NATIONAL BLOOD AUTHORITY
AUSTRALIA

HORIZON SCANNING

INFECTIOUS DISEASES

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Introduction

Infectious diseases pose a range of potential risks to the safety and security of Australia's blood supply. At the extreme end, there is a risk that a new unknown infectious disease could result in extensive contamination of the blood supply resulting in numerous cases of patient harm. An infectious disease incident or outbreak, such as a pandemic influenza event, has the potential to restrict the Australian donor pool, either because of imposed restrictions on donors to reduce the risk of blood contamination or because there is a dramatic reduction in the availability of healthy donors. The speed and gravity of the impact of an infectious disease incident on the National blood supply is likely to vary by product, the nature of the disease threat and geographical spread of the disease outbreak.

Ongoing monitoring of infectious disease trends, or horizon scanning, provides a valuable tool to anticipate and mitigate an emerging risk.

Aim

The aim of this report is to provide an overview of the status of risks of emerging diseases to the blood sector.

Scope

The Report provides an overview of trends identified from NBA horizon scanning website reports since July 2013. The background information from the reports is included as **Appendix 1**. These reports include only a selection of matters considered of greatest relevance to Australia, eg with dengue they focus mainly on the experience in countries in our own region, rather than Latin America; and offer occasional snapshots rather than a continuing story. The Report is structured in three main parts:

Overview of key trends

- Disease specific observations
- Strategic questions arising from the Report
- The Report does not identify recommended actions in relation to observed trends or risks.
- Overview of Key Trends
- The review of horizon scanning reports since July 2013 emphasise the following general trends:
- the spread of so-called tropical diseases as mosquito vectors spread, (whether it be from climate change or not);

- the continuing threat from ever-changing flu viruses, speculation on which one will cause the next pandemic, and whether anything can be done to slow its emergence or limit its effects;
- the emergence of new diseases (maybe zoonoses such as Middle East Respiratory syndrome-novel coronavirus), their transmissibility and hence pandemic potential;
- the uncertainty of the degree of threat to blood supplies by diseases known to be transmissible or suspected of being transmissible through transfusion;
- continuing infections in the developed world with diseases such as measles and whooping cough for which successful prevention through immunisation has long been available;
- sexually transmitted diseases whose incidence in Australia as elsewhere has been rising; and
- the emergence of Ebola Virus Disease (EVD) as a disease of newest significant concern.

Disease Specific Observations

Disease specific observations identified for specific comment include the following:

- Mosquito-borne diseases: dengue, chikungunya, Zika, malaria, Ross River virus and West Nile virus
- Influenza: strains, spread, prevention and treatment
- Mers-CoV (Middle East respiratory syndrome, novel coronavirus)
- Ebola Virus Disease (EVD)
- Other diseases of interest, including: Chagas disease, Variant Creutzfeldt-Jakob disease (vCJD), Human immunodeficiency Virus (HIV), Childhood Diseases: Measles, Mumps and Whooping Cough (Pertussis), Tuberculosis (TB), Polio, Hepatitis and Lyme Disease.

Mosquito-borne diseases

Diseases carried by mosquitoes are not a public health issue confined to countries round the equator. Species of mosquito which carry so-called "tropical diseases" are travelling to, and surviving in, other regions.

Dengue

Major outbreaks of dengue have been continuing to occur round the warmer regions of the world including countries from which Australia receives many returning travellers or visitors, such as Papua New Guinea, Indonesia, Malaysia[1], Singapore, Fiji[2] and India. Brazil, which had over one million cases of dengue reported last year, is to host football's World Cup during the dengue season this year. The Government of Hong Kong tested its preparedness for the possible community outbreak of dengue fever on 3 March in Exercise Coral", organised by the Centre for Health Protection of the Department of Health in collaboration with government departments.

1 Malaysia had 18,047 dengue cases and 36 deaths reported for the first two months of 2014 compared with 4,250 cases and eight deaths for the first two months of 2013. Experts are predicting 60,000 cases this year. The strain currently circulating is DEN-2, a more virulent strain than usual

2 The Secretariat of the Pacific Community, or SPC, says the number of dengue fever outbreaks in the region over the past year is unprecedented. Four types of dengue fever have circulated the region at different times. It is two decades since dengue three circulated widely so people have been particularly susceptible to it. New Zealand is concerned that its northern areas, including Auckland, may experience more dengue cases. Australia has donated $A1.5 to help Fiji fight dengue.

Northern Australia is at risk of frequent dengue outbreaks, as it is host to mosquitoes which can transmit the virus[3]. In Far North Queensland, for instance, recent outbreaks have included both returning travellers and people who have not left the country. The public health emphasis has been on eliminating mosquito breeding sites, while the research emphasis has included infecting the relevant mosquitoes with wolbachia bacteria.

Dengue has a significant mortality rate. There are several strains, and patients who have previously survived infection with one strain may die if infected with another. There is no definitive vaccine for dengue, although some are in clinical trials.

Chikungunya

This disease emerged in Africa but has spread widely. The Caribbean has probably been the most reported "naïve" site this year, where the virus has taken a firm hold. The US is expecting to be its next landfall, probably Texas. Australia's near neighbours have been experiencing dengue and chikungunya outbreaks co-incidentally, and commonality of some symptoms has made snap diagnosis difficult in some cases. Chikungunya is at the moment considered less lethal than dengue.

Zika

Making headlines this year has been the Zika virus. Zika fever is a disease of arboviral origin, expanding its geographic area. It usually presents as an influenza-like illness with skin rash[4]. The virus is mosquito borne. In some of Australia's near neighbours, it has been circulating along with dengue and chikungunya, with some common symptoms.

Malaria

Knowledge continues to be gained by researchers of the malaria parasite and its functioning, as a basis for developing vaccines to produce immunity. Despite the progress through funding, research and clinical trials, the world cannot yet expect soon to be malaria-free.

Ross River Virus

This circulates in Australia, along with Kunjin virus, Murray Valley encephalitis, and Barmah Forest virus.

West Nile Virus (WNV)

West Nile virus has been a significant concern in the US recently, because the proportion of cases developing serious neurological complications has been rising.

3 The Aedes aegypti mosquito, which spreads dengue fever and other diseases, recently reappeared round Darwin Harbour, after it was eradicated in 1969, and Asian tiger mosquitoes (Aedes albopictus) have also been trapped. They are thought to have arrived on cargo vessels. The port area was sprayed and "fogged".

4 Zika is asymptomatic in 80 per cent of cases. When the infection is symptomatic it may be mistaken for other arboviral infections like dengue or chikungunya. Symptoms include a low grade fever, arthralgia, myalgia, headache, conjunctivitis and skin rash. Post-infection weakness is usual.

Influenza: strains, spread, prevention and treatment

The major concern round the globe in the last few months has been A(H7N9) which broke out in China and appears to be associated with live poultry markets. However for a number of countries A(H5N1) continues to kill humans who have been associated with sick poultry.

Both farmed poultry and wild bird stocks have seen major culls round the world because of illness.

The question of mutation to facilitate human to human transmission remains a concern. Genetic reassortment occurs in nature, and one of the issues under discussion is whether, since this reassortment is facilitated by mixing species at live poultry markets, such markets should be phased out. The other benefit which might occur with this is limiting the opportunities for humans to become infected with avian viruses.

Some rearrangement of the influenza virus can occur in laboratories, and so-called "gain of function" studies have been a hot topic in recent times, as governments contemplate curbing scientific freedom to protect public health.

Vaccines for A(H7N9) and A(H5N1) have been popular projects in the last year, and the development of a universal flu vaccine remains a hope.

Mers-CoV (Middle East respiratory syndrome, novel coronavirus)

MERS–CoV is a relative of SARS, severe acute respiratory syndrome, also caused by a coronavirus. SARS was first reported in Asia in February 2003 and spread to more than two dozen countries in North America, South America, Europe, and Asia before the outbreak was contained. MERS emerged in the Middle East, affecting Saudi Arabia most of all. Camels are believed to be the source of the virus, although some researchers think bats may have a role. There appears to be some human-to-human transmission, particularly in healthcare settings and to some extent families. Like SARS, it has a high morbidity rate.

Ebola Virus Disease (EVD)

This is probably the emerging infectious disease of most concern the moment. There is a very high fatality rate, no vaccine, no widely recognised successful treatment and worst of all it seems more difficult to contain this time round. The priority in healthcare is to identify patients with Ebola symptoms and isolate them. Unfortunately Ebola can take up to three weeks before symptoms appear, then it kills very quickly from uncontrollable internal and external bleeding[5].

Ebola was first discovered in 1976 in what is now Democratic Republic of Congo. Until the current outbreak was noticed in Guinea on 7 February this year, there had been only around 2,200 cases of recorded, of which 1,500 had been fatal. The current outbreak has been identified as the virulent Zaire strain of the Ebola virus, the most deadly of the five known species. The virus is understood to reside primarily in bats between its outbreaks in humans[6].

5 The initial symptoms resemble those of other diseases endemic to West Africa, such as malaria and cholera, which can slow diagnosis. The virus initially causes raging fever, headaches,and muscle pain, before moving into more severe phases of vomiting, diarrhoea and fatal haemorrhaging.

6 Bats host hundreds of infectious agents, many of which affect human and/or animal health. Bats also are susceptible to diseases. The INFECTIOUS DISEASES OF BATS SYMPOSIUM, will be held 26-27 JUNE 2014, in FORT COLLINS at Colorado State University. The symposium will focus on the relationships of bats and the infectious agents for which they serve as hosts, the zoonotic cycles and ecology of bat-borne infectious agents, the molecular mechanisms of immune evasion and pathogenesis, and the clinical manifestations of human and veterinary diseases caused by infectious agents transmitted by bats. The symposium will follow on from the annual meeting of the American Society for Virology, also at Colorado State University.

Ebola outbreaks have so far been rare and have mostly arisen in rural areas of poor African nations, so Ebola has not attracted much attention from profit-seeking pharmaceutical companies. Research has been largely funded by the US government. The US Centers for Disease Control and Prevention (CDC) sees Ebola as so deadly and so contagious that it poses a risk to national security. The CDC lists the virus as a Category A bioterrorism agent, alongside anthrax and smallpox

Canadian company Tekmira Pharmaceuticals Corp. (TKM), began its first human trial of its drug in January financed by the US Department of Defense[7]. Mapp Biopharmaceutical Inc., of San Diego, is developing an antibody cocktail, along with the US Defense Advanced Research Projects Agency (DARPA), the US National Institutes of Health (NIH) and the Defense Threat Reduction Agency. That cocktail prevented 43 percent of monkeys with symptoms of Ebola from dying[8]. Earlier work found this treatment, MB-003, saved all of the monkeys when given an hour after exposure to the virus, and two-thirds of the animals when administered 48 hours after exposure. Another antibody cocktail is under development at Canada's National Microbiology Laboratory, though it is not yet ready for human testing.

What treatments are available for use? "There are already candidate cocktails that can be used in an emergency," said Erica Ollmann Saphire, a professor at the Scripps Research Institute in La Jolla, California, who is leading a consortium of fifteen public and private institutions to develop treatments to fight the virus .The US National Institutes of Health has given a five-year grant of as much as $US28 million to Saphire's group, which is collaborating on antibody cocktails to fight Ebola.

However WHO spokesperson Tarik Jasarevic says his agency has not requested emergency use of any experimental treatments that have not been through the necessary clinical tests. David Heymann, a professor of infectious disease epidemiology at the London School of Hygiene and Tropical Medicine has worked on Ebola since the first outbreak in 1976. He says that before any experimental treatments could be used in an emergency situation trials showing the drugs are safe, plus ethical and regulatory clearance from the health ministries of affected countries, and regulatory clearance from the country where the drug is made, would be needed.

Stephan Guenther, head of the Bernhard Nocht Institute for Tropical Medicine in Hamburg, led a team of researchers that showed an experimental treatment called favipiravir, developed[9] as a treatment against the flu, cleared Ebola virus and prevented death in mice[10].There would be some challenges in human testing.

Gleevec and Tasigna, cancer drugs from Novartis, were claimed to have fought the Ebola virus in laboratory experiments reported in 2012.

7 Tekmira's drug, TKM-Ebola, is being developed under a $US140 million contract with the Defense Department's Medical Countermeasure Systems BioDefense Therapeutics Joint Product Management Office. Tekmira has fast-track designation from the US Food and Drug Administration (FDA) to develop the experimental treatment.

8 Xiangguo Qiu, Jonathan Audet, Gary Wong, Stephane Pillet, Alexander Bello, Teresa Cabral, Jim E. Strong, Frank Plummer, Cindy R. Corbett, Judie B. Alimonti[2] and Gary P. Kobinger, "Successful Treatment of Ebola Virus–Infected Cynomolgus Macaques with Monoclonal Antibodies", Science Translational Medicine, 13 June 2012 .Vol. 4, Issue 138, p. 138ra81 .

Sci. Transl. Med. DOI: 10.1126/scitranslmed.3003876

9 by Fujifilm Holdings Corp. (4901)'s Toyama Chemical unit

10 Lisa Oestereich, Anja Lüdtke, Stephanie Wurr, Toni Rieger, César Muñoz-Fontela, and Stephan Günther, "Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model", Antiviral Research, Volume 105, May 2014, Pages 17–21.
http://dx.doi.org/10.1016/j.antiviral.2014.02.014

Are there vaccines in development? GlaxoSmithKline in 2013 paid $US345 million for Okairos AG, a Swiss vaccine developer with early-stage products against Ebola and other diseases. Inovio Pharmaceuticals says its experimental vaccine protects guinea pigs from Ebola, and is seeking a government partner.

Other Diseases of Interest

Chagas Disease

This is a parasitic disease endemic to South America, but spread round the world through migration. A study just published[11] reported that "Australia hosts a rapidly growing population at risk and had 1928 infected residents in 2011; New Zealand had 98 in 2006. These figures underestimate the real situation, as they do not consider non-permanent residents. The only existing policy in both countries is the identification of blood donors with a history of or a risk of infection via questionnaire. There is no programme of detection and care of patients. The lifetime economic burden of disease for society is potentially very high."

