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.

### 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) Baxter reported positive results from a Phase III trial evaluating prophylactic use of its anti-inhibitor coagulant complex FEIBA to treat haemophilia A and B. The data will underpin a biologics license application (BLA) to be filed with FDA in the first quarter of 2013. This trial showed a 72.5 per cent reduction in bleed rates for the prophylactic treatment group versus the on demand group. It reinforces the results of an earlier study showing that FEIBA can reduce bleeding events in patients with severe haemophilia A and inhibitors when compared to on-demand treatment (results published in *The New England Journal of Medicine* in November 2011).

b) At the 6th Annual Congress of the European Association for Haemophilia and Allied Disorders Biogen and Swedish Orphan Biovitrum released Phase III trial data confirming the ability of their investigational recombinant factors VIII Fc fusion protein (rFVIIIFc) and IX Fc fusion protein (rFIXFc) to provide people with haemophilia A and B with long-lasting protection from bleeding with fewer treatments than are required with the current standard of care. Biogen will file with the FDA in the first half of 2013 for approval of its fVIII; it has already filed in the US for its fIX.
c) Baxter announced in February that it had submitted to the FDA an Investigational
New Drug (IND) application for its haemophilia A treatment BAX 855, a full-length
longer acting rFVIII developed to increase the half-life of Advate. Baxter will begin a
Phase II/III study in adult patients in the first quarter of 2013. In a Phase I trial the
half-life was 1.5 times higher than that of Advate.

d) A recent study concluded that plasma-derived and recombinant fVIII products are
associated with similar antibody development in haemophilia A. However the
investigators found an increased risk of inhibitor development for second-generation
full-length products as compared with third-generation full-length recombinant
products. They found no increased risk was associated with the content of von
Willebrand factor in the products, nor was there a risk in switching among products.

e) Novo Nordisk announced that NovoSeven, its recombinant factor VIIa, is now
available in a pre-filled syringe.

Other

f) In January GlycoMimetics completed enrolling patients in its Phase II study of GMI-1070. This randomized, double-blinded study is examining the efficacy, safety and
pharmacokinetics of the drug in hospitalized sickle cell disease patients undergoing
g vaso-occlusive crisis. Some results are expected in the second quarter of 2013. The
US FDA has granted GMI-1070 fast track designation and orphan drug status.

g) In January Amgen announced top-line results of the Phase III trial of Aranesp
darbepoetin alfa) RED-HF (Reduction of Events With Darbepoetin Alfa in Heart
Failure) Phase III trial of Aranesp. The study did not meet its primary endpoint

h) Scientists from the department of engineering design at the Indian Institute of
Technology-Madras design say they have created enough red blood cells from stem
cells to be used as 'artificial blood' in transfusion. They say they have funding
approval from the Union ministry of science and technology to produce artificial blood
on an industrial scale, and they expect to be conducting human trials in three years.

i) A recent report suggests that fibrinogen concentrate or a fXIII concentrate combined
with a mini dose of tranexamic acid might prevent bleeding complications during
antithrombotic therapy.

j) rEVO Biologics announced a major retrospective study which demonstrated that
pregnant patients with hereditary antithrombin deficiency benefit from ATryn
Antithrombin (recombinant) therapy to prevent venous thromboembolic events.

2. Regulatory

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

a) Pfizer and Bristol-Myers Squibb’s Eliquis (apixaban) won the backing of the UK’s
health-cost regulator, the National Institute for Health and Clinical Excellence, for
people with an irregular heartbeat, putting the drug in line to be the third new
treatment recommended for such patients in the past year. NICE asked doctors to
talk with patients to talk before using Eliquis about whether to choose Xarelto or
Pradaxa or the long-established warfarin instead.


Haemocomplettan® (Ria stap® ) or a Factor XIII concentrate Fibrogammin® combined with a mini
dose of tranexamic acid can reverse the fibrin instability to fibrinolysis induced by thrombin- or FXa-

3 In a poster at the February 2013 meeting of the Society for Maternal-Fetal Medicine (SMFM). The
analysis was led by Dr. Michael Paidas, professor at Yale School of Medicine and co-director of the
Yale Women and Children’s Center for Blood Disorders.
b) On 22 January Octapharma USA announced that the FDA had approved Octaplas, its frozen, solvent/detergent treated pooled human plasma, for the management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors and for patients with coagulation deficiencies due to hepatic disease or who are undergoing cardiac surgery or liver transplantation. The FDA also approved the product for transfusion or plasma exchange in patients with congenital or acquired thrombotic thrombocytopenic purpura (TTP). Octaplas has been used in Europe and other countries for some time.

c) The European Union granted Accumetrics CE Mark approval for its next-generation VerifyNow II System. This measures at point of care platelet reactivity to antiplatelet agents. The current system is used in over 70 countries to reduce the occurrence of thrombotic events such as heart attack and stroke.

d) The FDA approved CSL Behring’s request to expand indications for Corifact (its FXIII concentrate- human), to include the peri-operative management of surgical bleeding in adult and paediatric patients with congenital FXIII deficiency.

e) The FDA sent a warning letter to Novo Nordisk concerning inadequacies it perceived during an inspection of a facility in Denmark.

f) By 28 January the contaminated drug scandal involving a Massachusetts compounding centre had a case count of 693 across 19 States, with 45 fatalities.

g) A meta-analysis has suggested that albumin infusion in patients with spontaneous bacterial peritonitis (SBP) decreased renal impairment and mortality." Dr Francesco Salerno, from Università degli Studi di Milano, and colleagues commented: "These salutary effects of albumin infusion were remarkably consistent from trial to trial4." The study was supported by CSL Behring.

