WHO global consultation of research related to Zika virus infection

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For further information on the R&D Blueprint, please visit:
http://www.who.int/csr/research-and-development/en/

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List of acronyms

ADE	Antibody dependent enhancement
ANVISA	Agência Nacional de Vigilância Sanitária/National Health Surveillance Agency, Brazil
BARDA	Biomedical Advanced Research and Development Authority
CCP	Clinical case characterisation protocol
CMC	Chemistry, manufacturing and controls
cRCT	Cluster randomized control trial
ECBS	Expert Committee on Biological Standardisation (WHO)
EMA	European Medicines Agency
EUAL	Emergency Use Assessment and Listing
EVA	European Virus Archive
EVAg	European Virus Archive goes global – online catalogue portal
FAO	Food and Agriculture Organization
GBS	Guillain-Barré syndrome
GM	Genetically modified
GOARN	Global Outbreak Alert and Response Network
IAEA	International Atomic Energy Agency
ICMRA	International Coalition of Medicines Regulatory Authorities
ICU	Intensive care unit
IDAMS	International Research Consortium on Dengue Risk Assessment, Management and Surveillance
IgG	Immunoglobin G
IgM	Immunoglobin M
IHR	International Health Regulations
IND	Investigational new drug
IRS	Indoor residual spraying
ISARIC	International Severe Acute Respiratory and Emerging Infection Consortium
IVD(s)	In vitro diagnostics
IVIg	Intravenous immunoglobulin
MERS-CoV	Middle East respiratory syndrome coronavirus
MTA	Material transfer agreement
NIBSC	National Institute for Biological Standards and Control (UK)
NRA	National regulatory authority
PAHO	Pan American Health Organization
PCR	polymerase chain reaction
PHEIC	Public health emergency of international concern
QMS	Quality management system
R&D	Research and development
RIDL	Release of insects carrying a dominant lethal
RT-PCR	Real time polymerase chain reaction
SARI	Severe acute respiratory infection
SOP(s)	Standard operating procedure(s)
TDR	Special Programme for Research and Training in Tropical Diseases

	(WHO)
TPP(s)	Target product profile(s)
UNICEF	United Nations Children's Fund
US FDA	United States Food and Drug Administration
VCAG	Vector control advisory group
VHF	Viral haemorrhagic fever
WHO	World Health Organization
ZIKV	Zika virus

Executive summary

As part of the emergency response to recent outbreaks of Zika virus, WHO initiated an emergency research and development (R&D) response plan addressing needs for Zika virus vector control, in vitro diagnostics (IVDs), vaccines, and therapeutics, along with coordination of supportive research activities. As part of its commitment to assisting relevant R&D efforts and its role as global convener, WHO organised a meeting in Geneva on 7-9 March 2016, bringing stakeholders from relevant fields together to expedite the development of the products required for a rapid, robust response to Zika virus. This meeting was the first major international opportunity for experts in Zika virology, clinicians, product development experts, modellers, funders and others to take stock together, identify knowledge gaps, and discuss joint planning for accelerated product development and evaluation.

On the first day, the meeting received an overview of current knowledge of flaviviruses in general and Zika virus in particular, including their origins, spread, classifications and symptoms. While Zika is the current focus, increasing globalisation and more frequent contact with wild animals mean that other flavivruses—familiar or obscure—may well emerge. The current situation regarding microcephaly and Guillain-Barré syndrome in Brazil was outlined and compared to the recent Zika outbreak in French Polynesia, where the presence of Guillain-Barré syndrome has been retrospectively evaluated as 24 per 100 000 Zika infections. A review of the major outcomes of the recent PAHO meeting on Zika was presented; a report on this meeting is imminent.

The consultation then explored the pathogenesis of microcephaly as a medical condition, not a disease, and the different aetiologies of the condition. The potentially helpful role of modelling in the development of countermeasures was outlined, but it was emphasised that such modelling relies on data collected in the field and this data must be of high quality.

The second day looked at specific R&D product pipelines for Zika vaccines, diagnostics and vector control. The product development community has responded energetically to the need for these resources, and the pipeline is expanding rapidly. One major advance compared to the recent response to the 2014/15 Ebola epidemic seems to be the speed at which data is being shared.

Product-specific summaries

While vaccines will come too late for countries currently affected by Zika outbreaks, development remains imperative for future outbreaks. All current vaccine projects are in their early stages, but experience with other flaviviruses suggests that the end goal should be technically feasible. Efforts are, however, hampered by a lack of basic tools for Zika vaccine development, including reliable animal models, reference reagents and assays. At the meeting, a draft target product profile (TPP) was presented for an emergency use vaccine; public consultation on this draft will start soon, with the goal of a finalised TPP in May 2016. This TPP should assist in reaching

consensus on regulatory requirements for evaluating prospective Zika vaccines, and provide orientation to vaccine developers.

In vitro diagnostics (IVDs)

Diagnostics development is busy, with manufacturers proposing many potential products. The meeting established general support for development of a TPP for multiplex IVDs able to provide differential diagnosis for Dengue, Chikungunya and Zika virus infections. A draft TPP is ready and about to undergo public consultation, with a final draft due in mid-April 2016. Such a product would complement Zika-specific tests. In this context, there is an urgent need for increased access to standards and reference materials and methods to facilitate product development. To help achieve this objective, benefits to encourage sample sharing should be improved and publicised. WHO encourages manufacturers to apply for Emergency Use Assessment and Listing (EUAL) of potential products, and promised to meet requests for more information on criteria used for evaluation under the EUAL.

Vector control

In the area of Zika vector control, the meeting heard strong arguments that thorough entomological investigations are imperative to fill obvious important knowledge gaps, particularly regarding the roles and behaviours of various mosquitoes in the transmission of flaviviruses in general, and Zika in particular. There is a surprising absence of evidence in literature that implementation on classical vector control interventions have had significant impact on Dengue transmission. It is imperative that investments be made in improving implementation of these interventions, notably through better community involvement, and in this regard the scientific community must be very rigourous in evaluating new and established vector control tools and methods. New tools would be discussed in depth at a WHO Advisory Committee on Vector Control emergency meeting, to be held a week after this gathering.

Therapeutics

Research into therapeutics was also presented, with emphasis on the outstanding need for more mature understanding of the stages of infection and the biology of the Zika virus, and the challenges of developing medications for use during pregnancy. There are still important roles for prophylaxis and therapeutics for other target populations; the goal must be to identify the different stages of Zika pathogenesis, enabling the identification of the window period for the various types of treatments. Known antivirals and immune-based interventions are being examined for their suitability for use as treatment, and similarities between the Zika and Dengue viruses raise the possibility of repurposing existing molecules. The cellular factors in Zika infection and the interplay with the immune system could provide valuable new pathways to developing treatments; in this context there is a pressing need for relevant animal models to complement various ongoing questions and studies.

Regulation and data sharing

Regulators present at the meeting established themselves as keen to innovate, and support innovation, in response to public health emergencies and the need for accelerated product development. Regulators always take risk/benefit factors into consideration and, as such, appropriate regulation can support rapid progress. Knowledge gaps were acknowledged that must be filled in order to evaluate products against Zika, including a particular need to investigate how prior exposure to related viruses impacts immune responses to Zika vaccines. Again, the lack of animal models—and especially access to non-human primate models—was raised: these are needed to improve understanding of the pathogenicity of Zika and its complications, especially regarding potential reproductive toxicity of candidate vaccines. There is a clear need for improved international collaboration, building on the lessons of the Ebola epidemic; major regulatory agencies, including Brazil's ANVISA, the European Medicines Agency, and the US FDA, have committed to expedited evaluation of Zika products, and will reach out proactively to developers to provide regulatory advice.

The need for international reference standards for preparation was again highlighted; the UK's National Institute for Biological Standards and Control (NIBSC) and the Paul Ehrlich Institute (Germany) are working on this as part of their role as WHO Collaborating Centres. Currently, the candidate standard for the NAT Assay is the more advanced, with plans for a collaborative study to evaluate suitability to be launched as early as April 2016.

Questions around data sharing, bio-banking and other sample-sharing issues arose throughout the meeting; these were addressed on Day three, where a number of existing data-sharing platforms and initiatives—including a WHO open publication channel specific to Zika virus—were laid out and the gaps in technologies and international agreements examined. Recent developments have greatly advanced the capacity for managed data sharing, and many funders are moving towards a position of expecting rather than encouraging it; but there remains a need for a culture of informed and constructive commenting underpinned by effective tools and platforms, as well as dependable mechanisms to provide credit and recognition to those who do share data.

