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The microcephaly epidemic and Zika virus: building knowledge in epidemiology

Epidemia de microcefalia e vírus Zika: a construção do conhecimento em epidemiologia

Epidemia de microcefalia y virus Zika: la construcción del conocimiento en epidemiología

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Abstract

In August 2015, pediatric neurologists at public hospitals in Recife, Pernambuco State, Brazil, observed an increase in the number of disproportional microcephaly cases associated with other congenital anomalies. The fact caused social commotion and mobilization of the academic community and led the Brazilian Ministry of Health to declare a national public health emergency, followed by the declaration of a Public Health Emergency of International Concern by the World Health Organization. The hypothesis for the phenomenon was congenital Zika virus (ZIKV) infection, based on spatial-temporal correlation and the clinical-epidemiological characteristics of the two epidemics. Further evidence accumulated, and within the scope of epidemiologial reasoning fulfilled criteria that gave support to the hypothesis. The plausibility of the hypothesis is based on the neurotropism of ZIKV, demonstrated in animals, affecting neural progenitors in the developing brain, and in humans, due to neurological complications in adults following infection. Isolation of viral RNA and antigens in the amniotic fluid of infected mothers and in brains of newborns and fetuses with microcephaly further demonstrated the consistency of the hypothesis. The criterion of temporality was met by identifying adverse pregnancy outcomes in a cohort of mothers with a history of rash and positive ZIKV serology. Finally, the first case-control study demonstrated a strong association between microcephaly and congenital ZIKV infection. The knowledge built with the epidemiological paradigm was supported by the scientific community, thereby establishing the consensus for a causal relationship between ZIKV and the microcephaly epidemic.

Zika Virus; Microcephaly; Epidemics

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Living the microcephaly epidemic

It is definitely a challenge for an essay to record all the historical milestones in the development of epidemiological knowledge in the new congenital microcephaly epidemic. The cluster of microcephaly cases detected initially in Northeast Brazil sparked intense social commotion in a short space of time. In our view, society's mobilization reflected the gravity of these events linked to women's reproductive health and to the infants' neurological, cognitive, and motor development, lack of knowledge on the cause and risk factors, and the epidemic's potential for national and international spread. Misinformation circulating in real time and the intense national and international news coverage reflected the panic during epidemics in an age of intense interconnectivity. Photographs of infants with congenital malformations and their young mothers circulated worldwide, moving the global community to action.

The gravity of this public health crisis resulted in intense mobilization of the scientific community, with the declaration of a national public health emergency in Brazil [1], followed by a declaration by the World Health Organization (WHO) of a Public Health Emergency of International Concern (PHEIC) [2]. The current essay reviews the first scientific discoveries that allowed characterizing the congenital Zika syndrome and the related developments in epidemiological studies. We tell this story with no pretense of the detachment of scientific articles, but as researchers working at the epicenter of the epidemic.

Which microcephaly?

It the field of health, new disease entities are frequently perceived by clinical observation. That was what happened in August 2015 when two pediatric neurologists from public hospitals in Recife, Pernambuco State, Brazil, detected an increase in the number of cases of neonates with microcephaly of unknown cause, some of which with other congenital malformations [3,4]. Data in the Brazilian Information System on Live Births (SINASC) confirmed the keen observation by these pediatric neurologists in Pernambuco, that there was indeed an increase in case reports of microcephaly [3].

In October that same year, an active search by neonatologists and clinicians in specialized maternity hospitals for high-risk pregnancy investigated and described 29 cases of infants with microcephaly admitted to these units [5,6,7], leading the Pernambuco State Health Department (SES-PE) to report this unusual outbreak to the Brazilian Ministry of Health [3]. Teams from the SES-PE and staff from the Training Program in Applied Epidemiology for Services of the Brazilian Unified National Health System (EPISUS) launched a preliminary epidemiological investigation of the cases.