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 made a net profit of $US627 million in the six months to December 31, up 24 per cent from the same period in 2011. It expects its full year profit to increase by around 20 per cent.

b) NuSep through its Singapore subsidiary Prime Biologics has successfully completed three trial production runs of human albumin in Singapore and will replicate these before trialling fractionation runs of human IVIg. These allow the company to prepare for the Good Manufacturing Practice certification required to produce the first batch of therapeutic plasma products for the clinical trials to start later this year. PRIME Biologics intends to produce albumin, IVIg, FVIII and FIX from human plasma in Singapore. NuSep will spin out this business as Prime Biologics opens up the Asian therapeutic plasma market, particularly in currently unprocessable plasma.

c) Haemonetics Corporation announced significant progress on key business initiatives in conjunction with the 31st Annual J.P. Morgan Health Care Conference in San Francisco. These included completing the acquisition of the whole blood collection, filtration and processing business from Pall Corporation and increasing the penetration of its Cell Saver Elite product in the Chinese market.

d) Ipsen and Inspiration Biopharmaceuticals announced they entered into an Asset Purchase Agreement whereby Cangene Corporation agreed to acquire the worldwide

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4 Their report appeared in *Clinical Gastroenterology and Hepatology*. 

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rights to IB1001, a rFIX for the treatment of haemophilia B. In July 2012 Inspiration announced that IB1001 was placed on clinical hold by the FDA, after irregular protein levels were found, an issue Inspiration said has been fixed by changing the way the drug is manufactured. Cangene will take over the trials and complete the approvals processes with the FDA and the EMA. Cangene will pay $US 5.9 million in cash upfront. Royalties and milestone payments are expected to reach $US 50 million. The backup bid for IB1001 was an offer from Kedrion Biotechnology.

e) At the end of January, Baxter announced financial results for the fourth quarter of 2012, and provided its financial outlook for 2013. Net income in the fourth quarter was $US 494 million compared with $US 463 million in the fourth quarter of 2011. Worldwide revenues grew 4 per cent in the fourth quarter to $US 3.8 billion compared with $US 3.6 billion in the fourth quarter of 2011. Sales within the US of $US1.6 billion increased 7 per cent, and international sales increased 4 per cent excluding the impact of foreign currency.

i) For the full year 2012, and excluding special items in both years, Baxter’s net income was $US 2.5 billion in 2012, an increase of 2 per cent over 2011.

ii) During 2012:

(1) Baxter increased its investments in research and development to $US 1.2 billion, an increase of 22 per cent.

(2) The company announced investments to enhance future plasma products production capacity with its new manufacturing facility in Georgia and an agreement with Sanquin in the Netherlands to support growth of its plasma-based treatments5.

(3) The company entered into a public-private partnership in Brazil to expand its market for haemophilia therapies6.

(4) BioScience revenues increased 7 per cent (9 per cent excluding the impact of foreign currency) from the same period in 2011. There was strong growth in demand for Advate, particularly in the US Gammagard Liquid (intravenous immunoglobulin), FEIBA, and albumin. Baxter received milestone payments related to the development of influenza vaccines.

iii) In 2013, the initial data release from Baxter’s first Phase III trial evaluating IVIg therapy in mild to moderate Alzheimer’s disease will occur in the second quarter. The company continues enrolment in a second, confirmatory Phase III trial.

f) Bayer plans collaboration with Portola Pharmaceuticals to study a number of drugs that reverse the effects of its blood-thinner Xarelto, completing the study in the second half of this year.

g) In February, GRIFOLS celebrated 25 years of its Prolastin as augmentation therapy for treatment of alpha(1)-antitrypsin deficiency.

5 Commercial production in Georgia is expected to commence in 2018, with the new plasma fractionation facility adding up to 3.0 million litres of new capacity annually, and with the flexibility and infrastructure to expand further to support growth in world demand. Baxter announced in July that it had entered into a manufacturing services agreement with Sanquin that would it (Baxter) with up to 1.6 million litres of incremental plasma fractionation capacity annually. Baxter will pay Sanquin a fixed fee to fractionate plasma supplied by Baxter into bulk material for Gammagard Liquid (marketed as KIOVIG outside the US and Canada), and Flexbumin (human albumin). Sanquin will also indertake filling and finishing for IMMUNATE. The initial term of the agreement is 10 years, with production beginning in 2014 and Sanquin reaching the full 1.6 million litres a year by the end of 2016.

