

Scientific Policies and Ethical Economies in the Development of Vaccines Against Zika

*Políticas Científicas e Economias Éticas no Desenvolvimento de Vacinas
contra Zika*

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Abstract

The Zika epidemic alarmed international health authorities, who responded by calling for efforts to develop a vaccine. The goal was to produce a biotechnology that would especially protect pregnant women and women of reproductive age, in order to prevent more babies from developing the Congenital Zika Syndrome. In this context, scientists' arguments about the need to include pregnant women in biomedical studies have been intensified as a means of ensuring that this group receives drugs with proven safety and efficacy. Here, we prioritize the perceptions of women from two states in Brazil about their hypothetical participation in a vaccine trial against Zika. Considering their hesitations concerning medical experiments and their hopes for developing a treatment for Zika, we strain the production of biotechnologies based on specific perceptions about body, risk and ethics that neglect the knowledge and the experiences of the same women they are, supposedly, seeking to protect.

Keywords: Zika. Vaccines. Women. Ethics. Clinical Trials.

Resumo

A epidemia de Zika alarmou as autoridades sanitárias internacionais, que responderam convocando esforços para o desenvolvimento de uma vacina. O objetivo era produzir uma biotecnologia que protegesse especialmente mulheres grávidas e em idade reprodutiva, a fim de evitar que mais bebês desenvolvessem a Síndrome Congênita do Vírus Zika. Nesse contexto, os argumentos de cientistas sobre a necessidade de incluir mulheres grávidas em estudos biomédicos foram intensificados como forma de garantir que esse grupo receba medicamentos com segurança e eficácia comprovadas. Aqui, priorizamos as percepções de mulheres de dois estados brasileiros sobre sua participação hipotética em um teste de vacina contra o Zika. Considerando suas hesitações em relação aos experimentos médicos e suas esperanças no desenvolvimento de um tratamento para o Zika, nós tensionamos a produção de biotecnologias com base em percepções específicas sobre o corpo, risco e ética que negligenciam o conhecimento e as experiências das mesmas mulheres que supostamente buscam proteger.

Palavras-chave: Zika. Vacinas. Mulheres. Ética. Pesquisa Clínica.

1 Introduction

As 2014 gave way to 2015, an epidemic with never-before-seen characteristics quickly spread throughout the Brazilian Northeastern region. A few months later, the Zika virus was identified not only as the cause behind fever and physical pains, but also as the reason for the development of a severe fetal malformation, later named Congenital Zika Syndrome (CZS). Between 2015 and 2017, approximately 3000 children were diagnosed with CZS, thus establishing a demand for health services and social assistance to care for the various babies' brain lesions. Women have taken on the role of central caregivers for these children, and eight in ten mothers of babies with CZS are black (MAISONNAVE, 2016). The dissemination of the epidemic to other Brazilian states and 28 other countries in the Americas (PLOURDE; BLOCH, 2016) alarmed international health authorities, whose response was an explicit convocation of the international health and industrial-pharmaceutical communities for a gathering of efforts around the development of a vaccine. Their main concern was launching an immunization alternative that would especially protect pregnant women and women of reproductive age, so as to avoid thousands more babies developing CZS. In this context, the Zika epidemic in Brazil "was the emergence of a new way of getting sick", resulting in a double-burden for mothers of children with CZS "as caregivers and research subjects" (DINIZ; AMBROGI, 2017, p. 142).

Vaccines are part of complex relationships with health policies and the construction of the national state in Brazil. From immunization strategies against smallpox, which extended from the end of the 19th century to the eradication of the disease by 1970, vaccines increasingly

participate in health policies and the different configurations of the state, from the most centralized to the most democratic. Throughout the second half of the twentieth century, especially after the promulgation of the 1988 Constitution, vaccines abandoned the coercive character with which they were identified by the population in previous periods of the republic to become an artifact that brings together trust and popular adherence to national immunization campaigns (HOCHMAN, 2011). This scenario has only undergone changes in the last decade, with the emergence of vaccine hesitation practices and its consideration of vaccines as technologies with more iatrogenic than therapeutic effects (SATO, 2018). Formerly an artifact of state interference on the population and passing through the status of a technology that contributed to the affirmation of biological citizenship, currently the vaccine is ambiguously considered a hope in combating national endemics and a potential iatrogenic threat to health.

Experimental vaccine production in Brazil articulates these challenges to international and gender issues. In the case we address, the eruption of the Zika epidemic updated the historical debate on the participation of pregnant women and women of reproductive age in biomedical research. Arguments for the inclusion of pregnant women in trials gained traction, emphasizing the need to guarantee that the most dramatically affected group would benefit from scientifically proven protection (HOMBACH *et al.*, 2016). On the other hand, the race for the production and publication of scientific evidence brought about ethical dilemmas. How can one balance the inclusion of women made highly vulnerable by their racial, socioeconomic, regional, and gender characteristics with the intentions of transnational enterprises of technological development that, at times, ignore the contexts, histories, anxieties and hesitations of the families that live with the consequences of the epidemic? (DINIZ; AMBROGI, 2017).

Considering the ethical dilemmas involved in developing a Zika vaccine, what might Brazilian women struck by the epidemic have to say regarding the experiments? Faced with the adversities of caring for a child suffering from CZS and the difficulties in accessing health services, would they be willing to participate in such tests? Under what

conditions would they give their consent, and when would they refuse recruitment for clinical trials? What specific traits of an immunizing technology might make research seem to them as either a risky or therapeutic endeavor? These questions, although fundamental to the development of the vaccine, seem to be absent from debates on ethics of research with pregnant women as well as from the definition of priorities in global and local health actions. Centered on generalist and poorly contextualized perceptions of the body and of risk and protection, such controversies silence and make obsolete the perceptions and conceptualizations of women who are the target audience of the R&D process. In this article, we will put forward some ethical elaborations of Brazilian women in the contested field that makes up the international setting of technological policies adopted for the fight against Zika in Brazil. More precisely, we attempt to “put them first” (BIEHL; PETRYNA, 2013).

