

1 **Uncertainty in times of medical emergency: knowledge gaps and**
2 **structural ignorance during the Brazilian Zika crisis**

3
4 **Abstract**

5 Uncertainty was a defining feature of the Brazilian Zika crisis of 2015-2016. The cluster
6 of cases of neonatal microcephaly detected in the country's northeast in the second half
7 of 2015, and the possibility that a new virus transmitted by *Aedes* mosquitoes was
8 responsible for this new syndrome, created a deep sense of shock and confusion in Brazil
9 and around the world. When in February 2016 the WHO declared a Public Health
10 Emergency of International Concern (PHEIC), it noted that it did so on the basis of what
11 was *not* known about the virus and its pathogenic potential. To better understand the role
12 that non-knowledge played in the unfolding of the Brazilian Zika crisis we differentiate
13 between three different kinds of uncertainty: global health uncertainty, public health
14 uncertainty, and clinical uncertainty. While these three forms of uncertainty were difficult
15 to disentangle in the early weeks of the crisis, very soon each one began to trace a distinct
16 trajectory. Global health uncertainty centered on the question of the causative link
17 between Zika virus infection and congenital malformations, and was officially declared
18 resolved by the time the PHEIC was lifted in November 2016. Public health and clinical
19 uncertainty, in contrast, persisted over a longer period of time and did in some important
20 ways become entrenched. This taxonomy of uncertainties allows us to explore the
21 systematic *nonproduction* of knowledge in times of medical emergency, and suggests
22 structural limitations in the framework of "emergency research" that global health
23 institutions have developed to deal with unexpected threats.

Keywords: Brazil; Zika; microcephaly; public health emergency; ignorance

1. Introduction

For the better part of a century, the Zika virus (ZIKV) remained at the margins of public health attention. First isolated in sentinel rhesus monkeys in Uganda in 1947 and soon identified as a flavivirus transmitted by *Aedes* mosquitoes, ZIKV was infrequently detected in human populations, and never in significant numbers or associated with distinct clinical symptoms. The emergence of the virus in the Micronesian island of Yap in 2007 attracted the attention of the US Centers for Disease Control and Prevention, but as the infection appeared to cause only mild clinical manifestations, the virus was deemed a relatively innocuous pathogen with minor public health implications (Hayes 2009; Duffy et al 2009). A subsequent outbreak in French Polynesia in 2013-2014 demonstrated ZIKV's striking epidemic potential – serosurveys suggested that nearly 50% of the population had been infected – and was associated with a cluster of cases of Guillain-Barré syndrome (Oehler et al 2014). Evidence collected during this outbreak also indicated that the virus might be transmitted sexually (Musso et al 2015).

It was, however, the confirmation in May 2015 of a large outbreak in the northeast region of Brazil that placed national and international health organisations on alert. When in August 2015 reports began to emerge of an unusual cluster of microcephaly and other neurological disorders among newborns in areas where the virus had been circulating, the alert turned into a full-blown public health crisis. News of a “microcephaly epidemic” and

1 photographs of infants with unusually small heads flooded Brazilian and international
 2 media (Lowe et al. 2018), and on 11 November the Brazilian Ministry of Health declared
 3 a Public Health Emergency of National Importance (*Emergência de Saúde Pública de*
 4 *Importância Nacional*, or ESPIN). Reports of the rapid spread of ZIKV into the
 5 Caribbean region and Central America appeared to herald a new global health disaster, on
 6 the heels of the still raging West African Ebola epidemic.

7 Zika's rapid transition from object of minor scientific interest to catalyst of an
 8 international public health crisis was partly spurred by the emotional salience of the
 9 images attesting to its teratogenic power. Clinicians and health authorities repeatedly
 10 expressed shock at the severity of ZIKV's impact on foetal development (Carneiro and
 11 Fleischer 2018). This shock was compounded by the lack of hard evidence on virtually
 12 any aspect of the virus and its physiopathological potential, and by the absence of
 13 diagnostic tools and protocols capable of characterizing the extent and severity of the
 14 epidemic (Castro 2016).

15 In this paper we look deeper at the role that uncertainty and ignorance played in
 16 the unfolding of the 2015-2016 Zika crisis in Brazil. Initial reports of a microcephaly
 17 outbreak in Brazil's northeast were met with a widespread sense of bewilderment and
 18 confusion. Cláudio Maierovitch Henriques, who was at the time in charge of the agency
 19 responsible for infectious disease surveillance at the Brazilian Ministry of Health,
 20 summarizes the situation towards the end of 2015 as follows: "There were no figures, but
 21 a large number of clinical reports, anxious looks, doubts, disorientation. Images that
 22 impregnate memory: children, photos, tomography and ultrasound exams" (Henriques,
 23 2017). This sense of anxiety and disorientation was echoed by international

1 organizations. When in February 2016 the WHO issued a Public Health Emergency of
 2 International Concern (PHEIC), its Emergency Committee made clear that the decision
 3 “was not made on the basis of what is currently known about Zika virus infection,” which
 4 was very little, but rather “on the basis of what is *not* known about the clusters of
 5 microcephaly, Guillain-Barré syndrome, and possibly other neurological defects”
 6 (Heymann et al 2016). Months after the alarm was first raised, the situation was still
 7 dominated by a pervasive sense of uncertainty about the origins, scope and implications
 8 of the crisis.

9 Yet as the sociology and the anthropology of ignorance remind us, ignorance and
 10 uncertainty never describe a generic absence of knowledge, but always refer to highly
 11 specific forms of *unknowing* (Gross and McGoeys 2015; Kerwin 1993; Mair et al 2012;
 12 Will 2019). Ignorance and uncertainty, that is to say, do not describe “a simple
 13 background failure to acquire, store and retrieve knowledge” (Rayner 2012, 108), but
 14 should be seen as the result of purposive courses of action, an effect of social
 15 arrangements of power. Each form of unknowing is historically specific, as it emerges
 16 out of a particular institutional configuration, and is sustained over time through active
 17 choices (Proctor 2008; McGoeys 2012). Understanding how certain events, phenomena or
 18 domains become more or less knowable requires that we attend to the production of what
 19 Michelle Murphy calls “regimes of imperceptibility,” the epistemic and political
 20 conditions under which some realities are “imbued with uncertainty” while others appear
 21 clear and distinct (Murphy 2006: 7).

