

Real-time Evaluation of Research and Development (R&D) Response to Zika

Second Review Mission: 28th to 30th June 2016

Introduction

Background details to this mission are found in the concept note related to real-time evaluation of the R&D response to Zika. A preliminary scoping mission was conducted in Geneva from 19-22 April 2016. This second mission sought to collect evidence on progress towards agreed milestones and indicators and also to answer a number of generic and specific questions. Details of these are presented in Annex 1 (p11). During the mission, a number of documents were reviewed (see Annex 2, p12) and interviews were held with a number of key informants (see Annex 3, p14). This report is organised as follows. First, it identifies and highlights a number of issues relating to the R&D response to Zika, in general, before considering more detailed issues relating to scientific evidence and progress on R&D related to diagnostics, vaccines, vector control and treatment. It ends with suggested conclusions and recommendations. The extent to which progress towards specific milestones has been assessed and particular questions answered is covered in Annex 4 (p15).

Acronyms

ANVISA	National Health Surveillance Authority (Brazil)
ELISA	Enzyme Linked Immunosorbent Assay
EUAL	Emergency Use Assessment and Listing
FDA	Food and Drug Administration
Fiocruz	Fundação Oswaldo Cruz
GLOPID-R	Global Research Collaboration for Infectious Disease Preparedness
IVM	Integrated Vector Management
MPTF	Multi-Partner Trust Fund
NAT	Nucleic Acid Testing
NTD	Department of Control of Neglected Tropical Diseases
OHE	Outbreaks and Health Emergencies
PAHO	Pan-American Health Organization
PCR	Polymerase Chain Reaction
R&D	Research and Development
RDT	Rapid Diagnostic Test
TDR	Special Programme for Research and Training in Tropical Diseases
TPP	Target Product Profile
UN	United Nations
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
US	United States
VCAG	Vector Control Advisory Group
VLP	Virus-like Particles
WHO	World Health Organization

General issues

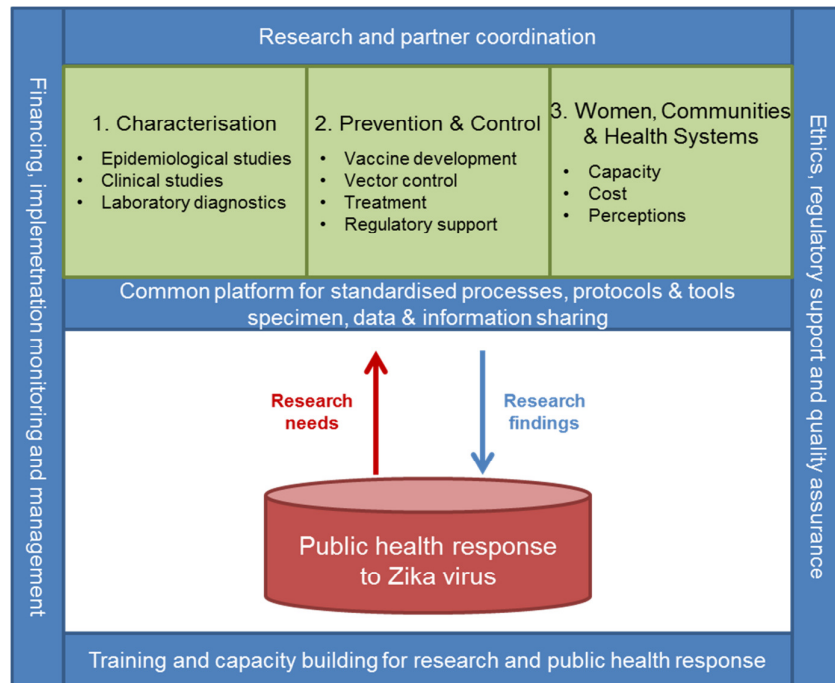
Role and scope of the Blueprint

In the work done for planning for the Blueprint to identify and prioritise pathogens that were likely to cause severe outbreaks in the near future and for which few or no medical countermeasures exist, Zika was identified as a serious threat requiring action by WHO to promote R&D as soon as possible. The prioritisation meeting also noted that if the link to microcephaly was confirmed, this would mean Zika would need to be moved to an even higher priority. In addition, work on regulatory environments conducted under work-stream 2 of the Blueprint has proved relevant and useful for the R&D response to Zika. Similarly, work carried out under the Blueprint's work-stream 4 meant that this real-time evaluation was able to be rapidly established. One external respondent commented that the Blueprint has resulted in R&D being brought to the forefront much more quickly than previously. They noted that had the Blueprint been in place prior to the Ebola outbreak, less time might have been spent in pursuing conventional but ineffective approaches.

