Parliamentary and Scientific Committee

Zika Meeting – 10.3.16

Event held as a contribution towards British Science Week

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Introduction to Zika virus

- Zika was first identified in Uganda – first in monkeys (1947), then in humans (1952). At first confined to equatorial Africa, then moved into South East Asia and to the Pacific Islands. In 2015 it was recorded in Central and South America.
- Zika is a flavivirus generally transmitted by the *Aedes* genus of mosquitoes (these also carry dengue, chikungunya and yellow fever), although some sexual transmission occurs.
- Symptoms of Zika are usually mild and may include a rash, itching, fever, muscle pain and conjunctivitis, however there are two conditions thought to be associated with Zika which are especially worrying:
    - **Microcephaly** - babies born with small and malformed craniums, and a non-fully developed brain
        - So far an increase in microcephaly cases, other neonatal malformations and adverse pregnancy outcomes has been reported only in Brazil and Columbia (about 1000 cases confirmed)
        - **UPDATE** as of April 13th, 2016, the link between Zika and microcephaly has been confirmed. See http://www.nejm.org/doi/full/10.1056/NEJMsr1604338?query=featured_home
    - **Guillan-Barre syndrome (GBS)** – a temporary ascending paralysis, which is seen on recovery from a number of viral infections
        - 8 countries have reported an increased incidence of Guillain-Barré syndrome and/or laboratory confirmation of Zika virus infection among GBS cases (about 1000 reported)
- These additional conditions are only seen in Central and South America, and the Caribbean
- Genetic analysis of the virus showed it arrived in Brazil in 2014, and the geographical distribution has steadily widened since. It was not noticed and recorded until 2015.
    - There were 1 million cases in Brazil in 2015, and 4 million are expected in 2016.
- Active transmission has been reported in 31 countries.

Actions on Zika in Active Transmission Zone

- A Public Health Emergency of International Concern was declared by WHO in February 2016 – their highest emergency category – due to the possible links to microcephaly and GBS, rather than the infection itself. Launched a Strategic Response Framework, which incorporates:
    - coordination, surveillance, care, vector control
    - risk communication and community engagement
    - research at global, regional and country levels
- $56 million over 6 months has been requested by the WHO (World Health Organization) for the response in the active transmission zone

Actions on Zika outside active transmission zone

- Zika virus is likely to be transmitted and detected in other countries within the geographical range of competent mosquito vectors, especially *Aedes aegypti* – so there is a need to assess and mitigate the risk of spread by looking at:
    - Mosquito distribution
    - Preparedness of health services
    - Anti-mosquito measures and plans
    - Disinsection of aircraft – spraying of insecticide inside planes
- Travel – infected humans or mosquitos can spread the infection
    - 10 countries have reported imported cases from this outbreak
    - 9 imported cases in the UK
    - Evidence of sexual transmission, and transmission via blood transfusion

What is the UK Government currently doing about Zika?

- Public Health England are supporting WHO control activities through expert assistance
- Contribution to WHO Contingency Fund for Emergencies
- Funding research through rapid response calls (MRC, DFID, EC)
- DFID is:
    - helping African countries prepare for future potential spread of Zika
    - providing health sector support in Caribbean
    - assisting disease surveillance in SE Asia
    - Contributing to outbreak response in Haiti

What more do we need to be doing about Zika?

- Urgent:
    - Develop a reliable diagnostic test – ideally we need diagnostics that can be used at the bedside to give a quick answer, rather than in the lab, but at the moment any reliable test would be an advance
    - Assess modern anti-mosquito measures – currently relying on old methods
    - Assess risks of microcephaly and GBS – currently not able to give accurate risk predictions
        - Also need to understand when transmission from mother to foetus occurs in pregnancy
    - Community engagement and communication – need to get messages around risk clear – hard to do for a disease which is usually mild, but can have devastating consequences
    - Need to work out how best to provide information and advice on risks, pregnancy, contraception, abortion
- Medium term:
    - Vaccine development – vaccines are at least 18 months away
    - Drug development - although if developed, could possibly be problematic – how do you persuade people, especially those who are pregnant, to take drugs for a disease which generally has mild symptoms?
    - Establish host range in vectors – need to establish which mosquitoes could start acting as vectors
    - Plans to care for those with disability – those with microcephaly will need life-long support