To this end, we will establish a dialogue between international debates led by biomedical scientists from the United States and Europe, and the formulations of Brazilian women hit in different ways by the Zika epidemic. Confronting different criteria, reasonings and considerations, we reflect critically on the clear limits of betting on a “magic-bullet approach” (BIEHL, 2007) which, by prioritizing the development and offering of a high-technology alternative with no consideration for, or articulation with, the racial, social, economic, political and gender factors involved in the epidemic, might risk the vaccine’s very process of development – and, graver still, the women and children cruelly hit by the Zika epidemic in Brazil.

2 Fast Epidemic, Speedy Research, Quick Vaccine

In late 2014, doctors in the Brazilian Northeast went on a scientific mission to visit the region’s hinterlands and collect biological and epidemiological material for the construction of a protocol for the handling of a new epidemic: chikungunya fever. The disease held both similarities and differences compared to dengue, which was widely known among the public and whose periodic outbreaks are already expected during rainy seasons in the summer. Chikungunya fever is also

transmitted by the *Aedes aegypti* mosquito; however, its symptoms are different: high fever, intense physical pains and prolonged prostration. According to Debora Diniz's (2016) detailed ethnographic record, when doctors sought out people with this new disease, what they found was surprising: recurring cases of low fever, itching and redness of the body, and conjunctivitis. The symptoms disappeared after a few days, leading experts to consider multiple nosological possibilities, nonsufficient for a definitive diagnosis. "Weak dengue" and "frightening allergies" were among the hypotheses, but neither accounted for the specificities that afflicted men and women in states like Bahia, Alagoas, Paraíba, Pernambuco and Rio Grande do Norte (DINIZ, 2016).

Everything happened surprisingly quickly between the gathering of biological samples and the identification of the disease's causal agent. Laboratories from different Brazilian states ran tests and, still in 2015, scientists involved in varied efforts revealed to the press and the scientific community that the Zika virus was behind the outbreak (CAMPOS *et al.*, 2015; ZANLUCA *et al.*, 2015). The epidemic's most surprising and dramatic chapter unfolded simultaneously, bringing with it greater concerns and equally agile developments. In the second half of 2015, hundreds of cases of fetal microcephaly were reported in Northeastern states, leading several specialists to investigate the causes behind the sudden and elevated malformation rates. The identification of the Zika virus in amniotic fluid by a doctor in the state of Paraíba, and its qualification as the motivator behind the cerebral lesions in fetuses happened before 2015 was over (DINIZ, 2016). The group of scientists responsible for the discovery published the findings in an international journal in the very beginning of 2016 (MELO *et al.*, 2016), thus establishing the scientific parameters for the identification of the Zika virus as the protagonist of a public health emergency of alarming proportions¹.

The establishment of a correlation between gestational infection by the Zika virus and CZS was preceded by a series of provisional hypotheses, chief among them the suspicion of use of vaccines during pregnancy². Some mothers of babies with CZS and some health professionals insisted for some time on the hypothesis that the region's public health service had incorrectly administered an expired batch of

rubella vaccines to pregnant women (CARNEIRO; FLEISCHER, 2018). Doctors, scientists and the Ministry of Health rushed to announce that this connection was nothing but a “dangerous rumor”. As such, they simultaneously reinforced that vaccines were absolutely safe and that the Zika virus was the main culprit behind the epidemic. They advised women to avoid pregnancy during that period, but that those already pregnant should protect themselves from the *Aedes aegypti* mosquito with long sleeved garments, repellents and proper home hygiene (MINISTRY OF HEALTH, 2015; COSTA, 2016).

As information on the clinical manifestations of CZS grew, so did uncertainties, fears and reproductive strategies among women. Several women all over Brazil delayed their pregnancy plans, in fear of catching the disease and dealing with serious repercussions during gestation (FOLHA DE SÃO PAULO, 2016). On the other hand, those who had delivered babies diagnosed with CZS were involved in new circuits of intensive care, uncertainty regarding the development of the disease, and precarious assistance from health and social security services (DINIZ, 2017; FLEISCHER, 2017; SCOTT *et al.*, 2018). Beyond new caregiving attributions, these women also had to deal with harassment from scientists over their own bodies and those of their children (DINIZ; AMBROGI, 2017). Putting basic and clinical research efforts in motion played into not only the interest in leading a scientific discovery and beating back the disease, but also into the national agenda of public health for the fight against the Zika epidemic (BRASIL, 2017)³.

The Zika epidemic also received considerable attention from international health authorities (CARVALHO, 2017). Faced with rising infection rates across Latin America and the Caribbean, the World Health Organization (WHO) gathered 18 experts in an Emergency Committee in February 2016. After analyzing available scientific data, the committee “agreed that a causal relationship between Zika infection during pregnancy and microcephaly is strongly suspected, though not yet scientifically proven”. When the meeting ended, WHO general director Margaret Chan publically declared the situation a Public Health Emergency of International Concern (WHO, 2016a). In this situation, the WHO singled out the need to produce research and

develop technologies specifically suited for the understanding of the causal conditions of Zika infection and CZS and for fighting the risk of the disease spreading globally: “The lack of vaccines and rapid and reliable diagnostic tests, and the absence of population immunity in newly affected countries were cited as further causes for concern” (WHO, 2016b)⁴.

The announcement of the international public health emergency and of the investment in the development of a vaccine led to the nearly immediate start of a technological race (HOMBACH *et al.*, 2016). By mid-2018, just two years after the announcement of the epidemic in Brazil, research institutes and pharmaceutical companies had already registered 45 vaccine candidates in the WHO’s Research & Development pipeline – at least nine of which had already advanced to phases I and II of human clinical trials (BARRETT, 2018). The initiatives are led both by national public funders, such as the United States’ National Institute of Health and Brazil’s Butantã Institute, and multinational pharmaceutical laboratories – with room for public-private partnerships (WHO, 2018; WILDER-SMITH *et al.*, 2018). Results so far seem promising, with good tolerance shown to vaccine candidates and their immunizing potential considered favorable in clinical and pre-clinical research (MARQUES; BURKE, 2018).