22 To explore this idea further in the particular context of medical emergencies we
 23 propose to differentiate between three different varieties of non-knowledge during

1 Brazil's Zika crisis: *global health* uncertainty, *public health* uncertainty, and *clinical*
 2 uncertainty. Each form of uncertainty registered a specific set of unknowns, invoked a
 3 different level of intervention, and proved more or less amenable to scientific elucidation
 4 (Kelly and Lezaun 2013). Global health uncertainty was defined, most notably by the
 5 WHO, around the question of whether a causative link could be convincingly established
 6 between congenital ZIKV infection and microcephaly. Public health uncertainty and
 7 clinical uncertainty, in contrast, were defined, respectively, by the difficulty in drawing a
 8 clear picture of epidemiological risk distribution, and by the struggle to offer a stable and
 9 equitable standard of supportive care for those most affected by the outbreak.

10 While the three forms of uncertainty overlapped and were largely
 11 indistinguishable in the early phases of the emergency, as the crisis unfolded they quickly
 12 diverged and began to trace distinct trajectories. Global health uncertainty was construed
 13 as a "gap" in the existing body of scientific knowledge about Zika, and this gap was filled
 14 effectively by a rapid mobilization of investigational resources. When in November 2016
 15 the WHO lifted the PHEIC, it justified its decision on the basis that the core uncertainty
 16 at the heart of the international emergency, the question of causality, had been
 17 successfully resolved.

18 In contrast, public health uncertainty and clinical uncertainty proved more
 19 intractable; they persisted over a longer period of time and continued to impede an
 20 effective response long after the PHEIC came to an end. This is because they reflected
 21 deficits in technical capacities of detection, surveillance, and care that are not easily or
 22 quickly tackled through "emergency research," epistemic shortfalls that cannot be readily
 23 categorized as "knowledge gaps." Disentangling and characterizing these three different

forms of uncertainty during the Zika crisis in Brazil thus allows us to explore “the systematic nonproduction of knowledge” during medical emergencies (Frickel et al 2010). That is, how certain areas of ignorance are successfully addressed, while others remain relatively neglected despite a heightened level of global attention and concern (Nunes 2016).

The analysis that follows draws on more than twenty-five interviews with scientists directly involved in the epidemic, and with officials from the Brazilian Ministry of Health and other federal institutions, such as the Oswaldo Cruz Foundation (Fiocruz) and the Evandro Chagas Institute, as well as discussions with policy-makers at the WHO. We also analyzed documents (ordinances, protocols, guides and epidemiological bulletins) issued by the Brazilian Ministry of Health during the 2014-2017 period. We have complemented this material with a close reading of the scientific literature on Zika published since 2015, particularly publications authored by researchers affiliated with Brazilian institutions.

We start by elaborating the three forms of uncertainty in turn, before discussing how their trajectories diverged as the crisis unfolded. We conclude by reflecting on the (in)ability of “emergency research” to redress structural forms of ignorance – that is, systemic deficits of knowledge and knowledge production that precede the crisis itself and are rooted in the limitations and unequal distribution of institutional capacities.

2 Global Health Uncertainty

On 1 February 2016, the WHO declared a Public Health Emergency of International Concern (PHEIC) in response to the cases of microcephaly and other neonatal malformations detected in areas of Brazil and neighbouring countries that had experienced ZIKV outbreaks. This was the fourth time the WHO had declared a PHEIC since its power to do so was established by the International Health Regulations of 2005. According to these regulations, a PHEIC designates a situation that 1) carries implications for public health beyond the affected state's national border, and 2) is serious, unusual or unexpected. The Zika crisis appeared to bear out both criteria. As WHO Director-General Margaret Chan noted, “the clusters of microcephaly and other neurological complications constitute an extraordinary event and a public health threat to other parts of the world” (WHO 2016a).

The extraordinary nature of the event was made immediately evident by the images of newborns with abnormally small heads that circulated in international media towards the end of 2015 and the start of 2016. This fast-spreading imagery was an essential element in making the Zika crisis a “global” emergency, and points to the central role that media and communication technologies play in defining the contours of an international health crisis, long before its scope and nature can be established by experts (Ribeiro et al 2018). As for the potential of the virus and its associated syndrome to spread beyond national borders, evidence had been mounting of ZIKV circulation across South America and the Caribbean. Cases of imported infection were reported from all around the world, and evidence of sexual transmission was now available from a number of different countries. ZIKV's potential for international spread echoed the epidemiological pace and scope of the Ebola epidemic—an outbreak that had been

1 classed as a PHEIC by the WHO in August 2014 and still remained at the center of global
 2 health concern. Reeling from widespread condemnation of its sluggish response to the
 3 Ebola emergency, the WHO sought to act as firmly as possible to tackle a crisis of
 4 obvious international scope. Brazil’s planned hosting of the 2016 Summer Olympic
 5 Games added a further dimension of urgency to the rapidly evolving crisis.

6 The declaration of a PHEIC in response to the Zika crisis was unusual, however,
 7 because at the time it was still unclear what sort of clinical risk ZIKV infection posed to
 8 the general public. The WHO’s Emergency Committee (EC) noted that its
 9 recommendation to declare an emergency was motivated by the radical uncertainty that
 10 characterized ZIKV and its potential pathogenic effects. “Our advice to declare a
 11 PHEIC,” the EC members wrote, “was not made on the basis of what is currently known
 12 about Zika virus infection” (Heymann et al. 2016). The recommendation, they continued
 13 “was rather made on the basis of what is *not* known about the clusters of microcephaly,
 14 Guillain-Barré syndrome, and possibly other neurological defects” (*Ibid*; emphasis
 15 added). The EC drew here an explicit contrast with the Ebola emergency: “The Director-
 16 General declared the Ebola outbreak a PHEIC because of what science knew about the
 17 Ebola virus from many years of research during outbreaks in the past, whereas she
 18 declared the current PHEIC *because of what is not known* about the current increase in
 19 reported clusters of microcephaly and other disorders, and how this might relate to
 20 concurrent Zika outbreaks” (*Ibid*; emphasis added).