The authors concluded that "Chagas disease is an emerging health risk with potential high human and economic costs in Australia and New Zealand in the absence of public health attention. Implementing strategies to screen high-risk groups and prevent transmission should be considered. Moreover, migration between the Western Pacific and Chagas endemic regions and the presence of vectors means this risk applies in the whole region."

Screening tests for Chagas disease are available, and have been used in other countries, such as Brazil and the US.

Variant Creutzfeldt-Jakob disease (vCJD)

Research continues round the globe into causes and hence possible prevention of, or treatment for, this disease. In the absence of major breakthroughs, the emphasis in public health has been on preventing transmission. French research supported the concern that C JD could be transmitted by blood transfusion and blood-derived products. In the UK, research suggested that 1 in 2000 people nationally carry vCJD proteins. The House of Commons science and technology committee opened a parliamentary investigation into measures to improve the quality of screening of blood and organ donors. Inadequate sterilization of instruments used in neurological surgery continues to be a means of transmission, and a research grant in Scotland is directed towards assessing the best way of cleaning surgical instruments to prevent infection.

One encouraging step in the challenging fight against this disease was taken by the University College of London Institute of Neurology. Dr Graham Jackson and his colleagues reported on a blood test screening for infection with the agent responsible for vCJD[12], performing well enough to be used to screen populations at risk for the disease.

Human immunodeficiency Virus (HIV)

When two men who had undergone routine bone marrow transplants in Boston appeared to have become free of HIV after around eight months of antiretroviral therapy, there was hope that a cure may have been found. However they have now tested positive for the virus. Perhaps

11 Jackson Y[1], Pinto A, Pett S, "Chagas disease in Australia and New Zealand: risks and needs for public health interventions." Trop Med Int Health. 2014 Feb;19(2):212-8. doi: 10.1111/tmi.12235. Epub 2013 Dec 3.

12 InJAMA Neurology, published online 3 Mar 2014, doi:10.1001. They said the assay was of sufficient sensitivity and specificity to warrant a major study comparing vCJD prevalence in the UK with a population unexposed to BSE.

there is still hope for children born with the virus and treated within hours after birth. Two babies in the US treated thus appear disease-free and a clinical trial will be conducted on a further 60 babies.

Childhood Diseases: Measles, Mumps and Whooping Cough (Pertussis)

These are sometimes called childhood diseases, but they are by no means confined to children. What they do have in common is that people in the developed world with ready and affordable access to vaccines do not need to suffer from them; but some choose to take a chance for themselves or their children, so herd immunity is not as high as it could be. Hepatitis A and B are other diseases where immunisation is not always accessed when available. All of these have been circulating in Australia during the last year.

Tuberculosis (TB)

Australia accepts residents and visitors from a number of countries where TB is endemic, such as India and China which together account for forty per cent of the world's known TB cases. The fact that our hospitals have TB clinics is testimony to the presence of the disease has a presence here. Our most vulnerable point of entry may be Far North Queensland, for Papua-New Guinea (PNG) is seeing increasing multi-drug resistant and extra-drug resistant cases. Our culturally sensitive border arrangements with PNG regarding free movement between settlements in the Torres Strait provide opportunities for disease transmission and create a treatment burden for Queensland Health.

Polio

WHO South-East Asia Region [SEARO] was certified polio-free in March. Polio is regarded as endemic in Afghanistan, Pakistan and Nigeria. Concerns in the Middle East have recently led to major vaccination campaigns. In 2013 there were 190 cases in Somalia, and multiple cases in Ethiopia, Cameroon and Kenya.

Hepatitis

Figures revealed in the Kirby Institute's Annual Surveillance Report, released at the Australasian HIV & AIDS Conference in Darwin in November, suggest that nearly half of the estimated 207,000 people living with **chronic hepatitis B** in Australia continue to remain undiagnosed, while 15 per cent of people living with **chronic hepatitis C** in Australia have not yet been diagnosed[13]. A study of silent **hepatitis E** infection amongst blood donors in the Netherlands[14] found 17 HEV RNA-positive donations among 45 415 donations, equivalent to one HEV-positive blood donation per day in the Netherlands.

13 The report found that almost 400 deaths in 2012 were related to hepatitis B-related liver disease despite the rate of diagnosis of newly acquired hepatitis B infection declining among those aged 30 years or older as well as reducing substantially among people aged 15-29 since 2003. In 2012, NSW had the highest number of diagnoses of hepatitis B infection, with 34.7 percent of the national total. The report also found that an estimated 310,000 people living in Australia in 2012 had been exposed to hepatitis C, with it thought that 173,500 had chronic hepatitis C infection and early liver disease, 51,500 had chronic hepatitis C infection and moderate liver disease, and 6,500 were living with hepatitis C related cirrhosis. The other 80,000 people believed to have to have been exposed have cleared their infection. The Kirby Institute estimates that almost 80 per cent of all infections for hepatitis C occur among people who inject drugs, with only one per cent of those people currently receiving treatment. Unlike other types of hepatitis, there is currently no vaccine to prevent hepatitis C, and medication is the only way to manage the disease. It is believed that 10-15 percent of all people living with HIV in Australia may also have hepatitis C and that co-infection remains a serious issue.

14 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

Lyme Disease

Work continues on vaccines[15] against **Lyme disease,** carried by ticks and increasing in notifications in the US. 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. The CDC says of Lyme disease and blood donation: Although no cases of Lyme disease have been linked to blood transfusion, scientists have found that the Lyme disease bacteria can live in blood from a person with an active infection that is stored for donation. Individuals being treated for Lyme disease with an antibiotic should not donate blood. Individuals who have completed antibiotic treatment for Lyme disease may be considered as potential blood donors.

Is Lyme disease present in Australia? If not, is something very close to Lyme disease present in Australia? For a detailed discussion visit a webpage of the Department of Medical Entomology at the University of Sydney which deals with serological investigations, clinical investigations, and vector and reservoir host investigations: http://medent.usyd.edu.au/fact/lyme%20disease.htm

15 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

Strategic Questions

Strategic questions raised by this Report include the following:

- Can we limit the emergence of new zoonoses? Zoonoses are infectious diseases transmitted, sometimes by a vector, from animals to humans. In direct zoonosis the agent needs only one host for completion of its life cycle, without a significant change during transmission[16]. Over a decade ago, a systematic review of 1,415 pathogens known to infect humans found 61 per cent were zoonotic[17]. Most experts agree that zoonoses are assuming greater importance.
- How do we increase "herd immunity"? There is incomplete acceptance of vaccines in communities even where vaccines are available and affordable, and in a large section of the world's population availability and affordability themselves remain challenges.
- In a world characterised by migration, travel and trade, and even medical tourism, what role, if any, do national borders play in limiting the spread of infection? What can global co-operation[18] achieve?
- Can we limit genetic reassortment opportunities in influenza? Should we try to limit gain-of-function studies by researchers?
- Can we speed our response to emerging diseases and emerging strains, eg by faster development of vaccines and treatments? What is the role of public/ private partnerships? What are the implications for public funding of research[19]?
- Could Australian blood donations be tested for additional transfusion-transmissible diseases? When does could become should?

16 The emergence of a pathogen in a new species is known as disease emergence disease invasion.

17 Taylor, L. H.; Latham, S. M.; Woolhouse, M. E. J., "Risk factors for human disease emergence". Philosophical Transactions of the Royal Society B, Biological Sciences 356 (1411): 983–989. doi:10.1098/rstb.2001.0888. PMC 1088493. PMID 11516376. 2001

18 Eg The Centers for Disease Control and Prevention (CDC) and the Pentagon will fund the US effort in the Global Health Security Agenda, which aims to strengthen disease-monitoring links between countries, to limit the number of laboratories that handle dangerous microbes and to boost vaccination programs. The Agenda involves 26 countries, and the World Health Organization (WHO); it follows on from a 2005 agreement by 194 countries to improve their disease detection and response by a June 2012 deadline, which many failed to meet. The Obama administration will spend $US40 million in 10 countries this year to upgrade laboratories and communications networks. Thomas Frieden, director of the CDC, said the President will seek another $US45 million next year.

19 The US government through a number of agencies has carried a large proportion of infectious disease research. In 2007 the share of the US in global biomedical research spending was 51 per cent. By 2012 this had fallen to 45 per cent. While the National Institutes of Health had suffered some reduction in purchasing power, it was primarily reduced industry funding driving the decline in the US share.

Appendix 1.

Recent items on infectious diseases reported on the NBA website.

Mosquito-borne diseases: dengue, chikungunya, Zika, malaria Ross River virus and West Nile virus

Dengue

April 2014

a) In contrast with a number of other countries round the tropics, the Philippines has recorded a drop in dengue cases so far this year. It reported 11,000 dengue cases to 1 March, a 52 per cent decrease over the same period last year. 40 fatalities were reported in the first two months of this year.

b) There has been a continuing high incidence of dengue in West Jakarta..

c) Britain's wet winter and warm spring has raised dengue fears as Aedes aegypti mosquitoes are known to be present.

d) There is concern in Japan that rising temperatures are expanding the habitat of the dengue-carrying tiger mosquito across the northern part of the country and that dengue may have returned for the first time in six decades. It appears that a German traveller contracted dengue in January.

e) Transmission of dengue relies on mosquitoes (Aedes aegypti) living long enough for the virus to infect the salivary glands. Survival rates of wild mosquitoes are difficult to measure. Hon Mieu Island in central Vietnam has been the site of a pilot release of Aedes aegypti infected with a strain of Wolbachia pipientis bacterium that induces virus interference and mosquito life-shortening. The bacterium was initially studied as a dengue control in Queensland, and has also been deployed in Indonesia. In the Vietnam trial, mosquito survival was found to be highest in the dry/cool (January-April) and dry/hot (May-August) seasons, when more of the Hon Mieu mosquitoes survived to an age that they were able to transmit dengue. The work led to season specific Aedes aegypti survival models to improve mosquito control strategies to break the dengue transmission cycle.[20]

f) Sanofi Pasteur hopes to be first to market with a dengue vaccine in 2015[21]. It began producing the vaccine last July to ensure it is ready to ship if the product is approved by regulators. Based on earlier clinical trial results, approval may not be assured. Data released in 2012 from a trial in Thailand showed Sanofi's vaccine did not protect against one the disease's four strains, which was the most prevalent in the country at the time. The vaccine, which is given in three shots six months apart, is currently being tested in 20,000 children aged 9-16 in Latin America and in 10,000 children aged 2-14 in southeast Asia. Guillaume Leroy, who heads the dengue vaccine project at Sanofi Pasteur, said the results of this final

20 Leon E. Hugo, Jason A. L. Jeffery,Brendan J. Trewin, Leesa F. Wockner, Nguyen Thi Yen, Nguyen Hoang Le, Le Trung Nghia, Emma Hine, Peter A. Ryan, Brian H. Kay, "Adult Survivorship of the Dengue Mosquito Aedes aegypti Varies Seasonally in Central Vietnam", PLOS Neglected Tropical Diseases, February 13, 2014. DOI: 10.1371/journal.pntd.0002669

21 Sanofi has invested over ($US1.38 billion) in research and development over two decades, and has prepared a dedicated production plant outside Lyon. This will have a capacity of up to 100 million doses per year from late 2017.

trial would start "trickling in" from mid-year Sanofi hopes to present consolidated clinical results at a conference on tropical diseases in November. Where will Sanofi market first if results are positive? "It's hard to predict which one could be first, but one can easily imagine it'll be one of the bigger countries, such as Brazil, Mexico, Malaysia, maybe the .Philippines," Leroy said.

g) Takeda, Merck, GlaxoSmithKline and Novartis are also working on dengue vaccines, but these are not yet in phase III trials.

h) Researchers at the Florida campus of The Scripps Research Institute have a $US2.3 million grant to study a family of viruses ("flavivirus") that cause dengue fever, West Nile, yellow fever and other diseases spread by mosquitoes and ticks. These diseases cause flulike symptoms, severe pain and sometimes encephalitis. Flaviviruses are estimated to affect 2.5 billion people globally each year and cause hundreds of thousands of deaths each year. There are no treatments but a small number of vaccines provide protection against a few.

i) The University of Alabama at Birmingham has been awarded $35 million from the US National Institute of Allergy and Infectious Diseases (NIAID) to establish a research centre developing new drugs for global infectious disease threats. The Antiviral Drug Discovery and Development Center, or AD3C, will focus on four virus types: flaviviruses, coronaviruses[22], alphaviruses and influenza.

March 2014

a) As at 11 March, Queensland Health reported that so far this season there had been 17 confirmed cases of dengue type 3 in Port Douglas, 117 Confirmed cases of endue type 1 in Cairns/Innisfail and 10 confirmed cases of dengue type 1 in Townsville.

b) Aedes aegypti have been found at Melbourne airport in the plastic, water-filled bollards used for traffic management.

c) Researchers at the University of North Carolina, in the labs of Dr Ralph Baric, and Dr Aravinda de Silva, showed that a molecular hinge where two regions of a protein connect is where natural human antibodies attach to the dengue 3 virus to disable it[23]. Now Drs Baric and de Silva are collaborating with vaccine developers at two pharmaceutical companies to test potential dengue vaccines now in clinical trials. If these investigational vaccines don't bind to their molecular hinge, then they will probably less effective than desired.

d) De Silva and Baric are also attempting to deal with dengue's particular phenomenon called antibody dependent enhancement. People infected with one type of dengue usually develop a natural immune response that overcomes the virus and prevents a repeat infection. But if they are later infected with a second type of dengue, the virus is enhanced because of that first immune response. This can result in dengue haemorrhagic fever and death. A large clinical trial of a dengue vaccine, conducted in Thailand in 2011, therefore contained a mix of the four types of dengue then known. However the vaccine proved only partially protective. If these researchers can isolate the major epitopes (binding sites) for each dengue type, they know from their experiments so far that they could modify a virus with all the epitopes and have the basis for a vaccine against all types[24].