Congenital microcephaly is defined as small head circumference present at birth [8]. In most cases this clinical finding is associated with involvement of the central nervous system (CNS) and cognitive disorders. However, congenital microcephaly does not necessarily indicate abnormal brain development, and some neonates with microcephaly are otherwise normal [9]. Head circumference (HC) is a screening tool for the detection of microcephaly, independently of cause. One accepted definition for microcephaly is an occipitofrontal circumference (OFC) one standard deviation (SD) below the mean for sex and gestational age [9,10,11]. HC below the normal growth curves suggests the existence of a small brain, and neuroimaging and laboratory tests assist the investigation of congenital anomalies [3,10]. Congenital microcephaly can result in abnormal brain growth during intrauterine life, associated with genetic syndromes or hypoxic injuries, metabolic disorders, and exposure to pesticides and infections that can interfere in normal brain development. The main congenital infections that can cause microcephaly are those traditionally known as TORCH: toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and syphilis [9,10].

An epidemic is defined as the occurrence of cases of a disease, specific behaviors, or other health-related events that are clearly above normally expected levels for a given community or region [12]. The evidence in this case pointed to an unusual and strange microcephaly epidemic in Pernambuco, with a nearly fivefold increase in reports in the SINASC database in just three months (August to October 2015). In November 2015, when the increase in the number of cases was detected in other states of Northeast Brazil, the Ministry of Health assumed the existence of an epidemic of this

congenital malformation and declared a national public health emergency [13] after a meeting in Brasília with representatives from Pan-American Health Organization (PAHO) and researchers with various health backgrounds, exemplifying interaction between the Brazilian Ministry of Health and the academic community.

Despite the alarming increase in cases of this congenital malformation and the public health emergency declared by the Ministry of Health, there was no consensus in the scientific community concerning the existence of an epidemic. An example of this skepticism over the event's definition was an interview by Brazilian researchers from the Latin American Collaborative Study on Congenital Malformations (ECLAMC), published in *Nature* in its "on-line first" edition on January 28, 2016. The experts contended that "*a rise in reported cases of microcephaly might largely be attributable to the intense search for cases of the birth defect and to misdiagnoses*" [14] (p. 13). A few days later, on February 1st, WHO Director-General Dr. Margaret Chan declared that "*the recent cluster of microcephaly cases and other neurological disorders* (...) *constitutes a Public Health Emergency of International Concern*" [2]. The situation posed a public health threat to other countries of the world, and due to the severity and lack of knowledge of the etiology, it required a coordinated and immediate response [15].

What, how, and where?

At the epicenter of the events, there was much speculation and rumor in society and academia, with still unanswered questions. Researchers faced an unusual scenario, both a social tragedy and an enormous scientific challenge. As an operational development, the Health Surveillance Division of the Brazilian Ministry of Health, PAHO, and the SES-PE invited some researchers to lead a research agenda focused on elucidating the epidemic. An interinstitutional agreement was thus signed between the Oswaldo Cruz Foundation in Pernambuco (Fiocruz-PE), Federal University of Pernambuco (UFPE), University of Pernambuco (UPE), SES-PE, and Professor Fernando Figueira Institute of Integral Medicine (IMIP). An international partnership was also established with the London School of Hygiene and Tropical Medicine (LSHTM; London, United Kingdom) and the University of Pittsburgh (Pittsburgh, United States). The agreement aimed to lay the groundwork for interinstitutional research cooperation to conduct epidemiological projects and studies. This group of researchers and health professionals called itself the Microcephaly Epidemic Research Group (MERG) (http://www.cpqam.fiocruz.br/merg/). The leadership by Fiocruz-PE, realizing the severity of the public health problem, opened the doors to MERG and to partnership in the day-to-day development of the clinical and epidemiological studies.

Epidemiology is the science that studies the distribution and determinants of health events and diseases in human populations [16]. Two premises are central to epidemiological theory and method: disease distribution is not random, and the determinant factors and processes can be identified by systematic investigation of population groups in given space and time [17]. For infectious diseases, it is also crucial to know the transmission mechanism(s) (direct, sexual, vector-borne, etc.), reservoirs, and complex network of contacts in the population. Such knowledge allows estimating the transmission rate and the potential for spread of the infection in different human populations, as well as developing strategies for prevention and control [18].