21 In highlighting the unknowns surrounding the Zika epidemic, the WHO ascribed
 22 an explicitly *instrumental* role to the PHEIC. The declaration was seen as a means of
 23 accelerating the production of the evidence necessary to fully characterize the nature of

1 the threat. In its recommendation, the EC alluded specifically to the need to increase and
 2 standardise the reporting of microcephaly cases, enhance the capacity to detect infection,
 3 and intensify efforts against the mosquito vector. But resolving the uncertainty at the
 4 heart of the crisis, the EC emphasized, required above all a full clarification of “the
 5 aetiology of confirmed clusters of microcephaly and neurological disorders to determine
 6 whether there is a causative link to Zika virus, other factors, and cofactors” (Ibid.). In the
 7 words of David Heymann, Chairman of the EC, “there was an urgent need to know
 8 whether there was an epidemiological link between the neurological disorders and the
 9 rapidly spreading Zika epidemic” (Heymann, quoted in Maurice 2016).

10 Considering that three months earlier, in November 2015, the Brazilian
 11 government had officially confirmed that link (see next section), this implied that the
 12 evidence gathered up to that point did not meet WHO’s own “global” standard of
 13 certainty. In the press conference in which she announced the declaration of the PHEIC,
 14 Margaret Chan noted that a causal link was “strongly suspected” but was “not yet
 15 scientifically proven” (WHO 2016a). A key objective of the emergency declaration, she
 16 pointed out, was precisely to activate “international coordinated efforts to investigate and
 17 understand this relationship better” (Ibid.). In an editorial, the journal *Nature* echoed the
 18 argument, noting that “the most urgent priority on the ground is research to answer basic,
 19 but crucial, questions, including whether the birth defects are caused by the virus, and if
 20 so, how frequently” (Nature 2016).

21 Several research reports circulated or published in February and early March 2016
 22 provided important insights into the question of causality. Data from a case-control study
 23 coordinated by the epidemiologists Celina Turchi Martelli that compared 200 children

1 born with microcephaly and 400 born without the syndrome in the state of Pernambuco
2 appeared to rule out alternative explanations for the malformation (Souza et al 2016).
3 Preliminary results from a study of pregnant women in Rio de Janeiro reported foetal
4 abnormalities in a high percentage (29%) of ZIKV-positive women (Brasil, P. et al
5 2016a). A third report from a laboratory study showed that the virus was able to target
6 and destroy the foetal cells that form the brain's cortex (Tang, H. et al 2016). Reacting to
7 the first of these studies, Anthony Fauci, Director of the U.S. National Institute of Allergy
8 and Infectious Disease, noted in early March that any lingering uncertainty about the
9 existence of a causative link between ZIKV infection and microcephaly had virtually
10 disappeared. "Now there's almost no doubt that Zika is the cause" (quoted in McNeil and
11 Saint Louis 2016).

12 At a press conference following the second meeting of the WHO's Emergency
13 Committee, on 8 March 2016, Chan similarly noted "the increasing strength of the
14 evidence showing a likely association between Zika infection and foetal malformations
15 and neurological disorders." She also remarked, however, that the experts on the
16 Committee had "pinpointed the types of studies needed to establish a causal
17 relationship," implying that conclusive evidence of the nature of the association was still
18 lacking. Chan ended the press conference by emphasizing that "strong public health
19 actions should not wait for definitive scientific proof" (WHO, 2016b).

20 In a later exchange with a journalist during the same presser, David Heymann
21 provided a more extended answer to the question of when the WHO would consider it
22 had "definitive proof that Zika causes these problems":
23

1 Regarding the second question which was on definitive proof, we asked all the
2 different advisers, the seven different advisers today, what they would consider as
3 definitive proof. And they couldn't really give any specific criteria which is what we
4 were looking for, but what they did say was that there needed to be consistency in
5 different studies over time and that there's only a few studies now but that other
6 studies must be done which are repeated, which are consistent with what's going on
7 now in the case-control area and in other areas. So that was one of the answers we got
8 (WHO 2016c).

9

10 This exchange suggests that at this point the EC still held a variety of views on what
11 would constitute definitive proof of a causative link. The gold standard was case-control
12 prospective investigations of pregnant women, but that evidence would be slow in
13 coming. In the meantime, the EC came to rely on systematic reviews of multiple forms of
14 evidence, including a reanalysis of data gathered during the outbreak in French Polynesia
15 (Cauchemez et al 2016). The first systematic review used the Bradford Hill criteria – a
16 synthesis of nine considerations allowing a reasoned judgment “that the most likely
17 explanation is causation” (Hill, 1965) – and came to the conclusion that more information
18 was needed before a final determination of causality could be made (Franck et al. 2016).
19 A second review, drawing primarily on Shephard's criteria for establishing proof of
20 teratogenic effects, reached a different conclusion, and asserted “that a causal relationship
21 exists between prenatal Zika virus infection and microcephaly and other serious brain
22 anomalies” (Rasmussen et al. 2016). This second review was published in the *New*

1 *England Journal of Medicine* on 16 April 2016, and that same day the CDC announced it
2 had concluded that ZIKV was the cause of microcephaly and associated brain defects.

3 On 18 November 2016, the EC met for the fifth time and recommended lifting the
4 PHEIC. The emergency declaration, the Committee noted, had “led the world to an
5 urgent and coordinated response,” and this response had been successful in “providing
6 the understanding that Zika virus infection and associated consequences represent a
7 highly significant long-term problem” (WHO 2016e). Since the key unknown at the heart
8 of the PHEIC had been resolved, it was no longer necessary to define the crisis as an
9 emergency of international concern. “Because research has now demonstrated the link
10 between Zika virus infection and microcephaly, the EC felt that a robust longer-term
11 technical mechanism was now required to manage the global response.” It was now
12 necessary to create the conditions for “sustained research” to address the “many aspects
13 of this disease and associated consequences [that] still remain to be understood” (*Ibid*).