22 eg Middle East respiratory syndrome-novel coronavirus, or MERS-CoV

23 The finding was published in the Proceedings of the National Academy of Sciences,

24 de Silva and Baric's also believe their research could be relevant in other fields where there is no vaccine.. "The general idea is that a complex protein-interaction site can now be moved from one virus to another," de Silva said. For instance, an epitope from a virus like hepatitis C could be moved onto the live virus used in the measles vaccine. This new chimeric virus would simultaneously offer people protection against hepatitis C and measles. He went on to suggest that a virus might not even be needed. "We might just need to create the epitope that we know antibodies

e) Since dengue fever infects only humans, scientists have not had animal models on which to work in their search for vaccines and treatments. Now researchers from MIT and the Singapore-MIT Alliance for Research and Technology (SMART) have developed a "humanized mouse" that mimics features of the human immune system. The team may have found the cause of one of the major symptoms of dengue—the depletion of the blood platelets essential to clotting. The researchers found that in the bone marrow of dengue-infected humanized mice, cells that eventually become platelets (megakaryocytes) were also depleted[25].

February 2014

a) Following field trials in Far North Queensland and Vietnam of mosquitoes carrying Wolbachia bacterium to stop the spread of dengue, trials are in progress in Indonesia.

b) A team of scientists at the University of Michigan and Purdue University has described for the first time the structure of a protein (NS1) which is produced inside infected cells and helps flaviviruses such as dengue and West Nile replicate and spread infection. Team leader Janet Smith of the University of Maryland Life Sciences Institute said: "Seeing the design of this key protein provides a target for a potential vaccine or even a therapeutic drug." [26]

January 2014

a) Panama government authorities have asked media to reduce their reporting of the country's dengue epidemic because of the effect on tourism.

b) French Polynesia has been experiencing twin epidemics-dengue and the zika virus. The latter is similar to dengue fever, chikungunya, yellow fever and Japanese encephalitis.

c) A run of dry weather helped slow the spread of dengue in Cairns.

d) Texas has had its first outbreak of dengue since 2005.

e) Scientists at the University of Hawaii at Manoa have found that the US Food and Drug Administration (FDA) approved InBios dengue virus IgM ELISA kit detects anti-dengue virus IgM antibodies in under five hours[27].

f) The Bill Gates-backed antibody therapeutics developer Visterra has acquired an exclusive license to a family of four early-stage monoclonal antibodies that target dengue virus. They were discovered at MIT, using protein engineering approaches.

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can bind to. And that would serve as the vaccine."

25 A Sridharan, Q Chen, KF Tang KF, EE Ooi , ML Hibberd, J Chen J., "Inhibition of megakaryocyte development in the bone marrow underlies dengue virus-induced thrombocytopenia in humanized mice", J Virol. 2013 Nov;87(21):11648-58. doi: 10.1128/JVI.01156-13. Epub 2013 Aug 21.

26 D. L. Akey, W. C. Brown, S. Dutta, J. Konwerski, J. Jose, T. J. Jurkiw, J. DelProposto, C. M. Ogata, G. Skiniotis, R. J. Kuhn, J. L. Smith. "Flavivirus NS1 Structures Reveal Surfaces for Associations with Membranes and the Immune System." Science, 2014; DOI: 10.1126/science.1247749

27 The study was published in the Journal of Clinical Microbiology,

November-December 2013

a) A confirmed case of dengue in New York is said to be the first instance of local acquisition of the infection. "Given the recent introduction of Aedes albopictus into New York State and the high level of travel in New York to areas of the world endemic for dengue, it is not surprising that a locally acquired case of dengue has been found in the state," said State Health commissioner, Nirav R. Shah.

b) Western Australia had its first case of locally-contracted dengue for seventy years.

c) The EMA has awarded orphan drug designation[28] to DengueCide, NanoViricides' drug candidate for the treatment of dengue and dengue haemorrhagic fever.

d) Nikos Vasilakis, a virologist at University of Texas Medical Branch in Galveston, told the Third International Conference on Dengue and Dengue Haemorrhagic Fever in Bangkok: "We discovered and characterized a new dengue serotype". Researchers screening dengue viral samples collected during an outbreak in Malaysia's Sarawak state in 2007 suspected they were different from the four known serotypes. Sequencing proved them to be phylogenetically distinct from the other four types. Experiments found that monkey antibodies produced against the new type differed significantly from those resulting from the previously known dengue viruses. The existence of a new type which may spread can be expected to complicate vaccine development further.

September 2013

a) NanoViricides announced that an Orphan Drug Application has been submitted to the European Medicines Agency (EMA) for DengueCide, a drug candidate for the treatment of dengue and dengue haemorrhagic fever.

b) Johnson & Johnson's Janssen unit has purchased global rights to compounds from a three-year alliance between the Rega Institute and the Centre for Drug Design and Discovery at KU Leuven. The compounds have been effective in animal tests in preventing replication of the dengue virus.

c) In Singapore, a "humanised mouse" has been developed to test dengue drugs.

d) The ban on Townsville residents donating blood because of a dengue outbreak was lifted at the end of August.

e) Scientists at the International Centre for Genetic Engineering and Biotechnology in New Delhi say they have developed a non-infectious dengue vaccine from yeast, and that animal trials of the vaccine have yielded satisfactory results. Dr Navin Khanna, group leader of the Recombinant Gene Products Group, said that "Efforts to develop a live attenuated vaccine (a vaccine created by reducing the virulence of a pathogen but still keeping it viable) have encountered unexpected interactions between the vaccine viruses, raising safety concerns. This underscored the need to experiment with non-replicating vaccine options." Partners in the project are the University of North Carolina School of Medicine and Ranbaxy research laboratories[29].

28 One of the benefits of orphan drug designation is ten years of exclusivity in marketing.

29 The research has been published in the journal, PLOS One.

August 2013

a) Restrictions on whole blood donations in Cairns were lifted in August after a nine-month ban because of the local dengue fever outbreak.

b) NIH have awarded $US 11.4 million to the University of Rhode Island for an additional five years of research on the dengue virus.

c) 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[30].

d) Meanwhile, Siga Technologies announced in New York that it has selected a lead candidate for its dengue anti-viral program.

e) Arbovax has applied to the FDA to begin human trials of its dengue vaccine.

f) Florida Keys has been investigating the use of drones to locate remote mosquito-breeding areas.

July 2013

a) The number of people contracting dengue in Singapore this year had passed the five figure mark by 17 June with 10,258 cases diagnosed. There was hope then that the rate of new infection had plateaued.

b) Thailand's health ministry predicted the country would see at least 100,000 dengue cases and more than 100 deaths this year, a three-fold increase from 2012.

c) In early June, health authorities said unseasonal wet weather may be prolonging the dengue outbreak in Cairns. By 26 June there had been 170 cases in the Cairns region.

a) NanoViricides filed an Orphan Drug Application to the FDA for DengueCide, a drug candidate for the treatment of dengue and dengue haemorrhagic fever.

Chikungunya

April 2014

a) Chikungunya is an alphavirus, first isolated from the blood of a febrile patient in Tanzania in 1953, and has since caused epidemics in Africa and Asia and has been seen in limited areas of Europe. This year it has spread to the Caribbean. The European Centre for Disease Prevention and Control (ECDC) on 28 March reported that the number of confirmed and suspected chikungunya cases in the Caribbean was continuing to increase; so far there had been 3211 confirmed chikungunya cases reported, including 5 deaths, and there had been 15 282 suspected cases. The US is expecting locally acquired cases of chikungunya in the next year or two.

February 2014

a) In 2013 there were 127 cases of chikungunya reported amongst Australians, an increase from the 19 in 2012. The disease is now prevalent in South East Asia, Papua New Guinea and the Pacific, leading to a spike in cases among Australians travelling to these countries. There is also a danger that the virus could cross the Torres Strait, with the short distance and frequent population movements between Papua New Guinea and Cape York.

30 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.

January 2014

a) There is a significant outbreak of chikungunya in the Caribbean. US health officials are concerned that infected travellers returning home can introduce the virus into local Aedes aegypti and Aedes albopictus populations when bitten by the mosquitoes.

b) Chikungunya, which was thought to have been eradicated from Singapore, appears to have become endemic again. In the Philippines, the number of cases in 2013 was three times the number in 2012.

c) In Western Australia the number of people diagnosed with chikungunya in the year to December 16 was 54, with most contracting it in Bali.

November-December 2013

a) A vaccine against chikungunya has been developed by Vienna-based Themis Bioscience, and is undergoing a phase I clinical study at Vienna General Hospital. The vaccine is based on a standard anti-measles vaccine. The company´s own Themaxyn platform also forms the starting point for a vaccine against dengue.

b) A chikungunya outbreak in Papua New Guinea is one factor causing scientists to worry that chikunguya coming into Australia with returning travellers could soon be locally transmitted by mosquitos already present here.

July-August 2013

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 chkingunya suggested to be a very real threat[31].

b) By 26 June, 11 people in Queensland had been diagnosed with Chikungunya, ten of them contracting it in Papua New Guinea and the eleventh in Indonesia. Because Queensland has mosquitoes that can transmit the disease, Tropical Public Health Services Director Dr Richard Gair said "Every import is a potential outbreak".

c) An Australian team says its experimental malaria vaccine protected mice against several strains of the disease. The vaccine caused existing white blood cells, or T-cells, to attack the malaria parasite inhabiting red blood cells[32].

Zika

April 2014

a) AT 26 March, the European Centre for Disease Prevention and Control (ECDC) estimated that more than 30,000 people in French Polynesia had sought medical care for Zika-like symptoms since the outbreak began in October[33]. By then there were 8,600 confirmed cases.

b) In New Caledonia, the first locally acquired case of Zika was reported in mid-January. The number of confirmed cases by 18 March was 276.

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

32 Journal of Clinical Investigation

33 It was recognized some of these could have been dengue.

c) By 25 March there had been 49 confirmed cases of Zika virus (a flavivirus) in the Cook Islands, while 630 people were believed to have suffered from the mosquito-borne disease.

March 2014

a) As of 7 March there were outbreaks on at least 15 Polynesian islands, including Tahiti and Bora Bora. The European Centre for Disease Prevention and Control also confirmed one case and reported 40 suspected cases on Easter Island. The virus is thought to have come with tourists from other islands, picked up by local Aedes aegypti mosquitos. Chilean health authorities who have responsibility on Easter Island decided not to raise a health alert, claiming the outbreak was contained and under control. However, experts fear the spread of the virus by unknowing tourists to a wide range of localities with host mosquitoes.

b) One confirmed case of Zika in French Polynesia led to hospitalisation for Guillain-Barre syndrome (GBS). The patient also had serological markers of resolute dengue which raised the question of a sequential arboviral immune stimulation. There had been observed an unusual clustering of GBS cases during concurrent circulation of Zika [virus] and 2 dengue [virus] serotypes. Experts warned that "in endemic areas, clinicians should be aware of the risk of diffuse demyelinating disorders [disorders involving damage to the myelin sheath of neurons] in case of Zika [virus] infection[34].

Malaria

April 2014

a) The Bill & Melinda Gates Foundation has awarded $U23 million over five years for University of Notre Dame research that seeks to prevent malaria and dengue fever.

January 2014

a) GlaxoSmithKline and Medicines for Malaria Venture have received from the FDA breakthrough therapy designation for tafenoquine, an investigational drug for treating Plasmodium vivax malaria and preventing relapse. This designation is designed to speed development and reduce review times for drugs for life-threatening conditions.

b) A team from Nanyang Technological University in Singapore has found a way to block access to red cells by the malaria parasite and hopes this can lead to development of an effective vaccine.

August to October 2013

a) Trials of a malaria vaccine developed by GlaxoSmithKline almost halved the cases of malaria in children aged between five and seven months and reduced by one quarter the number of cases in babies aged six to twelve weeks.

b) Two new tests have been developed which will help in tracking drug resistant malaria[35].

34 Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastere S, Valour F, Baudouin L, Mallet HP, Musso D, Ghawche F. Zika virus infection complicated by Guillain-Barre syndrome-case report, French Polynesia, December 2013. Eurosurveillance, Volume 19, Issue 9.

35 Witkowski B, Amaratunga C, Khim N, et al. "Novel phenotypic assays for the detection of artemisinin-resistant Plasmodium falciparum malaria in Cambodia: in-vitro and ex-vivo drug-response studies". Lancet Infect Dis 2013 Sep 11 and Sibley CH. "Tracking artemisinin resistance in Plasmodium falciparum". (Editorial) Lancet Infect Dis 2013 Sep 11.

c) 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.

Ross River Virus

September 2013

a) The West Australian Health Department announced that 31 Perth residents were diagnosed with Ross River virus (RRV) in the 4 weeks to 19 August, with a further 8 cases diagnosed outside the Perth area. A candidate RRV vaccine has been tested in humans. The adjuvanted, inactivated whole-virus Vero cell-derived vaccine is highly immunogenic in RRV-naive adults and well tolerated at all dose levels. This vaccine is not commercially available[36].

West Nile Virus

February 2014

a) CDC researchers have estimated health care costs and productivity loss from West Nile Virus to have been $US778 million from 1999 to 2012 inclusive[37].

August 2013

a) The 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.

a) 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[38]. The 2012 WNV outbreak with 286 deaths was the deadliest since the virus emerged in the US. It 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,

36 Aichinger G, Ehrlich HJ, Aaskov JG, Fritsch S, Thomasser C, Draxler W, Wolzt M, Müller M, Pinl F, Van Damme P, Hens A, Levy J, Portsmouth D, Holzer G, Kistner O, Kreil TR, Barrett PN. "Safety and immunogenicity of an inactivated whole virus Vero cell-derived Ross River virus vaccine: a randomized trial". 2011. Vaccine 29(50):9376-84.

37 J. Erin Staples, Manjunath Shankar, James J. Sejvar, Martin I. Meltzer, and Marc Fischer, "Initial and Long-Term Costs of Patients Hospitalized with West Nile Virus Disease" Am J Trop Med Hyg 13-0206; Published online February 10, 2014, doi:10.4269/ajtmh.13-0206.

38 Lyle R. Petersen, Aaron C. Brault, Roger S. Nasci, "West Nile Virus: Review of the Literature". 2013. JAMA 310:308-315.