The meeting then heard of the importance of sample sharing and bio-banking for priority diseases to advance disease knowledge, improve interventions and increase international capacity. Epidemic responses generate a wealth of samples that could be used to illuminate research needs, and work is underway to develop guidance on principles and considerations for material transfer agreements and Memorandums of Understandings that allow this while reflecting the needs of all stakeholders. The European Virus Archive already offers a non-profit online catalogue of quality assured resources, and has mobilised a task force to respond to the recent peak in applications for materials in response to the Zika emergency.

Note to the reader

Because of the rich discussion and in an attempt to keep this report simple and readable, comments are not attributed unless their content renders attribution necessary.

This report condenses the themes of each session – including the interventions from the floor – according to the themes addressed, rather than attempting to provide a chronological summary of the dialogue.

Summaries of presentations and of points made in discussion are presented as the opinions expressed; no judgement is implied as to their veracity or otherwise.

Background

As part of the broader emergency Zika response, WHO has initiated an emergency research and development response plan.

This plan is the first attempt since the Ebola virus outbreak of 2014-15 to implement the WHO's research and development (R&D) Blueprint. Established in 2015 at the request of the WHO Executive Board, and subsequently welcomed by the World Health Assembly, the R&D Blueprint aims to develop and implement a roadmap for R&D preparedness for known priority pathogens, and to enable roll-out of an emergency R&D response as early and as efficiently as possible for emerging pathogens for which there are no, or insufficient, preventive, and curative solutions. In December 2015 WHO convened a workshop to identify a short-list of pathogens to be prioritized immediately. Zika was identified as serious risk, necessitating further action as soon as possible.

The emergency research and development plan has been tailored to the current state of understanding of Zikavirus-induced fever and addresses research and development needs for novel means of vector control, IVDs, vaccines, and therapeutics. The plan further includes coordination of supportive research activities such as the establishment and validation of appropriate animal models, and sharing of information. WHO remains committed to working with all those involved in relevant research and development efforts, and in bringing them together to contribute solutions to this international health concern. This meeting was convened as part of that commitment.

Day 1: opening remarks

Dr Bruce Aylward, *Assistant Director-General (ADG), Health Systems and Innovation Cluster (HSI), World Health Organization (WHO)*

Dr Aylward provided a brief overview of WHO's approach to the Zika virus outbreak recently designated a public health emergency of international concern (PHEIC), pointing out that the emergency is the microcephaly and Guillain-Barré syndrome (GBS) possibly associated with Zika virus infection, not the infection itself. A recent visit by Dr Aylward, WHO Director General Margaret Chan and others to Brazil confirmed the certainty that new and more tools are needed. He outlined his hopes for the meeting: consensus on the research agenda and aetiology of microcephaly; a better understanding of the related natural history; improved understanding of absolute risk; and a focus on public health tools to address the problem.

Introduction

Dr Marie-Paule Kieny*, Assistant Director-General (ADG), Health Systems and Innovation Cluster (HSI), World Health Organization (WHO)*

Dr Kieny explained that an R&D blueprint was under development by WHO to enable better response to epidemics, and that this would develop in parallel to the R&D response to Zika. She then outlined the meeting agenda, pointing out that it would build on the recently-concluded Pan American Health Organization (PAHO) meeting on regional aspects of the Zika epidemic; and that it would serve as a stepping stone to two further meetings on vector control and pathologies. Concrete steps are already under way: target product profiles (TPPs) for diagnostics and vaccines are in development; WHO's regulatory team are accepting Zika-related applications from manufacturers of diagnostics under the emergency use authorization listing (EUAL); and the *WHO Bulletin* is allowing Zika-related papers to be published online while peer review is ongoing. Other sharing initiatives are also under way. Dr Kieny ended by expressing her hopes for identification of the most promising products, drugs, vaccines, treatments, vector control methods and medical countermeasures.

Opening session: current knowledge; feedback from PAHO meeting; microcephaly & neurological disorders

The session consisted of a series of presentations to set the context for the meeting.

- **Flaviviruses: an overview**. Duane Gubler (Chairman, Partnership for Dengue Control) introduced flaviviruses, summarizing their history, classification, evolution and epidemiology. He explained the principal clinical syndromes caused by flaviviruses, and what is known of their transmission cycles. After providing examples of hosts, habitat associations and enzootic vectors and their global distributions, Prof. Gubler looked at Zika-related viruses transmitted by Aedes mosquitoes. Zika has several vector associations. He finished with a summary of further modes of proven flavivirus transmission, suggesting that preliminary data suggests that Zika

could have multiple modes of transmission—which could partly explain why transmission has been so rapid in Brazil.

- Current epidemiological features, timeline of events and major concerns: Zika virus syndrome. Dr Celina Turchi (University of Pernambuco) outlined current epidemiological features of Zika virus; timelines of its emergence and of microcephaly in Brazil; major concerns and challenges; and relevant ongoing studies.

- **Feedback from PAHO meeting: Flaviviruses—an overview**. Ludovic Reveiz (PAHO) presented the results of a PAHO meeting convened under the auspices of the Global Outbreak Alert and Response Network (GOARN) a week earlier, and sketched out high priority research gaps.

- Pathogenesis of microcephaly. Geoff Woods (Cambridge University) explained the classification of microcephaly, the cellular processes that cause the condition, the potential infection process, and the progression to foetal abnormality.

- Associations between Zika virus infection, microcephaly & Guillain-Barré Syndrome. Nathalie Broutet (WHO) summarised work on the causality framework linking Zika virus with neurological disorders, particularly GBS and microcephaly.

Discussion

- Updates were provided on epidemiological research, including a retrospective analysis of the French Polynesian Zika outbreak in 2013/14. More work is needed to demonstrate causality (a number of studies are ongoing); Polynesian results are consistent with what is seen in Brazil.

- The precedent for "living reviews"— systematic reviews that are periodically updated and publicly available—was discussed, and it was argued that the necessary platforms, protocols and systematic strategies do not yet exist. The point was also made that the living framework approach poses challenges related to critical appraisal and the fact that the studies are not standardised. As well as data, therefore, pre-publication models are also required for methodologies, allowing transparency of methods, end points, and burdens of proof. WHO has argued that sharing of pre-publication data should be the norm in an emergency; this has been followed by supportive statements from major journals (see day three). The *WHO Bulletin*'s open application system for Zika-related articles is allowing this now and should be followed. Questions related to bias were raised, and it was said that there should be some way to publish and access negative and inconclusive results for critique and evaluation. It was asked that the whole community address the important question of selecting what studies are required, and what must be considered in reviews and in the development of protocol. Throughout all these arguments it was stressed that data originators must be acknowledged so people—particularly researchers in lower-income countries—are not exploited.

- The need was emphasised for descriptive neuropathology not only of the brains but also the peripheral nervous systems of affected infants, in an attempt to apply the historical lessons of Dengue, Chikungunya and other infections.

- A number of researchers "have an intuitive sense" that there may be more to the current picture than just Zika virus; this cannot be investigated without understanding which Dengue virus types are circulating. Additional information is requested to characterise a polyarboviral environment, enabling examination of confounders and risk factors.

- Beyond foetal conditions we are dealing with a constellation of neurological disease in adults that may constitute "the tip of the iceberg;" neuroinformation can extend back to conditions like schizophrenia and depression and researchers must look out for things other than discrete high profile diseases.
- With regard to vector control, it was pointed out that addressing controlling factors requires a broader view that addresses all potential risks, including insecticides and a range of environmental and sociological factors.

Research protocols; epidemiological modelling; pathogenicity

- **Research protocols: roadmap towards implementations**. Nathalie Broutet (WHO) provided an overview of key public health research questions and priority areas.
- Elements to consider in research protocols for diagnostic tools and methods. Christopher Oxenford (WHO) listed features of Zika virus infection, the serological response and some of the issues complicating interpretation.
- Research considerations re. pathogenesis. Alan Rothman (University of Rhode Island) sketched out a requirement for clinical studies to improve vector control, vaccine production and the ability to control Zika virus syndrome as it occurs.
- Elements to be considered with regard to vectors. Frédéric Simard (UMR MIVEGEC, IRD, Montpellier) highlighted a need for knowledge of natural amplification cycles in the forest in order to understand risk of transmission to humans; he also suggested that other viruses are also candidates for emergence, and researchers should not focus exclusively on Zika.
- **Clinical characterization, natural history, and complications of Zika in the context of co-circulating arboviruses in Latin America - the WHO-IDAMS-ISARIC[1] protocol.** Thomas Jaenisch (Heidelberg University) specified the primary objectives of a CCP for Zika, along with the accompanying framework and the next steps.
- Epidemiological modelling: Implications for Zika control measures. Neil Ferguson (Imperial College) sketched out the challenges of modelling flaviviruses and the lessons of existing models.
Zika pathogenesis and the design of novel interventions. Cameron Simmons (Oxford University) outlined flavivirus replication cycle in cells, the points in the cycle in which interventions are possible, and the nature of potential interventions, as well as the natural history of arboviral transmission and the latest knowledge of Zika.