6 Baxter has established an exclusive 20-year partnership with Hemobras (Empresa Brasileira de Hemoderivados e Biotechnologia). Baxter will be the exclusive provider of Brazil’s recombinant FVIII treatment over the next 10 years while the companies work together on a technology transfer to support development of local manufacturing capacity by Hemobras.
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) The US, along with much of the northern hemisphere, has experienced a severe flu season. Boston Mayor Tom Menino said "I am declaring a public health emergency in the city of Boston."

b) Two reports in the January 17 issue of The New England Journal of Medicine bring to public attention the fact that Lyme disease is not the only infection humans can acquire from deer ticks. *Borrelia miyamotoi* may also be a cause for concern7.

c) CSL Behring awarded $US 78,750 in Local Empowerment for Advocacy Development grants to patient advocacy organizations in New York and Ohio, and to the American Plasma Users Coalition.

Other

d) The UK National Health Service recently issued an appeal for O negative blood after a major outbreak of norovirus sparked a decrease in donations.

e) Thailand is to establish a local plasma fractionation plant. It is a collaborative venture between four major organisations, the National Health Security Office, the Thai Food and Drug Administration, the Government Pharmaceutical Organisation and the Thai Red Cross Society. The facility is expected to produce albumin; intravenous immunoglobulin (IVIG); and Factor VIII. It is expected to be operational by 2015. The plant will have a production capacity of over 200,000 litres of plasma per year. In July 2011, the Thai Red Cross signed a memorandum of understanding with Green Cross Corporation, a Korean pharmaceutical firm, covering the transfer of technological know-how to manufacture the three products. The two parties have now signed an agreement on the construction of the plant.

f) Health Canada is reported to have approved an application by Canadian Blood Services (CBS) to change their blood donor screening model after a two-year pilot project. Now "multi-skilled clinic employees" can perform all clinic functions – from accessing a vein to donor screening – instead of a registered nurse.

a) A study of narcolepsy rates in six European countries before and after 2009 H1N1 pandemic vaccine campaigns confirmed that the countries which first reported an increase- Finland and Sweden- were not alone. A rise was also found in Denmark8. The countries in the study were Denmark, Finland, Italy (Tuscany and Emilia Romagna regions), the Netherlands, Sweden, and the United Kingdom. Finland and Sweden recommended the pandemic vaccine for the whole population. The others recommended the vaccine mainly for people in particular risk groups. The authors noted that in Finland and Sweden there were mismatches with age-specific diagnostic rates and pandemic vaccine coverage rates so factors other than the vaccine may have been associated with the increase in narcolepsy cases identified by health officials. The most common vaccine for H1N1 used in Europe was

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8 The study was conducted by members of the Vaccine Adverse Events Surveillance and Communication (VAESCO) consortium based on a request from their partners at the European Centre for Disease Prevention and Control (ECDC). Wijnans L, Lecomte C, de Vries C, et al. “The incidence of narcolepsy in Europe: before, during, and after the influenza A(H1N1)pdm pandemic and vaccination campaigns”. *Vaccine* 2013 Feb;31(8);1246-54
5. Safety and patient blood management

*We follow current issues in patient safety.*

a) Research led by Ryan Nofziger⁹, of Nationwide Children's Hospital in Columbus, Ohio found that among critically injured paediatric patients, a blood transfusion suppresses the immune system, and this is exacerbated when older blood is used.

b) A paper¹⁰ published online January 24 in the *Canadian Journal of Anesthesia* reported that hip and knee replacement patients who were transfused had longer hospital stays as did coronary artery bypass graft patients who were transfused. The risk of infection doubled in transfused patients. The author called anaemia a “silent killer”, as low oxygen levels in vital organs could lead to heart attacks, strokes and kidney failure. The key is early diagnosis and treatment of anaemia before surgery.

c) In 2002 the Ontario government established the Ontario Transfusion Coordinators (ONTraC). ONTraC figures published in January show the number of patients requiring blood transfusions after undergoing knee surgery fell from 24.5 per cent in 2002 to 10.1 per cent in 2011. The number requiring transfusions after undergoing coronary artery bypass grafting fell from 60.2 per cent to 25.2 per cent in that time.

d) A recent study found that tiny premature babies who were given iron supplements did not do any better than those who were not – there were no differences in mortality, transfusions or red blood cell count¹¹.

e) Masimo told the annual meeting of the Society for Technology in Anesthesia that using its haemoglobin monitoring technology to reduce the number of transfusions during surgeries could save hospitals up to $US 1,000 per patient. The company outlined its study of 106 neurosurgery patients monitored using the noninvasive continuous total haemoglobin measuring technology. The group had a 56 per cent reduction in multi-unit red blood cell transfusions and a 47 per cent reduction in the average number of red blood cell units used, compared with patients monitored without the Masimo technology. The company said the technology helped the surgical team initiate transfusions 82 per cent more quickly.