One recurring issue is the scope of the Blueprint. While it is agreed that the focus is on research and development, there does not seem to be consensus as to precisely what this means and this may need to be clarified.

WHO has also been developing separately an overall research agenda for Zika. The research agenda has three main pillars – characterisation; prevention and control; and women, communities and health systems (see Figure 1).

Figure 1: WHO Zika Virus Research Agenda Implementation Framework (from Zika research agenda)



Clearly, elements of product research and development that are included in the Blueprint are reflected in the Zika research agenda, particularly the second pillar focused on prevention and control. Elements relating to research and development of diagnostic tests (including landscape analysis, target product profiles and emergency assessment procedures) are included under the first pillar focused on characterisation.

Implementing the full research agenda would be expected to cost around \$12m over two years. Work already conducted under the research agenda includes harmonisation of research protocols. Challenges identified include:

- Ensuring someone is responsible within the emergency response for developing a research agenda for the specific pathogen causing the outbreak.
- Quickly identifying people with the appropriate research skills and experience to conduct necessary research identified in the research agenda. Building up (and establishing framework contracts with) a network of outbreak investigators could be helpful in this regard.

Coordination

In general, respondents were positive about coordination of the R&D response to Zika drawing, in particular, positive comparisons to what had been the case for the R&D response to Ebola. One respondent highlighted that there was better coordination across WHO, including headquarters and

regional/country offices. There had been strong leadership from the management team centrally and from PAHO.

One external respondent commented that WHO had used their convening authority well and pointed to the meeting that was held in March 2016. This meeting brought together more than 130 experts from 30 countries to focus on issues relating to R&D of vaccines, treatment and vector control for Zika. One external respondent commented that this meeting went very well and brought people together to seek consensus. They noted that it would have been good to be clearer as to how WHO would communicate and coordinate after the meeting.

Concerning coordination within WHO among those working on Zika R&D, there have been regular meetings of the Blueprint team in relation to Zika with the next meeting scheduled for 7th July. These meetings bring together those working on the R&D of diagnostics, vaccines, treatment and vector control.

In addition, there has been coordination between those working on Zika R&D and those working on the Zika response more broadly. These two elements are managed by different departments within WHO. The coordination arrangements are reported to be the same as they were at the beginning of the response to Ebola, i.e. R&D is considered part of the overall Zika response.

In terms of WHO communications with other actors and partners, external respondents appreciated the regular donor calls but commented that these could be documented more systematically. In general, WHO could communicate more clearly and regularly about what it is doing in relation to Zika R&D. For example, some of the external respondents reported that they had not seen the WHO Zika research agenda. A regular email update with clickable links to access more detailed information might be the best way of sharing such information. One respondent commented that meetings convened by WHO had been a good way of sharing up-to-date information. Another commented that it was important for WHO and its partners to understand each other's structures and communication channels to ensure that communications are both effective and efficient.

Respondents did highlight a number of issues related to coordination:

- There are some areas where efforts appear to be duplicated, e.g. different companies developing similar vaccines.
- Substantial efforts have been made to coordinate work on diagnostic R&D between UNICEF and WHO, including at a meeting organised by UNICEF in Copenhagen.
- External respondents expressed some uncertainty about potential overlaps and duplications between the work of the WHO Blueprint and the Global Research Collaboration for Infectious Disease Preparedness (GLOPID-R) and the desire that these two bodies work more closely together. This may involve delineating more clearly the boundaries between the two bodies, i.e. who does what, to avoid unnecessary duplications and overlaps.

