



## PIP review group

### Speaker key:

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NB	Nathalie Broutet
BM	Bernadette Murgue
AC	Anthony Costello
MT	Marta Hurtado
UM	Jamil Chade
JS	Julie Steenhuysen
JK	Jamey Keaton
HB	Helen Branswell
TM	Tulip Mazumdar
LS	Lisa Schnoering
GV	Gretchen Vogel

MV I'm Marsha Vanderford, director of communications. I want to welcome journalists in the room, on the phone and others who are joining us via Facebook today. WHO's spokespersons for today's press conference include Dr Pete Salama, who is executive director of WHO's health emergencies programme. With Dr Salama and available for your questions are WHO's technical experts, who have been leading several areas of WHO's work on Zika, microcephaly, research, reproductive health and research and development. These include Dr Natalie Broutet, medical officer in the department of health and research for reproductive health. Also Dr Bernadette Murgue, project manager for research and development on the blueprint team, and from the health systems and innovation group. Dr Anthony Costello is also here. He is director of the department of maternal, newborn, child and adolescent health.

We will open the press conference with a brief statement from Dr Salama and then open the floor to questions to Dr Salama and other experts who are here in the room. For journalists in the phone, just in advance, you can signal your intention to ask a question at any time by signalling and dialling on your phone 01. Dr Salama, please.

PS Thank you so much and good afternoon, everyone. I'll provide a brief summary of the situation as it relates to the Zika virus and associated consequences this afternoon, summarise what we've discussed today with the member states and then open the floor to questions.

Today's meeting was an opportunity to update countries about the situation regarding Zika and particularly what WHO is doing about it. As you know, on Friday the emergency committee for Zika and associated complications recommended that although Zika and its consequences remain a significant and on-going public health challenge, that it no longer represents a public health emergency of international concern.

I think it's very important to understand that when the public health emergency was initially declared it was because the association between the virus and microcephaly was unproven.

Today we're in a very different situation. The association is clear. We know enough about the virus to know that it will continue to spread and we know that it causes microcephaly. Indeed there are many other things about the virus that we don't know and will be subject to a long-term research agenda and in that spirit we'll be transforming the Zika programme from an emergency programme into a medium to long-term programme of work that covers the programmatic priorities but also the research priorities.

The programme will need to be well-funded and in many ways this is actually an acknowledgement that the programme needs to escalate into a longer-term programme of work. As we enter into this latest phase of the response to Zika WHO is scaling up its work to ensure that even more countries are prepared to fight this virus and manage its complications. WHO continues to partner with countries to strengthen surveillance systems so that they can detect and track the virus. We work with countries to develop and strengthen their national response plans and we work to co-ordinate the global response of more than 60 partners to Zika virus.

Under the research and development blueprint we'll continue to facilitate research in all areas from characterisation of the epidemiology to fast-tracking medical countermeasures such as diagnostics and therapeutics, to really looking at qualitative studies around the barriers for women and communities to seek care.

We'll also continue to produce the expert guidance on how to treat and manage the virus' consequences and this is key. We'll continue to work with countries to prevent the adverse consequences of Zika virus infection, engaging communities directly.

And finally we'll continue to provide information to the public, to health workers and to policymakers. Much of the work that we do at WHO in terms of implementation is driven through our regional offices. To give you one example, in the Americas in 2016 our regional offices have supported 30 countries with more than 1,000 person-days of technical assistance on Zika and its consequences.

But we know that there are many unknowns that still need to be addressed, questions such as what is the natural history of this disease, are there variations in the adverse outcomes such as microcephaly and congenital malformations, depending on the particular virus strain, are there co-factors that make some of these adverse outcomes more likely, does previous infection with another Zika virus strain or a different flavivirus confer any protection against

Zika virus? Many outstanding questions that will only be answered by a co-ordinated and concerted long-term research agenda driven by WHO.

So in summary, Zika virus is here to stay and WHO will continue to work with countries so they're best prepared to deal with this acute public health priority, with new tools, with better data and with the best scientific advice possible to inform their response as we all collectively learn more about this public health threat. I thank you.