f) With some recent discussions associating blood transfusion with patient mortality, it is worth recalling an article in May 2012 which concluded that for patients undergoing cardiac surgery bleeding contributes to mortality through mechanisms unrelated to blood transfusion¹².

g) A recent study found that patients transfused with red blood cells after nonvariceal upper gastrointestinal bleeding are at an elevated risk for rebleeding¹³.

h) Researchers reported that “Administration of [tranexamic acid] TXA twice reduced postoperative blood loss after [total knee arthroplasty] TKA, and TXA was not

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¹⁰ By Dr Gregory Hare of St Michael’s Hospital

¹¹ The study was led by Dr Tiffany A. Taylor and Dr Kathleen A. Kennedy, from The University of Texas Health Science Center within Houston Medical School. It was published January 21 2013 in the journal *Pediatrics*.


associated with the risk of deep vein thrombosis or pulmonary embolism…….Further, administration of TXA twice may eliminate the need for blood transfusion during TKA."14

i) Researchers led by Dr Andreas Greinacher, of Greifswald University Hospital in Germany, have concluded that the increase in risk of blood-borne infection from platelet transfusions sourced from multiple donors rather than single-donor apheresis may not be as great previously thought15. Data from more than 12,000 patients suggested that the total increase in risk associated with pooled-donor platelets -- when receipt of other blood products was also factored in -- was only about 44 per cent. That differs from customary estimates which assume 100 per cent increase in risk associated with each donor beyond the first whose platelets are included in pooled-donor platelet units.

j) Dr. Simon Stanworth spoke at the annual meeting of the American Society of Hematology on the Trial of Prophylactic Platelet Transfusion (TOPPS), funded by National Health Service Blood and Transplant. He said "This multicenter trial has not shown that a no-prophylaxis platelet transfusion policy is noninferior to prophylaxis." It is expected that the wide use of prophylactic platelet transfusions in adults with haematologic malignancies and severe thrombocytopenia will be narrowed following this randomized, international trial. Dr. Stanworth drew attention to the need for new strategies to minimize bleeding in these patient groups, and suggested that antifibrinolytics and tranexamic acid should be explored.

k) A study conducted by the UK's blood transfusion service suggested that red blood cells treated with the P-Capt prion removal filter do not increase the risk for alloimmunization or transfusion reactions.

l) The Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) study found16 that transfusion in the 10 days preceding low- or medium-risk elective surgery significantly reduced the risk for clinically significant complications in patients with haemoglobin SS subtype or Sβ thalassaemia sickle-cell-disease subtypes. The rate of serious adverse events was also significantly reduced with preoperative transfusion, said Jo Howard (Guy's and St Thomas' Hospital, London) and co-authors.

m) A Danish study found that people with the AB blood type showed a higher risk of venous-blood clotting compared with those with the O blood type. In the AB blood type, both A and B factors appear on red blood cells. This correlates with increased levels of von Willebrand factor in the blood, and this concentration promotes clotting. The authors say that compared with people with type O blood, individuals with a non-O blood type have 25% to 30% higher plasma levels of von Willebrand factor17.

n) At the Society for Maternal-Fetal Medicine’s annual meeting in San Francisco researchers reported results of a study performed at Dignity Health, the fifth largest health care system in the US, with 31 obstetricsl units. These showed that the implementation of a standardized comprehensive maternal haemorrhage protocol significantly reduced blood product utilization and resulted in a 45 per cent reduction in puerperal hysterectomy. The approach included having a dedicated haemorrhage cart allowing immediate availability of all the commonly used items in the event of a maternal haemorrhage18.

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16 Findings were published in The Lancet.
17 The study is published in the Canadian Medical Association Journal.
18 Nearly 21,000 deliveries were included in the study, which found standardised protocols reduced red blood cell units used by 22.4 per cent, platelet units by 31.4 per cent, and the need for cryoprecipitate by 58.1 per cent. There was an 88 per cent reduction in the number of patients transfused with four or more units of blood.
Australia is to allow beef imports from Europe, a decade after it banned meat from countries with a history of mad cow disease. Food Standards Australia New Zealand has decided that consumers face a “negligible” risk of catching BSE from eating Croatian or Dutch beef\textsuperscript{19}. Eight other countries, including Mexico, Turkey, Brazil and Lithuania, have applied for approval to sell their beef in Australia. Food Standards is conducting desk assessments.