Landscape analyses

WHO conducted an initial landscape analysis in March 2016 related to Zika diagnostics, vaccines, vector control and treatment (see Box 1). Since that time, these analyses have been kept regularly updated.

Box 1: More detail of initial landscape analysis conducted by WHO on Zika diagnostics, vaccines, vector control and therapeutics¹

For diagnostics, WHO has mapped what diagnostics are being developed by whom. This includes nucleic acid test kits (for both Zika alone and in combination with other viruses); integrated nucleic acid testing (NAT); immunoassays (enzyme-linked immunosorbent assays [ELISA]); and rapid diagnostic tests (RDTs). This mapping includes those products submitted to WHO for EUAL but it also includes others. The landscape analysis notes that information may be incomplete because companies may choose not to disclose the current state of their development. WHO updates this information on a weekly basis with a focus on those products submitted for EUAL.

For vaccines, WHO conducted a landscape analysis based on feedback from 25 developers related to at least 15 active programmes. A range of different technologies were identified including inactivated purified virus; live vectored; live attenuated/recombinant; subunit/peptides; virus-like particles (VLP); and nucleic acid based vaccines. The landscape analysis considered potential advantages and disadvantages of the different technologies. All programmes were at an early preclinical stage with phase 1 clinical trials expected towards the end of 2016. Following the landscape analysis, WHO began a consultative process to develop a target product profile (TPP) for a Zika vaccine.

For vector control, the landscape analysis focused on identifying new tools including mechanical, chemical, biological and genetic approaches. It also examined how vector control methods could be made more efficient, effective and ecologically sound and referred to the work of the Vector Control Advisory Group.

For therapeutics, given the lack of understanding of Zika virus infection, clinical progression and pathogenesis, the role for therapeutic products is uncertain. Nevertheless, the landscape analysis did include a product pipeline for a number of therapeutic agents including Amodiaquine, Chloroquine, Ribavirin, Interferon A, BCX4430, GS-5734, NITD008 and monoclonal antibodies.

¹ Sources include "Current Zika Product Pipeline" produced March 2016

Comparisons to Ebola

In general, WHO and others have learned many lessons from their experiences of responding to Ebola which have proved extremely useful in responding more effectively to Zika and other outbreaks that may occur. For example, lessons learned through Ebola concerning WHO's programme of prequalifying products led to the introduction of processes for EUAL which are being used in the response to Zika.

While lessons have been learned for R&D from the response to Ebola that are relevant to the response to Zika, there are significant differences between the two diseases and their outbreaks which mean that the amount of cross-learning may be limited. For example, there were candidate vaccines available when the Ebola outbreak occurred. In addition, case mortality rate was very high in Ebola meaning there was a major focus on treatment. In terms of diagnostics, there were fewer problems of cross-reactivity because although there is potentially some cross-reactivity with other viruses, e.g. Marburg, this proved not to be a major issue in practice. Conversely, in relation to Zika, there was no candidate vaccine or treatment at the time of the outbreak. Zika also differed from Ebola in terms of being a relatively minor disease in most people but with potentially severe effects in fetuses. Consequently, potentially recommending vaccination for pregnant women has implications in terms of the risks and ethics of using a relatively untested vaccine in that group. In terms of Zika transmission, vector control has proven to date to be relatively ineffective. In addition, there are real practical problems for Zika diagnostics because of cross-reactivity with other viruses. In addition, the Zika virus is present in a person's blood for a relatively short period of time.

Funding and resources

A key concern raised by respondents was that, to date, it has proved difficult to raise funding and resources needed for the response to Zika. The strategic response plan identifies that at least \$122m is required by WHO and its partners from July 2016 to December 2017. However, the plan also notes that these figures are not exhaustive as some partners have not yet developed and finalised their plans. The budget is sub-divided into five objectives (see Figure 2). Although the plan is said to represent the work of more than 60 partners, almost all the budget (89%) is focused on the work of six UN agencies (see Figure 3).

Of the total budget, around one third (33%, US\$40m) is specified for research. Of this, almost all (95%) is allocated to either UNICEF (US\$25.4m) or WHO (\$12.3m).