Questions

- Q: Sir Peter Bottomley – What was the historic impact of Zika? Why has it only just come to our attention?
    - A: The disease used to be fairly inoffensive. It was only in Polynesia (5 years ago) that we started to see epidemics
- Q: Stuart Taylor (Royal Society) – Is it known when in pregnancy that birth defects arise?
    - A: It is known from studying Rubella that the first trimester is the most risky stage of pregnancy. But early work on Zika seems to suggest any stage is risky – Zika infection in pregnancy has led to miscarriage at 37 weeks.
- Q: Baroness Tonge – have we seen microcephaly associated with Zika virus before?

- A: It is not thought there were the same epidemics in humans before – the virus was mainly endemic in primates, only 7-10% of the human population in endemic areas would have caught it.

- Q: Claire Mouchot (French Embassy) – does the virus stay in the body and have longer term effects?
  - A: Currently no evidence of such.
- Q: How long after infection is the virus found in semen?
  - A: Known to stay in blood in urine for a week. Longer in semen, but not known how long exactly.

Dr James Logan

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The main vectors

- Primary vector: *Aedes aegypti* – a mosquito species highly adapted to the urban environment
  - Aggressive biters – bite even through clothing, and will take multiple blood meals
  - Bite during day and night, indoors and outdoors
  - Do not fly far: ~50m – so control measures around homes/schools can be effective
  - Mainly absent from Europe – too cold here
- Secondary vector: *Aedes albopictus*
  - Less adapted to urban environment – forest dwellers
  - Less aggressive biters
  - Usually smaller populations
  - Can survive in temperate regions
    - There are populations in southern Europe – probably only a matter of time before they arrive in the UK

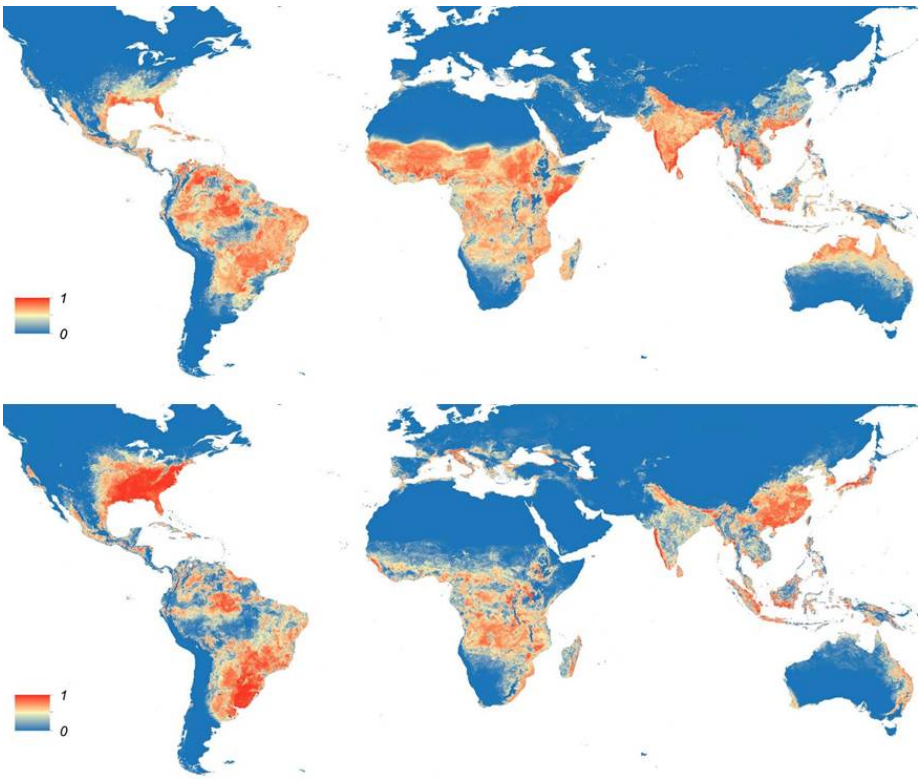

Figure 1 - Global map of the predicted distribution of the two main vectors: *Aedes aegypti* top, and *Aedes albopictus* bottom. The maps depict the probability of occurrence (from 0 blue to 1 red) at a spatial resolution of 5 km × 5 km. Taken from (Kraemer et al. 2015)