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[39].

b) 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.

Influenza: strains, spread, prevention and treatment

H7N9

April 2014

a) As of 29 March, a total of 393 human cases of avian influenza A(H7N9) had been confirmed in m inland China. Hong Kong reported, "All boundary control points have implemented disease prevention and control measures. Thermal imaging systems are in place for body temperature checks of inbound travellers. Random temperature checks by handheld devices have also been arranged. Suspected cases will be immediately referred to public hospitals for follow-up investigation.

March 2014

a) In January and February of 2014, 72 people had died from H7N9 in China, more than in the whole of 2013[40]. Total cases in China had been 226 in those two months.

b) By the first week of March, Hong Kong had confirmed its sixth case of H7N9, with infection identified once more as having occurred on the mainland in a live poultry market. Hong Kong had banned live poultry imports from the mainland. Given that for 2013 and 2014 combined, 389 cases of H7N9 had been confirmed on the mainland up to 10 March, Hong Kong implemented other border protection measures[41] and offered advice for travellers[42]. The Centre for the Health Protection of the Hong Kong Department of Health continued to advise anyone visiting China to avoid live poultry markets and to cook poultry and eggs thoroughly.

c) By the end of February South China's Guangdong province had selected Guangzhou, Shenzhen and Foshan as pilot cities to allow only frozen poultry to be sold at markets. In the Zhejiang province capital of Hangzhou city officials closed the main poultry markets on February 15, some permanently, with those in two outlying districts are closed for 3 months. The city also banned the transport of live poultry on public transport and the

39 "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.

40 In 2013 there were 144 cases and 46 deaths recorded.

41 A spokesperson said: "All boundary control points have implemented disease prevention and control measures. Thermal imaging systems are in place for body temperature checks of inbound travelers. Random temperature checks by handheld devices have also been arranged. Suspected cases will be immediately referred to public hospitals for follow-up investigation."

42 Through airport posters, in-flight announcements, health inspections and advice to the travel industry. Travellers returning from avian-flu infected regions with fever of respiratory symptoms were asked to wear masks, seek medical attention and reveal their travel history. Healthcare professionals were asked to question whether presenting patients had had contact with poultry, other birds or their droppings

raising of poultry in urban areas. To allay consumers' concerns, authorities are developing a tag for frozen poultry to show that it has passed rigid inspection and quarantine.

d) A Chinese vaccine for H7N9 may be available by May, according to Li Lanjuan, of the Chinese Academy of Engineering. Adimmune, Taiwan's producer of human vaccines, will launch the second phase of human trials of its H7N9 vaccine in March and expects to begin mass production in June. It will be able to make 3 million doses of vaccine per month. In March, Novavax announced in the US the initiation of a Phase I/II clinical trial of its H7N9 avian influenza VLP (virus-like particle) vaccine candidate.

a) The European Centre for Disease Prevention and Control (ECDC) provided a risk assessment of human avian influenza A infection in China, dated Feb 24. It said the faster pace of human infections in the second wave might point to enhanced transmissibility of the virus, a larger wild or domestic bird reservoir, an increase in the number of exposed people, a seasonal pattern, or multiple influences.

b) The Public Health Agency of Canada (PHAC) noted that in the second waves, cases were less skewed towards the elderly, though males still predominated. Limited person-to-person transmission was noted with close contact, but PHAC noted that could change.

c) In the northern hemisphere Spring of 2013 H7N9 virus was isolated from a seemingly healthy tree sparrow in a Shanghai park, highlighting the need to monitor the presence of the virus in a number of species[43].

d) Chinese researchers suggested online in The Lancet that H9N2 avian flu appears to be an "incubator" for flu viruses of wild bird origin so that culling poultry infected with H9N2 might curb human infection. They noted that H10N8 –which recently killed two people in Jiangxi province has a genetic lineage similar to H7N9, including internal genes from H9N2 in poultry. They called on health officials everywhere to close live poultry markets or disinfect them regularly.

e) A report funded in part by the US Geological Survey [44] says the North Atlantic region is a significant pathway to allow the movement of avian influenza between Europe and North America in either direction. Birds congregate in Iceland's wetlands during migration, providing opportunities for transmission and comingling of viruses.

February 2014

a) In early February, the H7N9 outbreak case total passed 300 (with 67 deaths) since the disease emerged in humans, with up to 10 cases a day being reported from Chinese provinces[45]. WHO said the most active calendar year for the continuing H5N1 strain, 2006, saw 115 cases[46].

b) By 12 February, there had been five confirmed cases in Hong Kong, which appeared to arise from travel to China. Malaysia confirmed in mid-February its first case of H7N9 in a Chinese tourist.

43 Zhao B, Zhang X, Zhu W, Teng Z, Yu X, Gao Y, et al. "Novel avian influenza A(H7N9) virus in tree sparrow, Shanghai, China, 2013" in Emerging Infectious Diseases 20 (5), May 2014

44 Robert J. Dusek, Gunnar T. Hallgrimsson, Hon S. Ip, Jón E. Jónsson, Srinand Sreevatsan, Sean W. Nashold, Joshua L. TeSlaa, Shinichiro Enomoto, Rebecca A. Halpin, Xudong Lin, Nadia Fedorova, Timothy B. Stockwell, Vivien G. Dugan, "North Atlantic Migratory Bird Flyways Provide Routes for Intercontinental Movement of Avian Influenza Viruses",PlosOne, March 19, 2014.DOI: 10.1371/journal.pone.0092075

45 31 patients on the Chinese mainland died from H7N9 in January. Live poultry markets in Hangzhou and Shanghai had been ordered to close permanently.

46 Between 2003 and 2013, the bird flu H5N1 is known to have infected 648 people, with 384 deaths.

c) The United Nation's Food and Agriculture Organization (FAO) warned on 5 February that cross-border spread was increasingly likely.

d) In early February the South China Morning Post reported that China's poultry industry wanted public health agencies to cease reporting individual H7N9 cases, to "avoid excessively detailed reports" of H7N9 infections, and to refer to "H7N9 flu" or "H7N9 virus" rather than "H7N9 bird flu." The industry was anxious to reduce consumer concern about buying and eating poultry.

e) Vivaldi Biosciences and the US National Institute of Allergy and Infectious Diseases (NIAID) have signed a cooperative research and development agreement to develop and evaluate in preclinical studies live attenuated influenza vaccines against H7N9.

f) China's Sinovac Biotech in January announced the acceptance by the China Food and Drug Administration of its clinical trial application for its H7N9 vaccine.

g) Queensland researchers believe that surveillance and mapping of internet searches and social media topics would provide more up to date information on developing epidemics than the current method, which relies on physicians reporting relevant patient visits[47]. Google publishes search data for flu and dengue[48], but does not publish search terms. The Queensland researchers are working on their own system, which they hope will encompass all communicable diseases recognised in Australia, about 65. They believe Australia offers an ideal trial site, because of high internet penetration and high dependence on Google.

January 2014

a) There was a resurgence of H7N9 flu in China. By 20 January 204 human cases of avian influenza A (H7N9) had been confirmed on the Chinese mainland, including Zhejiang (77 cases), Shanghai (40 cases), Jiangsu (30 cases), Guangdong (23 cases), Fujian (12 cases), Jiangxi (six cases), Anhui and Henan (four cases each), Beijing, Hunan and Shandong (two cases each), and Hebei and Guizhou (one case each).

b) On 18 January a medical worker in a Shanghai hospital died from H7N9, fuelling concern that the strain may be spreading from person to person.

c) A patient in Hong Kong (who had travelled to the mainland) died on 13 January. His close contacts had earlier been quarantined and given Tamiflu and his other contacts were under medical surveillance. Hong Kong borders Guangdong province and Hong Kong's secretary for food and health on 12 January called on people in Hong Kong not to visit markets in Guangdong or the eastern mainland when they visited their relatives during the Lunar New Year holiday.

d) On 5 January, Xinhua reported that samples of goose flesh taken from a Guangzhou market tested positive for H7N9 flu.

e) On 30 December Hong Kong had its first H7N9 death.

f) A study published in the Proceedings of the National Academy of Sciences[49] suggested ethnic differences in the ability to mount an immune response to the H7N9 virus. This is due to genetic differences in a protein complex involved in cell-mediated immune responses. Professor Peter Doherty said the findings were supported by experience during the 1918-19 influenza pandemic, when 100 per cent adult mortality was seen in some remote Alaskan villages; and between ten and twenty per cent of Indigenous Australians died, compared with

47 Gabriel J Milinovich, Gail M Williams, Archie C A Clements and Wenbiao Hu, "Internet-based surveillance systems for monitoring emerging infectious diseases", The Lancet Infectious Diseases, Volume 14, Issue 2, Pages 160-168, February 2014 doi:10.1016/S1473-3099(13)70244-5

48 https://www.google.org/flutrends/about/how.html

49 Sergio Quiñones-Parra, Emma Grant, Liyen Loh, Thi H. O. Nguyen, Kristy-Anne Campbell, Steven Y. C. Tong, Adrian Miller, Peter C. Doherty, Dhanasekaran Vijaykrishna, Jamie Rossjohn , Stephanie Gras, and Katherine Kedzierska, "Preexisting CD8+ T-cell immunity to the H7N9 influenza A virus varies across ethnicities", doi: 10.1073/pnas.1322229111

fewer than one per cent of non-Indigenous Australians. Similarly, during the 2009 H1N1 outbreak, 16 per cent of hospitalized Australians were Indigenous. Katherine Kedzierska[50] explained that "The genetic susceptibility of Indigenous Australian and Alaskans would have resulted from isolation of indigenous populations from the viruses like influenza. The indigenous populations were not subjected to evolutionary pressures caused by the viruses over the centuries".

November-December 2013

a) The H7N9 strain of avian flu which emerged in China in the previous northern hemisphere winter saw 137 confirmed cases and 45 deaths through to late October, but the new northern hemisphere flu season is producing more cases, including the first two cases in Hong Kong.

b) Results from an early stage trial of a Novavax virus-like particle (VLP) vaccine against the H7N9 strain of avian flu were published online in the New England Journal of Medicine. Scientists said the vast majority of subjects produced protective antibodies very quickly. The VLP nature of the vaccine facilitates large scale rapid production

c) Novartis announced that early tests on its H7N9 vaccine showed that 85 per cent of subjects had a protective immune response after two doses.

d) A study has found that closure of live poultry markets is the best way to slow the spread of H7N9[51].

e) Chinese researchers announced they have developed a vaccine against the H7N9 virus. The vaccine was jointly developed by the First Affiliated Hospital under the School of Medicine of the Zhejiang University, Hong Kong University, the Chinese Centre for Disease Control and Prevention, the National Institute for Food and Drug Control, and the Chinese Academy of Medical Sciences.

October 2013

a) By 26 October, the WHO, had been notified of 137 laboratory-confirmed cases of H7N9 flu, originating in China. There had been 45 deaths.

b) H7N9 pandemic bird flu vaccines are being tested in the US. Taiwan says it will roll out its H7N9 vaccine in late 2014.

September 2013

a) In September WHO had selected an A/Anhui/1/2013-like virus for the development of H7N9 vaccines for pandemic preparedness. It noted that A/Shanghai/2/2013 is an A/Anhui/1/2013-like virus. The candidate vaccine virus and other H7N9 strains are being shared under the WHO's Pandemic Influenza Preparedness Framework.

b) Visterra Inc. told the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy that its monoclonal antibody VIS410 can neutralize both the H5N1 and H7N9 strains of avian flu.

c) A study has found that the avian-origin H7N9 influenza A virus attaches to the epithelium of both the upper and lower respiratory tracts. This has not previously been observed for other avian influenza A viruses[52]. Thijs Kuiken, of the department of viroscience at Erasmus

50 Of the Department of Microbiology and Immunology at the University of Melbourne

51 Hongjie Yu, Joseph T Wu, Benjamin J Cowling et al., "Effect of closure of live poultry markets on poultry-to-person transmission of avian influenza A H7N9 virus: an ecological study", The Lancet, Early Online Publication, doi:10.1016/S0140-6736(13)61904-2. See also Wu Y, Gao G F. "Lessons learnt from the human infections of avian-origin influenza A H7N9 virus: Live free markets and human health", Sci China Life Sci, 2013, 56: 493-494, doi:10.1007/s11427-013-4496-y.

52 The report was published in the October 2013 issue of The American Journal of Pathology. See also Y Yi Shi et

University Medical Centre, said in a press release that "Abundant virus attachment to the human upper respiratory tract correlates with efficient transmissibility among humans." This could lead to a pandemic. The virus causes severe pneumonia.

d) Researchers at nine US sites began human testing of an H7N9 avian influenza vaccine. The two concurrent Phase II clinical trials were sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. A possible role for adjuvants is being examined.

e) Japan says experts at the Health, Labor and Welfare Ministry will begin producing a vaccine for the H7N9 strain of avian influenza. The vaccine will be based on a strain produced by NIAID. The Ministry will test the vaccine on animals before deciding whether to conduct clinical trials on humans.

f) University of Hong Kong microbiologist Yuen Kwok-Yung advised that H7N9 bird flu may be spreading through human faeces, as researchers found the virus in the stools of 4 out of 6 people who died in Zhejiang. In Kowloon during the 2003 SARS outbreak the virus spread through sewage pipes. Yuen emphasised the implications of the discovery for infection control strategies[53].

August 2013

a) 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.

b) 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[54].

c) Scientists have found H7N9 transmissible between ferrets by respiratory droplets.

d) 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.

e) A recent study in mBio[55] 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.

f) 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.

g) 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.

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al, "Structures and Receptor Binding of Hemagglutinins from Human-Infecting H7N9 Influenza Viruses. Science DOI: 10.1126/science.1242917 <http://www.sciencemag.org/content/early/2013/09/04/science.1242917

53 Clinical Infectious Diseases, 13 August 2013.

54 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>).

55 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.

h) 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, 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.

i) 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.

j) 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.