While it is unclear how much of the required budget is available, the plan is clear that, of the \$25m that WHO and PAHO considered was needed for the first six months of 2016, only just over \$4m (16%) was received. It is also reported that only \$0.5m was made available for Zika R&D.

Figure 2: Breakdown of Zika Strategic Response Plan Budget (US\$122m) by Objective

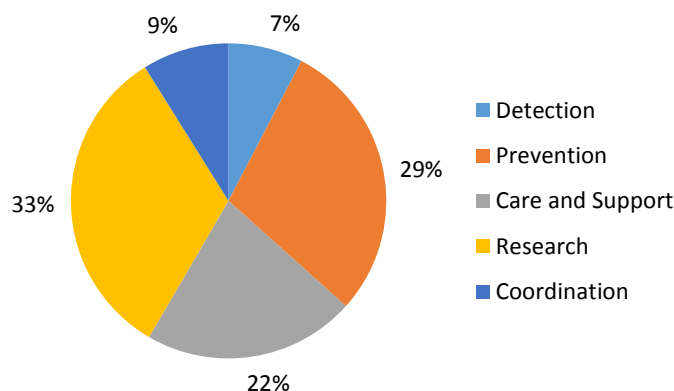


Figure 3: Breakdown of Zika Strategic Response Plan Budget (US\$122m) by Partner

Partner	Amount (\$m)
UNICEF	48.3
WHO	24.5
PAHO	15.1
UNFPA	10.0
UN Women	5.6
UNDP	5.2
Subtotal	108.7
Save the Children	6.3
Other	7.2
Total	122.2

In order to address this lack of funding, the UN established a Zika Multi-Partner Trust Fund (MPTF) in May 2016¹. The aim of this fund is to rapidly resource the UN system responses to Zika based on the needs and requirements of the Zika Response Framework. Although this framework is said to have three strategic objectives, i.e. surveillance, response and research, it is reported that the priorities of the MPTF needed to be “people-centred” so they focus on prevention, risk communication and care and support with no language specifically related to research.

¹ See <http://mptf.undp.org/factsheet/fund/ZKA00>

Role of WHO

One issue which continues to be discussed and debated is the role of WHO in effective R&D responses to Zika (and other pathogens). WHO is considered to have a comparative advantage in terms of coordinating and convening others and collating research done by others rather than in conducting research directly. One external respondent commented that it was not always clear from their documents what WHO is doing itself and what partners are doing.

WHO structure, rules, procedures and culture

WHO is currently reforming how it responds to emergencies². A new Executive Director has been appointed and is due to take up the post at the end of July. The Blueprint's manager has been representing R&D issues in that process.

Emergence of other threats

The response to Zika is not occurring in isolation. Some respondents noted that work related to Ebola is still ongoing and there is always a risk of other outbreaks occurring. Respondents expressed concern about the growing number of cases of Yellow Fever in Angola and the Democratic Republic of Congo. WHO is convening a research meeting at the end of September 2016 to seek to address the many things that are unknown about Yellow Fever.

R&D issues in more detail

Scientific knowledge

There has been interest in why Zika appears to be associated with a higher rate of neonatal microcephaly in North East Brazil than elsewhere.

Diagnostics

Substantial work has been done in relation to R&D of Zika diagnostics including landscape analysis, work on target product profiles (TPPs) and work on Emergency Use Assessment and Listing (EUAL) procedures. EUAL procedures were introduced during the Ebola outbreak and were opened for Zika in February 2016. WHO is currently processing 20 EUAL applications relating to Zika diagnostics (see Box 2). The initial timeline for receiving applications has been extended and these can still be received.

Box 2: Update on EUAL processes for Zika diagnostics (based on weekly update 1st July 2016)

Of the 20 diagnostic products submitted for EUAL, six had completed assessment of the manufacturer's quality management system. In five cases, additional information had been requested and in a further eight the process was ongoing.

In two cases, the documentary evidence review had been completed. In five cases, additional information had been requested and in seven cases the process was ongoing.

Three performance evaluations had been scheduled with a further seven in the planning phase.