14 A particularly salient aspect still to be understood was the sudden and surprising
15 decrease in the number of symptomatic ZIKV infections in areas of known transmission,
16 and the relatively low numbers of children born with severe neurological abnormalities in
17 the later months of 2016. The most pessimistic projections made at the height of the crisis
18 had failed to materialize. The caseload of congenital Zika syndrome in central Brazil was
19 much lower than that in the northeast, despite the strong presence of the virus in the area.
20 While there appeared to be a moderate “second wave” of ZIKV infections in Brazil in the
21 spring of 2016, it did not seem to have led to a rise in the number of cases of
22 microcephaly. In light of these developments, the cluster of cases that had triggered the
23 PHEIC appeared to be an exception, rather than the rule. This did not imply greater

1 certainty about ZIKV or its epidemiological and clinical implications, but the opposite:
2 the reasons for the “near disappearance” of Zika in Brazil remain mysterious and
3 unexplained to this day. The reduction in the number of reported clinical cases did not
4 appear to be related to any particular public health intervention, and seemed too sudden
5 to correspond to the normal patterns of immunity acquisition (Siedner et al 2018).
6 Knowledge of the kinetics of immune response, and the possible effect of immunity
7 against other flaviviruses, remained scant. In the meantime, , the virus continued to
8 spread around the world, with more than eighty countries reporting autochthonous
9 transmission in 2016-2017.

10 Uncertainty, in sum, was crucial in categorizing the Zika crisis as an international
11 emergency. This was a particular form of unknowing, however, understood by key
12 global health institutions, most notably the WHO, as the confusion created by the absence
13 of a scientific consensus on the nature of the association between ZIKV infection and
14 microcephaly. This lack of consensus was interpreted as a “gap” in the existing base of
15 scientific knowledge about the virus, an evidentiary deficit that a rapid mobilization of
16 investigational resources ought to be able to address in short order. Global health
17 uncertainty was in this sense an example of what Robert K. Merton called “specified
18 ignorance,” or “the express recognition of what is not yet known but needs to be known
19 in order to lay the foundation for still more knowledge” (Merton 1987: 1). Such express
20 recognition implies both a clear characterization of the unknown in question, and the
21 expectation that further knowledge will follow once it is addressed. Margaret Chan
22 captured this particular epistemology of health emergencies when she noted, in a
23 commentary marking the first anniversary of the ZIKA PHEIC, that she agreed to lift the

1 PHEIC in November 2016 because “research had addressed many of the questions that
2 made the disease so ‘extraordinary’ nine months earlier.” She conceded that “some
3 uncertainties remain, but many fundamental questions have been answered” (Chan 2017).

5 **3 Public health uncertainty**

6
7 As we have noted, the Brazilian Ministry of Health declared a Public Health Emergency
8 of National Importance on 11 November 2015 in response to the “alteration in the
9 epidemiological distribution of microcephaly in Pernambuco” (Ministério da Saúde
10 2015a). That same day, Brazilian scientists announced the detection of ZIKV RNA in the
11 amniotic fluid of two women from the state of Paraíba who were carrying fetuses that
12 showed severe abnormalities in brain ultrasounds (Oliveira Melo et al 2016). For many
13 Brazilian clinicians, these laboratory findings confirmed something they already thought
14 they knew or strongly suspected. Highly unusual and clinically unmistakable, the
15 multiple cases of microcephaly detected in the fall of 2015 were in their opinion
16 testimony of a new syndrome. Comments such as “I never saw anything like this,” it was
17 “like a tsunami,” “[the babies] all looked the same,” made by several of our interviewees
18 who were at the epicenter of the outbreak reflect the persuasive power of the symptoms
19 for local clinicians and epidemiologists. Many of these clinicians and epidemiologists
20 were, moreover, in direct contact via e-mail and WhatsApp groups, and had coalesced
21 around the view that they were witnessing an entirely new syndrome, likely caused by a
22 novel arboviral agent, weeks before the national public health emergency was declared
23 (Brito 2017).

Days after the declaration of the ESPIN, researchers at the Evandro Chagas Institute in Belém, in the state of Pará, identified ZIKV RNA in the blood, brain, and viscera of a newborn with severe microcephaly who had died minutes after being born. According to the Director of the Institute, this finding “unequivocally and irrefutably demonstrated” that the Zika virus was responsible for the malformations (Vasconcelos, 2017). On 28 November, the Brazilian Ministry of Health officially confirmed the link between microcephaly and congenital ZIKV infection and declared the outbreak “a unique situation in global scientific research” (Ministério da Saúde 2015b). Three days later, on 1 December, the Pan American Health Organisation (PAHO) issued an epidemiological alert (“Neurological syndrome, congenital malformations, and Zika virus infection”), recommending that its Member States “establish and maintain the capacity to detect and confirm Zika virus cases, prepare healthcare facilities for the possible increase in demand at all healthcare levels and specialised care for neurological syndromes, and strengthen antenatal care” (PAHO 2015).

The declaration of national public health emergency triggered “a huge political and institutional mobilization” (Maierovitch Herniques 2017). The Federal Government issued multiple sets of recommendations for health professionals, including new rules for ensuring the safety of blood transfusions, and then-President Dilma Rouseff created an inter-ministerial task force bringing together staff and resources from the Ministry of Health and the Ministry of Social Development to provide a comprehensive response to the crisis.

Still, in the absence of robust diagnostic protocols for ZIKV infection, crucial questions of public health relevance remained unanswered, and unanswerable, long after

1 the causative link between ZIKV infection and microcephaly had been officially accepted
2 in Brazil. While laboratory results demonstrated the capacity of the virus to infect the
3 foetus and attack its neurological system, adequate public health interventions required
4 population-wide measurements of infection and an epidemiological understanding of risk
5 distribution. It was impossible to know how many Brazilians were infected with the
6 virus, what percentage of those infections were symptomatic, what proportion of women
7 infected during pregnancy went on to give birth to infants with neurological
8 abnormalities, whether infection was especially risky at certain stages of the pregnancy,
9 or what percentage of microcephaly cases reported in the epidemiological bulletin
10 published by the Brazilian Ministry of Health could be plausibly associated with ZIKV
11 infection. Some anomalies in the regional distribution of congenital malformations were
12 quickly becoming apparent. The state of Bahia, for instance, where the first cases of
13 ZIKV infection had been detected, had reported no cases of microcephaly as of the end of
14 2015 (Triunfol 2016).