The study of distribution of diseases after a clear case definition addresses questions such as "where" and "when" the disease is occurring and "who" is being affected within a whole population or population subgroups. Epidemiology begins with the description of disease cases (or conditions), and the first question is whether they share certain characteristic(s). The next question is intuitive: why? Analytical studies are developed to test hypotheses and explain disease patterns in these populations [16,18]. Epidemiology is based on three lines: clinical and biological knowledge; a methodological base from statistics; and a social and demographic substrate. Based on such knowledge, the observations and queries become scientific questions. In the case of the epidemic of microcephaly appearing at birth, there were numerous unanswered questions.

Epidemiological surveillance required defining a "case" of microcephaly, and this definition initially aimed to identify the largest number of suspected neonatal cases for further investigation, prioritizing the criterion's sensitivity and based on HC. It was important at the time to identify all cases, and

this strategy allowed the investigation of children that strictly speaking would not be classified with microcephaly, with some presenting altered cerebral computed tomography results. This contributed to the realization that there was a broader spectrum of manifestations beyond just microcephaly.

In March 2016, the Ministry of Health aligned itself with WHO recommendations, adopting (for term infants) the HC cutoff values of 31.5cm for girls and 31.9cm for boys. Finally, in August 2016, WHO recommended the use of InterGrowth curve standards for both sexes [19], meaning HC cutoff values of 30.24cm for term girls and 30.54cm for term boys. The main justification for adopting these HC cutoff values was to prioritize specificity in the case definition for microcephaly, with a reduction in false-positive cases [11].

The first published case series described neonates with a rare phenotype involving microcephaly and other congenital anomalies. Microcephaly was characterized by craniofacial disproportion, sometimes accompanied by *cutis gyrata* (excessive scalp folds). At birth, the archaic reflexes (palmar and plantar grasp reflexes and sucking reflex, among others) were present and the infants generally fed normally, although in some cases they developed dysphagia. Neurological examination revealed hypertonia or spasticity, hyper-reflexivity, irritability, tremors, and seizures [20,21]. Some neonates presented macular atrophy on ophthalmological examination [22] and hearing disorders [20]. Imaging tests showed abnormalities of the central nervous system and presence of intracranial calcifications indicative of intrauterine infection [23].

Other alterations were soon reported, as part of the syndrome with characteristics of congenital infection, such as clubfoot (*talipes equinovarus*) and arthrogryposis, the latter defined as congenital joint contractures resulting from neurological abnormalities [24].

What was happening on the front?

In the face of such an unexpected phenomenon as the microcephaly epidemic, it was natural for controversies to appear concerning potential risk factors for the malformation. Vaccines during pregnancy [25,26]? Larvicide used in drinking water for vector control [27,28]? An arbovirus was emerging in the global public health scenario: the Zika virus (ZIKV).

In Brazil, in late 2014 and early 2015, epidemiological surveillance in the states of Northeast Brazil reported an outbreak of an exanthematous disease with clinical characteristics of early-onset rash, afebrile or with low fever, accompanied by arthralgia, joint edema, and conjunctivitis. Due to the presence of arthralgia, infection with chikungunya virus (CHIKV) was initially investigated but ruled out by serological tests and polymerase chain reaction (PCR). Case observation did not suggest classical exanthematous diseases or dengue, which led an infectious disease specialist from the University of Rio Grande do Norte to consider ZIKV infection [5,29]. The presence of ZIKV in Northeast Brazil was confirmed in April 2015 by PCR performed in samples from suspected cases in Bahia and Rio Grande do Norte [30,31].