Some of the greatest challenges for the development of the vaccine reside exactly in encompassing the vertiginous advance of ongoing research and the protection of pregnant women and women of reproductive age. The Zika epidemic has not kept up with the research’s accelerated pace. Contrary to recurrence projections, the number of people infected with the virus dropped significantly after the epidemic’s second year (BRASIL, 2019). With this in mind, in November 2016 the WHO declared the end of the Public Health Emergency of International Concern (WHO, 2016c). However, the recognition of a vaccine as a technological priority in the fight against future outbreaks held fast for the agency as well as for the scientific community:

Although a complex challenge, through concerted and proactive efforts, pregnant women and their offspring will benefit fairly from the global investments in ZIKV

vaccines, and the tragedy that is CZS will be maximally averted. (THE ETHICS WORKING..., 2017, p. 6.822)

The specificities of the epidemic, however, challenge the advancement of clinical trials, which need a large number of people infected with the Zika virus for the conduction of phase III experiments. Ironically, the lack of people infected with Zika to be recruited as research subjects has been read as a monumental challenge for the scientific community and for international public health authorities, who recognize that the very viability of the technology is at risk due to the retreat of the epidemic (WHO, 2018; WILDER-SMITH *et al.*, 2018)⁵.

Particularities related to the profile of research subjects in efficacy studies are also cause for concern. The fact that pregnant women and women of reproductive age are the main target audience of vaccination initiatives raises fundamental questions regarding their inclusion in experiments. Considered a “vulnerable population” (WILDER-SMITH *et al.*, 2018, p. 13), these women are usually spared participation in clinical trials, given the risks posed by unknown drugs to the gestation and the fetus. However, the specific risks of the Zika virus during pregnancy forced the scientific community to face the historical discussion regarding the adequate ethical stance to be taken in relation to the inclusion of pregnant women or women with childbearing potential in experimental studies (THE ETHICS WORKING... 2017). Would it be ethical to maintain the historic position of excluding from experiments pregnant women and women of reproductive age, thus avoiding any physical, psychological, moral and legal risks of harming the mother or the fetus? Or would it be more ethical to include these women in experiments, to guarantee that robust experimental evidence supports their use during pregnancy in case a new outbreak occurs?

3 Viral Ethics: readdressing frameworks on biomedical experiments with pregnant women

Intensifying debates that gained traction in the context of viral epidemics starting in the 1980s, several scientists and bioethicists have sought to establish new scientific and ethical parameters for the conduction of studies. They advocate for the understanding

that new parameters, that prioritize women's health, should orient scientific rationale as a whole, as a "matter of fairness and respect" (THE ETHICS WORKING..., 2017, p. 6.821). In the case of the Zika epidemic, stakeholders from the field of global health clearly tend to defend the conduction of experiments with pregnant women and women of reproductive age as a scientific imperative and an ethical defense of these group's best interests (OMER; BEIGI, 2016; THE ETHICS WORKING..., 2017). Such strong defense is explained by how, historically and systematically, pregnant women have been deliberately interdicted subjects of experimental studies (BLEHAR *et al.*, 2013).

In one of its international reference guidelines for industry practices, the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) explicitly establishes that

[...] in general, pregnant women should be excluded from clinical trials where the drug is not intended for use in pregnancy. If a patient becomes pregnant during administration of the drug, treatment should generally be discontinued if this can be done safely. (ICH, 1997, p. 9)

Exceptions are foreseen only in research whose investigational product is intended for use during pregnancy, in which case the pregnant woman, the fetus and the child must be monitored for an established period. Thus, whether pregnancy is considered an exclusionary criterion in recruitment processes, or whether women of reproductive age are told to adopt birth control tactics during the study, the fact remains that pregnant women constitute a group whose participation in research is generally avoided.

The historical landmark for this international standpoint is the iatrogenic tragedy of thalidomide in the late 1950s. Functioning as a critical event, the thalidomide case resulted in "new modes of action" on the part of doctors, institutions, families, communities, bureaucracies, courts of law, the state and multinational corporations (DAS, 1995, p. 6); its main consequence being the exclusion of pregnant women from biomedical experiments. The event in which such a decision was made was the birth of at least ten thousand babies with congenital

malformations after the widespread prescription of thalidomide for the treatment of morning sickness in pregnant women (CARPENTER, 2010). This episode, along with the publicization of cases of abuse within research situations in the United States, like what happened in Tuskegee, had a determining influence in the conclusion that certain groups needed additional protection, following the understanding of “[...] participation in research as a burden which, therefore, must be distributed as equitably as possible in society” (EPSTEIN, 2004, p. 188). Specifically, for women, it became understood that those of reproductive age and their fetuses made up a “vulnerable population” that, therefore, required special defense in the context of scientific research (MASTROIANNI *et al.*, 1994; EPSTEIN, 2007). Thus, with the publication of the NIH Revitalization Act of 1977, not only pregnant women, but women with childbearing potential were systematically distanced from experimental scenarios (EPSTEIN, 2004). This decision was replicated by regulatory agencies in several countries and followed by multinational pharmaceutical laboratories (CARPENTER, 2010).