15 In the face of these uncertainties, the mobilization of governmental resources
16 focused on a familiar target: the mosquito vector. For a considerable period of time after
17 the declaration of the ESPIN, the only obvious course of action was to intensify measures
18 already in place to fight dengue and chikungunya, all diseases predominantly transmitted
19 by *Aedes aegypti* mosquitoes. Despite an inflow of resources and the mobilization of
20 military personnel to assist in mosquito control efforts in several large cities, this strategy
21 faced evident challenges. Not only had similar interventions failed to reduce transmission
22 of other arboviruses in the past, but the specific nature of the relationship between ZIKV
23 and its mosquito vector remained uncertain. The effect of interactions between different

1 viruses on the mosquito capacity to transmit ZIKV, for instance, had yet to be
2 investigated. Studies published in the first months of 2016 even suggested that ZIKV
3 might also be transmitted by *Culex* mosquitoes, further complicating the design of
4 targeted mosquito abatement campaigns in urban centers.

5 Clarifying the public health implication of the ZIKV outbreak and developing
6 strategies to protect those exposed to the highest risk required, among other things, robust
7 evidence from large prospective case-control studies of pregnant women. Yet that
8 evidence would take months to arrive. The first cohort study with pregnant women who
9 had experienced symptoms of ZIKV infection had been launched in September 2015, and
10 preliminary results would not be available until March of the following year (see next
11 section). The first prospective cohort study started in January 2016 in the city of Recife,
12 Pernambuco, with initial results appearing around April of that year (de Araujo et al
13 2016). A second case-control study on the association between ZIKV infection and
14 microcephaly, supported by the US Centers for Disease Control (CDC), started in March
15 2016 in several municipalities in the state of Paraíba (Krow-Lucal et al. 2018). As these
16 and other studies progressed, public health uncertainty remained a central feature in the
17 evolution of the governmental response to the crisis in Brazil.

18 In fact, public health uncertainty was initially exacerbated by the intensification of
19 surveillance efforts. The need to standardize clinical reporting protocols brought greater
20 scrutiny to practices of prenatal and perinatal care, revealing shortcomings across the
21 country, including limitations in the national system for registering congenital and birth
22 abnormalities the SINACS (*Sistema de Informações sobre Nascidos Vivos*). The
23 reliability of SINACS had come into question in the past, as Brazilian scientists would be

1 the first ones to point out in some of the earliest publications on microcephaly (Schuler-
 2 Faccini, L. 2016), and many epidemiologists suspected that microcephaly had been
 3 historically under-reported in the country, which made it difficult to appreciate the true
 4 implications of the numbers published during the second half of 2015 (Triunfol 2016).

5 The very definition of microcephaly remained in flux during the early months of
 6 the crisis. SINASC had originally defined microcephaly as a head circumference ≥ 3
 7 standard deviations below the mean for age and sex, which corresponded to 30.3 cm for
 8 full-term females and 30.7 cm for full-term males. This definition, however, excluded a
 9 significant number of the neonates who were being born in the fall of 2015 with obvious
 10 physical abnormalities. In mid-November, the Ministry of Health introduced a new “ad
 11 hoc” surveillance system for the identification of cases of microcephaly in neonates born
 12 since 1 January 2015, which defined microcephaly as a head circumference ≤ 33 cm for
 13 both sexes. Before the end of the year the definition of microcephaly changed again, and
 14 from 8 December onwards full-term infants with a head circumference ≤ 32 cm were
 15 registered as suffering from microcephaly.

16 The choice of a 32 cm threshold did not mean, however, that the actual
 17 measurements taken in maternity wards across Brazil suddenly became more accurate.
 18 The new emphasis on a precise measurement of head circumference coexisted with a
 19 wide variety of measurement methods, different levels of skill, and lack of access in
 20 many cases to proper equipment. Researchers conducting case-control studies on the
 21 relationship between ZIKV infection and microcephaly had to bring specially designed
 22 measure tapes to the hospitals and maternity wards to be used on neonates. As one
 23 epidemiologist put it to us in an interview: “We bought some tapes that are neither paper

1 nor plastic, they measure exactly – they have no flexibility. We left a box of them in the
 2 delivery room, and asked the doctors to use only this tape, to not measure with sewing
 3 tape measure or any other kind of tape” (Interview, 18 April 2018). Measurements of
 4 head circumference made at birth, moreover, often proved inaccurate: the case-control
 5 study conducted in Paraíba found that only 55 per cent of the infants who had been
 6 reported to have microcephaly at birth had the diagnosis confirmed in follow-up
 7 measurements (Krow-Lucal 2018).

8 The combination of historical underreporting of microcephaly and the possibility
 9 of false positives due to shifting definitions of the category muddled the epidemiological
 10 picture and undermined international trust in Brazilian claims of a “microcephaly
 11 epidemic” in the early weeks and months of the crisis. In December 2015, the Latin
 12 American Collaborative Study of Congenital Malformations concluded that “the current
 13 data, affected by the change of criterion determining the measurement of head
 14 circumference to suspect microcephaly, do not allow to assess whether: 1. a real increase
 15 in microcephaly prevalence at birth occurred in Northeastern Brazil; 2. what was the
 16 magnitude of this increase; 3. was this increase due to exposure to the ZIKV or increased
 17 exposure to one or more environmental causes of microcephaly (STORCH, alcohol,
 18 prematurity, diabetes, etc.)” (ECLAMC 2015). A retrospective review of data from the
 19 northeast published in February 2016 showed previously undetected seasonal peaks of
 20 microcephaly since 2012, with the number of severe cases increasing from 2013 onwards
 21 (de Araújo et al 2016). These and similar reports gave credence to the notion that factors
 22 other than ZIKV infection might be at work in the observed cluster of congenital
 23 malformations, or that Brazilian clinicians were “overcounting” cases of microcephaly

1 due to the panic triggered by media reports, fueling international skepticism about the
 2 severity of the crisis (McNeil 2016).

3 Even after Brazil declared an official end to the national Zika emergency in May
 4 2017, key areas of public health uncertainty persisted, severely constraining the ability of
 5 national authorities to formulate precise and targeted interventions. In the press
 6 conference in which he announced the lifting of the ESPIN, Adelfson Cavalcante,
 7 National Secretary for Health Surveillance, noted that “the end of the emergency doesn’t
 8 mean the end of surveillance or assistance.” Yet he incorporated the threat of Zika into a
 9 “triple epidemic” of *Aedes*-borne arboviruses. “The health ministry and other
 10 organisations involved in this area,” he remarked, “will maintain a policy of fighting
 11 Zika, dengue, and chikungunya.” The grouping of Zika with other mosquito-borne
 12 diseases once again framed Zika as a vector control problem, sidelining its very specific
 13 clinical and public health implications (Nunes and Pimenta 2016). Proclamations of a
 14 renewed effort to control the mosquito vector did nothing to suggest, moreover, that the
 15 authorities would this time be more effective than in the past (Löwy 2017). Dengue and
 16 chikungunya, and presumably ZIKV, continued to spread across Brazil, and in 2017 the
 17 country would also experience one of the largest outbreaks of yellow fever in recent
 18 history.