One question was whether the virus had been introduced into Brazil during the 2014 FIFA World Cup, although no endemic country for ZIKV had competed in the event. Another hypothesis was that ZIKV had been introduced into Brazil during a world canoeing championship in Rio de Janeiro, when teams from the Pacific region competed (French Polynesia, New Caledonia, Cook Islands, and Easter Island) [32,33]. A third hypothesis, more plausible (because it was based on a ZIKV genomic study), showed by phylogenetic and molecular analysis that the virus had entered the country a single time, between May and December 2013. The estimated date coincided with the Confederations Cup and an increase in airline passengers from French Polynesia, during the peak of the ZIKV epidemic there. The team from Tahiti (French Polynesia) had played in the Pernambuco Arena in June 2013. This would also explain the larger size of the epidemic in that particular state [34]. The viral phylogenetic study shows that the origin of the Brazilian strain was Asian, sharing a common ancestor circulating in French Polynesia [33]. Despite published studies, the topic still sparks controversies among some specialists in the area.

ZIKV is a flavivirus of the Flaviviridae family, transmitted mainly by the *Aedes aegypti* and *Aedes albopictus* mosquitos and isolated for the first time in 1947 in the Zika Forest of Uganda [35]. Following the first human infection confirmed in Uganda between 1962 and 1963 [36], sporadic cases were

reported elsewhere in Africa and in Asia, and ZIKV spread silently for decades, with few reports of human infection for 60 years [35]. Thus, the impression that ZIKV infection only causes a mild febrile disease persisted for several decades [37], until the first documented outbreak occurred in Micronesia, on the Yap islands, in 2007 [38], appearing later from March 2013 to September 2014 in French Polynesia [39]. During the latter epidemic, cases of Guillain-Barré syndrome were reported, with an incidence approximately 20 times higher than expected [40,41].

The same phenomenon was observed in Pernambuco. Following the disease outbreak, emergency services and neurology departments detected an increase in cases of acute neurological syndromes in adults. Seven patients with neurological syndromes tested positive for ZIKV by RT-PCR, six in serum and one in cerebrospinal fluid (CSF), with tests performed by the virology laboratory (LAVITE) of the Fiocruz-PE. Of these patients, four were diagnosed with Guillain-Barré syndrome, two with acute disseminated encephalomyelitis, and one with meningoencephalitis [2,42,43]. Months later, the first microcephaly cases emerged. The causal hypothesis was based on this spatial-temporal correlation between the microcephaly epidemic and ZIKV outbreaks months earlier, besides clinical and epidemiological characteristics of the epidemic. The existence of numerous cases in a short period, occurring simultaneously in several cities, indicated a disease with a high attack rate and rapid spread, suggesting the possibility of mosquitos that were responsible for the transmission and spread of dengue virus, another flavivirus in urban areas. The main diseases known to be associated with microcephaly and among the specialists' initial hypotheses (toxoplasmosis, rubella, and cytomegalovirus) are not associated with large outbreaks, due to their mode of transmission. This evidence served as the basis for a clinician with a public health background to propose the hypothesis of an association between ZIKV and microcephaly. The history of this process was recorded in an article by Brito [5].

The association between congenital ZIKV infection and microcephaly was an apparently surprising hypothesis, since there were few previous records of malformations associated with congenital flavivirus infection [44]. Microcephaly cases associated with the ZIKV epidemic on the Pacific islands were only investigated and reported retrospectively [45]. Thus, the existence of a spatial-temporal association between the ZIKV epidemic and fetal malformations was identified and quickly acknowledged in Brazil [5,46].

The same factors that pushed the spread of the virus in the dengue pandemic are probably also responsible for the emergence and spread of the ZIKV [35]. Global urbanization and poorly planned urban growth in low- and medium-income countries have left urban areas prone to the proliferation of vector-borne diseases [47].

Clinical characteristics were also important for consolidating the hypothesis. The initial investigation of microcephaly cases in a specialized maternity hospital for high-risk pregnancy in Pernambuco showed that 70% of the pregnant women reported an infectious condition involving rash, with a similar pattern to the clinical symptoms of Zika: predominant rash, little or no fever, conjunctivitis, and swollen joints [5,48,49]. Another clinical characteristic that supported the researchers' ZIKV hypothesis was the existence of reports of an association between the virus and neurological syndromes in adults [40], confirmed just months before in Pernambuco [50].