MV Thank you, Dr Salama, for that important information. We'll now open the floor for questions both for those here in the room and also for those on the phone. We would like to remind you that if you'd like to ask a question and you are on the phone you will need to dial 01 on your telephone and that will put you in the queue to ask a question.

We anticipate taking two questions at a time before going on to the next set so do we have something? Yes, Marta, please go ahead. We'll ask everyone who's asking a question to please state their name and their agency.

MT Marta Hurtado Spanish News Agency. I would like to know, all these open questions; do you have a dialogue, do you have a priority, how are you going to work from WHO with all the scientists around the world to try to get any answers to all these questions? Thank you.

UM This is Jamil Chade from from Estado de Sao Paulo, Brazil. My question is about the funding; how much do you need, not in the short term but in the long term as well, and how much do you have at the moment? There were many questions in Brazil related to funding; people, especially scientists, are very worried that the end of the emergency will mean drying up of the resources. Thank you.

PS Thanks for the questions. Let me start and then I'll ask some of my colleagues to complement. Firstly, on the research and development issues, it's really a key question because this is so much at the centre of what we need to do in coming years. One of the critical lessons learned from Ebola was that developing a blueprint that all partners could contribute to and see themselves within on research and development in these kinds of contexts is critical and so we've learnt from that experience of Ebola and now in key high-threat pathogenic areas we're developing a similar blueprint so we have a research and development blueprint for Zika virus and it's categorised in three areas; further work needed on the characterisation of the virus so the epidemiology, the cohort studies required to address some of those questions I mentioned.

We have a set of research on the medical countermeasures so the diagnostics, the therapeutics and the other areas of product development. And then we have a set of issues around women, communities and health systems so the quality of studies associated, for example, with perceptions and bottlenecks to seeking care. And so that R&D blueprint is published and available and does indeed prioritise according to the critical questions that we want to answer and engages the scientific community involved in Zika in helping us answer these questions in a very deliberate and strategic manner. We're happy to share with you that document. Perhaps Nathalie wants to add on that question.

NB Thank you. To respond to the research questions that are still pending and principally with regard to the risk of complication following a Zika virus infection, the WHO research

agenda permitted us also to gather researchers around the world so that we can share data between us and we can do specific analyses that will give us, provide information about these things.

So, you know, microcephaly or Guillain-Barre syndrome, when you look at the incidence following a Zika virus infection it's quite a rare event and because it's a rare event and because co-factors are very numerous we need really to gather evidence as much as possible and that's what we're doing with the work on the meta-analysis of the different research protocols and also with the generic protocols that are published in the WHO research website for Zika virus. So it's really about the co-ordination and putting strengths together and partners together to look at these questions.

PS On the question about funding, in the strategic response plan, which is the overarching plan of WHO's 60 partners working on Zika, we asked for around \$112 million. So far just over \$50 million has been garnered so there is a funding gap. For WHO alone the funding gap is around \$19 million.

What's critical here though is that most of the money to date has come from emergency-orientated donors. As you can imagine, with some of these longer-term research questions we need to have multi-year funding because it's going to take several years of sustained financing to really address these questions and so we really need to be engaging now with the development donors, the research donors that are really going to look upon this issue as a long-term development issue and that's really what we're seeking to do in the new programme.

As we transition to the new programme we'll be looking at the funding gaps beyond the end of 2017 because currently our planning goes to the end of 2017 so as we transition to the new programme we'll be looking at the multi-year funding gaps and we note the concern from Brazil. It is critical that the world responds to this issue as what we see it now, an on-going public health threat for which there are many unknowns that need to be addressed by the scientific community.

T If I can just follow up, you just said that we're going to need a few years to answer all these questions and you said that you had the priorities but can you outline them now, at least to say some of them? Thank you.

PS So yes, I did say it's going to take several years and some questions will be answered more quickly than others because some questions we can answer just by following cohorts of infected people over time and following them for outcome measures. But some issues are very complicated; the issue of the genetic lineages of Zika, where they occur. It's going to require a series of seroprevalence studies around the world to determine what those genetic sequences are, what previous exposure of populations has been to Zika virus and indeed that will take many years to address all of the complex questions with Zika.