Discussion

- Case definitions are of crucial importance at this early stage: they will inform later research by others, including clinical intervention trials.
- Harmonisation of protocols should not be discussed without considering harmonisation of data collection tools and agreeing a minimal core data set. ISARIC has prepared forms for pregnant women and microcephalic children: all are welcome to use these and feedback to help improve them is encouraged.

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[1] The International Severe Acute Respiratory and Emerging Infection Consortium

- It is difficult to differentiate in recruitment between symptomatic and asymptomatic pregnant women; developers of clinical studies must think how to confirm cases. Good reasons to use diagnostics include surveillance and defining a clinical spectrum; but there is a need for certainty that confirmed cases are due to Zika, not cross-reactivity. We must also understand the proportion of asymptomatic disease. Researchers must ensure that cohorts look at past infections. Sample banking is important, providing possibility of more accurate serological diagnosis.
- WHO's potential roles in response were repeatedly raised. A case was made for a large, rapid study on pregnant women to be completed before the next peak of the outbreak. NIH, PAHO and WHO should move quickly to harmonise consortia. In the context of a fluid epidemic in which current clusters of microcephaly represent infections occurring 6-8 months ago, WHO could coordinate efforts to identify early stage outbreaks, then use those imperfect diagnostics that are currently available.
- This emergency is a valuable opportunity to improve maternal and child health and prenatal care. In several contexts throughout the day the point was made that while the meeting discussed responses in emergency situations, a parallel vision was also required taking into account longer-term questions of processes and structures.
- It was hypothesised that the current vector is less competent than expected, but that the frequency of mosquito bites explains transmission. Other vectors can also be important. A call is needed assembling different consortia across countries to prepare SOPs for virus detection in mosquitoes and run vector competence studies; a great deal of work remains to be done on standardisation. This could be relevant to diagnostic early warning systems for detection of virus circulation in mosquitoes.
- There was some discussion of why diagnostics addressed were limited to PCR and IgM, when it was argued that following the titre of IgG taking regular samples from patients, you can differentiate viruses through neutralisation tests. The counterpoint was made that in Asia IgG has not been found to be able to discriminate infections, and that the meeting was obliged to focus on tests applicable anywhere.
- Sexual transmission and neonates have not been included in modelling as sources of infection; the former is unlikely to contribute significantly, but neonates might.
- Zika virus might be more similar to yellow fever than to Dengue, and could have the ability to sustain in human populations for a time without reintroduction. All modelling is currently tentative due to the limitations of existing data.
- Zika might be hidden under Dengue fever in south east Asia; but it was argued that while symptoms overlap, they are distinct, and unless the virus has recently changed significantly it is unlikely. However Zika is generally associated with mild illness, and can be misdiagnosed; and many old Dengue papers report neurological illness. Zika could have been there the whole time, without causing epidemics that would have meant it was picked up. The Western Pacific epidemic may have been caused by a strain that came about as a result of a genetic change, and while microcephaly is a consequence of the virus it could have been missed due to low case numbers. Even in the French Polynesian epidemic, microcephaly was only picked up in retrospect. The biggest question of the next few years will be around changes in transmissibility.
- Zika may be a pan tropic virus with a broad vector range. Future work should examine the possibility of a range of mosquitos involved in transmission, and existing entomological knowledge gaps should be filled, particularly around vector surveillance and sampling and monitoring of mosquito species in the field. But

entomological work is not included in the research plan presented after the PAHO meeting. Even for modelling, it was argued, field data is required; experimental infections and extrapolations done in the lab are not sufficient on their own.
- Many historic Zika strains have been passaged multiple times in mouse brains, causing deletions and glycosylation sites of which all should be aware; incomplete passage histories may be associated with those isolates. Researchers are requested to keep all samples in -80 degree freezers so isolations can be done in future.

Day 2: Landscape analysis for future Zika medical technologies

Preparing for the inevitable—a blueprint for research and development

***Dr Marie-Paule Kieny**, ADG, Health Systems and Innovation Cluster (HSI), WHO*

Dr Kieny outlined the development of a blueprint for R&D in epidemics. WHO, as coordinator and secretary, has two main objectives: develop and implement a roadmap for R&D for known priority pathogens; and enable rollout of an emergency R&D response as early and as efficiently as possible in public health emergencies. The project's expected benefits include R&D preparedness for diseases that might lead to epidemics and for R&D needs during emergencies, along with improved coordination and pathways for new products, and improved ethical and regulatory capacity. Work began in September 2015. First deliverables are: prioritisation of key pathogens; development of a platform for technical consultation; development of R&D roadmaps for priority pathogens; and governance and coordination processes. Data sharing approaches are moving fast, as are consultations. A report was made to the WHO Executive Board in November 2015 and a series of meetings is ongoing around the Zika outbreak, including on vector control, pathology and ongoing work.

Zika virus mouse model

***Johan Neyts**, University of Leuven, Belgium*

Dr Neyts introduced the 7DMA molecule, which can be studied in cell culture and animals and is active in inhibiting Zika viral reproduction, plaque reduction, and blocking viral antigen expression. He also introduced a new vaccine concept being developed, borne of work on yellow fever vaccines where the goal was to create something thermostable and easy to produce; this approach can be used for other flavivirus vaccines and progress is being made with Japanese encephalitis. With regard to mouse models, the AG129 ZIKV model is validated for antiviral studies and can probably also be used for initial assessment of vaccine efficacy. In addition, assays are available for HTS (in 384well plate format) and validation; and new vaccine technology may allow production of heat stable flavivirus vaccines as efficient as the parent vaccines. Pan-flavivirus drugs are needed that can be used for the treatment/prophylaxis of Dengue, Zika, Japanese encephalitis, etc.

NIAID efforts in Zika animal model development

***Cristina Cassetti, Ph.D.,** Programme Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, NIH*

Dr Cassetti outlined an ongoing study that began on February 15 to establish viraemia in primates. Data is available online; summary results to date are: "Asian lineage" ZIKV establishes experimental infection and causes mild symptoms in rhesus macaques at all three doses tested; plasma viraemia is detectable as soon as one day post-infection and peaks higher than 1 million viral RNA copies/mL in 2/3 macaques; infected plasma is available for collaborators; viral RNA is also detected in urine and CSF; macaques will be monitored to 28d, rested for ~6 weeks, and rechallenged to assess protective immunity elicited by primary infection. The day before this talk the first infection had also taken place in a trial on pregnant monkeys; Dr Cassetti outlined the design, as well as that of a trial in AG129 mouse models to evaluate broadly effective antivirals that work against Zika. Of options tested in the latter trial BCX4430 stood out: Mice were significantly protected through 28 days post-virus injection (dpi) when treated with BCX4430 at a dose of 300 mg/kg/d; a lower dose of 150 mg/kg/d significantly delayed the mortality curve of infected mice; weight change at the higher dose was similar to treatment of sham-infected controls; and no morbidity was observed in surviving mice up to 28 dpi. Surviving mice were rechallenged with virus on 28 dpi, a process currently ongoing.

Zika Viruses for vaccine development

***Rick Bright**, PhD, Biomedical Advanced Research and Development Authority (BARDA), US Department of Health and Human Services*

Each week more Zika vaccine candidates are made available. Considerations are: genetic characterization; antigenic characterization; manufacturability; virus pedigree; and freedom to operate. Zika viruses from the French Polynesian outbreak are not highly related to other flaviviruses; there are two genetic lineages of Zika with a lot of similarities and very high homology; and it should be borne in mind that some old Zika strains have been passaged hundreds of times and may have mutated to the point that they are not really Zika any more. Work is under way to establish whether older strains induce antibodies that cross-react with currently circulating strains; informative data is expected in weeks. Neutralizing antibodies mediate long-term protection from disease; their measurement provides the best correlate of flavivirus immunity. Domain 3 of the virus presents the best target for vaccination. It is important for researchers to know where a virus comes from and how it has been handled since isolation, including full characterisation of virus seed and cell banks. It is also important that researchers respect all restrictions applicable to given virus strains and always acknowledge sources of viruses, sequences or other components. There is no need for a specific Zika strain recommendation but it is advisable that strains used for reduction be based on the recent Asian lineage, whether from south America or French Polynesia. Careful monitoring of genetic and antigenic characteristics from new viral isolates is warranted; timely data sharing is critical.