19 Public health uncertainty, in sum, pertained primarily to areas of ignorance and
 20 non-knowledge that impeded or limited effective action by national authorities, and
 21 followed a strikingly different path from global health uncertainty. It persisted well after
 22 the lifting of the PHEIC, because it was shaped by the enduring technical challenge of
 23 detecting the virus, the difficulty of accurately recording cases of microcephaly and other

1 birth abnormalities across the country, and the impossibility of drawing robust
 2 epidemiological inferences from fragmented and sometimes unreliable case data. The
 3 relative intractability of public health uncertainty is most evident in the centrality that
 4 mosquito control initiatives occupied in the governmental response to the crisis: this was
 5 a self-evident course of action, in the sense that it did not require any new knowledge but
 6 simply an intensification of already-existing measures, even if those measures had failed
 7 to check the spread of other arboviruses in the past.

9 **4 Clinical uncertainty**

10
 11 The clinical profile of ZIKV infection changed quickly and dramatically as the crisis
 12 unfolded. When, towards the end of 2014, a cluster of generally mild symptoms began to
 13 be identified in patients in Brazil's northeast, the syndrome was classified as
 14 "undetermined exanthematous" or "exanthematous acute" disease, on the basis of its
 15 most visible manifestation: skin rashes. The aetiology of the symptoms was unknown –
 16 local media speculated about an outbreak of rubella, while most reports and many official
 17 authorities described it as a form of "mild dengue."

18 Even after the Zika virus was detected in serum samples from patients in
 19 Camaçari, Bahia, in May 2015, and evidence began to mount that the "mild dengue"
 20 might in fact be caused by a new arbovirus, the clinical implications remained uncertain
 21 (Campos et al 2015). The main known potential complication was Guillain-Barré
 22 syndrome, as had been observed during the 2013-2014 outbreak in French Polynesia. Yet
 23 the number of cases of this autoimmune disorder reported in the states of Pernambuco

1 and Bahia in the second quarter of 2015 was relatively small, and involved predominantly
 2 adults. The novel syndrome was still characterized as “acute maculoexantematic illness,”
 3 and given the assumed clinical similitude with dengue, several health surveillance
 4 authorities in northeastern states recommended that new cases be reported as dengue even
 5 when ZIKV infection was suspected (Governo do Estado de Pernambuco 2015).

6 The identification of a cluster of microcephaly cases spatially and temporally
 7 associated with ZIKV circulation radically altered the tenor of the response. Yet the
 8 declaration of a national public health emergency in November did little, at least initially,
 9 to change the clinical profile of the disease. Accurate diagnosis of infection was
 10 hampered by the fact that many of the symptoms in adults resembled those for dengue or
 11 chikungunya, the cross-reaction of serological tests to antibodies produced by those
 12 viruses, and the narrow temporal window for detection of viral RNA in maternal sera. For
 13 several weeks, the capacity for reliable detection of the virus was limited to sentinel and
 14 reference laboratories and required expensive quantitative reverse transcriptase
 15 polymerase chain reaction (qRT-PCR) analysis. More portable tests, specifically a quick
 16 IgG immunochromatographic assay, proved difficult to develop and standardize. It was
 17 not until September 2016 that the Ministry of Health was able to purchase a new rapid
 18 test for use in primary health facilities, and the product did not arrive until early 2017.
 19 This test, however, has a long detection time and a low sensitivity, and its distribution
 20 across the country was uneven (de Vasconcelos et al 2018; Kameda de Carvalho 2019).

21 As to the most critical clinical issue, the proliferation of neurological birth
 22 abnormalities, it was impossible for a long time to obtain a clear view of the risk. In
 23 addition to the challenge of detecting the virus, hypotheses proliferated about the role of

1 potential co-factors or effect modifiers – from exposure to teratogenic drugs or
 2 pyriproxyfen-based larvicides, to co-infection by other arboviruses or administration of
 3 the rubella vaccine during pregnancy. Uncertainty also persisted about the relationship
 4 between time of infection during pregnancy and the severity of fetal disorders. Initial
 5 reports suggested that only infection during the first trimester of gestation led to
 6 microcephaly. This claim that would be contradicted in March 2016, when evidence from
 7 the first cohort studies suggested that, while the first trimester was indeed the period of
 8 highest risk, damage to the foetus could occur regardless of the period of pregnancy when
 9 the mother was infected by the virus (Brasil, P. et al 2016).

10 These and other uncertainties explain the most notorious and controversial piece
 11 of “clinical” advice given to women during the first months of the crisis: the
 12 recommendation to postpone pregnancy and wait for a clearer picture of the disease to
 13 emerge. Cláudio Maierovitch Henriques, director of infectious disease surveillance at the
 14 Ministry of Health, issued this advice in November 2015. “Don’t get pregnant now,” he
 15 said. “This is the soberest advice that can be given.” Although the Ministry of Health
 16 denied that this recommendation represented official policy, the same advice was
 17 conveyed publicly by many policy-makers, including the then-Minister of Health
 18 Marcelo Castro, who on 18 November declared to the newspaper *Folha de S. Paulo*:
 19 "Sex is for amateurs, pregnancy for professionals. Anyone who is going to get pregnant
 20 needs to take the necessary precautions. No one should get pregnant by chance, she must
 21 have a plan for a responsible maternity". The *Frente Parlamentar da Saúde*, an
 22 influential group of deputies in the National Congress, issued a similar advice: “Whoever
 23 is planning to have a baby now, should postpone that plan, should let some time pass and

1 give us an opportunity – give the government an opportunity – to defeat this very
 2 serious epidemic, primarily by eliminating the vector.” Similar recommendations were
 3 made by countless clinicians and medical experts. “Whoever is planning a pregnancy and
 4 can wait a month or two until we discover the cause of this outbreak would be acting
 5 prudently,” a neuropsychiatrician from Recife noted in the national *O Globo* newspaper.