And indeed to follow up children in the long term, not just for when they're born to assess whether they have microcephaly or not, but actually over time to see what that really means for their development is going to take tracking those cohorts for years to come.

MV Thank you. Dr Murgue, Dr Costello, anything to add on these two?

BM Just really quickly, in terms of product development, of course the main issue is vaccine development and a vaccine for women of child-bearing age and that's the main topic that we are working on in the vaccine field so diagnostics is also an issue but it's quite a long process as well but for the moment there are already two diagnostic tests in nucleic acid tests that have been validated by the emergency use assessment and listing process established by WHO.

AC And this may not be any longer a public health emergency in official terms but it's a public health problem of huge concern for the world. 69 countries have seen Zika virus emerge in the last two years. We're talking about a virus that causes brain damage and potentially lifelong disability, which is a huge blow to families. We know in Brazil where the problem was first picked up that there are now 2,100 confirmed cases but there are many others still being investigated and on current trends we expect another 1,000 cases to be picked up.

We know that the problem has not gone away even in Brazil, that every month between 150 and 200 cases of microcephaly are being identified. We know that we have to do extensive investigations which take many months to try and identify the size of the problem. Each case must be investigated by neurologists, by scans. Then we need to follow them up, we need to think about all of the inputs we need for rehabilitation, which Brazil has started with.

But many countries of the world do not have surveillance systems, they do not have mechanisms for monitoring microcephaly and they do not have the services that you need to really monitor what happens to these children or to provide the support to their families. So this is a very serious problem. Even one affected child has a very big impact on their community, their family and to say nothing else there's a big economic impact on countries as well.

PS If I had to list the priorities - the second part of your question - the natural history of the disease, we need to learn more; the co-factors that are potentially associated with complications once Zika virus is contracted; issues around the genetic lineages and their association with complications. Particularly we're interested in the African lineage, what that means for that continent which, as Anthony was referring to, many countries may be very unprepared for Zika virus outbreaks because of weaker health systems.

Levels of protective immunity from previous exposure or exposure of other flaviviruses; and then a series of programmatic-related research around the efficacy of certain vector control measures, programmatic research that's more qualitative in nature around perceptions of women and families, whether it's to do with contraception and its use or risk perception about exposure to the virus; and then of course the research around the medical countermeasures, diagnostics, vaccines particularly.

MV Thank you to all. We have now two more questions from the telephone. The first is from Julie from Reuters. Please go ahead but start with your full name, please.

JS Yes, hi, it's Julie Steenhuisen from Reuters. I just wanted to follow up on this question - it actually also follows up on some things Dr Salama was saying on Friday. I want to clarify, have you established that some of the babies in Asia who were born with

microcephaly were infected with the older Asian lineage of the virus? It sounded to me like you had said they were. And what exactly do we know about the capability of the older Asian lineage of Zika for causing microcephaly? Thanks.

MV Thank you. The second question in this comes from Jamey Keaton from AP.

JK To follow up on some of the things that have been said, first of all, what is the chance that a woman who had contracted Zika at any point during her pregnancy will give birth to a child with neurological problems?

And then, Dr Costello, if you could also elaborate on what the figures that I hadn't yet heard, about how you expect another 1,000 cases to be picked up in Brazil; over what time span are you talking about and does that mean that you're capping your estimate for the number of microcephaly cases at 3,100? Thank you.

PS Okay, let me start and then, Anthony, I'll ask you to comment on that second question. So, Julie, the first question is really one of those top-priority research subjects. There has indeed been microcephaly confirmed in Vietnam and Thailand associated with the Zika virus. The ongoing genetic studies are in play at the moment so I won't give you a definitive answer as to whether the older Asian strain causes microcephaly because we really are waiting for that information.