Discussion

- While there are currently no specific Zika strain recommendations, pre-clinical work under way at a number of different labs may cause that to change in coming weeks.
- Dengue vaccine clinical trials suggest that besides neutralizing antibody, cellular immunity may play an important role in protection.

- Experiments are ongoing in Brazil to establish whether Zika virus infects new world monkeys, in the hope of establishing an alternative animal model.
- A clearly documented passage history is needed before selecting a virus strain as vaccine seed, as mutations may accumulate through passaging processes. Earlier isolates have been passaged through mouse brain, and their use is discouraged. It is also unwise to focus all initial efforts on a single vaccine strain. With access to more than one, comparability analysis allows better business decisions to be made.
- Analysis is ongoing to determine whether the 2007 Yap Island strain of Zika has equivalent pathogenicity to the French Polynesian and recent strains. There are some differences in the 2007 Yap isolates and understanding their pathogenesis will be important; immunogenicity effects are still unclear.
- The macaque model shows results that are difficult to interpret, including secondary peaks of viral load. Autopsies will be carried out to see in what tissues the virus is residing and for how long. It could also be due to genetic differences. Another study is also planned for reinfection of primates months later. Work on alternative small animal models, including hamsters and guinea pigs, is ongoing.
- The possibility was discussed of Zika virus infection increasing susceptibility to Dengue; interactions between immunity to Dengue and to Zika are an important issue. The point was also made that we should look at the implications for Zika of yellow fever and yellow fever vaccination.
- Research is ongoing in Nicaragua on the interaction of Zika in previously infected Dengue patients, to establish whether T cell response contributes to persistent immunity. Clinical trials of Dengue vaccines have shown strong T cell responses.
- Rick Jackson of Sanofi Pasteur highlighted long-term follow-up of a phase 3 vaccine cohort for Dengue in 30,000 individuals across a number of countries, for which good data has been gathered including tens of thousands of samples with clinical notes going back to 2011 and—eventually—forward two more years. This data could provide valuable insight into the natural history of Zika virus disease.

Zika virus vaccines

Landscape analysis on Zika virus vaccine development: preliminary findings

***Joachim Hombach**, WHO Initiative for Vaccine Research*

A large number of Zika vaccine projects are building on established technologies. Dr Hombach explained the landscape survey methodology and listed the main technologies envisaged (the majority are inactivated purified virus and live vectored vaccines). Four projects, respectively run by Bharat Biotech, InOvio/GeneOne, US NIH and Novavax, were picked out as more advanced. Dr Hombach outlined general advantages and disadvantages of each technology, drawing attention to developers' concerns about bottlenecks, and identified areas requiring support, including: virus isolates and seeds (access, characterization, choice); reference reagents (serology, monoclonals); assay and protocols (neutralization); and pre-clinical models. WHO is working on the following areas: TPPs for emergency and routine use; landscaping and facilitating partnering for vaccine development; and action against bottlenecks.

WHO DRAFT target product profile for a vaccine to protect women of child-bearing age and pregnant women from Zika virus

***David Kaslow**, PATH*

Dr Kaslow introduced WHO's Product Development for Vaccines Advisory Committee (PDVAC), which oversees activities related to global vaccine R&D including the development of target product profiles (TPPs). A PDVAC working group is developing a TPP for a Zika vaccine for emergency use, with priority on mass vaccination of women of childbearing age and potentially pregnant women. He outlined current assumptions in development of an emergency vaccine; vaccine attributes related to the target population; attributes related to immunogenicity and efficacy; and attributes related to programmatic suitability. A first TPP draft has been developed; this will undergo online consultation, then be finalised by May 2016.

Discussion

A period of panel-led discussion opened with a series of presentations of companies' ongoing work. **Bharat Biotech** (India) has been running a development programme for flavivirus vaccines for a year and has two Zika virus vaccine candidates. **Newlink**, a company focussed on immunotherapy for cancer and infectious disease, has assembled a product development strategy. **Sanofi** has three licensed flavivirus vaccines and is taking forward a number of constructs for Zika vaccine development, including their ChimeriVax technology and a number of parallel workstreams including different animal models. **GeneOne** has one DNA-based candidate vaccine that will be in clinical trials by the end of the year. **Instituto Butantan** in Brazil is looking at inactivated vaccine in alum and with adjuvant, collaborating with **NIH** in work on a chimeric with Dengue vaccine expressing the E protein from Zika virus.

The following themes emerged from open discussion.

- As well as women of childbearing age, trials should also pick up girls about to enter puberty, and look at vaccinating males to prevent sexual transmission. Collaborative groups could be formed to get this going as soon as possible.
- Development of a correlate of protection was discussed, given that a simple immunological assay may be difficult to interpret as basis for licencing. Protection is required against congenital malformations; supporting data is required to allow a linkage. A cluster randomised trial was proposed to establish protection against disease and possible birth defects and infection. Better understanding of incidence is also required, and this may necessitate broader definitions; once a trial is designed, it will be hard to predict where to have sites relative to incidence. Efficacy endpoints (pre or post-registration) may initially be based on efficacy against disease. Test negative case control designs might work for birth defects.
- Regulatory agencies are key in the planning of evaluation strategies, and have committed to expediting review of these products; but a public health emergency does not alleviate the duty to deploy products as responsibly as possible. Large volumes of product can be rolled out quickly but this must be done in a way that assesses safety and efficacy. To help regulators, the international scientific

community can provide joint advice. A request was also made for special effort to include regulators in planning stages, especially in Africa.
- The question was raised of whether primary Zika disease can be used as an endpoint for powering clinical trials. Targets must be properly defined – do people with lowered symptomatology have same risk of birth defects? The definitions of 'disease' must be fleshed out; the challenge of subclinical disease is real.
- It was asked how much the TPP should limit platform technology in terms of safety, as this can limit choices. It was also asked whether head to head comparisons of different candidates could be possible in phase 2 trials. Realism is paramount—there is no vaccine for use in pregnant women; to rely on technology backed by data showing no problems with such use, focussing on avoiding contraindications, is a good approach.

Zika virus diagnostics

Zika diagnostics product development landscape and needs

***Bill Rodriguez**, FIND*

IVD development is a competitive space in which urgent product development is hard. It is difficult to make risk/reward assessments in an outbreak when the necessary structures are missing or in flux, resources are unavailable and regulatory frameworks are not established: outbreaks are unsustainable markets, and emergency needs are not the same as long term needs. In the context of those lessons, Dr Rodriguez provided a needs analysis for the current outbreak. Three types of test are possible: Zika virus-specific; flavivirus panels; and multi-pathogen fever panel tests that include other pathogens with similar presentations. There is current activity in a number of different product profiles: 10+ companies with molecular platforms are interested in developing Zika virus IVDs; at least eight have commercially available molecular based IVDs, with many more in development; two ELISA based IVDs have received regulatory clearance in US and Brazil, with more in development; and two rapid diagnostic tests have received regulatory clearance in the same jurisdiction, with more in development (especially pan-flavivirus IVDs and multi-fever pathogen IVDs). Several gaps remain. Pregnancy risk classification is required, and there is range of unmet scientific needs. For mapping and natural history studies serological tests are needed, as well as for studies on prevalence and immunity in populations and the protective effect of immunity. For natural history studies, molecular based IVDs are needed followed by the need for development of biological reference standards. To frame IVD development, product prioritisation and performance specifications must specify 'how good is good enough?' Guidance is needed on how the IVDs should be effectively used, especially in settings with pregnant women, as are mechanisms to accelerate regulatory approval and uptake. A repository of curated, highly characterised, accessible samples is crucial.

Overview of draft diagnostics TPP

***Francis Moussy**, WHO*

WHO is working with partners to create a TPP for Zika virus IVDs. Dr Moussy explained the rationale for the TPP of differential diagnosis of acute fever with focus on Dengue, Chikungunya and Zika. Two initial intended use cases—test for infection/exposure in asymptomatic pregnant women and a Zika diagnostic test for all patients—were considered through stakeholder feedback. As diagnostics must be developed in relation to current pipelines—and with no multiplex tests for acute fever at point of care in this landscape—the TPP was focussed on differential diagnosis of fever for case management, including pregnant women, children and infants at point of care. The test should be suitable for use during outbreaks of febrile illness in settings where one or more of the viruses are endemic, or an outbreak has been reported. Arguments for the relevance of this test were: better clinical management to prevent deaths for Dengue infections; importance of surveillance for all three pathogens; potential to reduce pressure on public health structures, especially during simultaneous outbreaks; potential to improve understanding of the spectrum of disease caused by Zika, including concurrent infections; use in implementing clinical intervention strategies for acute Zika infection as evidence from research emerges; and use in monitoring the impact of vaccination campaigns when vaccines become available. Dr Moussy then demonstrated the TPP itself. Hard copies were available, and interested parties were asked to provide feedback that could be used to develop the final version. The TPP does not specify what technology to use, but Dr Moussy suggested it would benefit from a combination of NAT and serology in blood specimens. Either technology used alone would fail to capture the full temporal spectrum of patients with acute fever for the three viruses; a test that could cover all three would be ideal. The next steps in the TPP process will be collation of stakeholder feedback; public consultation via WHO's website; publication of the final TPP by the start of April 2016; broad dissemination; and assisting diagnostics companies in developing tests.

