The United Nations said aid workers in Somalia are struggling to contain an outbreak of the crippling poliovirus, with rampant insecurity hampering efforts.

- x) Researchers at St Louis University have been testing a vaccine against plague, caused by bacteria usually carried by rodents. These bacteria are considered a potential weapon in a bio-terrorism attack.
- y) Work continues on vaccines<sup>40</sup> against Lyme disease, carried by ticks and increasing in notifications in the US.
- z) Although a vaccine against Hendra virus is now available, the take-up has been low although Queensland, New South Wales and Western Australian police forces have all vaccinated their horses.
- aa) Western Australia's Department of Agriculture and Food has been investigating the cause of lesions that were found in some horses south of Perth. Since then, lesions have appeared in humans who have had contact with the horses, although the people have been otherwise well. The Department of Health is assisting with the investigation of the affected humans.
- bb) Researchers have synthesised the sugars on the surface of the parasite that transmits Chagas disease. These trigger the human immune response, and the researchers hope their discovery will improve diagnostic tests and even lead to a vaccine<sup>41</sup>.
- cc) Queensland Health has faced particular difficulty in containing the legionella bacteria in facilities in the south west which use artesian water. This comes out of the ground warm, and is therefore an ideal breeding ground while it cools in tanks.
- dd) More and more travellers are returning to Australia bringing typhoid home with them, says Dr Anita Heywood, an infectious disease expert at the University of NSW, who identifies many of the cases are Australians of Indian descent returning from visiting family and friends on the subcontinent. She says pre-travel immunization helps to prevent diseases in the travellers and hence protects the general population to which they will return.
- ee) Victoria's Chief Health Officer warned of a potential measles outbreak after an infected man travelled through several public crowded locations in Melbourne.

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<sup>40</sup> Nina Wressnigg et al, "Safety and immunogenicity of a novel multivalent OspA vaccine against Lyme borreliosis in healthy adults: a double-blind, randomised, dose-escalation phase 1/2 trial", *The Lancet Infectious Diseases*, Volume 13, Issue 8, Pages 680 - 689, August 2013. doi:10.1016/S1473-3099(13)70110-5

<sup>41</sup> R A Ashmus et al, *Org. Biomol. Chem.*, 2013, DOI: 10.1039/c3ob40887f