We're in a similar situation, by the way, in the investigation in Guinea-Bissau on the African lineage, where there's some preliminary genetic information but it's not yet conclusive enough to make a formal statement so this is really one of the top priorities for our research agenda; do these other strains cause microcephaly and if so do they cause microcephaly and indeed other elements of the Zika virus congenital syndrome at the same rate as the newer Asian strain that has hit the Americas? It's an absolutely critical question because it has real public health implications for African countries, for Asian countries that already have Zika virus transmission and so we are all following this extremely closely and it's, as I say, one of the top-priority questions.

In terms of the specific question around the numbers, you know, it's a very difficult question to answer definitely today. We believe that most children born to women infected with Zika virus will not have neurological complications. However we know that infections in the first trimester cause a higher risk than infections later in pregnancy and we're also learning a lot every day about the types of neurological complications.

A few months ago we were very focused on determination and diagnosis of microcephaly at birth. Today we know that actually children can be born with normal head size but can either later develop microcephaly postnatally or can remain with a normal head circumference and develop other neurodevelopmental problems so it really is an ongoing area of research because it really depends on how you define the congenital malformations associated with Zika virus and we're seeing that that definition is expanding, that that syndrome is expanding and so we may need to continue to update whatever number we would choose to give you today in terms of the risk. It's small but significant but it's definitely a moving target as well. Anthony?

AC Yes, just on the chances of transmission, I believe in Brazil yesterday there was a report of a study where they looked at 57 cases of women who were known to have Zika virus in pregnancy, I think in the south near Sao Paulo, of whom 20 went on to have problems with their baby.

The only problem with those kind of reports are that we don't know whether the original group are a selected group. We know for example that the earlier you get an infection in pregnancy, it's more likely to have a serious impact so we need to wait for some of the systematic studies that are ongoing right now in Brazil and elsewhere, the cohort studies that Natalie might mention.

Just on the Brazil risks, to the question, just in case you misunderstood, so in the last situation report we had 2,106 cases of confirmed microcephaly associated with Zika in Brazil. What I referred to was when you look at the Brazilian data there are another over 3,000 cases being investigated and previously we know that roughly one-third of suspected cases become confirmed. If that's the case then we could expect another 1,000 to emerge from the cases under investigation, which would take the figure up to over 3,000.

Does that mean a cap? No, not at all. It's certainly true that the number of microcephaly cases that are being reported month by month have gone right down in all regions of the country but that may also be a seasonal thing so we need to watch and wait and see what happens over the next few months and obviously that will depend on the extent to which immunity is kicking in into populations or the extent to which the population are taking control measures or termination of pregnancy or whatever.

PS I think extremely important when interpreting any of this data is to remember that it's subject in large part to under-reporting, that 80% of infections are asymptomatic, which makes it extremely difficult to get at the denominators, and it's very complex and if we take the Brazil example, one of the more complex epidemiological puzzles at the moment is that when we had the initial real surge of microcephaly cases it occurred around six months after the surge of Zika virus infection.

But in the past few months we haven't seen the same surge in microcephaly in response to increasing cases of Zika virus that have been confirmed so what's happening, is the virus changing, is people's behaviour changing? There're a lot of outstanding questions even on the basic epidemiology that still need to be addressed so very hard to interpret the data, which is why you see us hesitating and giving you very definitive statistics on some of these numbers. We're all learning a lot and I think we have to approach these data with a level of humility.

MV Thank you. Dr Broutet, Dr Murgue, either one, something to add? Okay, thank you. Our next question then comes from Helen Branswell at Stat.

HB Hi, thanks very much. Can I ask two questions, please? Dr Salama, today and on Friday you mentioned that this needs to go from being funded by emergency funders to a sort of a more programmatic approach. Do you have any reason to believe that it's going to be easier to raise funds for the Zika response now that it's a programme as opposed to when it was an emergency?

And my second question relates to sharing of research findings. The journals have all very graciously allowed researchers to share even in pre-print before publication and they have put all their Zika papers in front of their paywalls because it was a public health emergency. Have you talked to them; do you know if that will continue now that this is no longer an emergency?

MV Thank you. The second execution in this set comes from Tulip Mazumdar , BBC, please.