In the following decades, some viral epidemics threw suspicions on the notions of protection, ethics and risk present in this global interdiction. The HIV pandemic in the 1980s was probably the historical landmark that gave way to demands for changes in the restrictive stance of pregnant women in clinical trials. Faced with the spread of the HIV epidemic to pregnant women and the risks of vertical transmissions, women’s movements in healthcare and U.S. congresswomen denounced the white male body as the paradigm for clinical research. They argued that such reference resulted in the underrepresentation of women and ethnic minorities in the production of safe and effective health technologies (EPSTEIN, 2007). Furthermore, they accused public authorities of implementing regulations and actions imbued with a “governmental paternalism” (EDGAR; ROTHMAN, 1990), which stripped them of their right to participate in research and made them victims of inadequate or suboptimal treatment, that failed to take into account the physiological specificities of the female body. Advocating for the transition from one protectionist emphasis to another, AIDS

activists in the United States caused a shift in the debate over the regulation of clinical trials. In this new setting,

[...] some of the same groups that had been singled out for protection in the earlier era, including women and children, were now portrayed as victims of substandard care – at risk both because of research indifference to the particular manifestations of the illness among them and their inadequate access to potentially lifesaving drugs. (EPSTEIN, 2004, p. 188)

More recently, the pandemic caused by the Influenza H1N1 virus in 2009 hit pregnant women especially hard and added weight to the opinion of scientists who claimed it was necessary to have women of reproductive age participate in clinical studies. Authorities involved in fighting the pandemic recognized the need for quick development of a vaccine – one that could be safely used by pregnant women (TAMMA *et al.*, 2009). Scientists claimed there was a contradiction in the practice of excluding pregnant women from clinical trials as a strategy to guarantee their protection:

Ironically, the effort to protect the fetus from research-related risks by excluding pregnant women from research places both women and their fetuses at greater risk from understudied clinical interventions and may also result in a dearth of therapeutic options specifically developed for pregnant women. (GOLDKIND *et al.*, 2010, p. 2.242)

The H1N1 pandemic seems to have brought about a fundamental inflection: the emphasis on the biological specificity of the pregnant body and its function as an immunizing vector for the whole human population. When compared to other women, pregnant women have hepatic, renal, hormonal and metabolic particularities, and their underrepresentation puts them at risk of suboptimal treatment, making the reversal of pregnancy as an exclusionary criterion an urgent matter – under the condition of putting not only pregnant women and their future children, but also the whole of global population, at heightened risk.

The Zika epidemic breathed new life into this discussion. The idea that there are specificities to the pregnant body proved relevant

to scientists involved in the debate (OMER; BEIGI, 2016; THE ETHICS WORKING..., 2017). Moreover, the absence of specific scientific and ethical standards for the conduction of research with this group was qualified as a fundamental barrier to be transposed as it

[...] poses a challenge for conduct of clinical trials, generalizability of safety data, and merging of large safety data sets. This last point is critical because large multilocation data sets could optimize the evaluation of rare but clinically important outcomes, such as microcephaly. (OMER; BEIGI, 2016, p. 1.228)

On the other hand, attention was given to the fact that researchers and IRBs insisted on the perception of clinical trials during pregnancy as particularly risky, under “[...] misinterpretations or overly cautious interpretations of what is allowed under research regulations and international norms, as well as concerns about legal liability” (THE ETHICS WORKING..., 2017, p. 6.819).

In such an effervescent context, the Pan-American Health Organization (PAHO) took a perhaps unprecedented position. After consulting with experts, of whom at least three were Brazilian, the agency launched the “Zika Ethics Consultation: Ethics Guidance on Key Issues Raised by the Outbreak” (PAHO, 2016). The document takes a wider look at ethics – health care delivery; public health; and research – and highlights the moral duty of making available updated information, relevant reproductive options and social aid to women of reproductive age in regions hit by the epidemic (SAENZ, 2016). Dealing specifically with the conduction of trials, the guide explicitly states that

[...] research with pregnant women is ethically acceptable and should be actively promoted because it is critical to providing pregnant women with safe and effective medical treatment, which is imperative for their own health and the health of their offspring. (PAHO, 2016, p. 13)

With this ethical imperative in mind, some specificities of the epidemic were taken into consideration, such as the need to obtain consent for experiments with women and their babies, the

recommendation that communities be consulted in discussion regarding the initiatives to be prioritized, and the sharing of research capacity in cases of transnational enterprises that include low- and middle-income countries.

The HIV epidemic in the 1980s and the Influenza H1N1 pandemic paved the way for the ethical discussion that was to be revived with the recent Zika epidemic. The scientific and ethical inflection is evident: currently, it is held that the pregnant body is specific, and therapies applied to it must be scientifically developed through tests with pregnant women; it is unfair for them to continue receiving medications and vaccines with no basis in evidence. The restrictive stance of yesteryears is now held to be inadequate for pregnant women, “they deserve better” (LYERLY *et al.*, 2008, p. 19). Such position is not unanimous, as main stakeholders like ICH, whose documents guide major pharmaceutical industries, regulatory agencies and IRBs worldwide, still seem likely to pose pregnant women as a ‘vulnerable population’. However, the positions and protocols followed by scientists and international bodies have failed to incorporate the perspectives of the women they seek to protect. Do Brazilian women afflicted by the Zika epidemic share the scientists’ understanding and perceptions on risks and benefits? Do their pathways for demanding rights, treatments and healthcare include participation in research?

4 Ethical Economies: where do Brazilian women affected by the Zika outbreak stand?

Faced with international investments and challenges for the development of therapies and vaccines against the Zika virus, we turned our attention to the perspectives of Brazilian women from the Federal District (DF) and Pernambuco (PE), two different states⁶. We sought to understand their perceptions of Zika as well as their understanding of a possible participation in a clinical study for the development of a vaccine. Five focus groups (FG) were held in October 2016. Around 15 questions/propositions were presented to the group,⁷ with an average time of 62 minutes of conversation. In total, 27 people agreed to speak with us, of which 12 were from the cities of Brasília and Ceilândia (DF)

and 15 were from Recife (PE). Only two men participated, with little said by one of them, who accompanied his wife. In the Federal District, all women were students or alumni of the University of Brasília, either from a central campus (Brasília) or from another, geographically as well as economically peripheral one (Ceilândia) and aged between 19 and 30. In Recife we met with a group of feminist activists between the ages of 20 and 40, as well as with another group of women with different political views, but with no tertiary education. Among this last portion were women who had recently contracted Zika during pregnancy, some of whom had had babies with CZS.