ZIKV was found in the amniotic fluid of pregnant women, with fetuses with microcephaly detected in utero [51] and in brain tissue and placentas from neonates and stillborn infants [52]. The first 42 microcephaly cases investigated in Pernambuco tested positive for anti-ZIKV IgM in 90.5% of cases in serum and 100% in CSF, confirming congenital and neurological ZIKV infection in neonates, since maternal IgM does not cross the placenta or the blood-brain barrier [7,53]. Studies by Brasil et al. [54] and Mlakar et al. [55] further demonstrated the ZIKV infection in pregnant women preceded the finding of microcephaly and other brain abnormalities in fetuses and neonates. A retrospective investigation in French Polynesia identified an increase in cases of severe congenital malformations, including microcephaly, following the ZIKV outbreak in 2013 and 2014 [45].

Evidence thus pointed to a probable causal association between congenital ZIKV infection and the microcephaly epidemic, although epidemiological studies with more adequate designs were needed to establish causal inference [56]. Without analytical studies including control groups, to interpret the observed association between ZIKV infection and microcephaly as causal would be to infer an association at the individual level, based on observation at the aggregate level of a spatial-temporal correlation, that is, an "ecological fallacy" [16,57].

Meanwhile, even after the Brazilian Ministry of Health assumed the relationship between the ZIKV and the microcephaly epidemic in the Northeast [13] and the WHO declared that microcephaly cases and other neurological alterations possibly associated with ZIKV infection constituted a PHEIC [2,15], some Brazilian and international researchers still questioned this daring hypothesis, although not considering it "entirely irrational" [58].

Specialists questioned why the explosions of cases had not occurred in other areas of Brazil that year or in subsequent years, suggesting that something other than the ZIKV was causing these differences, possibly explained by other environmental, socioeconomic, or biological factors [59,60,61,62].

Pernambuco was considered the epicenter of the epidemic, with many more cases than other states of Northeast Brazil affected by the outbreak during the same period. As shown in Table 1, Pernambuco recorded a total of 399 confirmed cases from epidemiological week 45/2015 to epidemiological week 52/2016, far more than the other states except for Bahia. Prevalence rates in Sergipe (31.5/10,000 live births) and Paraíba (27.3/10,000 live births) were also higher than in Pernambuco (23.8/10,000 live births) [63].

During the period analyzed, this variation in microcephaly prevalence between states of the Northeast was small and sometimes statistically insignificant. This can be explained by the geographic proximity of the cities of Northeast Brazil, with intense population mobility, and the possible random fluctuation that occurs when calculating rates for rare events.

However, the interpretation of these reporting data should consider possible differences in the application of the case definition and operational diversity in the laboratory confirmation of cases, recalling that this surveillance system was built and implemented during the first outbreak of microcephaly and subject to both underreporting and overreporting. The recently created information system for monitoring congenital Zika syndrome was still necessarily the object of assessment and improvement, like any system for a new disease.

We propose that the rapid response by the SES-PE in alerting neurologists and the declaration of a public health emergency by the Brazilian Ministry of Health and later by the WHO served as a watershed for mobilization of the scientific community and coordination of the Brazilian and global public health responses. Researchers and health professionals and administrators drafted clinical protocols for pregnant women and infants and developed operational studies and field assessment instruments. The event's magnitude and the potential for expansion broke through institutional barriers, creating the space for data- and knowledge-sharing in real time. The first case-control study to

Table 1

Mean annual prevalence of Zika virus-associated microcephaly in the States of Northeast Brazil, 2015-2016.

Federation Units	Live births *	Confirmed cases **	Mean annual prevalence (per 10,000 live births)
Maranhão	117,564	157	11.6
Piauí	49,253	99	17.4
Ceará	132,516	109	7.1
Rio Grande do Norte	49,099	126	22.2
Paraíba	59,089	186	27.3
Pernambuco	145,024	399	23.8
Alagoas	52,257	86	14.3
Sergipe	34,917	127	31.5
Bahia	206,655	420	17.6
Total	846,374	1,709	17.5

* Live births in 2015 according to mother's Federation Unit of residence (Information System on Live Births. Brazilian Health Informatics Department; http://www.datasus.gov.br).

