Pregnancy, Research, and Public Health Emergencies

ZIKA AND BEYOND

Toward Guidance for Ethically Addressing Pregnant Women in Zika R&D

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On Behalf of the
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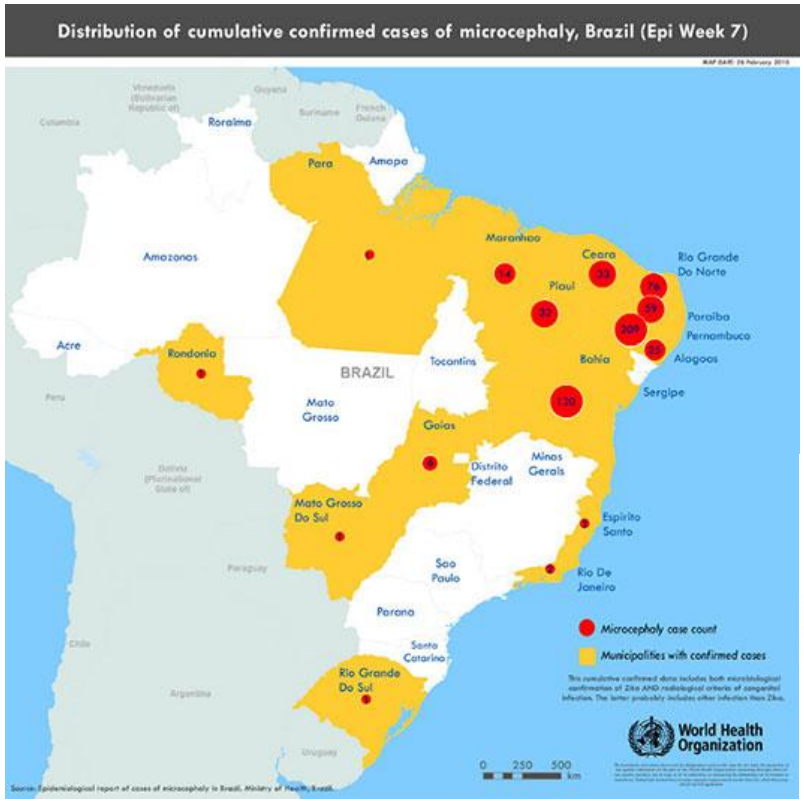
- Introduction
- Pregnant women and the Zika R&D Agenda
- Toward Guidance for Ethically Addressing Pregnant women in Zika R&D

The Zika Epidemic

- Fall 2015: Reports from Brazil of unusual spike in microcephaly cases, believed to be associated with local Zika - National Public Emergency in Brazil declared November 11, 2015