The focus groups showed the following characteristics: 1. Woman who had not had Zika and had not gotten pregnant during the epidemic (Brasília/DF); 2. Women who had not had Zika and had not gotten pregnant during the epidemic (Ceilândia/DF); 3. Women who had not had Zika and had gotten pregnant during the epidemic (Ceilândia/DF); 4. Women who had had Zika, had gotten pregnant during the epidemic and had children with SCZ (Recife/PE); 5. Women who had had Zika and had not gotten pregnant during the epidemic (Recife/PE). Due to Zika cases being more common in Pernambuco than in the Federal District, groups with women who had contracted Zika were only conducted in the city of Recife (PE).

There is a big difference between GF 4 and the others. Aspects like their class condition, having a child with CZS and their increased burden of care duties associated to poor state policies to care for their children's disabilities meant they had a hard time making ends meet with the need of items such as drugs, specific tests, circulation around the city, etc., – especially after leaving the job market to assume almost always exclusive care for this child. The isolation in distant neighborhoods, with little access to public transport, and the impairment of mental health, with the progressive consumption of anxiolytics to take care of the child, family and home also crossed by these different and significant nuances.

The FGs were conducted by the three coordinators of the research, aided by a team of researchers in keeping a record of participants' contributions, their non-verbal reactions during interactions and checking recording equipment. Before discussions began, guided by a

set of questions previously established and pre-tested, participants were informed about the research project, the researchers, the methodology and the structure of clinical studies. All of them were allowed to clear occasional doubts and consented to participating in the study by signing a Term of Informed Consent. This research project was approved by the Social and Human Sciences IRB of the University of Brasília. In publications with results from the study, we adopted the use of pseudonyms.

The women we spoke to knew the epidemic from the television, newspapers, social media, stories of people close to them or from self-experience. At the time of the study, they were not participating in any trials for the development of a Zika vaccine. Thus, they were prompted to imagine themselves in this experimental scenario and, from their own perspectives, gave heterogeneous answers about the conditions under which they might or might not participate in such a trial. In this article, we will attempt to highlight their different positions on risks and benefits of taking part in a clinical trial, thus avoiding an essentializing description of their positions.

Generally speaking, all 27 people showed roughly similar reactions to the idea of participating in a hypothetical medical experiment. In all five focus groups, the first answer to the question “if a Zika vaccine were being tested, would you consider participating in the trials” was a resounding, sometimes unisonous, “no”. In most cases, they claimed to have never taken part in clinical research, to never have known anyone who had, and showed an automatic aversion to the experimental setting. Their reasons for such a strong refusal varied significantly, encompassing questions and preoccupations related to risks to their own health, the possible damage to their day-to-day lives with the children they already had, and potential harm if participation happened during pregnancy. In FG 3 (Ceilândia/DF), for instance, Carolina, a Veterinary Medicine alumna, mother of one child and not suffering from Zika, explained to the research coordinator that under no circumstances would she participate in a clinical study due to the risk of unforeseen adverse reactions:

Researcher: You wouldn't participate, right, Carol?

Carolina: Not a chance.

Researcher: Not even if you weren't pregnant?

Carolina: Not even then.

Researcher: Why?

Carolina: Because, I mean, these reactions, they're very... They might [run tests] on a thousand people and nothing will happen. [But], they might run them on me, something might happen. So I wouldn't participate. And as for the vaccine... I think that's so complex... Like, I have a baby who had a reaction to the 5-in-1 vaccine.⁸ If you look it up... That doesn't happen often, but my baby had a reaction to the 5-in-1. So, I mean, I wouldn't, I'd be afraid. Even though I know it [testing] needs to happen, I wouldn't risk myself.

The fear of possible deviations in reproductive physiological functions was a particularly specific concern present in the statements of a few women in the groups conducted in PE and the DF. In FG 5, for instance, Carina, a biologist and feminist activist from Recife, who had not had any children recently but who had contracted Zika, mentioned that she would not participate in a clinical study, out of both mistrust of the state's immunization policies and the fear of not being able to bear children in the future:

Oh, I'm afraid of, I don't know, I'm wary of things the State offers... I hesitate mostly out of suspicion; I don't trust absolutely anything that comes from the State. When you asked me, the first thing that came to mind was that maybe I wouldn't have, if anything went wrong, the possibility of getting pregnant. I so want to gestate a person inside me, and I keep thinking if something went wrong with that, I'd be very upset.

In the case of women with children, in both states, the risk of harmful side effects during research was viewed through the lens of consequences that falling ill might have on maternal duties. This was made clear in the only group with "micro mothers"⁹, FG 4 (PE): "I wouldn't [participate] either, because you need to give 100% of your time to the child. What if I get sick from the injection, whose effects I don't know? That complicates things, exactly because it's a test!" In FG 3 (DF), the three participants voiced similar concerns:

Carolina: I wouldn't participate yet, because I still breastfeed. So I'd be afraid because of my baby. Because we have this problem when it comes to how tests are run on people who breastfeed and who are pregnant, so I wouldn't risk myself. Which is sad, because you do need people who are brave enough. But I wouldn't be.

Juliana: I wouldn't do it either. Because I breastfeed too.

Valéria: If I were pregnant and breastfeeding, no. Maybe if you excluded those two scenarios, I might consider it.

Valéria, who at the time was on her way out of nursing school, refers to two fundamental factors behind a series of refusals from participants from all groups: pregnancy and breastfeeding. When we asked about a possible participation in trials and when we specifically mentioned pregnancy in this setting, several “noes” were said in all groups and justified with concerns for the health of the fetus and the baby. Noteworthy, although not included in our range of questions, breastfeeding was spontaneously considered as a practice that requires care regarding contagions, diseases and treatments because it is also seen as surrounded by risks. Not only pregnancy and childbirth, but in the post-partum, the maternal body continues to be perceived in a dyadic way, mother and child, with a strong potential for transmitting positivity and harmfulness, through the circulation of various substances, including breast milk.