- The disease has also been isolated from certain species of the following genera of mosquito, but not to the extent to prove them as vectors:
    - *Anopheles* (malaria vector)
    - *Aedes* (other) (vector of dengue, chikungunya, yellow fever)
    - *Culex* (vector of filariasis and West Nile virus)

What vector control is being done?

- Insecticides are used to kill adult mosquitoes
    - Results of 'fogging' with insecticides are often short lived – resident mosquitoes killed, but there is influx of mosquitoes from surrounding populations
        - More of a PR exercise? Very visual, but evidence for effectiveness is sparse.
    - Residual spraying is long lasting but expensive
    - Insecticide resistance is an issue – mosquitoes can adapt to survive treatment with insecticides
- Can also use insecticides to target the larvae, which grow in stagnant water
    - Temephos – resistance has developed
    - Bti and Pyriproxifen show no resistance
- Can also just remove stagnant water from neighbourhoods – cheap but very labour intensive
    - Water pools in rubbish, tyres, flat roofs, etc
- Promotion of bed net usage – good for malaria (as the vector mosquitoes bite at night), but not so helpful for Zika, which is vectored by day biting mosquitoes
    - But importantly they still have a role for those sleeping during the day – eg. children napping, shift workers, those taking a siesta – so should be recommended
- There is evidence that vector control reduces mosquito populations, but in practice there are many challenges:
    - Resistance
    - Education of communities

- Co-ordination and sustainability
- Lack of evidence for effectiveness in containing the disease due to lack of studies – more research needed

- Insect repellents are highly recommended to provide personal protection. Are being given out to pregnant women in Brazil by government and clinics.
  - Four main active ingredients:
    - **DEET** (diethyl-m-toluamide): a synthetic repellent - the best and most widely used. 20-50% concentration recommended. Recommended for pregnant women. Safety proven.
    - **PMD** (p-menthane diol): a natural repellent from lemon eucalyptus
    - **Icaridin** (Bayrepel): synthetic repellent
    - **IR3535** : synthetic repellent
      - Latter three are effective but require more frequent reapplication than DEET
  - However, resistance to DEET has been shown to develop after just one generation in the lab (Stanczyk et al. 2010), so needs to be monitored in the wild. Repellents have not been used on this scale before, so need to watch closely for resistance.
  - Jury is out on effectiveness of repellents in controlling disease. There have been eight trials of the effectiveness of repellents against malaria, four of which are adequate for meta-analysis. Meta-analysis found there was a non-significant reduction of 30% in risk of *P. falciparum* infection (Wilson et al. 2014) - more trials needed.
- Aircraft disinsection – cabin crew spray inside cabin with aerosol insecticide. Very little evidence this works; further trials needed – yet recommendations (for usage) have been made.
- Wearable technologies – clothing impregnated with repellent or insecticide provides 50-100% protection against bites, and lasts for 4-5 months. Affective even against resistant mosquitoes.
  - Could be used to protect against mosquitoes that transmit malaria, Zika, dengue and other insect-borne diseases
  - Further work underway at LSHTM and via arctec and a new spin-out company from LSHTM called Vecotech to develop this technology further