** Microcephaly cases related to Zika virus infection in the 60-week period from epidemiological week 45/2015 to epidemiological week 52/2016 [63].

explore the possible causes and factors associated with the congenital malformations was financed during this public health emergency and in the midst of a heated economic and political crisis in Brazil (the impeachment of President Dilma Rousseff) [64,65].

Testing the hypothesis

One way that scientific thinking explains the origin of a phenomenon is by identifying its cause. Although social epidemiology has drawn on philosophy to incorporate broader definitions of "cause", such as structural cause and ultimate cause [66], classical epidemiological method usually deals with the concept of efficient or direct cause. That is, the study of causality in epidemiology is based on the search for the "specific" cause of the disease. This approach found legitimacy through the identification of etiological agents of infectious diseases. Beginning in the latter half of the 20th century, with the decline of infectious diseases and the increase in cardiovascular diseases and cancer, the study of causality in epidemiology shifted to probabilistic risk quantification. This model became more adequate for these diseases and conditions which lack a "single cause" and allowed "solving problems" based on a given theory [67].

Testing a causal hypothesis involves analyzing the statistical association between a particular exposure and a disease or event. The estimated measure of effect, the risk, is a probabilistic measure that attempts to determine whether the probability of developing a given disease or event in the presence of an exposure is different from the corresponding probability in its absence [16]. In other words, "association" refers to the statistical dependence between two variables, that is, the extent to which a disease or event rate in persons with a specific type of exposure is greater or lesser than the disease rate in those without the exposure. However, the presence of statistical association does not guarantee the existence of a cause-and-effect relationship. Causal judgment is not "direct" and involves a logical chain that involves issues of the association's validity and the elaboration of a theoretical framework to support it. The association's validity is verified when the role of chance is minimized by testing statistical significance, when the presence of biases is avoided or minimized by planning an adequate methodological design, and when potential confounding factors or alternative explanations are controlled [19]. Hence, risk is a measure of statistical association, insufficient for directly inferring causality. Bradford Hill, in 1965, defined the criteria, adapted from the causal canons of John Stuart Mill, to assess the causal nature (or lack thereof) of an observed epidemiological association.

In the case of the association between ZIKV infection and microcephaly, authors performed this exercise of verifying Hill's criteria, at a stage of in the knowledge when few of the criteria for causality could be considered met [2,56]. However, the results of studies soon added knowledge in this direction.

As for biological plausibility, the existence of a plausible explanation for the hypothesis of association is anchored in the neurotropism of ZIKV, already demonstrated in animals at the time of its identification [68,69], which also came to be suspected in humans, as verified in observations of the association between ZIKV infection and neurological complications [70]. Viral RNA and antigens were also isolated in the amniotic fluid of infected mothers and in the brains of neonates and fetuses with microcephaly, demonstrating that congenital ZIKV infection reaches the placenta and crosses the fetal blood-brain barrier [51,52,55]. The association's consistency, represented by the repetition of findings in different population groups, was backed by the report of a case of congenital microcephaly and ZIKV infection in a pregnant woman who had visited an epidemic area [55] and microcephaly case series in newborns with reports of the pregnant woman's probable infection with ZIKV [23,44]. The criterion of temporality, i.e., that cause precedes the effect or event, was demonstrated in a cohort of 182 pregnant women with history of rash and positive serology for ZIKV, of whom 58 (46%) presented unfavorable pregnancy outcomes including abortions, stillbirths, and imaging abnormalities in liveborn infants [54]. As for the criterion of analogy, a resource used in scientific thinking, among flaviviruses, the Japanese encephalitis virus caused congenital infection associated with teratogenic effects during epidemics in Uttar Pradesh, India, signaling introduction of the virus in an immunologically susceptible population [44]. Animals experiments have also backed the causal hypothesis in recent studies. ZIKV appears to mainly affect neural progenitors in the developing brain [71], and in primates, maternal infection with prolonged viremia causes fetal malformations [72,73].