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) Researchers\textsuperscript{20} have described a process using sickle-shaped red blood cells to select and target oxygen deprived cancer tumours in mice and block the blood vessels that surround them. 

b) Scientists already knew of two major genes that partially regulated levels of von Willebrand factor in the blood. However, they explained only a small part of the inherited differences in von Willebrand factor levels between people. Now a study of twins at the University of Michigan has identified the specific parts of the genome responsible for levels of this key substance in blood clotting\textsuperscript{21}.

c) Researchers at Northwestern University have produced blood platelets from stem cells in the laboratory environment. Their challenges now are the efficiency and scalability of the production.

d) The Worldwide Network for Blood and Marrow Transplantation reported that one million hematopoietic stem cell transplants have been performed worldwide. The first was reported by the late E. Donnall Thomas in 1957. He received the Nobel Prize in 1990 for pioneering the use of this innovative approach to treat leukemia and other life-threatening diseases. More than 70 malignant and non-malignant diseases are now routinely treated with HSCTs.

e) \textit{TechNewsDaily} reported that rhæsus monkeys given a patch of microneedles coated with a DNA vaccine had a 140-fold higher gene expression response than monkeys that received the vaccine through an injection.

f) Research from the Hotung Molecular Immunology Unit at St George’s University in London has found that tobacco plants can be genetically modified to produce antibodies against the rabies virus. It is hoped this finding can deliver a rabies treatment which will be less expensive than human rabies immunoglobulin\textsuperscript{22}.

g) Seven European drugmakers\textsuperscript{23} are to pool their research efforts with academic scientists\textsuperscript{24} and smaller companies in a new 196 million euros project backed by the European Union. Pharmaceutical companies will contribute at least 300,000 chemical compounds from their in-house collections. The US National Institutes of

\textsuperscript{19} The Food Standards assessment of the Dutch application found 88 cases of BSE had been detected in The Netherlands since 1997 and rated The Netherlands as having a "negligible BSE risk". It rated Croatia as a "controlled BSE risk".

\textsuperscript{20} Reporting in the January 9 2013 journal, \textit{PLoS One}.

\textsuperscript{21} Online report December 24 in the \textit{Proceedings of the National Academy of Sciences}.

\textsuperscript{22} The study was published in \textit{The FASEB Journal}.

\textsuperscript{23} Bayer, AstraZeneca, Sanofi, Lundbeck, Merck KGaA, UCB and Janssen, the European arm of Johnson & Johnson.

\textsuperscript{24} From universities in Germany, Britain, the Netherlands and Denmark.
Health (NIH) last May launched a similar project to test experimental drugs provided by manufacturers and other public-private drug research partnerships.

h) Researchers at Georgia Tech are attempting to develop artificial blood platelets laced with chemicals that could be delivered by an injector device the size of an iPhone. Some wounded soldiers may be able to treat themselves, initiating the clotting process.

i) With IVig being trialled as a treatment for Alzheimer’s disease, the NBA, concerned about market pressure if the trial result is positive, takes an interest in research on other possible treatments for Alzheimer’s, on the identification of genetic predisposition for the disease, and on improvements in diagnostic tools. Some recent developments are outlined in an appendix to this article.

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-born diseases

b) Dengue fever is caused by any one of four different but related viruses. A US government-funded Phase I trial of a new vaccine was involved 112 healthy adults. The purpose was to see whether the experimental vaccine, composed of live but weakened viruses, was not only safe but also stimulated an antibody response against all four dengue types. Researchers at Johns Hopkins School of Public Health in Baltimore formulated four different versions of the combination vaccine, and tested a separate vaccine in each of four groups. All of the vaccines produced an antibody response, but one, called TV003, induced an immune response against all four dengue viruses in 45 percent of participants. An immune response to three viruses was seen in about 90 percent of participants. The experimental vaccine will face more safety and effectiveness testing in Phase II and Phase III trials, with scientists testing how well it creates an immune response against all four dengue viruses in Brazil and Thailand, where dengue is endemic.

c) The count of dengue cases in Cairns this summer reached 55 by early February. A report from Cairns on 31 January had said residents were refusing to allow the Dengue Action Response Team to treat their homes; all the recent confirmed cases of dengue fever occurred at houses that had not been treated by DART.

Influenza

d) Forty flu researchers globally decided to lift their voluntary moratorium on studies into the airborne transmission of the H5N1 strain of avian-flu. Their moratorium from January 2012 followed an outcry about the dangers to public health and safety inherent in their work. Professor Lord May, a former chief scientist to the UK government and past president of the Royal Society, said the moratorium should continue on the research which is directed towards making the virus more infectious to humans. “As this research becomes more widely known and disseminated, there is the opportunity for evil people to pervert it. My other concern is the statistics of containment are not what they ought to be,” Lord May told The Independent.
e) The severity of the North American flu season was such that both Canada and the US faced apparent shortages of oseltamivir (Tamiflu), with release from government stockpile one solution; sale of Roche's reserve stock in different packaging was another. In the US local shortages of flu vaccine, particularly for young children, were reported.

f) A number of countries have had massive official bird culls because of the detection of avian influenza in their flocks. Mexico culled some 300,000 poultry when H7N3 avian influenza was detected in January.