6 The recommendation to delay or avoid pregnancy placed the onus of
 7 responsibility for prevention squarely on individual women, yet did not provide any
 8 clarity as to the nature of the risk of ZIKV infection, nor was it associated with any policy
 9 to increase contraceptive options (Borges *et al* 2018; see also Sanabria 2010). The advice
 10 also laid bare the socio-economic disparities that structured the distribution of risks and
 11 healthcare provision. Not only were the majority of cases of microcephaly reported in
 12 some of the poorest states in the country, but within the same state or even the same city
 13 the risk of ZIKV infection and subsequent congenital abnormalities was strongly
 14 associated with the quality of living conditions, as a result of the differential level of
 15 exposure to mosquitoes. A study of the distribution of microcephaly cases in Recife
 16 showed a much higher prevalence rate in the poorest sections of the city (de Souza *et al*
 17 2018). Tellingly, cases from the wealthier district tended to be reported during the early
 18 weeks of the crisis, suggesting that women of higher socio-economic status had easier
 19 access to contraception and/or abortion, which is illegal in Brazil except when there is a
 20 direct risk to the mother’s life or in cases of rape (Löwy 2018). In fact, the private
 21 healthcare sector – which serves a quarter of the population but mobilizes almost half of
 22 healthcare expenditure – was mostly absent from the early history of the crisis. Upper-
 23 and middle-class women escaped the state’s epidemiological gaze and were better able to

1 assert sexual and reproductive rights in the face of the epidemic (Diniz 2016; Castro et al
2 2018).

3 Finally, the longer-term clinical implications of the disease remained – and remain
4 – uncertain. Brazilian scientists soon noted that microcephaly was only “the tip of the
5 iceberg,” and that less apparent neurological malformations were common among
6 newborns exposed to the virus *in utero* (Oliveira Melo et al 2016). This led to
7 increasingly broader definitions of the disease, such as “congenital Zika syndrome” or
8 “syndrome associated with congenital infection with Zika” (Brito 2016). Extensive
9 investigations of several hundred infants suggested that a significant number of those
10 born *without* microcephaly did suffer significant developmental abnormalities (França, G.
11 V. et al 2016). A new term, “postnatal microcephaly,” was introduced into the lexicon of
12 Zika-related symptoms to describe children born with normal heads who went on to
13 experience brain growth failure. As a 2018 review of the field suggested, “[d]espite the
14 intense scientific investigation of congenital microcephaly, we are only beginning to
15 understand the greater spectrum of ZIKV-associated injury and neurodevelopmental
16 outcomes for non-microcephalic fetuses” (Waldorf et al 2018). As the infants born in
17 late 2015 and early 2016 continue to grow, the range of abnormalities associated with
18 congenital ZIKV syndrome (musculoskeletal malformations, seizures, dysphagia, hearing
19 and vision impairments) has continued to expand, and the protocols for the care,
20 stimulation and rehabilitation of children have continued to evolve as the true extent of
21 the malady reveals itself. (Kuper et al 2018).

22 Clinical uncertainty, in sum, registers the unknowns that hamper the
23 implementation of robust standards of supportive care for individuals exposed to ZIKV

infection, specifically pregnant women and their children. The recognition of a causal association between congenital ZIKV infection and microcephaly did not in and of itself expand the range of therapeutic or support options for affected individuals and families. Similarly, the end of the ESPIN in May 2017 was not associated with any clarification of the standard of care or any strengthening of healthcare provision. Clinical protocols remain fluid to this day, as the spectrum of neurological and developmental abnormalities linked to congenital ZIKV syndrome continues to expand, and the care of affected individuals becomes the concern of an expanding set of institutions, including educational ones, thus implicating ever more sectors of Brazilian society (Sá et al 2019). The implementation of these protocols, moreover, has been fragmentary and inconsistent, often contingent on and socio-economic status or regional origin (Albuquerque et al 2019). At the clinical interface of the emergency, then, epistemic deficits have been thoroughly mediated by inequalities and inequities in the distribution of access to information and care.

5 Discussion: diverging uncertainties and the selective impact of ‘emergency research’

An epidemic is almost by definition defined by a sense of epistemic deficiency. As Charles Rosenberg suggested in relation to the HIV/AIDS crisis, “fear and anxiety create an imperative need for understanding,” and the explanatory efforts triggered by epidemics “necessarily reflect a particular generation’s cultural and intellectual assumptions, its repertoire of available tools” (Rosenberg 1992: 294).

1 The Zika crisis threw this dynamic into sharp relief. Perplexity and dread
2 dominated the initial response: a largely unknown virus, transmitted by a species of
3 mosquito endemic across Brazil and neighboring countries, had emerged unexpectedly,
4 and appeared capable of causing severe fetal malformations. This original shock, we have
5 argued, encompassed different kinds and modalities of uncertainty.

6 Global health uncertainty pertained primarily to the scientific question of
7 *causality*, whereas public health uncertainty revolved around *risk distribution*, and
8 clinical uncertainty concerned primarily the availability and adequacy of *supportive care*.
9 During the initial weeks and months of the Zika crisis in Brazil, it was easy to fuse and
10 conflate these very different forms of unknowing; they were simply different dimensions
11 of an unexpected and poorly understood situation.

12 Yet, as the crisis unfolded, each modality of uncertainty began to follow a distinct
13 path. Global health uncertainty, as articulated by the WHO's PHEIC, was officially over
14 by November 2016. The EC justified the end of the emergency on the basis that "research
15 [had] demonstrated the link between Zika virus infection and microcephaly" (WHO
16 2016e). Implicit in this reasoning was the claim that the achievement of a scientific
17 consensus on the causal nature of the link between ZIKV infection and microcephaly was
18 in itself sufficient to transform the status of the Zika crisis from "emergency" to
19 "significant enduring public health challenge" (WHO 2016e). The resolution of global
20 health uncertainty, it turns out, did not require the completion of large prospective case-
21 control studies; it was accomplished by piecing together data from a small number of
22 index cases and laboratory studies, along with retrospective studies of past outbreaks and
23 preliminary reports from cohort studies.