Finally, the first analytical epidemiological study, a case-control study designed to test the hypothesis of association between congenital ZIKV infection and microcephaly, was conducted in Pernambuco by the MERG, with the support of the Brazilian Ministry of Health and PAHO [64]. The preliminary results of the case-control study with prospective recruitment of infants at birth showed a strong association between microcephaly and congenital ZIKV infection (OR = 55.5; 95%CI: 8.6-∞). This initial academic announcement aimed to fill the knowledge gap at the time. The study recommended that the new congenital Zika syndrome be included in the TORCH group, a group of mother-to-child infections transmitted during pregnancy [64]. The study's final results, with a sample of 91 cases and 173 controls, confirmed the strong association (OR = 73.1; 95%CI: 13.0-∞). None of the controls (neonates without microcephaly) tested positive for ZIKV. In addition, neither vaccines nor larvicide use during pregnancy were associated with microcephaly. These findings strengthened the interpretation of the causal association between microcephaly in neonates and congenital ZIKV infection during the epidemic in Brazil. They also refute the hypotheses that household larvicide use or vaccines during pregnancy increase the risk of microcephaly [65]. A case-control study does not allow establishing the risk of ZIKV infection according to pregnancy trimester. This question has to be answered by follow-up studies, currently under way [74].

Analysis of the spatial distribution of microcephaly cases in Recife, considering the city's social inequalities, showed that the higher-income population was less affected by the microcephaly epidemic than other population groups with more precarious living conditions [75], highlighting the role of structural cause as proposed by social epidemiology in the determination of the health-disease process [66].

In a review of 1,501 neonates with microcephaly reported in Brazil, where the investigation by medical teams in their home states had been concluded as of February 2016, cases were classified in five categories based on neuroimaging results and laboratory tests for ZIKV and other relevant infections. Eight hundred and eighty-nine microcephaly cases were eliminated from the analysis due to lack of information. Of the remaining 602 cases, 76 (12.6%) presented laboratory evidence of ZIKV infection and were classified as "definitive", independently of other findings. Fifty-four cases (9%) were classified as "highly probable" because they presented brain lesions highly suggestive of congenital Zika syndrome in imaging tests and negative results for other congenital infections. Another 181 (30.1%) were considered "moderately probable", with brain lesions suggestive of congenital Zika syndrome, but in whom it was not possible to rule out other congenital infections. The fourth category, "somewhat likely", included 291 reported microcephaly cases (48.3%) in which the patient charts showed that imaging tests had been performed, but without describing the findings. Importantly, "*One in five definite or probable cases presented head circumferences in the normal range (above -2 SD below the median of the InterGrowth standard)*" [76] (p. 891). These findings highlight the difficulty in establishing confirmatory criteria for cases of this new syndrome. It is also evident that HC should not be the only screening criterion for investigation of congenital Zika syndrome.

More recent studies have shown that congenital Zika syndrome consists of a range of adverse neonatal outcomes, still not fully described, and that microcephaly is just the most evident clinical sign. A recent review of published case reports and case series identified characteristics that are probably specific to congenital Zika syndrome: phenotype of disrupted sequential brain growth (rarely described before 2015), thin cerebral cortex with subcortical calcifications, chorioretinal atrophy affecting the macula, congenital contractures, and early hypertonia with extrapyramidal symptoms [77].

From October 2015 to May 2017, 26 countries of the Americas reported confirmed cases of congenital Zika syndrome. During this period, 3,374 cases (82%) occurred in Brazil. Congenital Zika syndrome is confirmed when the liveborn neonate meets the criteria for a suspected case and ZIKV infection is proven in samples from the neonate, independently of the detection of other pathogens [78].