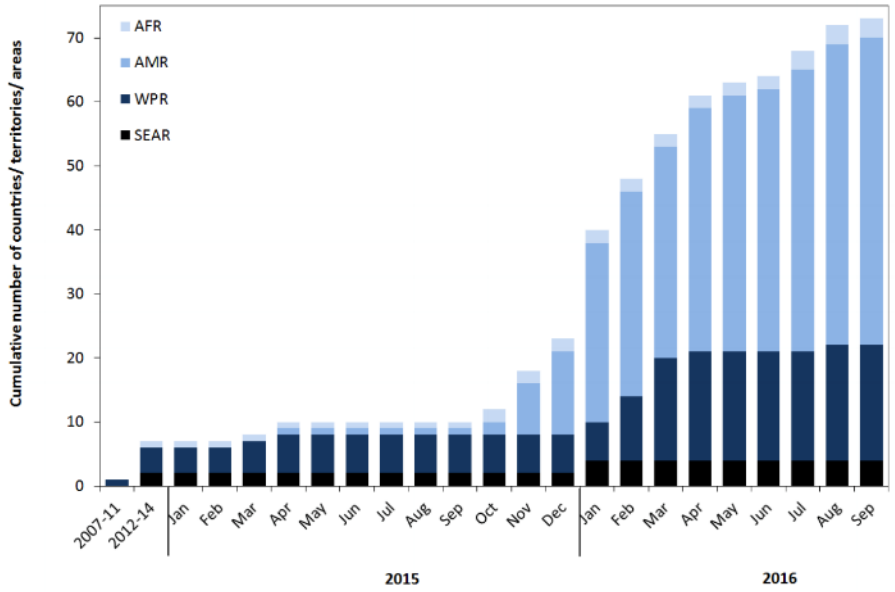


Zika Virus: State of the Epidemic

- 73 countries reporting evidence of mosquito-borne ZIKV since 2007
  - 56 with outbreaks in 2015 and later
- 12 countries reporting person-to-person transmission in 2016
- 21 reporting Zika-associated microcephaly and other adverse fetal outcomes - **>2000 cases of related microcephaly/CNS malformations**

February 1, 2016:
WHO declares Zika a Public Health Emergency of International Concern (PHEIC)

Figure 1. Cumulative number of countries and territories by WHO region[1] reporting mosquito-borne Zika virus transmission for the first time in years (2007–2014), and monthly from 1 January 2015 to 28 September 2016



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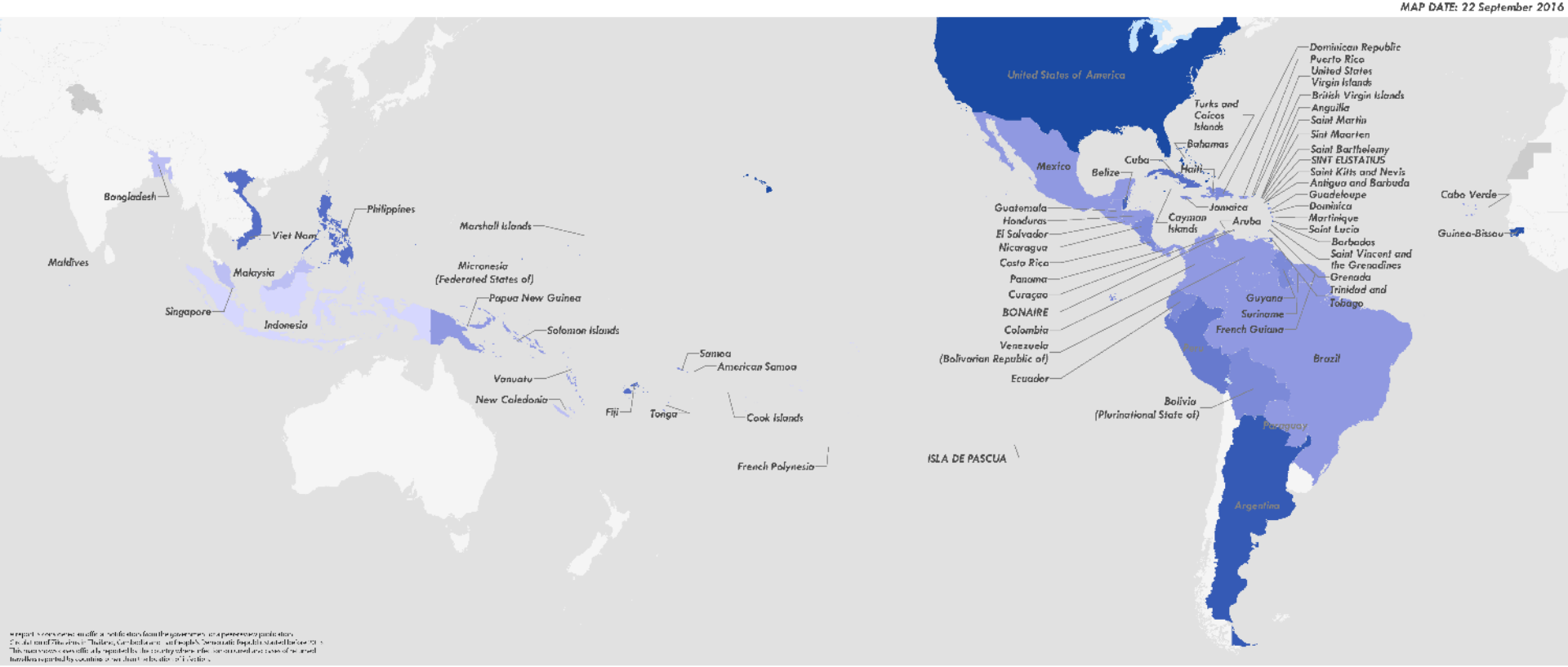
Zika Virus: State of the Epidemic