The EUAL process allows products to be assessed by WHO more quickly than the usual pre-qualification process which takes around 270 working days. The EUAL process has three main components (see also Box 2):

- Assessment of a product dossier, i.e. documentary evidence. Manufacturers submit evidence and this is reviewed by technical experts using a standard checklist.

² See http://www.who.int/about/who_reform/emergency-capacities/en/

- Assessment of quality management system – this component involves assessing the manufacturer. Unlike the standard prequalification process, the EUAL process does not require an inspection but relies on documentary evidence.
- Review of product performance – this requires independent assessment of the product in practice. This step is particularly important as manufacturers may not have full studies.

In March 2016, WHO organised a consultative meeting which brought together experts to agree the level of documentary evidence needed in the first step and the study protocols to test product performance.

One key challenge in relation to reviewing product performance of diagnostics is access to relevant clinical samples to build up a panel. It is particularly important to test diagnostics in Latin America because samples tested in other contexts, e.g. in Europe, might exhibit less cross reactivity because of other infections. It is reported that Brazil has passed a law which prevents samples being sent out of the country. This has made accessing and sharing samples more difficult. It means that product performance testing has to be done in country and WHO has been seeking to work with a laboratory in French Guiana and two laboratories operated by the Fundação Oswaldo Cruz (Fiocruz) in Brazil (in Recife and Rio). However, this is not straightforward because these laboratories, particularly the one in Recife, are overloaded and are targeted by others, e.g. manufacturers, researchers and national governments. It would be helpful if there were a network of laboratory centres which WHO and others could work with to gain access to specimens for product performance testing. Similar networks have been identified for specific diseases, e.g. influenza and dengue but it would be helpful to have such a network of laboratories that could be called on in different disease outbreaks. Such a network would allow WHO and others to identify laboratories to work with and could also allow sharing of specimens. Laboratories that are part of such a network would potentially benefit from increased visibility and recognition. Having such a network might also mean that requests, e.g. from companies, researchers and WHO, could be more coordinated. However, this might also involve more cooperation and coordination among those seeking to work with laboratories.

It would also be helpful if WHO were able to support these laboratories with “surge capacity”, i.e. additional staff. It is important that these staff have relevant experience and language skills. WHO has been working closely with Brazil’s National Health Surveillance Agency (ANVISA) who are reported to be very open on these matters.

It would be ideal if sample banks could be established and shared with those who need access to them. However, this has proved to be very difficult to agree because of issues relating to ownership and sharing benefits and risks. WHO might consider establishing a unit to promote biobanking. Such a unit would need to address issues of ownership and benefits. They might also need to promote a mindset in which drug manufacturers are seen as suitable partners and not the “enemy”.

Another key challenge is that while a number of steps have been speeded up under EUAL processes when compared with standard pre-qualification processes, there are a number of other elements, on which EUAL depends, which are reported to take as long as in non-emergency settings. These include ethical clearance and developing reference material.

Vaccines

WHO has developed a target product profile for a Zika vaccine and this has been posted and comments received. A first meeting of regulators has been held but there are many questions about

this vaccine including what the end point is, that is based on clinical findings or laboratory tests. There is need for a further meeting to resolve these questions as human clinical trials are due to start. There are also issues because the first vaccines tested are likely to be DNA vaccines and although these have been shown to be effective in animals they have not yet been shown to be effective in humans.

There are also issues about:

- Whether the vaccine can be given to pregnant women.
- The extent to which there is a commercial market for Zika vaccine.
- The extent to which vaccination with Zika might cause neurological problems and what the risks might be. There are also issues about how to assess these safety risks.
- Whether vaccination should be offered to men.

External respondents were extremely positive about the meeting which had been held to discuss the vaccine TPP. The meeting was relatively small and was well-organised. Those who were there had something to contribute and the meeting was quite representative. This was considered to be much better than during Ebola when meetings were very large and there were people in the meetings who had no experience or little, if anything, invested in the response. During Ebola, there were concerns that some meetings organised by WHO had pre-determined outcomes but this was not so in this case. There was vigorous discussion on some topics, e.g. whether Zika vaccine should be available to pregnant women but the conversation was considered helpful and productive.