Helena, a participant from Recife in FG 4, offered an illuminating synthesis of this concern, sometimes accompanied by a fear of living with guilt were the baby to be harmed or if it passed:

So, if I'm pregnant, I'm going to think of my baby, because it's a virus that will be administered to see if there are any reactions, and the reactions are going to be my baby's, so I'd be risking my child's future. We didn't know, but if we did know, we wouldn't take this vaccine.

Confronted with the same hypothesis of pregnancy during the imaginary experiment, some women, however, went from categorical refusals to considering the possibility of participation in a vaccine study. In four of the five focus groups, women mentioned that, if they were pregnant and already diagnosed with Zika and their children with CZS,

they would participate in trials, viewing them as possible treatments for their babies' condition. In this new setting, the vaccine, until then thought of as a significant risk, became a valuable hope for a cure for the syndrome, as can be seen with Cássia, then a student of a health course (FG 2, Ceilândia/DF):

Cássia: If it were really the last resort, I'd do it.

Researcher: What would be considered a last resort?

Cássia: An option if, say, I was at risk of losing the baby, or my life. Really, a last resort.

Researcher: So, in your case, if your baby had been diagnosed with microcephaly?

Cássia: Then, I would risk it.

Researcher: The vaccine would be a medication.

Cássia: Yes [...]. I don't know, at the same time that it might have side effects, it could also, I don't know, save its life in some way.

A similar reasoning emerged among women who had had babies with CZS in Recife (FG 4). Mayara mentioned that, if an experiment had happened while she was pregnant, she would have participated, since her child had already been diagnosed with microcephaly. In this case, understanding that the worst possible outcome of the infection had already happened, the experimental vaccine couldn't cause further harm – on the contrary, its only possible effect would have been to improve the baby's health.

When I was pregnant with her, if a vaccine like that had come around, I might take it because I knew my daughter already had it [microcephaly]. So, I would imagine she might get better. Then, yes, I would do it! But if I had a normal child, I would never risk it. [...] If my daughter has microcephaly, then the virus applied by the test injection wouldn't give her micro, because she already has it. So, what it could do would be to improve something in the baby's brain.

The weighted calculation between the risk of participating in a trial and the care for a child in the womb remained, in this setting, as the main variables to be considered. If faced with a healthy pregnancy, the more prudent and careful position would be to avoid subjecting the fetus to a drug with unknown effects; when considering the setting

of Zika infection and the subsequent diagnosis of fetal lesions, the better course of action, for a large portion of the 27 participants, was to “put themselves at risk” in the name of possible improvements, “encouraging themselves” in the name of a better (if only slightly) future for their baby. In this sense, Carina, from Recife, who at the start of FG 5 had said she would not participate in clinical trials out of suspicions towards the State and the fear of infertility, came around to say that, in the case of a critical situation such as CZS, she would make a different choice. Her dialogue with Liz, a feminist activist, and one of the coordinators of the research, is enlightening:

Liz: I keep thinking, also, that if you’re pregnant, there might be a greater chance of... thinking “No, this could work”, of being more positive. I don’t know.

Researcher: A more positive impetus?

Liz: Yeah, “It could work,” and going ahead with it, being braver.

Carina: And like I was saying, right, you’re pushed to it, because you’re in a condition where you need to solve that problem. You’re pushed to make that decision. You want results, preferably positive ones.

Transitions and slippages in participants’ ponderings, albeit strongly conditioned by the scenarios of pregnancy, the Zika epidemic and CZS diagnoses, took into account other conditions for a possible “yes”. Across all focus groups, university-led research was preferred, in keeping with suspicions towards studies done by the State or pharmaceutical companies. Concerns with State interests in immunizing the greatest possible number of women and with private companies’ thirst for profit were singled out as factors that would make them more comfortable with participating in studies done by universities (even if also public, generally maintained and funded by Brazilian State funds). Even though they considered universities to be spaces more fully committed to increasing knowledge on the disease and to improving the population’s health, some women still thought it necessary to know the research group responsible for the study (FG 5).

When considering participating in trials, questions were raised as to the need for guarantees of indemnity and lifetime support in the case of harm resulting from research. This aspect seemed particularly

significant to FG 4, with the “micro mothers”, who highlighted the importance of research sponsors offering guarantees that would allow them to care for their children were these to develop CZS:

Ana: In my opinion, I think that, in that moment, I wouldn't need to receive anything other than the guarantee that if, in the future, something was to happen to my baby because of that test, then I'd be compensated well enough to, at least, deal with the costs of caring for the baby.

Vera: Myself, I wouldn't want restitution, I would want everything covered, all his medication, his hospital bills, every last thing, because if you get paid compensation, you know you'll spend the money. I would want my son covered in all his needs. With a right to everything, because these days, even [public] hospitals are refusing [treatment].

Enaida: I think when they make this vaccine and test it, they should, for at least three years, keep up with people, running lots of exams.

For these women, a “study” needs to be responsible and maintain longer connections with its participants, beyond the specific moment of data collection. Results, follow ups, tests, medication, damage payments are the practical aspects that surround an idea of responsibility on the part of researchers. These participants from FG 4 seem to demand a relationship with the researchers, and not mere contact; they seem to expect that the involvement of one's life (or two, in the case of pregnancy) be accompanied by other lives – specifically, those of the researchers, and perhaps those of other women and babies who might, in the future, also benefit from the results. The massive presence of research and researchers in Recife helped the perception of science as a special and problematic place for these mothers of children with SCVZ. Specially because science was one of the places they appealed to, looking for answers for their sons and daughters' health situation. Troublesome because they underwent dozens of tests and protocols, without necessarily receiving the results. High expectations were created about the research results, which were, in our view, personified in the figure of researchers. So, the demand for a relationship is with the researchers, but regarding the results of their researches (SIMAS, 2020; FLEISCHER, in press).