Potential new methods of vector control

- GM Mosquitoes – developed by Oxitec, a startup based in Oxford. Engineered to not produce viable offspring.
  - Trials have been carried out in Brazil (several locations), Cayman Islands and Panama. They showed up to 90+% suppression of total *Aedes aegypti* mosquitoes (measured by direct counting of larvae).
  - Over 150 million Oxitec mosquitoes released worldwide; no adverse effects on people or the environment.
  - Potential issues: Social dislike, reinvasion of adults from other areas, technology is species specific, scale up is hard
    - This is not an immediate solution, but it has potential
    - There is a good opportunity now to take this technology to the next level and investigate its efficacy further
- Another potential method of control is the use of the bacteria *Wolbachia*. This is an endosymbiotic bacteria which lives inside cells and infects >65% of insects. It is maternally inherited and manipulates host reproduction to enhance transmission. Importantly it inhibits the replication of Dengue, Chikungunya & Zika viruses in *Aedes aegypti* mosquitoes.
  - Rapidly invades and establishes in wild mosquito populations
  - Released in wild mosquito populations in Brazil, Indonesia, Vietnam and Australia
  - This technology is currently in very early stages – but this outbreak is a good opportunity to develop it further.
- We may be able to exploit humans' natural differential attractiveness to mosquitoes. It has been estimated that 10% of the population are unattractive to mosquitoes – if we can understand why we may be able to make others unattractive to mosquitoes too.
  - This has never been investigated in disease endemic countries – again this is a good opportunity.
  - We know that pregnant women are more attractive to malarial mosquitoes – is it the same for *Aedes*?

- Attractiveness to mosquitoes is under strong genetic control – so could there be populations that have evolved natural repellency? (Fernández-Grandon et al. 2015)
    - If the genes can be identified, then a pill could be developed that upregulates the genes in question, and generates an 'aurora of repellency' around individuals.

Needs going forward

- Global mosquito database – currently no global database of mosquito vectors of disease
- Guidelines & training for vector control in S. America
- Community educational campaigns
- Guidelines for vector control for mitigation and rapid response in at risk countries
- Define accurate levels of resistance to insecticides & repellents
- Development and large trials of new technologies

Questions

- Q: Stephen Metcalfe MP – Are some countries better at vector control than others?
    - A: Yes – it's very much wealth dependant. Different countries also have different techniques they favour – and these are not necessarily the most efficient.
- Q: Lord Selbourne – How practical is it looking to scale up the production of mosquitoes by Oxitec?
    - A: They think it is feasible, just a matter of getting enough funding. They have just built a second factory in Brazil – will be able to protect 1 million people. Are also able to build temporary factories in trucks. However for scale up to be effective they need to develop methods of aerial deployment (currently just throw mosquitoes out of lorries) – and that will require more research.
- Q: Sally Cutter – Do we know how Zika virus interacts with the mosquito host?
    - A: Not yet – more research needed!
- Q: Are there reservoirs in other animals?
    - A: Don't yet know how wide the host range is – but primates are definitely important. Rio has forested areas in the city, which hold animals which act as reservoirs.

Professor Trudie Lang

Professor of Global Health Research; Director of the Global Health Network and Senior Research Scientist in Tropical Medicine, Nuffield Department of Medicine; Senior Research Fellow, Green Templeton College

Overview

- Drugs: could assess existing anti-viral drugs - nothing on the shelf as there was with Ebola as it was not seen as a threat
    - Could be effective too late to stop effect on pregnancies because anti-virals work best at early stages of infection and typically there are little or no symptoms to prompt treatment. Also issues in giving drugs to pregnant women, and so it is unlikely that drug therapy research will be a priority
- Vaccines:
    - Progress with DNA vaccine – NIH program has been in news – will have Phase 1 trails by the summer
        - But who do we target the vaccine at? How do we plan clinical trials and then scale it up? Issues with price and access – will it be affordable and available to the countries affected? Vaccine manufacture is also an important issue.
    - Traditional vaccine – slower – but work was underway to develop a vaccine for similar viruses like Western Nile disease.
- Need a diagnostic test to use in community settings - some progress has been made, but there is cross reactivity with Dengue or yellow fever
    - It is also important to include foetal scanning in the discussion on diagnostics. Here standardised assessments need to be agreed and validated to determine what is abnormal and what is happening

when in regard to the viral infection and developing baby. It needs to also be remembered that very few women in low-income countries have access to scans, and that abortion is illegal in most of the countries affected by Zika.