Countries, territories and areas showing the distribution of Zika virus, 2013 - 2016

MAP DATE: 22 September 2016



Disputed Areas

Disputed Borders

World Health Organization

2013	2014	2015	Jan 2016	Feb 2016	Mar 2016	April 2016	May 2016	Jun 2016	Jul 2016	Aug 2016
Indonesia French Polynesia	New Caledonia Cook Islands Bangladesh Malaysia ISLA DE PASCUA, Chile	Brazil Honduras Colombia El Salvador Guatemala Mexico Paraguay Suriname Venezuela (Bolivarian Republic of)	Papua New Guinea Vanuatu Solomon Islands Cabo Verde Martinique Panama Puerto Rico	Samoa Bolivia (Plurinational State of) United States Virgin Islands Dominican Republic Costa Rica Guinea-Bissau Saint Martin Nicaragua Barbados Maldives	Ecuador Guyana Jamaica Curaçao American Samoa Haiti Tonga	Peru Marshall Islands Saint Vincent and the Grenadines Trinidad and Tobago Aruba BONAIRE, Netherlands	Fiji Micronesia (Federated States of) Viet Nam Cuba Philippines	Saint Barthelemy Belize Saint Lucia	Argentina Grenada	Guinea-Bissau Anguilla	Bahamas Cayman Islands United States of America Turks and Caicos Islands Antigua and Barbuda SINT EUSTATIUS, Netherlands	British Virgin Islands Singapore Saint Kitts and Nevis

Zika Virus: What we “know” so far

- Flavivirus (dengue, chikungunya, yellow fever, etc.)
- Transmission: Mosquitoes, Sexual, Vertical, Blood, *other?*
- Zika in adults: generally mild, similar to seasonal flu, rash, conjunctivitis – 80% asymptomatic
  - GBS, other neurological complications
- **Congenital effects on fetus: CZS**
  - Microcephaly and other neurological effects
  - Other malformations and abnormalities: ocular, musculoskeletal
  - Most severe cases associated with 1st trimester infection - but emerging evidence suggests persistent risk throughout pregnancy

Questions & Priorities for the Global Health Response to Zika

- What can and should countries do now to address the epidemic and the needs of the population?
- What can be offered to babies and families affected by congenital Zika syndrome (CZS)?
- **What research should be done and what interventions should be prioritized for development?**
- **How can we ensure the response meets the needs of those at the crux of the epidemic: pregnant women?**

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Prioritizing Pregnant Women in the Zika Research Agenda

Research and Pregnancy

- Widespread, continued reticence to include pregnant women in biomedical research
  - Ethically and legally complicated
  - Scientifically challenging
  - Culturally embedded

Krubiner et al, *AIDS*, 2016

- A Question of Justice
  - Evidence gaps re: safety for woman and fetus
  - Evidence gaps re: dosing and toxicity
  - Reticence to use beneficial medications
  - Access to direct benefit

Research, Pregnancy and PHEs

- Research with pregnant women may be particularly important in PHEs, given **urgent need** for safe and effective interventions
  - Usual timeline (!) for safety and efficacy data unacceptable

- Pregnant women may face **different levels and types of risk** than non-pregnant women
  - In some cases (e.g., H1N1), significant implications for maternal morbidity/mortality and pregnancy outcome
  - In other cases (e.g. Zika), significant fetal effects

"… a practical and ethical nightmare" -- *The Guardian*, 2016

The Zika Research Agenda

- Diagnostics
- Therapeutics
- **Vaccines**

WHO Target Product Profile (TPP)