Despite significant differences in their justifications, during focus groups, the matter that seemed fundamental to women in their elaborations was care. Their attributions, be them in relation to the developing fetus or to their already born children, was an element that led them to both say “no” in the case of a healthy pregnancy or a child with disabilities and “yes” in the case of pregnancies with fetal CZS diagnoses. This slippage in perceptions seems less related to questions more categorically singled out in the international controversy as relates to the tension between women’s rights and the rights of the fetus (EPSTEIN, 2007) or the need to develop health technologies specifically to pregnant bodies. Women’s concerns were closer to a recognition of a calculation between risks and benefits that takes into account their role as caregivers (FLEISCHER, 2018) in a context of precarious access to healthcare.

5 Care and Ethics Beyond Evidence-Based Medicine

For these women, different from the emphasis given by scientists involved in ethical debates on Zika research, perspectives on the immunization of their own bodies seem to have been eclipsed by more urgent matters of care. The chances of having the Zika virus eliminated from their bodies, be it through participation in an experiment or through permanent medication, were not considered systematically as something for their own individual benefit. On the contrary, health benefits almost always figured in relation to the fetus – especially those diagnosed with CZS. Such diagnosis also played a crucial role in their regards concerning the technology under test. As the scenario transitioned from one where a possible prophylactic substance could harm the fetus whose Zika virus status was unknown to another where the CZS was certain, the risky possible vaccine would become a possible saving medicine. Pharmaceuticals, in this sense, were not recognizable to these women for any intrinsic properties they carry, but mainly for the variable status and effects they would enact as they moved from one assemble of factors to another (AKRICH, 1995; SANABRIA; HARDON, 2017).

However, the risks of taking part in an experiment were looked at through a double lens – on the one hand, the experimental vaccine might compromise the health of the babies, and on the other hand, the health of the women involved in the study. This latter aspect, in turn, was mostly considered negative in view of the need to care for children, be they planned, in gestation or already born. Such perceptions diverged from those presented in international guidelines for the development of Zika vaccines, which tend to emphasize the need for evidence about the pregnant body as an ethical goalpost for the inclusion of pregnant women in clinical studies. Without a definitive stance on the relevance of their participation in research, women in these focus groups prefer to evaluate each specific situation keeping in mind not so much perspectives and promises of future evidence-based treatment but their immediate caregiving attributions.

Although it was never emphasized in debates and protocols referring to the production of Zika vaccines, the matter of care is not new for scientists who advocate for the participation of pregnant women in clinical trials. Feminist approaches insist that the absence of evidence places women and their babies at risk, since both use medication without scientifically validated information (LYERLY *et al.*, 2008). Implications in this setting also include perceptions of female caregiving roles and responsibilities. Faden and colleagues (2018) research with the Ebola virus, for instance, indicates that not extending clinical vaccine trials to pregnant and breastfeeding women increases their risk of exposure to epidemic because, in most cases, these women are already mothers and/or the main caregivers of their domestic unit. As they assume duties for those most vulnerable (children, the elderly, the sick, people with disabilities, for instance), they are also more exposed to people already infected by a virus. Not protecting them means dismissing this gendered aspect of care and epidemiological exposure.

Additional concerns with the risk of infertility point towards another important aspect to be considered regarding research ethics with pregnant women. Such questions make clear how much reproductive projects should be taken into account. Both fear of losing reproductive

capacity and the risk of miscarriage were mentioned as elements that would drive women away from clinical trials. On the other hand, as stated by a participant of FG 5, the possibility of being assisted in the voluntary interruption of an unwanted pregnancy would make her consider participating in a study. She suggests that, due to a possible legal and ethical protection conferred by a clinical trial, there would be less risks associated to abortion illegality, and she could reevaluate certain “side effects” of the vaccine as favorable.¹⁰ In any of these cases, what is evident is that the discussion of reproductive rights is central when we talk about ethics in clinical research and the participation of women, especially, pregnant women. Whether they consent or not, the participants in these focus groups never give up deciding how to manage their reproductive projects during a supposed participation in an experiment. As a matter of fact, more recently, some “micro mothers” that took part in this research had children and still do not rule out having more.

Therefore, all the focus groups suggested that pregnant women with confirmed Zika and fetal CZS diagnoses would be the best suited for involvement in a study for the development of a vaccine. They imagined the later stages of pregnancy to be safer for the involvement in clinical trials. For mothers who saw pregnancy as a sensitive time, however, women considered that the test should happen right at the beginning since, if anything went wrong, they would have time to get used to the side effects affecting the baby or, as an alternative, to seek safe and legal ways to interrupt the pregnancy. This calculation took into account care and responsibilities towards their children, the contribution to other women and the specificities of the female body.

About this last aspect, it was noted that women’s bodies, pregnant or otherwise, need to be considered in their particularities. Thus, it was not considered possible that eventual studies with men might come up with evidence suited to the experiences of women – even accounting for sexual and hereditary transmission of Zika immunity. Here, they are in full political accord with the demands historically directed towards clinical research with specific groups, wishful of inclusion into such efforts (McCarthy, 1994). On the other hand, some participants said

it might also be better for women who did not want kids to volunteer for research, since the risk of infertility would not compromise their reproductive projects. In this case, however, though the specificity of the female body would be covered in clinical trials of medications, the same could not be said for the specificities of the pregnant body.

6 End Notes: when women come first

The continuity of the scientific interdiction on pregnant and breastfeeding women sheds light on a series of tensions that articulate matters of gender, science, ethics and disability. This exclusion is marked by the attempt to avoid repeating extensive cases of iatrogenesis, where adverse effects of medication ingested by the pregnant patients manifest vertically on the fetus. Meanwhile, questions emerge relating to the impacts of not conducting studies with pregnant women for the improvement of their and their babies and families' health. The interdiction of pregnant women in experimental research, in this context, is associated with a risk economy where the impact of not knowing the effects of medication on pregnancy and breastfeeding is counterbalanced with the potential teratogenic effects of the drug being tested. In this setting, according to Epstein (2007, p. 263), apparently the "rights" and 'interests' of the fetus obfuscate the mother's" and, in this sense, the exclusion of pregnant women from medical experiments remains the rule – including those studies on vaccines against Zika and other pathologies not yet covered by prophylaxis.