Vector control

Coordinating R&D on vector control in relation to Zika has involved liaising closely with two other groups with expertise in the more usual and established ways of vector control, including spraying and bed nets. These groups are the Department of Control of Neglected Tropical Diseases (NTD) and the Special Programme for Research and Training in Tropical Diseases (TDR). However, a number of new tools for vector control were identified during a landscape analysis of the research and development pipeline conducted under the WHO R&D Blueprint response to Zika. The subsequent WHO consultation in March 2016 on Zika R&D concluded “that extreme rigour needs to be applied in evaluating novel tools, such as Wolbachia, recombinant and irradiated mosquitoes”. The following week an emergency meeting of WHO’s Vector Control Advisory Group (VCAG), jointly established by the Global Malaria Programme and NTD in 2013, recommended “the carefully planned pilot deployment under operational conditions of two tools (Wolbachia-based biocontrol and OX513A transgenic mosquitoes) accompanied by rigorous independent monitoring and evaluation”. The VCAG has commissioned a set of guidance on the evidence base needed to underpin vector control field trials. The guidance, which will cover both entomological and epidemiological end-points, is being developed by external experts. A preliminary report is expected to be available in September 2016.

As part of the R&D Blueprint, a meeting will be organized in November, in close collaboration with NTD, to identify operational considerations when applying VCAG/WHO guidance in emergency settings

The Zika strategic response framework emphasises that prevention should not focus only on vector control but on a process of integrated vector management (IVM) which also protects pregnant

women and women of reproductive age from infection and unintended pregnancy. Elements of IVM include advocacy, risk communication for behaviour change and community engagement and legislation; collaboration with the health sector and with other sectors; integrated approach to disease control; evidence-based decision-making; and capacity building.

One external respondent expressed concern that WHO's messaging on this is confusing. On the one hand, strategic documents emphasise the need to move beyond conventional approaches to vector control while many programmes continue to emphasise these and work in this way. Clearer, evidence-based guidance is needed

Treatment

As noted above, there has not, as yet, been much focus on R&D of Zika treatment given that the illness is mild and self-limiting in most cases and there has been more focus on diagnostics, vaccines and vector control.

Conclusions and recommendations

This report concludes with a number of conclusions and recommendations for further discussion and potential action:

1. In relation to Zika, it would be useful to **clarify the link between the research and development Blueprint and the broader research agenda**. In particular, it would be helpful to have clear agreement on what falls within the scope of the R&D Blueprint and what falls beyond its scope.
2. It would be helpful if WHO could **establish a network of outbreak investigators** that could be available to provide research capacity in the face of emergencies. One option for doing this might be to establish a number of framework contracts with institutions with research capacity, e.g. universities and other academic institutions, that could be called on as needed.
3. There is need for **someone within the OHE cluster to be responsible for developing a research agenda in an emergency situation**.
4. It would be helpful if WHO were able to **improve its communications about Zika R&D particularly with key external stakeholders**. In the short-term, this should include sharing the Zika research agenda with them. In the medium-term, this should involve a regular email update focused on issues of concern and interest to them.
5. It would also be helpful if **WHO could clarify and explain how it is working and coordinating with other key partners working in this field**, e.g. UNICEF and GLOPID-R.
6. There is need to recognise that while lessons can be learned from one disease outbreak that can inform responses to future outbreaks of different diseases, **diseases and outbreaks differ from each other in many ways so may limit the transferability of lessons learned**, e.g. from Ebola to Zika.
7. Given the importance of research (including R&D) to effective responses to Zika, it is **crucial that efforts to raise resources for the response to Zika include resources for research**. This is particularly important as the MPTF is established.