g) The US Biomedical Advanced Research and Development Authority (BARDA) established Emergent Biosolutions in innovative manufacturing with an eight-year, $US 220 million contract to advance development of chemical, biological, radiological and nuclear medical countermeasures and domestic pandemic influenza vaccine, among other things. Emergent has acquired the exclusive right to manufacture and sell VaxInNate's next-generation flu vaccine. VaxInNate uses TLR technology to produce vaccines as soluble biopharmaceutical grade proteins in bacteria. These can be developed and manufactured quickly and on a large scale.

h) The FDA approved for use in adults Protein Sciences Corporation's Flublok, a trivalent influenza vaccine made using an insect virus expression system and recombinant DNA technology. Karen Midthun, director of the FDA's Center for Biologics Evaluation and Research, said that the new technology "offers the potential for faster start-up of the vaccine manufacturing process in the event of a pandemic, because it is not dependent on an egg supply or on availability of the influenza virus". Flublok contains three recombinant proteins to help protect against two influenza virus A strains, H1N1 and H3N2, and one influenza virus B strain.

i) A small study suggested that a gene variant prevalent in people of Chinese descent may partly explain the higher incidence of severe H1N1 infections in some populations. It did not suggest that the variant meant greater susceptibility to infection, but rather a greater likelihood of experiencing severe symptoms. The analysis considered the genotypes of 83 patients in Beijing hospital during the 2009 H1N1 pandemic. One variant of a particular gene was associated with a six-fold increase in incidence of severe infection. Of those with respiratory or renal failure 69 per cent had the variant, compared with only 25 per cent of those with milder symptoms such as fever, headache and lethargy. Researchers assume the variant lessens the capacity of one specific protein to deal with the flu virus. Nearly a quarter of Han Chinese (the most prevalent ethnic group in China) carry the variant, compared with fewer than 1 per cent of Caucasians.

j) The US NIH granted researchers at the University of Georgia $US 1.1 million to refine a method to fingerprint the flu virus with laser beams.

Other

k) Scientists at King's College London have shown how to deliver a dried live vaccine to the skin without a traditional needle, and that this technique can kick-start the immunising properties of the vaccine. The research team used a silicone mould to create a microneedle array. The team formulated a dried version of a live modified adenovirus-based candidate HIV vaccine in sugar (sucrose) and used the mould to create the microneedle array. They found that the dried live vaccine remained stable and effective at room temperature. The sugar dissolved when the microneedle array was inserted in the skin. A report on this early study was published in Proceedings of the National Academy of Sciences in January.

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25 In 2011, Emergent contracted to earn up to $US 1.25 billion over 5 years for providing 44.8 million doses of its BioThrax anthrax vaccine to the US government.

26 The work was published 29 January 2013 in the online journal Nature Communications.
l) The Lancet reported on 4 February that the promising new tuberculosis vaccine MVA85A failed to offer extra protection compared with the current vaccine when tested on infants. This experimental vaccine is designed to boost immune responses already initiated by the only existing vaccine, BCG (Bacille Calmette-Guérin). BCG was first used in 1921. It is given routinely to babies in countries with high rates of TB to prevent severe disease. BCG wears off after a few years and it does not protect against pulmonary TB, which is the form most usually seen in adolescents and adults. In earlier human trials, MVA85A produced a powerful immune response in adults. But now, in a randomized Phase II trial carried out on healthy, BCG-vaccinated South African infants, researchers saw only a negligible improvement in protection.

m) The US has had its worst year for whooping cough in six decades, and researchers have discovered some cases have been caused by a germ resistant to the vaccine. This new germ had already been reported from Japan, France and Finland.

n) Cangene’s antitoxin for botulism is safe and the benefits exceed the risks, FDA staff said in a report ahead of a meeting of agency advisers to discuss the product. Cangene, based in Winnipeg, Canada, currently supplies the antitoxin to the U.S. government under an exemption for use in an emergency situation. The company is now seeking FDA approval based on safety studies in humans, as well as efficacy studies in guinea pigs and monkeys. The U.S. government awarded Cangene in 2006 a contract now valued at $476 million for late-state development of the antitoxin and 200,000 doses, according to the arm of the Department of Health and Human Services responsible for the nation’s approach to preparing vaccines and drugs for national emergencies. A human dose used in monkeys “statistically increased survival” and median time-to-death,” FDA staff wrote. The FDA may decide on Cangene’s application for approval by March 20, according to the staff report.

o) An analysis published in the journal The Lancet Infectious Diseases says the annual cost of Chagas disease globally is about $US 7 billion. Chagas is widespread in Latin America, but about 300,000 Americans, mostly Texans, are thought to carry the parasite Trypanosoma cruz, and Europe and other destinations of Latin American emigrants are also affected. Chagas disease can be transmitted through blood