- In emergency use context, vaccination prioritized **to women of childbearing age/potential (WOCP)** as this group is considered at high risk due to the causal relationship between prenatal ZIKV infection and microcephaly, other nervous system malformations, and pregnancy related complications

- Theoretical risk **may not preclude the exceptional use during pregnancy** and lactation

July 2016

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The reasonableness of targeting WOCP

- Crux of concern: preventing congenital Zika
  - Maternal health effects mild
- High rates of unplanned pregnancy
- High rates of later prenatal care

- In general, vaccination before pregnancy is most likely to prevent congenital Zika syndrome

Not abandoning pregnant women

- Access to vaccine
- Access to trials
- Information on safety and efficacy

Access to vaccines

- Pregnant women will **want access to vaccines**
  - Many will not be vaccinated before pregnancy
  - No therapeutics currently available
  - Limited access to abortion
  - Pregnancy may entail higher risk of infection due to sexual transmission
- Access can **depend on evidence**
  - Lack of evidence in pregnancy could lead to exclusionary policies and practice in rollout
  - Incomplete or poor evidence can also lead to restrictions

Access to trials

- Pregnant women will desire **access to trials**
  - Prospect for **direct benefit**
    - Potential for congenital harm has been documented through gestation
  - ? Favorable **risk/benefit** ratio
    - Unknown risks of vaccination potentially less concerning to women than known risks of ZIKV infection and congenital syndrome
    - Particularly in endemic areas

Access to information

- Pregnant women will be **exposed inadvertently**
  - Women enrolled in **trials** may be or become pregnant
  - Pregnant women will be exposed in **rollout**
    - pregnancy tests may not be feasible
- Pregnant women will need **information about safety**
  - Platforms include live, killed, novel
  - Role of abortion? Enduring concern?
- Pregnant women will need **information on efficacy**
  - Pregnancy changes immune system functioning
  - May lead to reduced immune responses to vaccine in pregnant compared to non-pregnant women

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Our Project

Aim: To develop concrete, actionable, consensus-driven guidance for conducting ethically responsible biomedical research with pregnant women in the context of public health emergencies – starting with Zika.

Current focus is on Zika vaccines.

Funding support from the Wellcome Trust

Our initial guidance will address:

1. How to prioritize development of vaccine candidates given their likely use during pregnancy (inadvertent and intentional)
2. Whether and when pregnant women should be involved in vaccine trials
3. How to proceed with women who fall pregnant during trials
4. How data on inadvertent exposures can be prospectively collected to best inform future use

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Our Approach

- Consultations with experts in vaccine science, maternal-fetal medicine, flaviviruses, public health practice, etc.
- Scholarly legal research examining hard and soft law of clinical research during PHEICs
- Engagement with community of research ethics scholars
- Literature reviews
- Moral analysis
- Historical case analyses of pregnant women in past epidemics

Consult with Experts

Scholarly Research

Draft Guidance

Convene Vetting Groups

Consensus-Driven Guidance

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Draft Recommendations

1. Zika vaccine R&D should prioritize vaccine platforms that would be widely accepted for use in pregnancy. (killed vaccine with known adjuvants)

2. Pregnant women should be allowed to enroll in vaccine trials that pose little to no theoretical/biologically plausible risk, particularly when there is a prospect for direct benefit.

We are not, *at this time, in this particular context,* challenging the prevailing view among relevant experts and bodies that pregnant women should not be knowingly, prospectively enrolled in trials of live attenuated vaccines.

3. Women who identify a pregnancy or become pregnant during a study should be allowed to remain on study and have the opportunity to complete their vaccine schedule.

4. Vaccine trial designs should include a plan for prospectively studying maternal and child outcomes for women who fall pregnant during the trial or who are unknowingly pregnant at the time of vaccine administration.

Draft Recommendations

1) Prioritizing vaccines candidates under development

Activities supporting the research and development of Zika vaccines should prioritize vaccine platforms that would be widely accepted for use in pregnancy.