July 2013

a) At 7 July, WHO had been informed of a total of 133 laboratory-confirmed cases of H7N9, including 43 deaths. Chinese researchers have warned that the virus could re-emerge later this year[56]. Some live poultry markets closed when the disease emerged have now re-opened.

b) Chinese health officials have found co-infection of H7N9 and H3N2, and recognise co-infection as a possible source of reassortment of the virus.

c) A study published in the journal Radiology shows how the H7N9 virus differs from pneumonia in the way it rapidly and progressively changes in the lungs and pulmonary connective tissues.

d) Vaxart took twenty days to develop a recombinant oral H7N9 vaccine which was successful in preclinical testing. Taiwan vaccine provider Adimmune's H7N9 vaccine developed from a WHO-approved virus strain passed its Phase III clinical trial.

H10N8

January and February 2014

a) A study published in The Lancet on 4 February reported that a strain of the H10N8 avian flu had mutated and could now be carried by humans. H10N8 flu had been found in three people in China up to 14 February. Two of them had died. The study said the new strain had genetic similarities to H5N1 and H7N9, and that since it hasn't been responsible for major reported outbreaks in poultry it could be spreading silently in birds. The study said that H10N8 was not then known to have been transmitted from person to person but warned: "The pandemic potential of this novel virus should not be underestimated".

56 Hongjie Yu et al,"Human infection with avian influenza A H7N9 virus: an assessment of clinical severity", The Lancet, Early Online Publication, 24 June 2013 doi:10.1016/S0140-6736(13)61207-6

b) A woman in Nanchang died of this strain in December. She was known to have been in contact with live poultry. The strain was detected in water birds in China in 2007. Its transmission mode is not known, and the possibility of human-to-human transmission is thought to be low. Its symptoms are severe pneumonia and respiratory failure. WHO described this death as "worrisome".

c) Taiwan responded to news of this death by issuing a travel alert for the Chinese province of Jiangxi. Taiwan had already banned the slaughter of poultry at traditional markets.

H5N1

March 2014

a) Bird flocks, wild and farmed, continue to be found in a number of countries to be infected with H5N1, sometimes with associated culls[57]. Occasional human cases occur where there has been some association with infected birds. To the beginning of March, Cambodia had reported six cases this year, some fatal.

b) The Japanese Ministry of Health, Labour and Welfare last August awarded a cell culture vaccine production facility capacity building grant to the Daiichi Group in the expectation that H5N1 vaccine would be supplied by the end of March 2014. The company found that vaccine yields declined during the purification process and this has delayed the achievement of its goal.

February 2014

a) H5N1 can circulate in vaccinated birds without causing obvious disease. A Canadian woman who recently died of H5N1 had visited Beijing, which has not reported a case of H5N1 for some years.

b) A Japanese man has been found to have an antibody against H5N1, although he has no record of bird flu symptoms and no human infection with H5N1 has been reported in Japan. A research team led by Yoshikazu Kurosawa, president of Fujita Health University in Toyoake, believes the man had previously been infected with three different types of flu viruses, with two of them resembling the H5N1 strain.[58]

c) At the American Society for Microbiology Biodefense meeting in Washington DC in January the University of Alabama at Birmingham and Hemispherx's presented a poster entitled "Seasonal Influenza Vaccine and a TLR-3 Agonist, Rintatolimod (Ampligen(R). Given Intranasally Produced Cross-Reactive IgA Antibodies Against Pathogenic H5N1 Influenza HA". The presenter was Dr. E. Turner Overton, an infectious disease expert at UAB. Researchers hope that the use of Ampligen as an adjuvant combined with approved commercial vaccine FluMist may offer advantages. FluMist , due to its intranasal administration, imitates the natural entry of the influenza virus, to generate local 'first-line' immunity as well as traditional systemic immunity. The stimulation of cross-protection against pre-pandemic H5N1 avian influenza strains is an ongoing clinical research goal and the proposed "vaccine cocktail" will enable potentially wider immunity against a variety of highly pathogenic influenza viruses.

57 The website of the US Geological Survey lists round 170 bird species as affected by H5N1. (<http://www.nwhc.usgs.gov/disease_information/avian_influenza/affected_species_chart.jsp>).

58 Nobuko Ohshima, Ritsuko Kubota-Koketsu, Yoshitaka Iba, Yoshinobu Okuno, and Yoshikazu Kurosawa "Two Types of Antibodies Are Induced by Vaccination with A/California/2009pdm Virus: Binding near the Sialic Acid-Binding Pocket and Neutralizing Both H1N1 and H5N1 Viruses", PloS One, 5 February 2014 DOI: 10.1371/journal.pone.0087305

January 2014

a) A resident of Alberta, Canada, died of the avian flu strain H5N1, following a visit to Beijing. This was not only the first known H5N1 death in North America, it was also the first known case of H5N1 infection imported by a traveller into a country where the virus was not present in the poultry. WHO advised that while it is difficult to transmit the virus from person to person, when people do become infected, the mortality rate is about 60 per cent.

b) WHO confirmed that between 2003 and 2013 inclusive there were 648 human cases of H5N1 infection in 15 countries, and 384 deaths. If the H5N1 virus were to mutate and become easily transmissible between humans, the consequences for public health could be very serious.

c) In mid-January, Vietnam reported its first H5N1 death for 2014.

d) On December 18, 2014, 56 researchers wrote to the President of the European Commission asking that the Commission convene a meeting to discuss the risks of continuing research in which viruses are mutated to increase their transmissibility between mammals. This debate had begun with earlier "gain-of-function" studies with the H5N1 virus[59].

e) UK scientists[60] have developed a new flu test using gold particles. They found that a gold solution changes colour in the presence of the flu virus, and the colour it changes to differs according to the strain. The test can distinguish between human and avian flu, and it could be used to fight superbugs in hospitals and even to detect toxins like ricin used in bioterrorism. "We are now looking for a diagnostics company to help us bring it to market," said the researchers[61].

f) The Vietnam Health Ministry's Institute of Vaccines and Medical Biologicals says it has successfully produced vaccines against H1N1 and H5N1 flu and that production is underway, funded by WHO. The Institute is now conducting trials of another vaccine for the H7N9 flu virus.

October 2013

a) Replikins announced that it has successfully developed a vaccine against the influenza strain H5N1 that is now ready for testing.

August 2013

a) Vaxart has oral vaccine candidates for H1N1 seasonal flu and H5N1 avian influenza in Phase I trials.

H5N8 and H9N2

January and February 2014

a) New Scientist on 31 January carried a report on the H9N2 virus, which it says gave rise to H5N1, H7N9 and H10N8. Robert Webster of St. Jude Children's Research Hospital in Memphis, Tennessee, told New Scientist that "closing Asia's ubiquitous live poultry markets would be the key to controlling N9N2, as this is where H9N2 and its spin-off viruses spread, mingle and evolve – and where humans catch them. Beijing, Shanghai and three cities in Zhejiang Province temporarily closed their live poultry markets. Some reports suggest

59 In 2011, when a Dutch researcher was criticised for genetically manipulating the H5N1 strain so it could be transmitted by airborne particles between ferrets, the Dutch government used its export regulations to bar publication of full results. In October 2013 the European Society for Virology wrote to the European Commission supporting wide dissemination of research findings.

60 Professor Rob Field from the John Innes Centre and Professor David Russell from the University of East Anglia

61 Results were published in Organic & Biomolecular Chemistry

live markets in major cities may be banned permanently. Zhang Yonghui, head of the Guangdong Centre for Disease Prevention and Control, told China's official news service Xinhua that the government should change the country over to industrial chicken slaughter.

b) South Korean authorities have culled 3 million birds with A(H5N8) with no human cases reported.

c) A 7 year old boy in Hunan and an 86 year old man in Shenzhen were taken ill with avian flu H9N2. The boy had been in contact with poultry. He was treated in the local hospital and recovered. The man had no recent poultry contact, consumption of undercooked poultry, or contact with patients. He was treated in Hong Kong. The number of flu strains in circulation, including H10N8, may signal a higher risk of virus mutation and genetic swapping, said one expert. He said "Biosecurity measures and regulatory controls on the mainland have not caught up with increasing poultry numbers" as traders packed more birds into limited-space wet markets. Hong Kong in 2008 banned wet markets from keeping live poultry overnight. The H9N2 infection rate had been 5 per cent to 6 per cent but fell below 1 per cent after the ban.

H1N1

March and April 2014

a) Influenza came early to New Zealand this year. It is the same A (H1N1) flu strain that caused the 2009 "swine flu" pandemic and struck down 780,000 people in New Zealand, including one in every three school children.

b) A(H1N1) or swine flu which caused a pandemic scare has been the dominant flu strain during the US winter and has been experienced in other northern hemisphere countries. It can be expected to be around to some extent also during the Australian flu season. Queensland Health has already confirmed several cases on Palm Island.

c) Another study has examined disparate ethnic experience with 2009 pandemic H1N1 influenza, this time using data from Ontario[62]. While the study concluded that pH1N1 cases were more likely to come from certain ethnic groups compared with test-negative controls[63], further work is needed to establish whether these disparities arise due to social or biological factors, and to develop approaches to reduce the burden of a future influenza pandemic.

January 2014

a) North America's predominant flu strain in the current winter appears to be the 2009 H1N1 pandemic strain popularly known as "swine flu". It has been sickening and killing young adults, and people 49 to 64. Europe has had three strains of flu circulating.

62 Debeka Navaranjan, Laura C Rosella, Jeffrey C Kwong, Michael Campitelli and Natasha Crowcroft, "Ethnic disparities in acquiring 2009 pandemic H1N1 influenza: a case-control study", BMC Public Health 2014, 14:214 doi:10.1186/1471-2458-14-214. The electronic version can be found online at: http://www.biomedcentral.com/1471-2458/14/214

63 Ethnic disparities in hospitalization and death due to pH1N1 were known. This study examined ethnic disparities in acquiring the disease. The researchers found adult
cases were more likely than controls to be self-classified as East/Southeast Asian, South Asian and Black. Paediatric cases were more likely to be self-identified as Black). However, paediatric cases without risk factors for severe influenza infection were more likely to be South Asian, Black, and West Asian/Arab, Latin American or Multi-racial groups.

b) Japanese researchers have reported[64] an H1N1 cluster resistant to oseltamivir (Tamiflu) and peramivir. The viruses were however sensitive to zanamivir (Relenza) and laninamivir, two other neuraminidase inhibitors.

Influenza: general

March 2014

a) US firm VaxInnate has begun a Phase I trial of its recombinant quadrivalent vaccine for seasonal flu.

b) A meta-analysis published in The Lancet Respiratory Medicine[65] suggested Tamiflu reduced the death rate in the 2009 H1N1 pandemic. The research was led by Nyugen-Van-Tam, a professor of health protection at the University of Nottingham, and funded by Hoffman-La Roche, which makes Tamiflu.

c) Romark Laboratories is sponsoring a Phase III trial of a formulation of mitazoxznide, known as NT-300, alone and in combination with Tamiflu, as treatment for acute but uncomplicated flu.

January- February 2014

a) Israel's BiondVax Pharmaceuticals announced the completion of tests on its flu vaccine which show it is "universal" and suited to new flu strains that have appeared in the past few years, including H5N1, H5N8, H6N1, H7N7, H7N9 and H10N8. BiondVax says its new vaccine contains small doses of the flu virus, sufficient to teach the immune system to recognize all flu strains.

b) The European Commission reported that of the 18 European Union member states who provided vaccination statistics for older age groups for 2011-12, only the Netherlands met the target of 75 per cent coverage.

c) Visterra's lead experimental flu drug VIS410 will be trialled in humans. It is not a vaccine, because it provides antibodies to fight the flu rather than encouraging the body to produce them.

November-December 2013

a) The FDA approved a GlaxoSmithKline vaccine for use in an H5N1 epidemic. It will be added to the national stockpile for distribution by public health officials if required. It contains and adjuvant to boost the body's immune response to the vaccine.

b) A woman in Taiwan tested positive for the avian flu strain H6N1 which had not been considered able to infect people[66].

October 2013

a) WHO recommended that trivalent vaccines for use in the 2014 influenza season (southern hemisphere winter) contain the following: an A/California/7/2009 (H1N1)pdm09-like virus (a); an A/Texas/50/2012 (H3N2)-like virus (b); a B/Massachusetts/2/2012-like virus. WHO recommended that quadrivalent vaccines containing 2 influenza B viruses

64 January 9, in Eurosurveillance

65 doi:10.1016/S2213-2600(14)70041-4

66 See Lancet Respiratory Medicine

contain the 3 viruses above and a B/Brisbane/60/2008-like virus. WHO noted (a) A/Christchurch/16/2010 is an A/California/7/2009-like virus; (b) A/Texas/50/2012 is an A(H3N2) virus that following adaptation to growth in eggs has maintained antigenic properties similar to the majority of recently circulating cell-propagated A(H3N2) viruses > including A/Victoria/361/2011.

b) Avian flu (but not H5N1) has been found on two NSW egg farms.

c) Discovery of a novel influenza virus, H18N11, in several species of Peruvian bats suggests New World bats can be an important reservoir.[67]

September 2013

a) A US study showed that pigs vaccinated against one flu strain were worse off if later infected with a related strain[68].

b) Sanofi announced its Fluzone High-Dose vaccine is more effective at preventing influenza in adults aged 65 and older than a standard dose of Fluzone.

c) Researchers have found the avian-origin H7N9 influenza A virus to be both virulent and easily-transmissible between humans.

August 2013

a) 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.

b) Rather than develop a universal flu vaccine, some scientists are suggesting sequential vaccination with distinct strains isolated from the last century[69].