What did we learn from Ebola about drug, vaccine and diagnostic research and development during outbreaks?

- Scientists were only just starting to reflect on the Ebola response when Zika appeared – so they are having to apply lessons from Ebola straight away, before there has been time to embed them into international responses.
- In West Africa, for Ebola, there was very minimal clinical trial capacity and this slowed the response and resulted in outside organisations having to take the lead. Research infrastructure needs to be improved in low-resource countries so that they are able to respond to outbreaks locally.
    - Still managed to set up trials in 16 weeks (usually takes 18 months) – but this is not fast enough.
- We have to embed research into immediate response to a new outbreak in order that the disease can be understood and drug and vaccines can be evaluated within the very limited time within which an outbreak occurs
- Need to ensure this the research effort is coordinated and led by a neutral agency, such as the WHO, and not by any one country
- WHO have developed an R&D framework - http://www.who.int/csr/research-and-development/blueprint/en/
    - It is important that the response is strongly led and key questions such as which studies to prioritise are agreed by all. That way all stakeholders are able to contribute to the development of response.
- Collaborative efforts with Zika shows the need and importance of integrated research platforms – which typically cannot get funded. These need to operate outside of outbreaks to increase regional research capacity for tackling on going health issues and then are able to respond in outbreaks as they are already trained and active.
    - Zika has required coordination between maternal health researchers, epidemiologists, vector experts, which just shows how this ability to collaborate and share knowledge via research platforms is so important as so many different types of research and research disciplines are needed – and they need to communicate, share and engage.
        - For example, data capture standards are really important – eg. InterGrowth are working to unify how baby measurements are taken – important if we are to have worldwide knowledge of the extent of microcephaly. Now their tools – 'The International Fetal and Newborn Growth Standards for the 21st Century' - are recommended by the WHO and 11,728 have been downloaded, in 163 countries, from The Global Health Network (www.TheGlobalHealthNetwork.org). This means everyone is measuring in the same way, and therefore can agree what is abnormal and the situation can be properly assessed.
    - ISARIC are coordinating an international research response and developing sharing protocols and data capture tools. The Global Health Network is providing ISARIC with a secure, online, digital information platform for sharing these research documents, standards and as a mechanism for agreeing research priorities, logging who is doing what and for providing training, tools and guidance - www.zikainfection.org . This work is lead by researchers in Brazil and everything is translated into Spanish and Portuguese
- It is vital to put in place the ability to undertake research in areas of the world where the next outbreak is likely to be. There will be others new diseases and we are not ready for future outbreaks, because it takes too long to set up research studies
- In 2014 WHO said that unless low income countries become generators rather than receivers of research and data, then we are not prepared for future outbreaks. This has not happened.
    - Need a change in mind-set in low income countries – research is seen as a Western thing. Start with simple pragmatic trials, then build up research base. Health and laboratory workers in these regions need to be engaged, supported and trained.
- There will be other outbreaks – and we are not prepared. Global travel and urbanisation are raising the stakes on a future outbreak.
    - Therefore it is vital we work to develop (and get funding for) cross cutting research capacity development platforms. If we had these systems in place before Zika arose we would be much better able to answer all these unknowns much faster.

- Important that MRC, DFID and the Wellcome Trust need to change their funding frameworks to reflect this, and fund capacity development and research platforms that operate in between outbreaks and therefore have the ability to respond.
- We also need to look at what slows the process of setting up new studies. Delays such as regulatory approval and contracts can be solved ahead of time and this should be resolved through WHO working groups running cross-cutting projects to put solutions in place.