WHO Emergency Use Assessment and Listing (EUAL) procedure

***Robyn Meurant,* WHO**

Ms Meurant provided an introduction to the Emergency Use Assessment and Listing (EUAL) procedure created in 2014 for vaccines, medicines and IVDs. The EUAL is different to WHO Prequalification; decisions are made to list products based on minimal evidence of safety and performance, and immediate need. She explained how the EUAL works, and that its use requires a PHEIC. Submission requirements for each product type are specified in guidance documents, and applicants are encouraged to contact WHO early, with rolling submissions possible. Applicants must also attest intention to complete development and, if applicable, to apply for WHO Prequalification. The EUAL process for IVDs, where possible, consists of a desktop review of selected manufacturing and quality management system (QMS) documentation; a review of any existing documentary evidence of safety and performance; and a limited laboratory evaluation of relevant performance and operational characteristics of the product. If the decision is made to list, WHO publishes information about the IVD on the WHO website. The validity of the listing is generally 12 months; all decisions are reassessed within a year (or sooner if data becomes available). The EUAL experience for Zika virus has been similar to that

during the Ebola virus outbreak: invitations to submit have gone to 30 manufacturers; four applications are in to date. After finalising dossier requirements for the EUAL for Zika IVDs, input will be sought from NRAs and subject matter experts, and final laboratory- based performance evaluation protocols completed with assistance from reference laboratories and WHO collaborating centres. What is in process does not necessarily meet the aspirational parameters of the TPPs.

Panel discussion

- In lower-income countries, laboratories cannot necessarily purchase even those IVDs that are commercially available; so focus is required on the published assays that laboratories *can* access. Six are available and a seventh is recommended by PAHO. Better standards are required to allow test comparisons; viral loads in Zika virus are so low that we are currently testing using molecular methods at the border of technological sensitivity. Improved understanding is also required of what we should test: data so far is insufficient to advise testing urine only, so if urine is tested, this should always be done with blood.
- Data from studies looking back into Dengue virus infection allows the conclusion that a combination of RT-PCR/IgM or NS1 antigen/IgM allows diagnosis of over 90 per cent of acute infections on a single specimen collected within the first ten days. For diagnosis of Zika virus, combined tests are important because the onset of fever can be uncertain or intermittent.
- Zika virus serology is problematic; most pregnant women tested have antibodies to Dengue virus and multiple infections. There is therefore a need to increase diagnostic capacity up to primary health care. Rapid diagnostics are required that are sensitive and specific, and which show limited cross-reaction. The idea of a multiplex assay is good, but in the meantime we should work with existing tools; evaluation in field conditions, on all fluids and not just blood, should be ongoing.

Discussion

- Accessibility to well characterised samples is a hurdle to IVD development. Legal challenges must be addressed, tackling questions of ownership, transport, valuation, funding, and credit. WHO intends to play a role in this, leading collaboration to set up transparent mechanisms for curating and making samples available. A framework must be developed to recognise those providing the samples. The TB specimen bank set up by FIND and TDR provides one template.
- WHO recommends that manufacturers establish relationships with good regional labs for testing in countries, and use them; a group of different multi-country testing centres will be useful, as there may well be variability in some countries.
- With regard to EUAL, WHO asks for certain documentation to confirm that a quality management system is in place for applying manufacturers, and that they have the capacity necessary to meet orders and continue supply.
- Pregnant women presenting with rash illnesses could have other conditions requiring follow up, and systems must be in place to manage those conditions.

New tools for vector control

Review of the vector control landscape

***Philip McCall**, Department of Vector Biology, Liverpool School of Tropical Medicine*

The bulk of Dr McCall's presentation was drawn from a forthcoming systematic review looking at evidence for existing Dengue vector control methods published after 1980, a watershed for significant urbanization. The results contained surprises: no RCT has ever been conducted on the effect of vector control on Dengue incidence. Three methods had reliable evidence for impact on incidence: house screening significantly reduced it, indoor residual spraying (IRS) reduced it but not significantly, and environmental management plus water lids reduced it. For fogging, the most widely used method, no RCT had been done in the last 35 years. Huge gaps in knowledge were revealed, including but not limited to details of treatment, insecticide, frequency, and coverage. Very few studies examined insecticide susceptibility or resistance. Dr McCall's conclusion was that "there's no real evidence base to recommend anything." He identified the following needs: an increase in rigorously designed studies; appropriately designed RCTs for insecticide space-spraying/fogging as a priority; further evaluation of house/premises screening, IRS, and community-based approaches to improve delivery; elucidation of the relationship between vector indices and risk of Dengue transmission; and incorporation of insecticide susceptibility M&E into all relevant trials. In urban zones where vectors proliferate, to continue unquestioningly with what has always been used or pursue new approaches without supporting evidence would be wrong. A global independent advisory body is needed to guide selection of approaches and tools for control or prevention of infections transmitted by urban *Aedes sp.* vector populations, and guide the design of multi-centre trials to evaluate effectiveness.

Modelling the introduction of vectors designed to reduce disease burden

***Gemma Nedjati-Gilani & Pierre Nouvellet**, Imperial College, London*

This presentation examined the use of new tools for vector control in the context of Dengue through modelling quantifying the impact of wMel, a strain of the endosymbiotic bacteria Wolbachia with which mosquitoes are deliberately infected then released. Wolbachia reduces fecundity, increases mortality and reduces viraemia in infected mosquitoes. The presentation argued that the Wolbachia method could be expected to cause a 70 per cent reduction in R_0 for Dengue serotype. There has been limited field evaluation of new methods of vector control on incidence of disease (as opposed to vector population levels), but planned cRCTs are on the way, and slight modifications of protocol would allow estimation of impact on Zika transmission. Issues can be expected around scaling up, heterogeneity in transmission, vector density, cost effectiveness and operational research. Monitoring is of great importance. Research is required to generate epidemiological evidence of impact and cost-effectiveness analyses; and operational research is needed to address logistical challenges. All should be done with the goal of getting R_0 to less than one until vaccination is available. Finally, it should not be

forgotten that models need to be fed with data, so high quality data is of paramount importance; but analysis of data is also greatly enhanced by modelling.

New tools for vector control: target product profiles (TPPs)

Abraham Mnzava & Rajpal Yadav, *WHO*

This presentation mentioned the upcoming meeting of the emergency vector control advisory group (VCAG) to review available evidence, identify potential gaps and recommend and fast track potential emergency measures. The history and role of the VCAG were outlined: the group does not give recommendations on deployment of particular products; rather it provides technical advice to WHO on new forms of vector control with a view to developing recommendations. The concept of TPPs was then laid out, along with respective three-step processes for generating entomological and epidemiological evidence required to develop guidelines, and the wider pathway of assessment for developing new intervention concepts. An overview was provided of intervention concepts currently under review.

Panel discussion

- Oxitec are developing **GM mosquitoes** as a tool for *Ae. aegypti* suppression, and are currently at step three of the VCAG review process. Mosquitoes contain a self-limiting gene as well as fluorescent marker gene for tracking and tracing; males are released that mate with females and stop the population from developing. Approval for use has been granted in Brazil and discussion is ongoing with the US FDA.
- The **Eliminate Dengue project** is trying to develop **Wolbachia** in a not-for-profit consortium, aiming for a low-cost sustainable approach to Dengue elimination. Studies have shown Wolbachia causing significant reductions in mosquitoes. Recently use of a contemporary Brazilian Zika isolate was unable to infect the Wolbachia insects; reproducible and consistent reduction in infection has been shown with Wolbachia mosquitoes. 40+ field releases across five countries have shown that Wolbachia has been sustained in local populations in some areas for ten years; and there has been no evidence of significant local transmission of aegypti-associated diseases in any area where Wolbachia has been established. A two-year deployment in a major city would cost about $2-3 per person per year, with costs significantly reducing over subsequent years.
- The **FAO** and **IAEA** have developed the **sterile insect technique**, which they described as a safe, responsible sustainable approach to controlling the aegypti population by using ionising radiation to sterilise males, then releasing them over target areas. Through continuous release, the population diminishes and is suppressed. The last few years have seen development of mass rearing protocols; tools and equipment; radiation protocols for males and females; sex separation methods for males and females; methods to overcome problems associated with release; and methods for handling, transporting and release of sterile males over large areas. All of these are continuously updated and refined, and the full package is available for aegypti and albopictus. A combined approach with Wolbachia eliminates risk associated with release of females that might be fertile or disease transmitting and the risk of replacement with a new population.