July 2013

a) WHO has redefined what constitutes a flu pandemic to emphasise the risk it poses instead of its geographic spread. The definition is now "a period of global spread of human influenza caused by a new subtype". The new system uses four phases (interpandemic, alert, pandemic and transition) to describe the spread. WHO currently considers the world is at the "alert" level when it comes to both the H5N1 and H7N1 bird flus.

b) Swiss firm Viroblock has developed a face mask incorporating technology which it claims will trap and kill over 99 per cent of H1N1 and H5N1 flu vruses and a similar percentage of aerobic human corona viruses.

c) By 2 June Australia had already seen the second-highest number of flu cases for this time of year recorded in a decade, reported Ian Barr, the deputy director of the Australian WHO Collaborating Centre for Reference and Research on Influenza. The national register of laboratory-confirmed flu cases had identified 3379 infections, compared with just over 3000 at the same time last year. Infections are being driven by the H1N1 swine flu virus.

d) For the 2013-2014 influenza season in the US, vaccines will contain two A and two B strains. The FDA has now approved Sanofi's 4-in-1 influenza vaccine Fluzone Quadrivalent, which is approved for children 6 months and older, for adolescents and for adults. It joins

67 Tong S, Zhu X, Li Y, Shi M,"New World Bats Harbor Diverse Influenza A Viruses", by in PLoS Pathog 9(10): e1003657. doi:10.1371/journal.ppat.1003657

68 Dr Hana Golding of the Center for Biologics Evaluation and Research at Bethesda in Maryland and colleagues at the National Animal Disease Center published their report in Science Translational Medicine. "Vaccine-Induced Anti-HA2 Antibodies Promote Virus Fusion and Enhance Influenza Virus Respiratory Disease", Sci Transl Med 28 August 2013: Vol. 5, Issue 200, p. 200ra114 Sci. Transl. Med. DOI: 10.1126/scitranslmed.3006366.They cautioned that their results may not apply to humans, and that the vaccines they used were made from whole, killed viruses. Those used in humans are made from parts of killed viruses.

69 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

two other quadrivalent vaccines already approved, GlaxoSmithKline's Fluarix Quadrivalent and AstraZeneca's MedImmune vaccine. The latter two can be given to children only if they are aged at least 2 and 3 years respectively.

e) Medicago has received approval from Health Canada to begin a Phase II dose-sparing clinical trial of its virus-like particle (VLP) candidate vaccine for H5N1 bird flu. Medicago is now to be acquired by Mitsubishi Tanabe Pharma, an affiliate of Philip Morris International.

f) Studies published in the journal Nature Genetics in June described genetic factors affecting how ducks respond to bird flu. Ducks can catch more different strains than other animals. They survive bird flu not because they have more immune genes, but because they have specialised genes that resist the virus.

Mers-CoV (Middle East respiratory syndrome, novel coronavirus)

April 2014

a) WHO announced that genetic data show the MERS-CoV isolates in camels and humans are closely linked and "suggest the current observed pattern of disease in humans is the result of repeated introductions into human populations from camels, with subsequent limited human-to-human transmission, rather than sustained community transmission among humans. As such, discovery of the route of transmission between camels and humans remains critical to stopping the initial introduction into human populations."

b) From September 2012 to1 April 2014, WHO was informed of a global total of 207 laboratory-confirmed cases of infection with MERS-CoV, including 87deaths.

March 2014

a) WHO's global MERS tally, updated 14 March, was 196 cases and 83 deaths. Saudi Arabia's then accounted for 157 cases, with the death toll 63.

b) A study says the MERS virus has been "extraordinarily common" in camels for at least 20 years, and may have been passed directly to humans from the animals[70].

c) Health experts warned that MERS-CoV infections that may be acquired in healthcare facilities illustrate the need to continue to strengthen infection prevention and control measures[71].

d) WHO issued advice to member states about appropriate response to MERS-CoV[72]. It has

70 Alagaili AN, Briese T, Mishra N, et al: "Middle East respiratory syndrome coronavirus infection in dromedary camels in Saudi Arabia". MBio. 2014; 5(2). pii: e00884-14. doi: 10.1128/mBio.00884-14

71 The advice : Healthcare facilities that provide care for patients suspected or confirmed with MERS-CoV infection should take appropriate measures to decrease the risk of transmission of the virus to other patients, healthcare workers and visitors. Education and training for infection prevention and control should be provided to all healthcare workers and regularly refreshed. Early identification of the MERS-CoV is important, but not all the cases could be reliably and timely detected, especially when disease is mild or presents atypically. Therefore, it is important to ensure that standard precautions are consistently used for all patients and all work practices all of the time, regardless of suspected or confirmed infection with the MERS-CoV or any other pathogen. Droplet precautions should be added when providing care to all patients with symptoms of acute respiratory infection, and contact precautions plus eye protection should be added when caring for confirmed or probable cases of MERS-CoV infection. Airborne precautions are indicated when performing aerosol generating procedures. When the clinical and epidemiological clues strongly suggest MERS-CoV, the patient should be managed as potentially infected, even if an initial test on a nasopharyngeal swab is negative. Repeat testing should be done when the initial testing is negative, preferably on specimens from the lower respiratory tract.

72 WHO encourages all of its member states to continue their surveillance for severe acute respiratory infections (SARI) and to carefully review any unusual patterns. Healthcare providers are advised to maintain vigilance. Recent travelers returning from the Middle East who develop SARI should be tested for MERS-CoV as advised in the current surveillance recommendations. All WHO member states are reminded to promptly assess and notify WHO of any new case of infection with MERS-CoV, along with information about potential exposures that may have resulted in infection and a description of the clinical course. Investigation into the source of exposure should promptly be initiated to identify the mode of exposure, so that further transmission of the virus can be prevented. People at high risk of severe disease due to MERS-CoV should avoid close contact with animals when visiting farms or barn

not to date advised special screening at points of entry with regard to this event, nor does it currently recommend the application of any travel or trade restrictions.

e) Researchers reported in the Proceedings of the National Academy of Sciences that they have developed a mouse model for MERS-CoV infection, which could provide an opportunity for early testing of drugs and vaccines.

f) Scientists have analysed 32 MERS-CoV isolates from Saudi Arabia and found little genomic evidence that the virus is evolving to become more easily transmitted between humans.

February 2014

a) On 7 February, WHO said that since September 2012 it had been informed of 182 laboratory-confirmed cases of MERS, associated with 79 deaths.

a) Researchers led by Stanley Perlman, a microbiologist at the University of Iowa, have created the first mouse model for MERS-CoV for testing of drugs and vaccines.

b) An editorial in the journal Annals of Internal Medicine said the spread of MERS in hospitals is a significant problem, as was the case with SARS[73]. Health workers have made up around twenty per cent of cases, and some have been asymptomatic. In the same issue was a report on the disease course and outcomes of 12 intensive care patients in Saudi Arabia, three of whom were health workers[74]. A WHO report on 20 January said "more than half of all laboratory-confirmed secondary cases have been associated with health care settings. These include health care workers treating MERS-CoV patients, other patients receiving treatment for conditions unrelated to MERS-CoV, and people visiting MERS-CoV patients".

c) Camels have been seen as a possible source of MERS-CoV[75]. Now researchers have found another coronavirus in dromedary camels in the United Arab Emirates[76].

d) While MERS-CoV is the coronavirus of current concern, as was SARS-CoV a decade ago, there are other coronaviruses, some not yet known to infect humans[77].

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areas where the virus is known to be potentially circulating. For the general public, when visiting a farm or a barn, general hygiene measures, such as regular hand washing before and after touching animals, avoiding contact with sick animals, and following food hygiene practices, should be adhered to.WHO does not advise special screening at points of entry with regard to this event nor does it currently recommend the application of any travel or trade restrictions.

73 Trish M. Perl, Allison McGeer, and Connie Savor Price, "Medusa's Ugly Head Again: From SARS to MERS-CoV", Ann Intern Med. Published online 28 January 2014 doi:10.7326/M14-0096

74 Yaseen M. Arabi, Ahmed A. Arifi, Hanan H. Balkhy, Hani Najm, Abdulaziz S. Aldawood, Alaa Ghabashi, Hassan Hawa, Adel Alothman, Abdulaziz Khaldi, and Basel Al Raiy, "Clinical Course and Outcomes of Critically Ill Patients With Middle East Respiratory Syndrome Coronavirus Infection", Ann Intern Med. Published online 28 January 2014 doi:10.7326/M13-2486

75 Meyer B, Müller MA, Corman VM, Reusken CBEM, Ritz D, Godeke G-D, et al. Antibodies against MERS coronavirus in dromedary camels, United Arab Emirates, 2003 and 2013. Emerg Infect Dis [Internet]. 2014 Apr [print]. http://dx.doi.org/10.3201/eid2004.131746

76 Woo PCY, Lau SKP, Wernery U, Wong EYM, Tsang AKL, Johnson B, et al. Novel betacoronavirus in dromedaries of the Middle East, 2013. Emerg Infect Dis [Internet]. 2014 Apr [print]. http://dx.doi.org/10.3201/eid2004.131769

77 Coronaviruses are a large group of RNA viruses that can cause both respiratory and enteric signs of disease in various species. They are further classified into alpha, beta, and gamma coronaviruses based on genetic and serologic difference. The equine coronavirus, a beta coronavirus, has been responsible for a number of recent outbreaks across the US. In horses, this is an enteric disease. So far there has been no association with a respiratory component (although in cattle both enteric and respiratory effects are common). Researchers recently completed a study on equine coronaviruses in mature horses. At the 2013 American Association of Equine Practitioners' Convention, in Nashville, Tennessee, Nicola Pusterla, a professor at the University of California, Davis, School of Veterinary Medicine, presented the results of the study. "We consider this an emerging pathogen," Pusterla said, noting that disease outbreaks associated with ECoV and adult horses have rarely been described in the scientific literature prior to recent years. Coronavirus is spread faeco-orally, Pusterla said, "and likely passed from horse to horse via faecal contamination of the environment from clinically but also asymptomatic shedders.

January 2014

a) At January 3, 2014 WHO had been informed of a total of 177 laboratory-confirmed cases of infection with MERS-CoV, including 74 deaths[78]. Although camels are currently regarded as a probable reservoir for the disease, it has demonstrated human-to-human transmissibility. It also has a high mortality rate (42 per cent) and was called "a threat to the entire world" by Dr Margaret Chan, the Director-General of WHO at the 66th World Health Assembly in Geneva. In the US the Obama administration designated MERS-CoV a threat to public health and national security, and authorized the fast-tracking of approvals of tests and treatments for MERS-CoV.

b) A health worker who treated the first MERS case in Dubai contracted the disease.

c) Oman reported its second MERS case at the beginning of January.

November-December 2014

a) By early December the global total of laboratory confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) was 163 (and a dozen probable cases) with 70 deaths. Cases traced back to infections in a handful of countries on the Arabian Peninsula: Jordan, Saudi Arabia, Qatar, the United Arab Emirates and Oman. Camels in both Qatar and Saudi Arabia have tested positive to the virus.

b) On 18 November Spain announced its second case in a woman who participated in the recent Hajj in Saudi Arabia, had travelled to Saudi Arabia with Spain's first MERS case, and had shared sleeping quarters with her.

c) Scientists developed a strain MERS-CoV that could be used as the basis of a safe and effective live-attenuated vaccine against MERS[79]. "Our achievement was a combination of synthetic biology and genetic engineering," said co-author Luis Enjuanes of The Autonomous University of Madrid. "The injected vaccine will only replicate in a reduced number of cells and produce enough antigen to immunize the host," he says, and it cannot infect other people, even those in close contact with a vaccinated person.

d) Inovio reported positive results in preclinical tests for its MERS vaccine, whose production is based on its DNA (SynCon) vaccine technology.

e) WHO on 19 November placed all health care providers on red alert on possible outbreak of Severe Acute Respiratory Infections (SARI). It said recent travellers returning from the Middle East who develop SARI should be tested for Middle East respiratory syndrome coronavirus (MERS-CoV).

f) Scientists from Imperial College London, the University of Edinburgh and the Institut Pasteur in Paris, in a new analysis of MERS case data, suggest that for each case that is known, five to 10 may have been missed. The scientists further suggest that transmission of the MERS virus is occurring at a rate close to the threshold where it would be considered able to pass from person to person in a sustained manner. They said that on the evidence currently available they cannot rule out the possibility that person-to-person spread is the chief mode of transmission of the virus at this point. The other option is that viral transmission is through a combination of animal-to-person and then person-to-person transfer. They concluded "a slow growing epidemic is underway, but current epidemiological data do not allow us to determine whether transmission is self-sustaining in man"[80].

78 By 1 January, Saudi Arabia's case count was 141, with 57 deaths.

79 mBio

80 Lancet Infectious Diseases, 20 November 2013.

October 2013

a) WHO's International Health Regulations Emergency Committee unanimously decided on 2 October not to declare a Public Health Emergency of International Concern related to the Middle East respiratory syndrome coronavirus.

b) By 25 October there had been 144 confirmed cases of MERS.

August 2013

a) Concern continues about the pandemic potential of MERS-CoV, particularly with sizeable international gatherings of pilgrims to occur soon in the Middle East[81]. 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[82]. While there is a view that the virus originated in bats[83], 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[84]. The FDA approved a diagnostic test to detect MERS-CoV.

July 2013

a) The Obama administration in early June designated Middle East respiratory syndrome coronavirus (MERS-CoV) a potential threat to public health and national security. This permitted fast-track approval of treatments and tests. In March, Congress had passed the Pandemic and All-Hazards Preparedness Reauthorization Act, strengthening the policies on emergency health threat designations.

b) At the end of June, Saudi Arabia's Health Ministry announced seven further laboratory-confirmed cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and a death in a previously confirmed case. Virologists expressed concern about the possibility of transmission and geographic spread of the virus as a result of religious pilgrimages. Pilgrims were being encouraged to wear masks for the October Haj.

c) WHO on 6 July announced it would convene an International Health Regulations (IHR) Emergency Committee on MERS-CoV as there is a lack of knowledge about the disease. At that time there had been 77 confirmed cases and 43 deaths

d) On 12 July, the Saudi Ministry of Health announced that, in a measure to prevent the spread of MERS-CoV, the elderly and those suffering from chronic diseases would not be granted Haj visas this year, nor would they receive visas for the subsequent Umrah season.

e) On 13 July, WHO announced that a laboratory confirmed case in the United Arab Emirates brought the global total to 82 cases.

81 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.