Questions

- Q: Stephen Metcalfe MP – How much of this needs to be global?
  - A: It all does; and the UK takes a key leadership role, such as the work that the Wellcome Trust is doing. UK Organisations such as the MRC, DFID and the Wellcome Trust work alongside and in close partnership with WHO and Gates Foundation etc. to drive international effort and collaboration.
- Comment: Stuart Taylor (Royal Society) – There has already been a call for freedom of information surrounding Zika research. Nature and Springer [science publishers] have agreed – Zika papers are no longer behind a paywall.
  - Response: This is a very important and game changing announcement – is a huge shift in the workings of science. But it will take time to see the full impact. Important to remember the need to enable the collection of data in the first place, and that it needs to be standardised and of good quality so that it is ready for sharing.

Wider questions aimed at all the speakers

- Q: Stephen Metcalfe MP – Is our government doing enough?
  - A: JW - The UK is second in terms of funding donated (only the US have donated more), and have made a considerable contribution to the contingency fund for the emergency. But we are not acting in Central and South America (instead the focus is on strategic areas in Africa and Caribbean) – so the government should think about expanding their response into the Americas.
  - A: JL - Also need concrete plans for what to do if *Aedes albiopictus* is found in the UK – including where funding for a response would come from. Currently the only monitoring is through the public sending in samples – not good enough.
    - The mosquito has already been found in France and Belgium – could easily come over this summer, like Bluetongue disease did last year.
- Q: Lord Selbourne – If Oxitec's mosquitoes are so promising, should the UK be leading on the scale up research?
  - A: JL – Would agree that this is the time to focus on scale up – but warns that the trials will take around 2 years, and we need viable control solutions now. Good success from other techniques too – need to scale up accessible tech. Conventional tools should not be ignored.
- Q: Tim Roberts (Institute of Patent Attorneys) – The Nagoya protocol of 2014 requires the country of sample origin to give permission for any genetic research – does this raise difficulties for Zika research?
  - A: JW – At the level we work we haven't seen any impact. But there has been discussion going on at high levels in the WHO and Dept of Health. More likely to have an impact of influenza research? Thought article 4.4 – if research is for global health research in a pandemic then it is excepted – may be of help.
- Q: What are we doing about screening blood products for Zika?
  - A: Minimal risk in UK, so no need as yet.
  - A: This is an issue in Puerto Rico, and they are having to import blood from the US.
- Q: Baroness Tonge – Is there proof of the link between microcephaly and Zika? Could it not be other reasons – eg. Crop spraying?
  - A: TL – The link is indeed not proven yet, and 'normal' base levels of birth defects are hard to establish as recording is limited in many affected countries. Other factors are important to consider. Need more background research.

        - May be that in Africa the human population has been previously exposed to Zika and so there are lower cases of microcephaly because women become immune before they reach child bearing age – but this is not proven either.
    - **UPDATE** - as of April 13th, 2016, the link between Zika and microcephaly has been confirmed. See http://www.nejm.org/doi/full/10.1056/NEJMsr1604338?query=featured_home
- Q: Dr Jane Pritchard (GAIN) – GBS is treated with blood products, so do we need to mobilise such products from Zika-free areas?
    - A: The priority treatment for GBS in affected areas in currently ventilation in the ICU (intensive care unit) – patients get better over time without the need for blood products. But healthcare facilities are hugely variable in Central and South America.
- Q: Cheryl Tweed – when/why did all this hit the news?
    - A: TL – The outbreak was widely known about in the medical community in early December, but in the UK the press were only mobilised when patients brought Zika back to the UK. BBC response has been very responsible. Great opportunity to explain why research is needed in low income regions of the world and in neglected tropical diseases, which normally gets ignored.
- Q: is this incursion into South America of a certain subtype of Zika virus?
    - A: JW – There are two factors to consider:
        - The strain of Zika seen is the Asian strain (not the African strain), which is more transmissible.
        - The Central and Southern American population is naive – have not encountered the disease before – so more susceptible to the disease.
        - Hard to say which of these factors is more important in this epidemic.
    - A: TL – Recent research has shown that this virus is quite highly conserved (similar genetically to other strains) – so it seems likely that this has occurred because these populations have not previously been exposed to the virus and so the problems arise as women are being infected for the first time when they are pregnant, when the foetal damage is occurring – but this is still a theory.

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