- Africa contains no country with programmes for controlling arbovirus, but Dengue has been managed through **adaptation of malaria vector control programmes**. The core intervention is eradication through community participation; another is environmental management and nationwide indoor residual spraying. This approach has shown good results, though there have been issues with follow up, resistance, and failure to continue with IRS.
- In Brazil, the Ministry of Health recently convened an expert meeting to address perceived failures in vector control for Dengue. Three areas were recommended. **Approaches for whole populations** incorporated reinforcing community participation in environmental management, risk mapping for efficient use of resources, and mosquito-disseminated insecticides & ovitraps. **Protection of pregnant women** used screens, curtains, IRS and individual protection. **New approaches for evaluation** included biological control with Wolbachia, use of radiation, and spraying of biological live sites.

Discussion

- A recent block RCT for IRS showed 100 per cent effectiveness: IRS is probably the only effective vector control method for Aedes and should not be dismissed. It has not been part of famous Dengue interventions because outbreaks have tended to occur in urban areas without control programmes. When that is addressed, it was argued, there is no reason why it would be ineffective for Dengue and Zika control.
- Little is known about the basic behaviour of peridomestic mosquitoes; greater understanding is required of how to target them effectively. However, vector control is a preventive measure, not something that will curb an epidemic—at least with available existing means. Sustainability and cost are important.
- Vector control requires the participation of communities; but governments take care of the issues of environment, waste, sanitation and water that form much of the bigger picture. If these are ignored, vector control cannot function properly.

Regulatory concerns

Key regulatory issues for candidate Zika products

***Flávia Regina Souza Sobral**, ANVISA*

Dr Sobral characterized the main regulatory challenges of the Brazilian Zika outbreak as uncertainty; the urgency/emergency framework; the current lack of vaccines and therapeutics; and risk/benefit evaluation. In this context, the Brazilian regulatory body ANVISA has taken a number of actions: publishing guidance and technical recommendations; creating collaborative and cooperative processes with other bodies such as the US FDA; expediting registration and other regulatory processes; liaising directly with manufacturers; holding an international Zika teleconference with ICMRA, the International Coalition of Medicines Regulatory Authorities; and encouraging sharing of data and research. In addition, Anvisa and the FDA have signed a specific protocol to support and to expedite regulatory process in development of vaccines, therapeutics and diagnostic tests; strengthen monitoring and health care; research; and vector control. Dr Sobral listed key principles for progress in emergencies: cooperation; prioritization; transparency; ensuring

development is scientifically driven; achieving speed without loss of quality; protecting the safety, welfare and rights of clinical trial participants; ensuring trials are scientifically sound so that they can generate interpretable results; and ongoing discussion with stakeholders (NRAs, WHO, manufacturers, etc.).

Collaborative regulatory support for emerging infectious diseases

David Wood, *WHO*

Dr Wood expects the concrete benefits of WHO's R&D blueprint to include better and stronger scientific, ethical and regulatory preparedness. He listed examples of collaborative regulatory support providing technical assistance to countries, including the EUAL, joint clinical trial review processes, and regulatory pathways. In a second area of work, non-clinical evaluation of products, key strategies have included the development of international reference preparations for regulatory evaluations of products and facilitating collaboration between expert labs. Manufacturers need globally agreed technological specifications: as much agreement as possible should be in place for efficacy criteria. Here, WHO provides guidelines to protect blood supply during Zika outbreaks, and on quality, safety and efficacy for flavivirus vaccines. A number of multi-country studies are under way to support safety evaluations in collaborative regulatory support. Regulators are an integral part of the public health response to emerging infections, and their key message is that early dialogue with all stakeholders—academia included— is essential to emergency response. They have shown they can do this, working together well on H1N1 and Ebola; and they have shown that they are willing to innovate in emergency situations, based on appropriate benefit-risk assessments.

Offers of support from regulatory agencies to evaluate candidate Zika products

Marco Cavaleri, *Head of Anti-infectives and Vaccines, European Medicines Agency*

Dr Cavaleri summed up the ICMRA pledge to tackle Zika virus disease by supporting rapid development of diagnostic tests; exchanging information to review investigational vaccine and treatment options and expedite their development; and ensuring that the regulatory processes are as efficient as possible. He then listed EMA's Zika activities, including creation of an ad hoc expert group, the EMA scientific committee, to provide a basis for early interactions with potential developers of prophylaxis and treatment. In the meantime discussions are ongoing with the European Commission, the Health Security Committee, and European CDC; and work with FDA, HC, ANVISA and WHO is taking place on available treatments/vaccines and development pathways. He listed the tasks of the expert group, and the aspects of the Zika situation impacting the regulatory environment in which they are working. Of these, he highlighted efforts to develop a preclinical package, including reproductive toxicity and available animal models, as of particular importance to swift progress toward clinical studies. Dr Cavaleri outlined the regulatory pathways available for early approval in context of public health emergencies, all of which can be expedited in cases of well-justified urgency, and concluded with a list of key points: there is a need for expedited regulatory pathways in emergencies, and the EMA is working in this area; investigational products are not likely to be sufficiently

mature for fully informed regulatory discussion, but EMA is nonetheless advancing contact with developers; vaccines are expected to play a major role in the Zika emergency but antivirals are not excluded; a drug/vaccine development plan must be defined along with options for accelerating development; and the EMA is ready to support WHO and international regulators, including on the EUAL procedure.

Candidate reference preparations for candidate Zika products - serology

Mark Page, *NIBSC*

NIBSC makes about 95 per cent of international reference materials for WHO; Dr Page outlined their uses and listed the assay types for Zika serology. He pointed out that access to antibody reactive samples presents issues, and highlighted an urgent requirement for more samples from recently infected human patients. With respect to antibody cross-reactivity, Dr Page informed the audience that NIBSC has reference antibody standards for Dengue serotypes 1-3 and for Japanese encephalitis virus, and is also producing a panel of murine monoclonal antibodies raised against whole inactivated Zika virus. Reference reagents are established through collaborative studies; Dr Page explained how WHO standards are the gold standard, what is done to meet those standards, and—using the example of Ebola virus—the value of using a reference standard in the first place. He made the audience aware the NIBSC is running collaborative studies in which institutions are welcome to be involved; and listed the organisation's current needs. These are: serum/plasma for Zika virus antibody IgM/IgG (recently infected); antibody to Dengue virus serotypes; antibody positive specimens for yellow fever antibody; antibodies to Chikungunya and West Nile viruses; and diagnostic kits and reagents to evaluate candidate antibody preparations.

Development of a candidate WHO international standard for Zika virus for NAT assays

Klaus Cichutek*, Paul Erlich Institute*

Dr Cichutek explained the work of the Paul Ehrlich Institute regulating biomedicines and vaccines in Europe with the EMA, and its role as a WHO Collaborating Centre for standardisation and evaluation of vaccines and quality assurance of blood products and IVDs. He provided an overview of the relevance of NAT and why it is important that specific reference materials are used. He explained WHO international standards for NAT-based assays, and then outlined what has been done so far with Zika virus. High titre stock has been grown, and studies have been started to evaluate whether there is a matrix effect. An inactivated standard is better for shipping, so the Institute has started to look at virus stock inactivation, and has undertaken kinetic studies and large volume testing. Results so far are encouraging. Dr Cichutek then outlined the Institute's ongoing and future work in various areas, and pointed out that as well as preparing reference material, the Paul Ehrlich Institute also provides guidance for vaccine development; all are welcome to approach for advice.

Keynote lecture: Zika virus associated with microcephaly

***Dr Tatjana Avsic Zupanc**, Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Slovenia*

Day three started with an overview of the seminal paper on Zika virus associated with Microcephaly published in the *New England Journal of Medicine* on February 10, 2016. This case history concerned a 25-year-old previously healthy female who presented in mid October 2015 with assumed foetal anomalies. She had lived in Brazil since December 2013, and became ill in the 13th week of gestation, displaying symptoms of Zika infection, though no virological diagnostic was performed. Ultrasound at 14 and 20 weeks of gestation showed normal foetal growth; anomalies were detected at 29 weeks. A medical termination preceded an autopsy that provided strong evidence of a link between Zika virus and microcephaly; severe foetal injury associated with ZIKV vertical transmission; severe effects of Zika on the central nervous system and gross intrauterine retardation; damage of the placenta by the virus; neurotropism of the virus; possible presence of the virus in neurons; arrested development of the embryonic cortex apparent at 20 weeks; and persistence of the virus in the foetal brain. Thanks were given to the subject, who remained supportive of the foetal research and publication of these findings.