82 Including Professor Chris Baggoley, 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.

83 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)

84 The Lancet Infectious Diseases, DOI: 10.1016/S1473-3099(13)70164-6

f) A report in the New England Journal of Medicine says Middle East respiratory syndrome coronavirus is readily transmitted in health care settings, and represents a serious risk to hospitals[85].

g) By the end of June Greffex announced it had developed a vaccine against MERS-CoV. The company's proprietary GREVAX platform was developed with support from the US National Institutes of Health (NIH) and the US National Institute of Standards and Technology. GREVAX vaccines can be administered by injection or nasal mist.

h) Purdue University researchers who previously created a drug to block the SARAS virus have been working with MERS-CoV.

Ebola Virus Disease (EVD)

April 2014

a) As of 31 March 2014, Guinea's Ministry of Health had reported 122 clinically compatible cases of EVD, of which 24 were laboratory confirmed, and 98 were probable (78) or suspected (22) cases. The total included 80 deaths, of whom 13 have been laboratory confirmed for EVD with the remaining 67 regarded as probable. As of 30 March 2014, 20 patients were in isolation. Eleven health care workers were among the probable and suspected cases. Efforts were being made to prompt community awareness about the importance of hand washing, and using personal protective equipment when handling potentially contaminated blood and body fluids and during environmental and disinfection. Safe burial is a major concern[86]. This is the first Ebola epidemic to strike Guinea. Guinea has banned the sale and consumption of bats and other bush meat. It has banned public funerals forvictims. Volunteers from the Guinean Red Cross have been dealing with infected bodies and disinfecting the homes of victims.

b) At 1 April 2014 Liberia's Ministry of Health had reported eight clinically compatible cases of EVD, including two laboratory-confirmed cases. Two patients had died.

c) Sierra Leone's Ministry of Health said it is vigilant following the deaths of two probable cases of EVD in one family who died in Guinea but whose bodies were repatriated to Sierra Leone.

March 2014

a) A consortium including the University of Texas Medical Branch at Galveston (UTMB) has been awarded a grant by NIAID to develop vaccines and treatment for the Ebola and Marburg viruses. Researchers from the US Army Medical Research Institute of Infectious Diseases (USAMRIID) and their industry partners recently showed a small-molecule drug candidate protects macaques against Marburg[87].

85 Abdullah Assiri, M.D., Allison McGeer, M.D., Trish M. Perl, M.D., Connie S. Price, M.D., Abdullah A. Al Rabeeah, M.D., Derek A.T. Cummings, Ph.D., Zaki N. Alabdullatif, M.D., Maher Assad, M.D., Abdulmohsen Almulhim, M.D., Hatem Makhdoom, Ph.D., Hossam Madani, Ph.D., Rafat Alhakeem, M.D., Jaffar A. Al-Tawfiq, M.D.; Matthew Cotten, Ph.D., Simon J. Watson, Ph.D., Paul Kellam, Ph.D., Alimuddin I. Zumla, M.D., and Ziad A. Memish, M.D, "Hospital Outbreak of Middle East Respiratory Syndrome Coronavirus". June 19, 2013DOI: 10.1056/NEJMoa1306742

86 People can become infected during burial ceremonies involving close contact with the bodies ofEbola victims.

87 Travis K. Warren, Jay Wells, Rekha G. Panchal, Kelly S. Stuthman, Nicole L. Garza, Sean A. Van Tongeren, Lian Dong, Cary J. Retterer, Brett P. Eaton, Gianluca Pegoraro, Shelley Honnold, Shanta Bantia, Pravin Kotian, Xilin Chen, Brian R. Taubenheim, Lisa S. Welch, Dena M. Minning, Yarlagadda S. Babu, William P. Sheridan, and Sina Bavari. "Protection against filovirus diseases by a novel broad-spectrum nucleoside analog BCX4430": Nature, published

Chagas disease

January 2014

a) A Canadian team led by Deborah Nicoll-Griffith of the Merck Frosst Centre for Therapeutic Research in Kirkland, Quebec, has developed a class of compounds which may help eradicate Chagas disease[88]. The current standard of care, benznidazole, has significant activity against the invading parasite during the acute phase, but is less effective in the chronic phase.

July-August 2013

a) 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.

b) 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[89].

c) Chagas disease, endemic in Latin America, is now present in a number of countries. A recent case report from Canada, referring to the fact that Canadian Blood Services and HemaQuebec have both initiated blood donor testing for the Chagas antibody, describes an unusual "case of vertical transmission from a mother, most likely infected through blood transfusion, and detected as part of a concurrent seroprevalence study in blood donors"[90]. The US also tests donors for Chagas disease[91].

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online 2 Mar 2014 (1800 London time/1300 Eastern US time). DOI: 10.1038/nature13027.

88 The research was published online ahead of print in Antimicrobial Agents and Chemotherapy.

89 R A Ashmus et al, Org. Biomol. Chem., 2013, DOI: 10.1039/c3ob40887f

90 MA Fearon, V Scalia, M Huang, I Dines, M Ndao, P Lagacé-Wiens, "A case of vertical transmission of Chagas disease contracted via blood transfusion in Canada", Canadian Journal of Infectious Diseases and Microbiology, Spring 2013, Volume 24 Issue 1: 32- 34.

91 The CDC website on American Trypanosomiasis (also known as Chagas Disease) includes the following Blood Screening FAQs. Why are blood banks now screening for Chagas disease? The transmission of Chagas disease via blood transfusion is a recognized risk. Screening tests recently have been approved by the Food and Drug Administration. Screening for Chagas disease makes the blood supply even safer for everyone. How does the screening test protect people from Chagas disease? The blood screening test allows blood banks to destroy potentially infectious blood before it is given to anyone. Screening will prevent those who are found to have the disease from donating blood again.Will I be tested automatically? Yes. Most donors will only be tested once and if the result of their test is negative for Chagas disease, they will not be tested when they donate again.Can Chagas disease be spread through donated organs? Yes. Chagas disease can be spread to an organ transplant recipient if a donated organ came from a person with Chagas disease. If I test positive for Chagas disease, can I give blood again? No. You cannot donate again if you've tested positive for Chagas disease. If I was diagnosed with Chagas disease in the past, can I donate blood? No. If you have ever been diagnosed with Chagas disease, you will not be able to donate blood.If I have had a transfusion or a transplant, should I be concerned about getting Chagas disease? Probably not. The risk is very low. You should, however, be aware of the potential risk for Chagas disease infection and the need to monitor your health. If you have symptoms of Chagas disease or other concerns you should contact your health care provider.

Variant Creutzfeldt-Jakob disease (vCJD)

April 2014

a) Experts have reassured UK members of parliament that very few cases of vCJD are missed by doctors. However, as there has been no test for it, the precise number of people with the degenerative brain disease remains uncertain. This human form of bovine spongiform encephalopathy (BSE), appeared after widespread exposure to BSE prions in the late 1980s and early 1990s through contaminated meat. A recent study published in the BMJ[92] estimated that 1 in 2000 people in the UK carried vCJD proteins, although only 177 clinical cases had occurred thus far.

March 2014

a) Dr Graham.Jackson, of the University College of London Institute of Neurology, and his colleagues have reported on a blood test screening for infection with the agent responsible for variant Creutzfeldt-Jakob disease (vCJD)[93], performing well enough to be used to screen populations at risk for the disease.

January-February 2014

a) Novant Health Forsyth Medical Center in Winston-Salem, North Carolina, performed a procedure on a patient with neurological symptoms on 18 January. Subsequent tests revealed he had Creutzfeldt-Jakob disease (CJD). The surgical equipment used in the patient's procedure was not then sterilized up to the enhanced standards required in CJD cases, since prions can survive routine cleaning procedures. The hospital said in its statement: "There were reasons to suspect that this patient might have had CJD. As such, the extra precautions should have been taken, but were not." Eighteen neurosurgery patients at the hospital may have been exposed to CJD.

b) That the blood of patients affected by sporadic and the new variant of Creuztfeldt-Jakob disease (CJD) shows the presence of infectivity was established by scientists from the French National Institute for Agricultural Research and the French National Veterinary School and European partners. Results so far[94] support the concern that CJD might be transmitted (from people incubating the disease) by blood transfusion and blood derived products.

c) German officials identified a cow with a case of bovine spongiform encephalitis (BSE), the country's first reported case since 2009. The cow was killed and its body destroyed, with none of the meat entering the human food chain.

d) In Scotland a £90,000 study, funded by the Scottish Infection Research Network, will assess the best way of cleaning surgical instruments to prevent vCJD infection risk. Professor Andrew Smith of the University of Glasgow who is leading the study, said: "With new data suggesting that one in 2,000 people potentially carrying vCJD prions, the risk of transmission of the disease via surgical instruments remains a public health concern."

92 BMJ 2014; 348 doi: http://dx.doi.org/10.1136/bmj.g2425 (Published 28 March 2014) Cite this as: BMJ 2014;348:g2425

93 InJAMA Neurology, published online 3 Mar 2014, doi:10.1001. They said the assay was of sufficient sensitivity and specificity to warrant a major study comparing vCJD prevalence in the UK with a population unexposed to BSE.

94 published in the journal Emerging Infectious Diseases on 11 December 2013

e) In the UK, the House of Commons science and technology committee decided to open a parliamentary investigation into measures to improve the quality of screening of blood and organ donors. Amongst other experts, Dr Roland Salmon had told MPs the danger of variant CJD "becoming a self-sustaining epidemic"–because of the ever-increasing number of infected carriers–"has to remain a significant concern". The committee was told by a witness that the country's blood banks are "a ticking time-bomb" because donations are not properly screened for mad cow disease[95].

September-October 2013

Scientists from Case Western Reserve University have suggested a promising discovery for the prevention and treatment of prion diseases. They claim recombinant human prion protein stops the propagation of prions[96].

In the US, insufficient sterilization of instruments at a New Hampshire hospital has led to concerns about a possible "outbreak" of Creutzfeld-Jacob disease.

Cytomegalovirus (CMV)

March 2014

a) Chimerix announced enrolment of the planned 450 patients in their phase III SUPPRESS trial of brincidofovir is on track to provide results in mid-2015. Positive data would support accelerated approval of brincidofovir for the prevention of cytomegalovirus (CMV), the first approval of an antiviral for the prevention of CMV in recipients of bone marrow transplants.

July to October 2013

a) Chimerix announced the publication of results from its Phase II Study of CMX001-201 evaluating brincidofovir (CMX001) for the prevention of cytomegalovirus (CMV) infection in hematopoietic cell transplant (HCT) recipients[97].

b) Theraclone Science announced it had dosed the first patient in a Phase IIa trial of TCN-202 for the prevention of human CMV infection in solid organ transplant recipients.

c) Vical of San Diego and Astellas Pharma of Tokyo have initiated a multi-national Phase III trial of a vaccine to control cytomegalovirus. ASP0113, or TransVax, will be tested in about 500 hematopoietic cell transplant recipients.

95 A study of archived appendix samples (published in October 2013) postulated that 1 in 2,000 people in the UK may carry the abnormal prion protein associated with vCJD. Gill O, Spencer Y, Richard-Loendt A, et al. "Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey". BMJ 2013;347.f5675. Also Salmon R, "How widespread is variant Creutzfeldt-Jakob disease?" BMJ 2013;347:f5994

96 Published online in Scientific Reports. Senior author Wen-Quan Zou, associate professor of pathology and neurology at the University's School of Medicine.

97 "CMX001 to Prevent Cytomegalovirus Disease in Hematopoietic-Cell Transplantation," appears in the September 26(th) issue of the New England Journal of Medicine (N Engl J Med 369:1227-36).

HIV

March 2014

a) An HIV baby born in Los Angeles last April began treatment four hours after birth and is showing no signs of the disease. A child from Mississipi received similar treatment over three years ago and is also reported to be disease free. A clinical trial will be conducted with 60 babies who are born infected put on drugs within 48 hours.

b) Seattle BioMed, the University of Washington, Seattle Children's Hospital, the Fred Hutchinson Cancer Research Center, and Rockefeller University have together been awarded a grant from the US National Institute of Allergy and Infectious Diseases (NIAID) toward developing an HIV vaccine.

c) Scientists at the University of Illinois at Urbana-Champaign have developed a microchip that can diagnose the HIV virus. Their small device takes a drop of blood from a patient[98].

January 2014

a) Two men who underwent routine bone marrow transplants in Boston, and who appeared to have become free of human immunodeficiency virus (HIV) after around eight months of antiretroviral therapy, have now tested positive for the virus again. A study[99] has recently found T memory stem cells appear to hide a (HIV) viral reservoir long after treatment.

November-December 2013

a) Japan's health minister said blood donated by an HIV-positive man slipped through safety checks by the Japan Red Cross Society and was transfused into two recipients at separate medical institutions. According to the ministry, the man found to be HIV-positive during blood safety screening in November had also donated blood in February. While the blood he donated in November was not used in transfusions, HIV was detected in a stored sample of blood he had donated in February. The infected blood may have passed the virus-detection system because HIV levels are low during the early stage of infection. The donor admitted lying at the time of the February donation when answering a question concerning whether he had had risky sexual contact. The ministry now suspects the man donated blood to discover whether he was infected with HIV.

b) Figures revealed in the Kirby Institute's Annual Surveillance Report, released at the Australasian HIV & AIDS Conference in Darwin in November, suggest that nearly half of the estimated 207,000 people living with chronic hepatitis B in Australia continue to remain undiagnosed, while 15 per cent of people living with chronic hepatitis C in Australia have not yet been diagnosed[100].

98 Watkins NN, Hassan U, Damhorst G, Ni H, Vaid A, Rodriguez W, Bashir R. "Microfluidic CD4+ and CD8+ T Lymphocyte Counters for Point-of-Care HIV Diagnostics Using Whole Blood." Science Translational Medicine. 2013.

99 published online January 12 in Nature Medicine, corresponding author Mathias Lichterfeld, from the Division of Infectious Diseases, Massachusetts General Hospital.