TB Hi, there, hello, thanks for taking these questions. I've got a couple. Just with those numbers again, Dr Costello, you mentioned 200 to 250 new cases of microcephaly. I wasn't sure if they are being identified or you're expecting them to be identified every month in Brazil. Could I just get clarification on that?

And also on Friday a study was mentioned in Brazil that found that there were no co-factors involved there. I wondered if anyone could tell me a bit more about that.

And lastly, if I may, just how far off a vaccine is for women of child-bearing age.

PS Okay, I'll start and I think Nathalie and Anthony will come in. So on the question of the - Helen's question, the first one at least on the funding, you know, whenever we look at a long-term research agenda in other areas of public health we don't tend to look at the emergency donors to fund that kind of agenda; remembering that the emergency donors tend to fund us for between six and 12 months and these research questions are clearly multi-year questions.

So I can't tell you today, Helen, that there's hundreds of millions of dollars in the pipeline but when we look around the world at many of the big research funding organisations Zika is certainly at the top of their list and we would anticipate that these questions, given their enormous public health significance, will result in sustained research funding so we're all working towards that goal. I'll ask Nathalie to address the second point.

NB So thanks for the question about the publication and the data sharing. So as you know, there are a number of cohort studies that are being implemented over the world to look at the question of the risk of microcephaly and co-factors and I was mentioning the co-ordinating mechanism we are putting in place in WHO to gather the evidence and to analyse the evidence in a joint manner.

So in fact the agreement that was done at the beginning of the epidemic when Zika virus has been noted as a public health emergency will remain because all the researchers - so we have started this relationship with the researchers and all the researchers around the world are really conscious that it's really important to share data, principally now that we need to respond to these key questions that were raised by you and by others during the initial briefing this morning, so about the risk, about co-factors, about asymptomatic patients, about the risk for Guillain-Barre syndrome, about the evolution, the newborn so all that needs to be looked at and the sharing pre-publication will remain.

The other issue about the co-factors; I don't know if you are referring to the study or to the article in Nature. So that's something that has been said by one study in Brazil, that there were no co-factors necessarily but it's still something that we cannot confirm, neither affirm. In fact what we are doing; you know, we've been working on this causality framework for the last few months and we look at all the dimensions of causality to establish the link between Zika virus infection and microcephaly.

Other co-factors than Zika virus infection is part of this causality framework and we don't have the response now to be able to say there is no co-factor or there are co-factors. And again to look at this question, as it was mentioned earlier, you need lots of, lots of, lots of participants and lots of cases and that's the importance of having this co-ordination mechanism and to try to gather researchers on these questions. Thank you.

AC Just to answer Tulip's question, firstly about numbers of microcephaly, I'm just looking at the graph from the Brazilian ministry of health about notification of microcephaly from different regions and I'm having to do a quick sum in my head but roughly speaking over the last four or five months there've been between about 220 and about 450 cases per month reported of microcephaly. It hasn't gone down to zero. If the same proportion of suspected to confirmed persists then you would expect about a third of those cases to go on to be confirmed as Zika-related brain damage, many of whom, as I've said, would have a lifelong disability.

Just on the co-factor issue, a word of caution; Peter's absolutely right that it looks as though a lot of places have had Zika virus and haven't seen the consequences. Some of that may be delay. Remember there's the six to seven-month delay of pregnancy. You've then got the delay of looking for the problem.

If you take Colombia for example, earlier in the year they hoped that because there may be

some co-factor in north-east Brazil they weren't going to be similarly affected. There are now 57 cases reported of confirmed Zika-related microcephaly in Colombia and there are several hundred being investigated so we need to be a bit cautious, also because we don't actually know how many women were infected in the original epidemic because our diagnostic tools are still looking backwards for historical infections, are not reliable. So it's possible that there may be very few co-factors but this requires much more research

PS Do you want to comment on the vaccine question?

BM Yes. In terms of the - I suppose that you probably refer to the effect of a previous flavivirus infection in the development of vaccine so it's an issue that has been discussed many times and it's still discussed. Nothing is solved. For the moment we have no clinical evidence of any enhancement of a Zika infection when the patient has been previously infected by another flavivirus, though that's definitely an issue that needs to be considered more carefully but based maybe on clinical evidence rather than on individual experiments.