Medicines and blood products

Understanding Zika virus infections and pathogenesis for treatment product development

***Lisa F.P. Ng, PhD,** A*STAR, Singapore*

Dr Ng drew attention to a recent study showing that Zika virus infects human cortical neural pathogens, which she called proof of concept of the virus's involvement with neurons and related cells; she also cited a Brazilian study that found the virus can halt growth in neurospheres. She pointed out many challenges in developing medications for use during pregnancy, but highlighted the role for prophylaxis and therapeutics for other target populations—men, non-pregnant women, and children. Dr Ng's work and that of others has identified key markers responsible for acute clinical symptoms and for chronic disease. Several subsequent studies from various parts of the world have also reported the involvement of immune mediators. She listed some known antivirals and outlined what effect they might have on Zika virus, as well as immune-based interventions and their suitability for treatment use. She explained typical IgG and IgM presentations, speculating as to whether there could be a role for antibodies as treatment, perhaps via passive transfer to clear viral load. She then outlined the sub-neutralising virus-specific antibody response. Dr Ng's group also examined cellular factors in Zika infection and the interplay with the immune system that could provide new reagents and knowledge on infection and disease; generate animal models to study inflammation; identify biomarkers of diseases; help develop treatment; and allow comparative studies in arboviruses with similar manifestations. Their objectives are to gather knowledge on immune responses mounted against Chikungunya in order to develop new immune-based

preventive and treatment strategies, identify biomarkers enabling better prognostics, and improve understanding of disease pathology to devise appropriate treatments. She expressed the hope that they will also be able to identify novel targets that will allow development of novel assays; in all this there is a need for relevant animal models. Finally, Dr Ng noted surface similarity of over 40% between Zika and Dengue viruses, and raised the question of repurposing existing vaccines—in particular the yellow fever virus vaccine and the new Dengue vaccine Dengvaxia.

Immunopathology of Guillain-Barré syndrome

***L. Magy**, Service de Neurologie, Centre de Référence 'Neuropathies Périphériques Rares,' CHU Limoges, France*

Dr Magy outlined clinical and immunopathological details of Guillain-Barré syndrome (GBS), along with classic and diagnostic classifications. He described GBS as a post infectious disease with many linked infections (it can also be an epidemic disease, as in China in 1993). He sketched out its pathogenesis, then outlined treatment options, which are of two types: treatment in an ICU providing respiratory support to combat paralysis; and treatments targeting inflammation/autoimmunity. In the latter category approved treatments include intravenous Immunoglobulin (IVIg) and plasma exchange, both of which have strong logistic and/or cost implications. Promising possibilities include Eculizumab, which is effective in animal models. Dr Magy then addressed what is known of GBS in the Zika setting: a recent case control study shows strong association, with a clinical phenotype characterised by rapid evolution. The phenotypic presentation of GBS is quite homogeneous, with good overall prognosis provided ICU is accessible for respiratory support. The mechanism of GBS remains poorly understood.

Discussion

- It should be ascertained whether current GBS cases are related to Zika virus; but getting the right tissue is difficult—sensory nerve samples may not enable researchers to see the virus, but motor nerve samples cannot be taken for risk of inducing paralysis. Patients in the current outbreak had antibodies, but different virus strains have not been identified in these patients. Retrospective analysis showed that GBS increased by 17 times in the French Polynesia Zika virus outbreaks. In Amazonia and Colombia, large numbers of people have no access to ICU and no practical access to IVIg, suggesting potential for tragedy.
- The mechanism by which IVIg functions as a treatment for GBS is not completely understood, and in some classical cases does not work at all.
- It was suggested that researchers could go back to the brain bank and examine what is new and what is different about the described case, for fear that focus on microcephaly has caused the research community to “put the cart before the horse”; questions need to be answered about how current cases differ from other known syndromic constellations caused by virus insults. A case series was requested showing exactly how the pathology and the morphology differ in this respect.
- The meeting was then shown a draft, pre-emergency use authorisation target product profile (TPP) for a Zika virus prophylactic. Points were made about the possibility of different use cases, including targeting pregnant women; using treatment as chemoprophylaxis; and use in the setting of a rash. A low entry point

for therapeutic use, it was argued, would be in settings of sexually transmitted disease; timing may render consideration for prophylaxis impossible.

Advances in data sharing

ZIKA R&D: data sharing panel

***Vasee Moorthy**, WHO*

Dr Moorthy outlined data sharing considerations underpinning every agenda item in this meeting. He sketched out the data types that need to be shared, which he characterised as epidemiological/surveillance data; research data both raw and analysed; interim results subject to quality control; final research results; 'negative' and inconclusive results; and genetic sequence data (this last overlapping with questions related to sample sharing). Key stakeholders in agreements on sharing mechanisms include funders; journals; investigators and researchers; commercial entities and manufacturers; governments; ethics committees; and regulatory authorities. The 10 February 2016 statement by a number of major journals, funders and others on 'data sharing on Zika' committed that all Zika virus content could be made free to access without risk of pre-empting publication in signatory journals. Signatory funders required that researchers doing emergency-relevant work must have mechanisms to share quality-assured interim and final data "as rapidly and widely as possible… with public health and research communities and with WHO." In this context, WHO generated a three-step process for clinical trials: universal prospective clinical trial registration; public disclosure/dissemination of results; and sharing of individual participant data, subject to ethical and legal obligations.

Panel presentations

Larry Peiperl, Chief Editor of PLOS medicine, outlined how data sharing has evolved. He argued that it is important to distinguish between what journals can do alone and what requires support of the scientific community. Free access can be provided, and this is happening; and early sharing of results can be encouraged, as can rapid review and publication, and the speeding up of peer review processes while advance sharing is going on. But, he said, specific policies—data standards, etiquette with regard to scooping, etc.—must also come from specific research communities. There is a need for tools; development of a culture of informed, constructive commenting; and mechanisms for providing important credit to those who do share data. Current adherence to legislation for publishing within certain timeframes is poor.

Dr Lara Gollogly, Editor of the *WHO Bulletin*, explained WHO's data sharing initiatives in response to Zika. A data sharing site and protocol was announced in early February, three days after the declaration of the PHEIC, and subsequently promoted and publicised. This was followed by the 10 February statement. So far, 11 research papers had been submitted to WHO in the first five weeks, of which nine had been posted. She pledged that WHO would follow up with authors to try to determine the impact on their work, and publish the results of this research as well.

Lindsey Baden of the *New England Journal of Medicine* argued that sharing information rapidly is essential, but characterised current responses as struggling with disseminating information that meets key public health criteria. It was essential to define and separate goals; what various platforms allow; and methods by which to achieve those goals. Challenges in data sharing include balancing speed, accuracy and completeness. He used Dr Zupanc's paper as an example: the paper as received by the NEJM was very different to what was eventually published; and if data are incomplete then the implications have to be managed carefully. The discussion of data sharing must include quality control standards for data and protocols for dissemination. In this context, the data creator or originator must not be forgotten: the point of publication is important, but there is a large swathe of investigators that must be credited—as is apparent in the context of serologies for Zika.

Katherine Littler of the Wellcome Trust then argued that the 10 February statement was a 'sea change' for funders, moving them from encouraging data sharing to expecting it. The number of signatories is increasing, and the critical question for funders is now how to implement this new reality; so policy alignment between funders is important. Dr Littler argued for three key policy areas. Firstly, incentives and recognition, where mechanisms must be developed to promote good behaviour and ensure appropriate censure for those who misuse data or fail to acknowledge data sources. Secondly, in infrastructure and tools development, resources and gaps must be mapped; discoverability and re-use of data must be enabled; further development and uptake of innovative (pre-)publication platforms to enable sharing of data must be encouraged; and tools must be developed to enable this. Thirdly, ethical, legal and governance issues must be addressed, including through developing template data and material transfer agreements, streamlining processes, safeguarding research participants and promoting trust.

Rebecca Lawrence of the F1000 group argued that the Open Science Publicising Platform already offers a response to WHO's needs. She how the platform works and said that models already exist that fulfil the WHO criteria as expressed: constituting a paradigm shift; allowing immediate publication using post-publication peer review services; and providing incentives for sharing data and results.