100 The report found that almost 400 deaths in 2012 were related to hepatitis B-related liver disease despite the rate of diagnosis of newly acquired hepatitis B infection declining among those aged 30 years or older as well as reducing substantially among people aged 15-29 since 2003. In 2012, NSW had the highest number of diagnoses of hepatitis B infection, with 34.7 percent of the national total. The report also found that an estimated 310,000 people living in Australia in 2012 had been exposed to hepatitis C, with it thought that 173,500 had chronic hepatitis C infection and early liver disease, 51,500 had chronic hepatitis C infection and moderate liver disease, and 6,500 were living with hepatitis C related cirrhosis. The other 80,000 people believed to have to have been exposed have cleared their infection. The Kirby Institute estimates that almost 80 per cent of all infections for hepatitis C occur among people who inject drugs, with only one per cent of those people currently receiving treatment. Unlike other types of hepatitis, there is currently no vaccine to prevent hepatitis C, and medication is the only way to manage the disease. It is believed that 10-15 percent of all people living with HIV in Australia may also have hepatitis C and that

Measles, Mumps and Whooping Cough (Pertussis)

March-April 2014

a) On Fri 28 Mar 2014, the San Diego County Health and Human Services Agency reported 10 new cases of pertussis, where others in the county may have been exposed to the disease. This brings the total number of cases reported so far in 2014 to 154, a large increase compared to the only 33 reported cases during the same time in 2013.

b) The phrase "pertussis paradox" describes the rise in reported cases of pertussis (whooping cough) seen in the developed world after a switch was made to a more tolerable, less reactogenic vaccine[101]. The US and Spain are amongst countries which have seen increased pertussis cases this year in the northern hemisphere winter. Australian researchers have also looked at the vaccine pressure involved with the continued evolution of the organism[102].

February 2014

a) California has had its worst measles outbreak for twenty years.

b) NSW Health urged everyone planning on travelling to the Philippines to ensure they are up to date with their measles vaccinations before they travel. The Northern Territory Health Department said on 7 February that its nineteenth case of measles in three weeks had been infectious while on a flight from Manila to Darwin.

c) New Zealand had a number of cases of measles which it traced to one person who had visited Sydney and socialized with travellers from the Philippines.

November-December 2013

a) A number of Victorians were diagnosed with measles after returning from Bali, and passed on the disease to others. In South Australia six children and a 36 year old woman returned from Bali with measles. A Queensland prison had an outbreak of measles after a prisoner introduced it into the facility. The infected prisoners were in their late 20s and 30s, of an age group that avoided contracting the disease as children but were too old to have been vaccinated under a mass drive in the 1990s.

October 2013

a) In September, Queenslanders were urged to check their measles vaccination status after the fourteenth diagnosis for the year. West Australian travellers were warned to watch for symptoms if they had been in Bali, as returning travellers had contracted the disease.

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co-infection remains a serious issue.

101 Lutwick LI, Preis J:"Pertussis": In: Emerging Infectious Diseases: Clinical Case Studies. Ergonul O, Can F, Akova M, Madoff L (eds), 2014, Elsevier, (in press)

102 Lam C, Octavia S, Ricafort L, et al: "Rapid increase in pertactin-deficient _Bordetella pertussis_ isolates, Australia". Emerg Infect Dis 2014; 20(4)

September 2013

a) Queensland Health was notified of six measles cases in the month to September 6 and was concerned about the potential spread of the virus. By 11 September the NSW North Coast Public Health Unit was advising a Tweed area alert.

b) The CDC considered over a decade's worth of data on measles cases to the end of August 2013 and found that most patients had not been vaccinated. The report concluded that although the US declared measles eliminated nationally in 2000, anti-vaccination believers were causing a return of the disease.

c) Scientists from Curtin University and The University of Western Australia are hoping to develop a new whooping cough vaccine to be delivered via nasal spray. They say the vaccine should be more effective than current vaccines, have fewer side effects, offer long-term protection and require fewer booster doses. They hope it will be commercially available within five to eight years[103].

July-August 2013

a) Victoria's Chief Health Officer warned of a potential measles outbreak after an infected man travelled through several public crowded locations in Melbourne.

b) Public Health England has warned that waning immunity to mumps in those given at least one does of the two-dose MMR (measles, mumps and rubella) vaccine may be contributing to transmission.

c) In mid-June, NSW Health warned of an outbreak of mumps across the state.

Tuberculosis (TB)

April 2014

a) Health workers in Papua New Guinea fear a galloping tuberculosis epidemic, health workers say 15,000 new cases are recorded annually. WHO says a quarter of those are fatal. UNAIDS PNG coordinator Stuart Watson reports that it is people living with HIV in PNG who are most at risk of contracting TB. He said multi-drug resistant (MDR) and extra-drug resistant (XDR) TB are increasing in PNG.

b) India and China together account for almost 40 per cent of the world's known TB cases India had an estimated 2.8 million people infected with TB in 2012, whereas China had half that number.

c) Of the 40 000 TB cases recorded in Bombay in 2013, more than ten per cent were relapse cases. The annual count of relapse cases has remained constant for a number of years. Over the last three years, the count of MDR and extensively drug resistant (XDR) TB cases has increased substantially[104].

103 After an intensive vaccination campaign, the number of cases in Australia dropped from 38,500 in 2011 to 26,000 in 2012, but this is high for a preventable infectious disease which is potentially fatal in babies.

104 From 181 new patients diagnosed with MDR TB and 288 under treatment for it in 2011, the figure rose to 2195 new patients diagnosed with MDR TB and 1935 under treatment the next year. In 2013, 2903 patients were diagnosed with MDR TB and 2604 were on treatment.

January –February 2014

a) British and Swedish researchers have found that patients with "superbug" types of tuberculosis (TB) could in future be treated with undifferentiated cells taken from their own particular bone marrow.

b) A study found that the majority of children in the US at risk for tuberculosis were either born outside the US or born in the US to parents born outside the country[105].

September-November-December 2013

a) The EMA's CHMP recommended the authorization of Deltyba (delamanid) and Para-aminosalicylic acid Lucane (a new formulation of para-aminosalicylic acid), as options for use in combination with other drugs to treat multidrug-resistant tuberculosis.

b) Jean-Pierre Zellweger, of the University of Lausanne, and colleagues reported at the European Respiratory Society meeting on their tracing study of tuberculosis-exposed people. They confirmed the accepted wisdom that close family contacts of tuberculosis were more likely to acquire the disease than other contacts.

July 2014

a) Extensively drug-resistant tuberculosis in Papua New Guinea is a concern in Far North Queensland, with free movement between settlements in the Torres Strait.

b) An international team has identified a new anti-tuberculosis compound which it says is active not only against ordinary TB bacteria but also against non-replicating TB bacteria and even extensively drug-resistant TB strains[106]. The team was led by scientists from The Scripps Research Institute (TSRI), the Howard Hughes Medical Institute and Albert Einstein College of Medicine of Yeshiva University.

Polio

April 2014

a) WHO South-East Asia Region [SEARO], home to a quarter of the world's population, was certified polio-free on 27 March 2014 by an independent commission under the WHO certification process. It is the fourth of six WHO Regions to be certified, one more towards global polio eradication. Eighty per cent of the world's population now resides in certified polio-free regions.

b) With continuing incidence of polio in the Syrian Arab Republic with international transmission, the polio outbreak response in the Middle East remains in place to contain regional spread.

105 Jenny Pang, Larry D. Teeter, Dolly J. Katz, Amy L. Davidow, Wilson Miranda, Kirsten Wall, Smita Ghosh, Trudy Stein-Hart, Blanca I. Restrepo, Randall Reves, and Edward A. Graviss, on behalf of the Tuberculosis Epidemiologic Studies Consortium, "Epidemiology of Tuberculosis in Young Children in the United States", Pediatrics, Published online February 10, 2014. doi: 10.1542/peds.2013-2570.

106 Their paper appeared online in June ahead of print in the Proceedings of the National Academy of Sciences. Senior authors of the study were Peter G. Schulz and William R.Jacobs,Jr.

March 2014

a) To achieve the goal of eradicating polio by 2018, WHO recommended that by the end of 2015, all children receive routinely at least one dose of Inactivated polio vaccine in over 120 countries that use only oral vaccine. Oral Polio Vaccine. Sanofi Pasteur and the Bill & Melinda Gates Foundation are amongst organizations making financial contributions. Iraq has announced its first polio case in fourteen years.

February 2014

a) In Afghanistan, Kabul has seen its first polio case since 2001. Polio is regarded as endemic in the rest of Afghanistan, Pakistan and Nigeria. Concerns in the Middle East have recently led to major vaccination campaigns. In 2013 there were 190 cases in Somalia, and multiple cases in Ethiopia, Cameroon and Kenya.

November-December 2013

a) Mass polio vaccination campaigns have been occurring across the Middle East, targeting 22 million children in seven countries. This follows the confirmation of wild poliovirus cases in several locations. Two European infectious disease experts have warned that wild polio virus might endanger Europe, through the flow of refugees from Syria and through visitors returning from the Hajj in Saudi Arabia[107].

July-August 2013

a) 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). 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. 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.

b) WHO sent a mission to Israel following detection of wild poliovirus in sewage. It recommended surveillance in countries with contacts in Israel. A supplementary immunization campaign with oral polio vaccine will be undertaken locally.

Other diseases

April 2014

a) In the autumn of 1348 the Black Death reached Britain from central Asia and by late spring the following year it had killed sixty per cent of London's population. Scientists extracted the DNA of the bacterium, Yersinia pestis, from teeth in skulls found during excavations and compared the strain of bubonic plague with the strain that recently killed 60 people in Madagascar. Tthe fourteenth century strain was no more virulent than the modern disease. The DNA codes were an almost coinccident. Some scientists believe that for the plague to spread so fast it must have invaded the lungs of victims and was transmitted by

107 Artin Eichner and Stefan Brockmann in Lancet Infectious Diseases, 8 November 2013 (online).

coughs and sneezes, and was therefore a pneumonic plague as well as a bubonic plague. Infection was transmitted human to human, not just by the rat fleas that bit a sick person and transmitted the plague to the next victim. "As an explanation [rat fleas] for the Black Death in its own right, it simply isn't good enough. It cannot spread fast enough from one household to the next to cause the huge number of cases that we saw during the Black Death epidemics," said Dr Tim Brooks, who put his theory in a Channel 4 documentary, Secret History: The Return of the Black Death. . Antibiotics can today prevent rodent flea-associated bubonic plague the disease from becoming pneumonic.

March 2014

a) Given the spread of microorganisms with the New Delhi metallo-beta-lactamase (NDM) resistance mechanism, both across bacterial species and across geographic boundaries, the Pan American Health Organization/WHO emphasised again the need to establish prevention and infection control in health care settings, as well as surveillance and detection.

b) At least 2.7 million Americans currently have hepatitis C[108]. Many are not aware they are infected. More people in the US now die from infection with hepatitis C than from HIV, the virus that causes AIDS. Risk factors for hepatitis C include intravenous drug use, and having received a blood transfusion before 1992. With Baby Boomers being six times more likely than others to be infected with hepatitis C, the CDC recommends one-time screening for people born between 1945 and 1965. Screening, together with more effective and better tolerated medication becoming available, could reduce the death rate significantly.

February 2014

a) Daiichi Sankyo and UMN Pharma have entered into a collaborative research agreement to develop a vaccine against norovirus, one of the leading causes of infectious gastroenteritis globally[109].

January 2014

a) Six biosecurity experts have strongly supported[110] the omission of key genetic information from the October Journal of Infectious Diseases report of a newly identified Clostridium botulinum toxin. The six are either current or former members of the US National Science Advisory Board for Biosecurity. The toxin's genetic sequence data has reportedly been withheld until an antitoxin can be developed.

b) The CDC reported that the number of cases of primary and secondary syphilis in the US increased 11.1 per cent in 2012. Men-particularly gay and bisexual men-accounted for the spike. Gonorrhoea increased 4 per cent in 2012, mostly among men.

c) A study of silent hepatitis E infection amongst blood donors in the Netherlands[111] 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

108 Dr. David Bernstein, chief of hepatology at North Shore University Hospital in Manhasset, N.Y said: "Our methods of estimating the true prevalence of the disease is flawed. All [federal government] reports underestimate the true prevalence of hepatitis C infection as they do not include the homeless or the incarcerated-two large populations with a high prevalence of hepatitis C infection."

109 Patel MM, et. al. "Systematic Literature Review of Role of Noroviruses in Sporadic Gastroenteritis", Emerg Infect Dis. 2008; 14(8):1224-31.

110 Casadevall A, Enquist L, Imperiale MJ, et al. "Redaction of sensitive data in the publication of dual use research of concern". mBio 2014;5(1) (Early online publication Dec 31, 2013)

111 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

transfusion[112] 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".

November-December 2013

a) By 30 October, around 150,000 horses in Australia had received the newly-developed Hendra virus vaccine.

a) Two US universities have experienced outbreaks of meningococcal disease.

August 2013

a) Work continues on vaccines[113] against Lyme disease, carried by ticks and increasing in notifications in the US. 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.

b) 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.

c) Researchers at St Louis University have been testing a vaccine against plague, considered a potential weapon in a bio-terrorism attack.

d) 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.

July 2013

a) Legionnella was discovered in the hot water system at Wesley Hospital, Brisbane. One patient died, another contracted the disease. Testing of hot water systems at other Queensland hospitals led to sanitization work at a number of them. Queensland Health then 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.

b) The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended approval of a new smallpox vaccine. Imvanex (Bavarian Nordic) is for active immunization against smallpox in adults-for primary vaccination (for individuals previously not vaccinated against smallpox) or booster vaccination. It can also be used in immunocompromised people. Unlike traditional smallpox vaccines, Imvanex is nonreplicating, which means it does not proliferate in the body, the committee notes."It is a live attenuated virus which works by inducing the immune system to produce antibodies against the smallpox virus. It will be available as a suspension for subcutaneous injection," the committee said.

c) Hendra virus killed unvaccinated horses on the mid north coast of New South Wales and west of Brisbane. There is no vaccine for humans. The disease is spread by flying foxes.

112 And has been reported in Saudi Arabia, Japan, France and the United Kingdom.

113 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

NATIONAL BLOOD AUTHORITY
AUSTRALIA