Based on the current state of the science and accepted medical practice, this means priority should be given to killed vaccines – using known adjuvants with prior use in pregnancy. Secondary consideration should be given to non-replicating platforms that do not have scientific plausibility for harm to pregnant women and fetuses, but have not been approved before for use in pregnancy.

This requires having a sufficient number of these vaccine candidates in the development pipeline in order to ensure that there is at least one resulting efficacious and safe option.

Prioritization should be reflected in the funding for vaccines, decisions about which candidates can be fast-tracked through safety and efficacy trials, as well as other supporting research activities (preclinical, surveillance studies, and implementation science) needed to ensure these vaccines will be reasonably available to pregnant women.

Draft Recommendations

2) Prospective Enrollment of Pregnant Women in Trials

Pregnant women should be allowed to enroll in vaccine trials that pose little to no theoretical/biologically plausible risk, particularly when there is a prospect for direct benefit.

In particular, pregnant women should be allowed to participate in trials of promising killed vaccine candidates. These trials should aim to enroll sufficient numbers of pregnant women to ensure data can support scientific conclusions about vaccine efficacy and safety in pregnancy.

Even when sufficient numbers of pregnant women cannot or will not be enrolled, where there is significant background threat of CZS due to active local transmission of Zika, pregnant women should still be given the opportunity to participate in the trial. This would follow a similar rationale as employed in expanded access or "compassionate use" of investigational interventions. Data collection should be rigorous to ensure as much information as possible is collected about the vaccine's use in pregnancy, even if the findings will not be sufficiently powered for statistical significance.

Draft Recommendations

2) Prospective Enrollment of Pregnant Women in Trials

We will not, *at this time, in this particular context,* challenge the prevailing view among relevant experts and bodies that pregnant women should not be knowingly, prospectively enrolled in trials of live attenuated vaccines.

We make this recommendation for live attenuated Zika vaccines even though there has never been evidence of fetal harm resulting from exposure in pregnancy to live vaccines for other related diseases (e.g., Rubella and YF) and there may be a range of compelling advantages of a live vaccine as compared to other platforms (e.g., single-dose, quicker development of antibody response, more durable immunity) and other benefits of enrolling pregnant women (data that could prevent anxiety and pregnancy terminations due to inadvertent vaccination).

That said, with the current scientific understanding of the theoretical harms associated with this particular virus and multiple alternatives simultaneously under development, we will not at this time challenge the current dominant position to exclude pregnant women from these particular trials.

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Draft Recommendations

3) Women who fall pregnant on trials or for whom pregnancy is identified post-exposure

Women who identify a pregnancy or become pregnant during a study should be allowed to remain on study and, when applicable, complete their vaccine schedule if they so choose.

Many vaccines that require multiple doses are not protective until the series is complete. We know from past trials that many women become pregnant on trials, particularly when the target population is women of reproductive age. Most vaccine candidates requiring multiple doses will be non-replicating platforms, meaning they pose lower theoretical risks in pregnancy. Women participating in studies who fall pregnant should should be given any relevant information about the vaccine with regard to their pregnancy and re-consented – with the option for them to remain on study.

There may be some live vaccine options that require multiple doses, particularly in cases where the Zika component is combined with other existing vaccines – such as the tetravalent dengue vaccines or other flavivirus vaccines. In these instances, the option to allow continued enrollment should be informed by the known relevant risks and benefits of the specific platform as well as the background risks of those diseases.

Draft Recommendations

4) Study designs for any vaccine trial should include a plan for prospectively studying maternal and child outcomes for women who fall pregnant during the trial or who are unknowingly pregnant at the time of vaccine administration.

Because inadvertent exposures and pregnancies among enrolled participants are likely to occur in large numbers, it is important to have appropriate mechanisms in place to capture relevant data from these exposures to better inform future use of these vaccines.

This will require appropriate screening of other kinds of exposures that produce fetal harms, so that there is not misattribution of harms to a safe vaccine. Any relevant correlates of immunity used in the study should be monitored in these women to determine what, if any, level of protection they have received from their levels of vaccine uptake.

This also requires mechanisms for time appropriate follow-up of women and any resulting children.

Thank you!