Cathy Roth of WHO argued that for epidemics of severe emerging diseases, biological samples are a precious non-renewable source of opportunities to advance knowledge of disease, improve and evaluate control tools and interventions, increase capacity for research, and foster international collaborations. They also present a moral imperative for prudent use to illuminate priority research questions—with an attendant emphasis on safety and biosecurity. The Ebola epidemic provides useful background, having generated thousands of valuable samples in an international environment lacking plans and capacity for maintenance and handling. Most emerging diseases on the priority list and new diseases like Zika are in the same situation. She outlined considerations identified during the Ebola epidemic, both disease specific (e.g. biosecurity of Ebola samples) and more generic (issues of ownership and ethics), and sketched out options for a generic approach to sample sharing based on international collaboration; a distributed "virtual" resource

of [national] bio-banks linked by an information-sharing platform; a shared system of governance and decision-making; and a systematic design adapted for each priority disease. She outlined what infrastructure such a system would need, and listed the stakeholders who must work together to address this. All such work would have to be conducted in the light of complex issues including the need for consistency with principles of existing relevant international frameworks and principles of equity and benefit sharing. Work is underway to develop guidance.

Jean Louis Romette outlined the work of the **European Virus Archive** (EVA), a non-profit EU-supported organisation that collaborates with partners to share material with the scientific community. Together they offer a variety of high quality products accessed through the EVAg web catalogue. Researchers desiring material apply online, undergo background checks, and are supplied with resources through partners. Material transfer agreements stipulate recognition of sample ownership; a ban on commercial application without owner's consent; and a ban on further distribution to third parties. Since mid December 2015 the EVAg has received 190 enquiries for Zika-related materials related to development of 258 separate products in 190 labs in 30 countries—though none are in South America. EVA also has a strategy for supporting responses to emergencies through a task force, WAVE, which is developing Zika related materials through four European laboratories.

Discussion

- While traditionally a published virus can be requested by anyone for non-commercial use, in reality repositories are often unwilling to share. It was suggested that those present could collaborate in the creation of a database of existing strains for Zika, their locations and the relevant contacts. Dr Andrew Haddow asked that anyone willing to host or to help this initiative contact him (see Annex B).
- Researchers should submit protocols and guarantee to review results when they provide data, in order to allow publication decisions to be made; there was general agreement that the publication process needs rethinking and that a protocol providing a roadmap of where data is going would make that easier. Models exist: F1000 registered reports allow publication of what is planned and encourage researchers to publish their lead outcomes.
- Currently the International Health Regulations enable sharing information from national authorities with, but not beyond, WHO; there was discussion of whether they can be interpreted to enable open data sharing in a PHEIC. The IHR Review Committee is looking at Ebola lessons to see if revisions to the Regulations are necessary. It was suggested that WHO move from an 'opt in' to an 'opt out' default position on sharing national data.
- The importance of mosquitoes was again stressed, along with the desire that this importance be reflected in approaches to sample sharing. If WHO funding exists for networking activities around insecticide resistance in different populations, or with different mechanisms, that should become part of the information sharing.
- Languages can often form a barrier to information sharing; Portuguese and Spanish research should currently be accepted and shared.

- The meeting was then closed by Dr Kieny, who summed up discussions (see executive summary) and thanked participants for their attendance and their contributions.

Annex A – meeting agenda

WHO global consultation of research related to Zika virus infection

7-9 March 2016, Geneva, Switzerland

Day 1: Public health Research

11.00-12.00	**Opening session**	
11.00-11.20	Welcome & introductory remarks	Bruce Aylward, WHO Marie-Paule Kieny, WHO
11.20-11.40	Flaviviruses & Zika: current knowledge	Duane Gubler, Duke University
11.40-12.00	Current epidemiological features, timeline of events and major concerns	Celina Turchi, University of Pernambuco
12.00-13.30	**Lunch break**	
13.30-14.00	**Feedback from PAHO meeting – key issues** Discussion	Ludovic Reivez Herault, PAHO
14.00-15.20	**Microcephaly and neurological disorders** Pathogenesis of microcephaly Causality framework and Key results of literature review Discussion	Paul Garner, Liverpool School of Tropical Medicine Goeff Woods, Cambridge University Nathalie Broutet, WHO
15.20-15.50	**Coffee break**	
15.50-17.00	**Research protocols: roadmap toward implementation** Outline of research protocols discussed at PAHO Which elements should be considered in the research protocols with regards to: Diagnostic tools Pathogenesis	Eva Harris, University of California, Berkeley Nathalie Broutet, WHO

	Vector	Christopher Oxenford, WHO
	Standard clinical characterization protocol	Alan Rothman, University of Rhode Island, Providence Frédéric Simard, IRD, Montpellier Thomas Janish, Heidelberg University
17.00-17.20	**Epidemiological modeling: Implications for Zika control measures**	Neil Ferguson, Imperial College, London
17.20-17.40	**Pathogenicity for the design of novel interventions**	Cameron Simmons, Oxford Universit
17.40-18.00	**Discussion**	Marie Paule Kieny & Duane Gubler
18.00	**Cocktail reception**	

Day 2 and 3: Landscape Analysis for future Zika medical technologies

8 March 2016

09.00-10.30	**Introduction**	
09.00-09.20	Overview of the R&D Blueprint	Marie-Paule Kieny, WHO
09.20-09.50	Animal models for Zika infection	Johan Neyts, Leuven University; Christina Casseti, NIH
09.50-10.00	Virus strains for product development	Robin Robinson, BARDA
10.00-10.30	Discussion	
10.30-11.00	**Coffee break**	
11.00-12.30	**Zika virus Vaccines**	
11.00-11.15	Review of the vaccine product development landscape	Joachim Hombach, WHO
11.15-11.30	Overview of the draft vaccine TPP	David Kaslow, PATH
11.30-12.30	Panel and General discussion	Jorge Kalil, Instituto Butantan Sumathy Kandaswamy, Bharat Biotech Joan Fusco, NewLink

		Nick Jackson, Sanofi
12.30-13.30	**Lunch break**	
13.30-15.00	**Zika virus Diagnostics**	
13.30-13.45	Review of the diagnostic product development landscape and needs	Bill Rodriguez, FIND
13.45-14.00	Overview of the draft diagnostic TPP	Francis Moussy, WHO
14.00-14.10	The EUAL process for diagnostics	Robyn Meurant, WHO
14.10-15.00	Panel and General discussion	Laurence Flevaud, MSF Brazil
		Jan Felix Drexler, Bonn Institute Virology
		Jonas Schmidt- Chanasit, Bernhard-Nocht Institute
15.00-15.30	**Tea break**	
15.30-17.00	**New Tools for Vector control**	
15.30-15.50	Review of the new vector control tools landscape	Philip McCall, LSHTM
15.50-16.05	Modelling introduction of vectors designed to reduce vector burden	TBD
16.05-16.15	Presentation of the TPP development process	Abraham Mnzava/Rajpal Yadav, WHO
16.15-16.50	Panel and General discussion	Hadyn Parry, Oxitec UK
		Peter Ryan, Monash University
		Konstantinos Bourtzis, FAO/IAEA
		Mawlouth Diallo, Institut Pasteur Dakar
		Paulo Gadelha, Fiocruz
17.00-18:00	**Regulatory**	
17.00-17.10	Key regulatory issues for candidate Zika products	Flavia Sobral, ANVISA
17.10-17.20	Examples of collaborative regulatory support for emerging infectious diseases	David Wood, WHO
17.20-17.30	Offers of support from regulatory agencies	Marco Cavaleri, EMA

	to evaluate candidate Zika products	
17.30-17.40	Candidate reference preparations for candidate Zika products	Mark Page, NIBSC Klaus Cichutek, PEI
17.40-18.00	General discussion	
17:50-18:00	Review of discussions & wrap up	Marie-Paule Kieny, WHO

9 March 2016

08.30-09.00	**Key note lecture**	Tatjana Avšič županc
09.00-10.30	**Medicines and Blood Products**	
09.00-09.20	Review of the treatment product development landscape	Lisa Ng, A*Star
09.20-10.30	Panel and General Discussion	Sina, Bavari, USAMRID Christina Casseti, NIH Ichiro Kurane, Japan NIH
10.30-11.00	**Coffee break**	
11.00-12.00	**Advances in data sharing**	Vasee Moorthy, WHO Lara Gollogly, WHO Lindsey Baden, NEJM Larry Peiperl, PLOS Katherine Littler, Welcome Trust Rebecca Lawrence, F1000
12.00-12.30	**Advances in sample sharing**	Cathy Roth
	Discussion	Jean Louis Romette, European Virus Archive
12.30-12.45	**Closing remarks**	Marie Paule Kieny, WHO

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