Public health uncertainty, in contrast, persisted and continued to constrain state action over a much longer period of time – at the very least, until the large prospective case-control studies launched during the heyday of the emergency delivered their final results, towards the end of 2017. These studies were able to exclude other potential factors in the association between microcephaly and congenital ZIKV infection, and provided a more definitive, if not particularly reassuring, analysis of risk distribution. Despite these advances in scientific knowledge, however, the slow development and fragmentary roll-out of point-of-care Zika diagnostics meant that the epidemiological picture of ZIKV infection and its clinical implications has remained uncertain. The reasons for the exceptional cluster of microcephaly and congenital Zika syndrome observed in Brazil in 2015 and early 2016 are still a mystery, and the current distribution of infection and clinical symptoms across the country is largely unknown. Local data sets from this period continue to be mined to advance alternative interpretations of the “true” epidemiological picture of the crisis (Brady et al 2019).

Finally, clinical uncertainty has proven even more intractable. In fact, it has increased over time, as the range of abnormalities associated with ZIKV infection expands and they affect more and more aspects of the lives of those who were exposed to the virus *in utero*. The Zika epidemic unfolded during a period of economic downturn and reductions in government spending on federal, state and municipal-level public services. The emergency threw into sharp relief structural shortcomings in Brazil’s justly celebrated universal health system, the *Sistema Único de Saúde*, and drew attention to regional and socio-economic disparities in healthcare provision.

As these differential trajectories suggest, each form of uncertainty has benefited to different degrees from the “emergency research” efforts that the WHO and other international organizations marshaled during the peak of the crisis. The decision by the WHO to describe the Zika crisis as a global emergency helped catalyze multiple funding commitments and re-directed resources to Zika research. According to Bruce Aylward, Executive Director of WHO’s Outbreak and Health Emergencies Cluster at the time, the PHEIC “sparked an explosion of scientific work which is filling the gaps in our understanding of the virus and on possible ways of preventing its devastating effects” (quoted in Maurice 2016). The WHO extended to Zika diagnostics the Emergency Use Assessment and Listing Procedure established during the West African Ebola outbreak, and other global medicines regulators followed suit with emergency use and expedited review provisions for Zika diagnostics and therapeutics in an effort to encourage investment by private developers.

Yet this surge of scientific work did not address the three forms of uncertainty equally. The influx of international research funding allowed a rapid accumulation of data on viral genetics, molecular biology, historical circulation of the virus, and physiological effects of infection, especially in laboratory models (Faria et al 2016; Cugola et al. 2016; Ming & Song 2016). In Brazil, where research budgets were under pressure, international partnerships supported by foreign funders contributed to a rapid expansion of scientific work on the virus, its mosquito vector, and inborn malformations, and resulted in the creation or extension of multiple national and transnational collaborative networks (Glopid-R 2016; c.f. Martinez-Pulgarin 2016). At a time of political crisis and economic downturn, Brazilian scientists, including young researchers,

1 many of them based in the northeastern institutions, were able to gain international
2 visibility through participation in research collaborations, policy-shaping events, and
3 publication in prestigious scientific journals.

4 Despite this inflow of resources, however, key funding gaps remained
5 unaddressed throughout the critical period. International health organizations received
6 only a fraction of the funds they requested (WHO 2016d), and a majority of the ad hoc
7 funding mobilized by European and North-American agencies went to researchers based
8 in high-income countries (Goodridge et al. 2017). Many of these resources were directed
9 at the questions at the heart of global health uncertainty, the nature of the link between
10 congenital infection and microcephaly, while other aspects of the Zika crisis, such as
11 sexual transmission of the virus or the long-term clinical implications of congenital
12 infection, were relatively neglected. Furthermore, with the lifting of the PHEIC in
13 November 2016 resources were quickly diverted to other purposes. Diagnostic and
14 vaccine development efforts slowed down and in some cases were terminated, while the
15 reduction in the number of cases of symptomatic ZIKV infection and microcephaly has
16 limited the ability to conduct efficacy trials for new therapeutics. Despite the WHO's
17 repeated claim that Zika represents "a highly significant long-term problem," it is evident
18 that financial and scientific resources have been re-directed elsewhere. In Brazil, the
19 erosion of research and clinical capacity has continued apace.

20 There is, in other words, a conceptual and institutional affinity between
21 "emergency research," as currently defined by international organizations and funding
22 agencies, and global health uncertainty, at the expense of other modalities of unknowing.
23 By focusing on the issue of causality, and by more generally defining uncertainty as a

1 matter of scientific consensus on fundamental aetiological questions, global health
 2 institutions defined the problem in a manner they were confident they would be able to
 3 solve: as a “gap” in the existing scientific knowledge base, a clearly identifiable
 4 unknown, or *not-yet-known*, that incumbent institutions of knowledge production could
 5 tackle with a rapid surge in research funding. In the summer of 2016, six months into the
 6 PHEIC, Bruce Aylward was able to highlight the success of this strategy as far as the
 7 establishment of new scientific facts was concerned. “What impresses me most,” he
 8 noted, “is the short time it took for scientists to reach a consensus that Zika is the culprit”
 9 (quoted in Maurice 2016).

10 The relevance of “emergency research” for public health or clinical uncertainty is
 11 less apparent or immediate, however, partly because these forms of unknowing revolve
 12 less around questions of scientific knowledge and pertain instead to matters of technical
 13 and institutional capacity that the framework of emergency response is ill-equipped to
 14 tackle (Lakoff 2017; Kelly 2018). Public health uncertainty and clinical uncertainty speak
 15 to forms of structural ignorance, entrenched modes of unknowing, rather than the sort of
 16 “knowledge gap” that a rapid mobilization of scientific resources can quickly fill.

17 In sum, the example of the Zika crisis in Brazil reminds us once again that the
 18 revelatory power of medical crises is concentrated on specific dimensions of the problem
 19 at the expense of others. Critical aspects of the epidemic, from the role of sexual
 20 transmission, women’s sexual and reproductive rights, or the socio-economic inequalities
 21 that structured exposure to risk and access to care, remained largely external to the
 22 scientific agenda that emerged at the end of 2015. Some epistemic deficits were quickly
 23 and effectively addressed, while others were allowed to persist and become entrenched. A

more careful delineation of the multiple forms of uncertainty that define moments of medical emergency, and greater attention to how institutions prioritize some of those unknowns over others, are essential to formulating global strategies that are both responsive to the urgency of the moment and capable of strengthening the institutional capabilities that ensure long-term effectiveness.

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