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27 The disappointing result in infants may not mean that the vaccine will not work in adults. MVA85A is being developed by Oxford University researchers with support from Aeras, the Wellcome Trust, the European Commission and the Oxford-this summer Emergent Tuberculosis Consortium, a joint venture between Oxford and Emergent Biosolutions created to make the vaccine. It is one of 16 vaccines in human clinical trials. The pace of development has quickened in the last few years with the emergence of drug-resistant TB. Because treating TB is a long process, many patients do not complete the treatment and this leads to drug resistance. Extensively drug-resistant TB, which resists the most highly effective drugs, was reported in nearly 80 countries in 2011. Totally resistant TB, where no effective drugs are available, is being reported from India. MVA85A is a modified version of a smallpox virus that has been rendered harmless but can still evoke an immune response. Researchers added a component of TB bacteria to train the immune system to fight infection. Two other vaccines are worth mentioning—one backed by Aeras and GlaxoSmithKline and the other by Aeras and Crucell (owned by Johnson and Johnson). The Crucell vaccine most resembles MVA85A, based on a strategy which primes the immune system with the BCG vaccine and then boosts it. Crucell uses a cold virus to transport bits of the TB bacteria or antigen into the body. But Crucell uses three TB antigens. The GSK vaccine, M72, relies on an adjuvant to boost the immune system—coupled with proteins from the TB virus

28 In the study on the monkeys, 14 of 30 that received the Cangene antitoxin survived compared to none out of 30 in a placebo group that had been intoxicated with botulism.

29 Bruce Y Lee, Kristina M Bacon, Maria Elena Bottazzi, Peter J Hotez, “Global economic burden of Chagas disease: a computational simulation model” The Lancet Infectious Diseases, Early Online Publication, 8 February 2013 doi:10.1016/S1473-3099(13)70002-1
transfusions and during pregnancy. Dr Peter J Hotez, one of those who worked on
the study, said of the US: “There’s an astonishing lack of awareness with doctors
about this disease,” Hotez says. “They misdiagnose it as a form of cardiomyopathy.
Unless you specifically look for it, you won’t find it.”
p) Hendra virus has been detected in flying foxes (bats) in South Australia.
q) A Legionnaires’ disease outbreak in Victoria was thought to emanate from a cooling
tower in Footscray.
r) There have been several deaths in Australia from listeriosis blamed on soft cheese
produced by a firm operating in Gippsland.
s) An eight year old boy contracted Australian bat lyssavirus in North Queensland.
t) In mid-February Britain’s Health Protection Agency said a new coronavirus related to
SARS may have spread between humans. They confirmed the eleventh case
globally in a patient who they suspect caught it from a family member. The new virus
was identified in 2012 in the Middle, East and the ten people previously known to
have been infected had all travelled to Qatar, Saudi Arabia, Jordan or Pakistan. This
eleventh patient is a UK resident with no recent travel to any of those countries but
who had close personal contact with an earlier case. In Saudi Arabia last year, four
members of the same family fell ill and two died. The virus can cause acute
pneumonia and kidney failure. Of the eleven cases to date, five people have died.
WHO has advised countries to test any people with unexplained pneumonia.
u) Viruses related closely to the novel coronavirus that appeared in the Middle East in
2012 have been found in a number of species of bats found in Europe, Russia,
Africa, parts of Asia and the Middle East.30

Appendix: Alzheimer’s Disease Research
As mentioned earlier, with IVIg being trialled as a treatment for Alzheimer’s disease, the
NBA – concerned about market pressure if the trial result is positive- takes an interest in
research on other possible treatments for Alzheimer’s, on the identification of genetic
predisposition for the disease, and on improvements in diagnostic tools.

a) Can looking after cardiovascular health with beta blockers reduce the risk of
Alzheimer’s disease? Over 21 years, 774 elderly Japanese-American men
participated in a Honolulu-Asia Aging Study. After the men died, researchers
performed autopsies. The study31 found that men who had received beta blockers
as their only blood pressure medication had fewer abnormalities in their brains than
those who had not been treated for their hypertension, or who had received other
blood pressure medications. Study participants who had taken beta blockers alone
or in combination with another blood pressure medication had significantly less
shrinkage in their brains.
b) AstraZeneca’s Neuroscience Innovative Medicines Unit has exclusively licensed
rights to compounds developed by Vanderbilt University’s Center for Neuroscience
Drug Discovery that act on a certain brain receptor, and may be potential treatments
for psychosis and other psychiatric symptoms associated with diseases like
Alzheimer’s and schizophrenia. The early-stage drug compounds that are part of the
agreement were earlier supported by the National Institute of Mental Health.
c) EnVivo Pharmaceuticals announced the initiation of a Phase II clinical trial of its
selective gamma secretase modulator EVP-0962 in healthy volunteers and in

30 Annan A, Baldwin HJ, Corman VM, Klose SM, Owusu M, Nkrumah EE et al:” Human
beta-coronavirus 2c EMC/2012-related viruses in bats, Ghana and Europe”. Emerg Infect Dis Mar
2013 can be found at > <http://wwwnc.cdc.gov/eid/article/19/3/12-1503_article.htm
31 American Academy of Neurology’s 65th Annual Meeting, January, 2013. Study author Lon White
of the Pacific Health Research and Education Institute in Honolulu
volunteers with mild cognitive impairment or early Alzheimer's disease (AD). The Phase II trial is a randomized, double-blind, dose escalating study to assess the safety, tolerability, pharmacokinetics and effects of EVP-0962 on cerebral spinal fluid amyloid concentrations.