The Zika epidemic was understood as a critical event and a global health emergency (PAHO, 2016; WHO, 2016a), but the scientific, ethical and economic correlation of forces proved decidedly unequal and led to different ways of dealing with the multiple developments of the epidemic. Though authorities mobilized quickly and undertook practically unprecedented efforts to fight the epidemic, women are still the least involved and heard part of the process. Women from Pernambuco and the Federal District indicate that epidemics, prophylaxes, and treatments also must take into account their rights and interests as subjects, caregivers, and knowledge producers (BIEHL; PETRYNA, 2013). Their contextual and contingent elaborations, as their

considerations on the risks and benefits of taking part in experiments are, as the Zika epidemic itself, rebellious against the expectations of stable and bureaucratic responses to ethical dilemmas. Otherwise, they're founded on their shared and particular experiences of (mis) trust, (lack of) assistance and (unfulfilled) hope.

The women we met do not reject the scientific and ethical international debate on the participation of pregnant women in clinical studies but refract it based on their own immediate and chronic experiences, values and challenges (especially in the case of mothers of children with CZS). On the other hand, the scientific world seems uninterested in bringing them closer to the complicated global debate on body, ethics and evidence that has taken place at the center of the epidemic. Our effort, thus, is not to come up with insights to facilitate the persuasion and consent of women to take part in vaccine trials, but to invest energy into giving the proper attention to their needs and demands as a primary ethical exercise. We rely, therefore, less on hope in the construction of silencing protocols and consent of women in subaltern positions than in the potential of complicating the ethical presumptions of certain scientific practices – even those with the best intentions. As described here, their demands are broad and consider even stages rarely prioritized in clinical studies, such as post-study relationships and access to new treatments (CASTRO, 2018).

The experience that “micro mothers” have built imbues them with their own expertise, one which might contribute greatly to the outlining of new pharmacological research, even when the epidemic has (fortunately) receded, even when the tendency becomes the progressive abandonment of this research agenda and forgetting of these women as participants in trials or users of healthcare services. The experiences of these subjects, those most gravely affected by the epidemic, signals towards alternatives for the *future*, for fighting recurrences or related viruses, but above all signals towards the *present*, for the construction of public policies of assistance and of scientific protocols. Research such as ours, which reflected on hypothetical and dilemma-ridden scenarios, helps to see how imaginative debates are fundamental for the understanding of several time frames at once,

and for the complexification of epidemiological phenomena of such far-reaching and dramatic consequences.

Notas

- ¹ Causal associations were also established between Zika infection and the development of Guillain-Barré Syndrome in adults (WHO, 2016a).
- ² Other explanations for the birth of babies with the CZS included pesticide contamination, high blood pressure during pregnancy, inadequate behavior on the part of the mothers and obstetric violence (Diniz, 2016; Carneiro and Fleischer, 2018).
- ³ The development of pharmaceuticals is organized into successive stages of pre-clinical research, conducted on animals, and clinical research, conducted on human beings. In phase I, studies are done with healthy humans, while in phases II, III and IV evidence of safety and efficacy is produced with subjects suffering from the disease the technology aims to treat.
- ⁴ Aside from vaccines, the WHO established the following R&D priorities: diagnostic tests for flavivirus (Zika, dengue and chikungunya fever) and innovative tools for controlling vectors (WHO, 2016b).
- ⁵ Other challenges identified by the scientific community include the heterogeneity of Zika transmission across time and space, the unpredictability of the disease, immunological and medicinal interactions between a Zika vaccine and other diseases, a drop in interest from private laboratories and the eventual scarcity of resources for the complete development of at least one vaccine (Wilder-Smith et al., 2018; Barrett, 2018; Marques; Burke, 2018).
- ⁶ Between 2015 and 2018, 33 cases were confirmed in the Federal District and 462 cases in Pernambuco, with its state capital Recife accounting for close to half that total (BRASIL, 2018, p. 5).
- ⁷ Questions were organized in three large groups. One on “Zika and pregnancy” (Did you have Zika? Did these cases make you feel afraid of catching the virus too? Did you have plans to become pregnant?, for example). A second group on “Participation in clinical trial” (Has anyone participated in a clinical trial? If they were testing a Zika vaccine, would you participate? If you were pregnant, you would be willing to participate? Who would you consult to better reflect on this participation? Do you imagine that someone in your family or community would be against your participation in a test like this?, for example). And the last group on “Risks and benefits” (What reasons would make you give up your participation in a clinical trial, once having agreed to participate? If the test could also be done with women who have been pregnant in the past, would you think their participation would be more appropriate rather than pregnant women? What kind of feedback/compensation do you think would correct, fair and enough to participants of a vaccine trial? Do you think participating in a vaccine trial could benefit you and/or other groups of women? Would it matter to you if the research was carried out by a university, a drug company or the government?, for example).
- ⁸ Pentavalent vaccine is a combination of five individual vaccines against Haemophilus influenzae type B, whooping cough, tetanus, hepatitis B and diphtheria. In Brazil’s Universal Health System (SUS), this 5-in-1 vaccine is among the 13 vaccines offered to children free of charge.

- ⁹ “Compared to the several physical and neurological complications of babies born with CZS, microcephaly was afforded special attention, becoming an important political and identitarian category. The prefix was added by these women in several ways: they call themselves ‘micro mothers’, their babies are known as ‘micro babies’, and there are also ‘micro families’, ‘micro NGOs’, ‘micro clinics’ and so on” (Alves; Fleischer, 2018).
- ¹⁰ In Brazil, there are only three legal breaches for interrupting a pregnancy: sexual violence, death risks for the mother, and fetal anencephaly.

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