8. It is always important in documents to be **clear as to what WHO's role is in the response to Zika**. This will involve being as clear as possible as to what is done by WHO and what by partners.
9. A key priority for the new OHE Director should be to establish and communicate the cluster's structure. This should **include articulating whether research (including R&D) fits within the OHE cluster and if so how**.
10. It would be helpful if **WHO could establish a network of laboratories that could be available to respond to disease outbreaks when they occur**.
11. WHO might consider **establishing a unit to promote biobanking of laboratory samples**.
12. There are **a number of areas where streamlined procedures might be needed in emergencies** akin to the EUAL process in place of standard prequalification processes. These include ethical clearance, preparation of reference materials and WHO human resource procedures.
13. It would be helpful if WHO could review where **additional staff might be needed to allow R&D for Zika and other emergencies** to take place effectively. This could include dedicated staff for EUAL processes, for example.
14. It would be helpful for WHO and partners to have **further discussions relating to Zika vaccine development** including the appropriateness or otherwise of seeking to vaccinate pregnant women.
15. It would be helpful if WHO could produce **clear and consistent guidance as to the role of vector control in relation to prevention of Zika and other related diseases**. It may be particularly important to align policy statements and programme practices.

Annex 1: Proposed Zika review mission

Introduction

Background details to this mission are found in the concept note related to real-time evaluation of the R&D response to Zika. A preliminary scoping mission was conducted in Geneva from 19-22 April. Based on this, it is proposed that a further mission be conducted in early June. It is proposed that the dates for face-to-face meetings in Geneva would be either the week of 30th May or 6th June. Remote interviews could be conducted during that week or prior to the trip to Geneva.

Topics and questions

It is proposed that evidence will be gathered concerning progress towards certain milestones and indicators, namely

- Global consultation on R&D in relation to Zika
- Landscape analysis table(s) completed.
- Number of conference calls held.
- Number of target product profiles developed.
- Products listed through Emergency Use Assessment and Listing (EUAL).

It is also proposed that certain questions will be explored during each mission, namely:

- To what extent is progress being made on (1) diagnostics; (2) vector control; (3) vaccine development; and (possibly) (4) therapeutics?
- To what extent are supportive research activities being coordinated including the establishment and validation of appropriate animal models and sharing of information?
- To what extent have the conference calls held been valuable in terms of improving coordination?
- Has the regulatory support group been established? To what extent is this functioning well?

It is also proposed that certain specific questions will be addressed during this particular mission, namely:

- What happened once Zika was identified as a priority pathogen and the cluster of microcephaly cases in Brazil was recognized as an emergency? In particular, was an operational plan developed and implemented?
- Were the appropriate stakeholders identified and informed? If so, what were the strengths and challenges of this process? If not, why not?
- Can any lessons be learned, e.g. for the development of a decision tree for new pathogens, from experiences of Zika, i.e. as a known pathogen developing new associations with diseases

Stakeholders to consult

- Blueprint workstream leads
- PAHO
- Country offices Brazil, Colombia, Mexico
- Manica Balasegaram, MSF, Strategic Advisory Group
- Lucille Blumberg, National Institute for Communicable Diseases, South Africa
- Chris Lewis DFID

Annex 2: Documents Reviewed

General for the Blueprint

WHO (2016) An R&D Blueprint for Action to Prevent Epidemics: Monitoring and Evaluation Framework: Detailed Plans May 2016
WHO (2016) Questions for Team Leaders
WHO (2016) Blueprint Project Management Plan
WHO (2015/6) Notes of Blueprint leads meetings
WHO (2015/6) Notes from SAG meetings
WHO (2015) Notes of Blueprint Meeting
WHO (2015) Short Concept Note on the Blueprint
WHO (2015) Blueprint Proposal

Other similar initiatives

WHO (2016) Global Action Plan for Influenza Vaccines – see http://www.who.int/influenza_vaccines_plan/objectives/en/
WHO (2016) Pandemic Influenza Preparation Framework – see <http://www.who.int/influenza/pip/en/>

Issues relating to Global Research Collaboration for Infectious Disease Preparedness (GLOPID-R)

GLOPID-R (2016) Website – see <http://www.glopid-r.org/>
GLOPID-R (2016) Mind the Gap: Coordinating Funding in Public Health Emergencies – letter to Lancet and details of authors
Kieny, M-P, Rottingen, J-A. and Farrar, J. (2016) The Need for Global R&D Coordination for Infectious Diseases with Epidemic Potential – letter to Lancet

WHO and emergencies

WHO (2016) Website – see http://www.who.int/about/who_reform/emergency-capacities/en/