PS And just to summarise, we have around 30 potential vaccine candidates for Zika, around three of which are in phase one so in all likelihood we are still a long way off having a viable commercially available Zika vaccine.

MV Thank you. We have two more questions in the queue and we'll take them as the last two for this session. The first one in this set is from Lisa Schnoering from Citrap. Please.

LS Hi, thanks so much. There were a couple of animal studies recently suggesting possible damage to the male reproductive system and I'm wondering if that is on your research agenda for humans going forward. And also I'm wondering if you're hearing anything anecdotally that there might be a problem in humans with that, with the male reproductive system damage. Thank you so much.

MV And our last question will come from Gretchen Vogel from Science Magazine.

GV From Science Magazine. Hi. I want to ask a little bit more about diagnostics. Dr Costello mentioned that it's still really difficult to look back and tell who has and has not been infected with Zika virus; that seems like one of the key tools that we need to better understand what's going on and I wanted to hear from you what progress has been made, where the state of the art stands on that. When I talk with researchers I hear slightly different things but wanted to hear from you, yes, how close are we to having a test that can tell who has and hasn't had Zika in the past? Thanks.

PS I'm going to ask Nathalie to talk about the first and Bernadette the second.

NB Thank you. So yes, we are aware of this article from an animal model that looked at the impact of Zika virus infection on spermatogenesis. This raised a lot of questions of course and also maybe new hypothesis or new questions that we have to raise on the impact of Zika virus infection on fertility.

So how to respond to that question? The importance of having this cohort of pregnant women but also the cohort that we're setting up and that we're implementing in a few countries, which looks at the presence and the presence of Zika virus in body fluids will have to be set

up for maybe longer than we were expecting when we were planning at the beginning. And the longer term, when we will have - so in this cohort we will have men that will have been infected with Zika virus infection and we are following up for one year.

So if we can - and I think we should do that - follow up these men for more than two years and maybe ten years, maybe having this long-term follow-up cohort so that we can really understand better the long-term impact of this infection not only on fertility but also maybe on disease in general and the long-term complications. So that's something really we are analysing and thinking of at the moment and that probably the way forward to have this long-term cohort. Thank you.

BM So on diagnostic, yes, it's quite a difficult issue but for the moment there are two nucleic acid tests that have been approved through the emergency use assessment process established by WHO during the Ebola outbreak so of course there are nucleic acid tests. One is just with decal [?], the other one is a multiplex test for the diagnostic of an acute infection obviously.

For serological tests it's a bit more difficult because we need to have some standards to validate these tests and to develop these standards we also need to have samples from an epidemic area and that has been quite difficult for the moment. But anyway, there is a study going on in order to develop an international standard for a serological test but as you know, the difficulty is in endemic areas to be absolutely sure that antibodies are related to a recent Zika infection and not to another previous flavivirus infection. But the progress is ongoing and I suppose we will have more and more tests that will be developed within the next few months.

AC Just one final comment about the size of the problem of brain damage; one area that we do need to explore further is the children who don't have microcephaly who may be **presenting later in infancy with signs of brain problems, where scans may show evidence of Zika-related brain damage** and we have anecdotal reports of that in Brazil already, in north-eastern Brazil and I think we need to quantify the size of that problem to see whether women infected later in pregnancy have milder forms of the Zika virus syndrome.

MV Anyone have a final comment then from amongst our spokespersons?

PS No, just to re-emphasise here that what we're dealing with Zika virus today is a long-term programmatic and research agenda that requires all partners to galvanise around answering these questions while we continue to respond to the outbreaks simultaneously and it's critical now that we've recognised that Zika will continue to spread in all likelihood wherever there are competent vectors and we need to continue to be able to respond and to address the long-term research issues at the same time. Thank you.

MV Thank you. Thank you to all our spokespersons and thank you to all the journalists on the phone, in the room and the viewers on Facebook. Just a reminder; we'll be posting audio files of this conference on the WHO media centre website in about an hour. A transcript should be available at the same location tomorrow. So have a good day, thank you for attending.