d) Amorfix Life Sciences and QPS Holdings have partnered to develop and validate the diagnostic EP-AD assay for use as a biomarker, useful in AD related clinical studies, and also – if FDA approval is achieved- as an FDA-early-stage AD diagnostic. Cerebral spinal fluid from AD patients at different stages of disease will be analyzed.

e) Studies done in the 1980s revealed a decrease in the rate of glucose metabolism in the brains of patients with AD\textsuperscript{32}. This hypometabolism occurs early in the disease process and is found in the same areas of the brain that show amyloid deposits and cell loss\textsuperscript{33}. Recent results suggest that addressing underlying defects in glucose metabolism or insulin signalling may be a fruitful avenue for AD therapy\textsuperscript{34}. One suggestion is that brains with AD have become resistant to insulin, and observation suggests, intranasal insulin rapidly improves cognition in AD patients\textsuperscript{35}. Other studies have shown ketone bodies improve cognitive performance in patients with mild cognitive impairment (MCI) or mild-to-moderate AD\textsuperscript{36}.

f) Researchers at Weill Cornell Medical College have found in mice studies that amyloid peptides damage the blood vessels that supply the brain with blood—thus accelerating cognitive decline in AD\textsuperscript{37}. This is the first research to pinpoint the role that the innate immunity receptor CD36 plays in damaging cerebral blood vessels and promoting the accumulation of amyloid deposits in them, a condition called cerebral amyloid angiopathy or CAA. Importantly, the study provides the basis for targeting CD36 to slow or reverse some of the cognitive deficits in AD and to increase the effectiveness of amyloid immunotherapy.

g) Dr Barry Reisberg, clinical director of the New York University School of Medicine’s Silberstein Aging and Dementia Research Center, created a 7 stage framework for Alzheimer’s disease. (See www.alz.org)

h) Researchers from the Center for Alzheimer Research and Treatment at Brigham and Women's Hospital announced the selection of solanezumab as the first therapeutic drug to be evaluated in the Anti-amyloid Treatment in Asymptomatic Alzheimer's disease prevention clinical trial. The trial will enrol 1000 people aged 70 to 85 with evidence of amyloid in their brains detected by PET scans but who do not show clinical symptoms of the disease. The US National Institutes on Aging, the lead NIH institute on Alzheimer's research, announced partial funding for the three-year trial. The trial will be facilitated by the Alzheimer's Disease Cooperative Study (ADCS), a consortium of academic Alzheimer's disease clinical trial centers, led by Dr Paul Aisen of the University of California at San Diego. Eli Lilly’s solanezumab has already shown a modest clinical benefit in the mild Alzheimer's disease patients in Phase III


\textsuperscript{34} Henderson ST. Ketone bodies as a therapeutic for Alzheimer's disease, in Emerging Drugs and Targets for Alzheimer's Disease: Volume 1: Beta-Amyloid, Tau Protein and Glucose Metabolism A. Martinez, Editor. 2010


\textsuperscript{36} Krikorian R, et al. Dietary ketosis enhances memory in mild cognitive impairment. \textit{Neurobiol Aging}. 2010. Online; and


Their study was published February 4 online in the \textit{Proceedings of the National Academy of Sciences}. 13
trials. This study questions whether starting treatment earlier and treating longer will slow cognitive decline.

i) Intellect Neurosciences announced in February that it has begun in vivo proof of concept studies for its monoclonal antibody, TauC3, in a preclinical model of AD.

j) The FDA in February issued draft guidance to assist companies developing new treatments for patients in the early stages of Alzheimer’s disease, before the onset of noticeable (overt) dementia. “The scientific community and the FDA believe that it is critical to identify and study patients with very early Alzheimer's disease before there is too much irreversible injury to the brain,” said Russell Katz, M.D., director of the Division of Neurology Products in the FDA's Center for Drug Evaluation and Research. “It is in this population that most researchers believe that new drugs have the best chance of providing meaningful benefit to patients.”

k) European regulators approved the use of a radioactive imaging agent from Eli Lilly, Amyvid, which binds to beta-amyloid plaques and causes them to show up on positron emission tomography, or PET, brain scans. The presence of the plaques may help indicate that a patient with cognitive problems has AD, though the diagnosis will not be definitive. Amyvid was approved in the US in April 2012.

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38 Guidance for Industry, Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease explains the FDA’s current view of how researchers can identify and select patients with early Alzheimer's disease, or those who are at risk of developing the disease, for participation in clinical trials.

39 In the US at the end of January a Medicare advisory panel was sceptical whether radioactive imaging agents like Amyvid can improve outcomes for people with early symptoms of memory loss. This lack of confidence could deter reimbursement.