Specific to Zika

UNDP (2016) UN Zika Response Multi Partner Trust Fund see <http://mptf.undp.org/factsheet/fund/ZKA00>
WHO (2016) Zika: Strategic Response Framework and Joint Operations Plan
WHO (2016) Zika: Organisational Structure
WHO (2016) Zika: Research Agenda Matrix
WHO (2016) Zika Virus Research Agenda
WHO (2016) Zika: Finances
WHO (2016) WHO Global Consultation on Research Related to Zika Virus Infection: List of Participants
WHO (2016) Emergency Use Assessment and Listing (EUAL) Weekly Update: Update on Submission of Applications to the WHO EUAL for Zika Virus IVDs (in vitro diagnostics) – and another table with details
WHO (2016) Zika Vaccines – see <http://www.who.int/immunization/research/development/zika/en/>
WHO (2016) DNA Vaccines – see <http://www.who.int/biologicals/areas/vaccines/dna/en/>
WHO (2016) Landscape Analysis on Zikavirus Vaccine Development – Preliminary Findings
WHO (2016) Current Zika Product Pipeline

Lessons from Ebola

High Level Panel on the Global Response to Health Crises (2016) Protecting Humanity from Future Health Crises

Harvard-LSHTM Independent Panel on the Global Response to Ebola (2015) Will Ebola Change the Game? Ten Essential Reforms before the Next Pandemic – Lancet article

Issues relating to Yellow Fever

PATH (2013) Yellow Fever Vaccination: The Potential of Dose-Sparing to Increase Vaccine Supply and Availability

Annex 3: People Interviewed

WHO

Virginia Benassi
Nathalie Broutet
Henry Dowlen
Theo Grace
Marie-Paule Kieny
Robyn Meurant
Bernadette Murgue
Claudia Nannei
Irena Prat
David Wood

External

Lucille Blumberg, National Institute for Communicable Diseases South Africa
Luciana Borio, Food and Drug Administration (FDA)
Chris Lewis, Department for International Development (DFID)
Hilary Marston, National Institutes of Health (NIH)

Annex 4: To what extent have milestones been achieved and questions answered?

Milestone/question	Comment	Status
Global consultation on R&D in relation to Zika	Conducted in March 2016	Done
Landscape analysis table(s) completed.	These were done for diagnostics, vaccines, vector control and therapeutics. They continue to be updated, e.g. the diagnostics EUAL is updated weekly.	Done
Number of conference calls held	There are a number of consultative calls and meetings being held. In general, it is better to assess the value and merit of these rather than the number of calls.	
Number of target product profiles developed	Again, the absolute number of these may not be important but that they are being developed in areas where they are needed, e.g. diagnostics and vaccines.	
Products listed through EUAL	20 diagnostics are going through the EUAL process – details of progress are in Box 2.	20 diagnostics in process
To what extent is progress being made on (1) diagnostics; (2) vector control; (3) vaccine development; and (possibly) (4) therapeutics?	Excellent progress on diagnostics and some progress on vaccines and vector control. Less focus to date on therapeutics.	
To what extent are supportive research activities being coordinated including the establishment and validation of appropriate animal models and sharing of information?	Good material on extent of coordination and sharing of information. Nothing specific on animal models. Is this still important?	
To what extent have the conference calls held been valuable in terms of improving coordination?	Wide range of coordinating mechanisms reviewed and considered. Broader than conference calls only.	
Has the regulatory support group been established? To what extent is this functioning well?	Not assessed.	
What happened once Zika was identified as a priority pathogen and the cluster of microcephaly cases in Brazil was recognized as an emergency? In particular, was an operational plan developed and implemented?	Good material presented on this – although not conceptualised specifically as an operational plan.	
Were the appropriate stakeholders identified and informed? If so, what were the strengths and challenges of this process? If not, why not?	Good material on this from within WHO and small number of external stakeholders. Still need to consult more widely, e.g. PAHO and country offices.	
Can any lessons be learned, e.g. for the development of a decision tree for new pathogens, from experiences of Zika, i.e. as a known pathogen developing new associations with diseases	Not assessed.	