Much information is still lacking for a complete description of the spectrum of adverse events associated with congenital ZIKV infection. Researchers in Pernambuco are engaged in on-going investigations to answer some of these pressing questions, in partnership with Brazilian and international institutions: what is the mother-to-child transmission rate for ZIKV? What is the rate of malformations in ZIKV-infected fetuses? What are the long-term adverse effects of congenital ZIKV infection in neonates without detectable anomalies at birth? These and other questions can only be answered by epidemiology, the science devoted to analyzing and solving public health problems. A

recent publication addresses the emergence of the ZIKV, its spread, and the knowledge gaps from the Brazilian perspective [79]. We believe that research projects developed in Brazilian and international consortia and currently under way, like the *Clinical Cohort of Children with Microcephaly and Other Manifestations of Congenital Zika Syndrome in Brazil*, sponsored by the research consortium Zika Preparedness Latin America Network (ZikaPlan), and the multicenter cohort study *Zika in Infants and Pregnancy* (ZIP study) have much to contribute. These prospective study designs can produce answers to the currently unanswered questions, as mentioned above. This involves not only a robust scientific framework, but also encouragement for multicenter studies that minimize duplication of efforts, while optimizing financial resources and producing solid evidence in a short space of time, aimed at implementing public policies.

Conclusions

The knowledge produced thus far through the epidemiological risk paradigm has been backed by the scientific community, personified currently by reviewers and editors of scientific journals, constituting one of the indictors of shared values and consensus-building among researchers [80]. Making science in times of crisis means maintaining the studies' methodological rigor to guarantee the data's validity, while accelerating the traditional processes of planning, preparation, financing, and development of studies to produce immediate responses to urgent public health problems. Researchers rarely have the opportunity to participate in investigating a new disease entity and building knowledge on it, especially in the context of a national and international public health emergency. The research work done here was developed in the midst of national commotion and lively discussions and controversies on the phenomenon's etiology. ZIKV infection had still not been linked to congenital malformations. For the neurologists and other health professionals that cared for the patients, the public health experts that created surveillance systems to report and monitor the epidemic, and the epidemiologists who drafted and developed studies at "zero hour" to elucidate the etiology, it was a unique experience, writing science on a blank page.

Contributors

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Resumo

Em agosto de 2015, neuropediatras de hospitais públicos do Recife, Pernambuco, Brasil, observaram um aumento do número de casos de microcefalia desproporcional associado a anomalias cerebrais. Esse fato gerou comoção social, mobilização da comunidade acadêmica e levou o Ministério da Saúde a decretar emergência de saúde pública nacional, seguida pela declaração de emergência de saúde pública de interesse internacional da Organização Mundial da Saúde. A hipótese formulada para o fenômeno foi a infecção congênita pelo vírus Zika (ZIKV), com base na correlação espaço-temporal e nas características clínico-epidemiológicas das duas epidemias. Evidências se acumularam e no âmbito do raciocínio epidemiológico preencheram critérios que deram sustentação à hipótese. Sua plausibilidade está ancorada no neurotropismo do ZIKV demonstrado em animais, atingindo neurônios progenitores do cérebro em desenvolvimento, e em seres humanos devido às complicações neurológicas observadas em adultos após a infecção. O isolamento do RNA e antígenos virais no líquido amniótico de mães infectadas e em cérebros de neonatos e fetos com microcefalia contribuíram para demonstrar a consistência da hipótese. O critério de temporalidade foi contemplado ao se identificar desfechos desfavoráveis em uma coorte de gestantes com exantema e positivas para o ZIKV. Finalmente, o primeiro estudo caso-controle conduzido demonstrou existir uma forte associação entre microcefalia e infecção congênita pelo ZIKV. O conhecimento construído no âmbito do paradigma epidemiológico recebeu a chancela da comunidade científica, construindo o consenso de uma relação causal entre o ZIKV e a epidemia de microcefalia.

Zika Vírus; Microcefalia; Epidemias

Resumen

En agosto de 2015, neuropediatras de hospitales públicos de Recife, Pernambuco, Brasil, observaron un aumento desproporcional del número de casos de microcefalia, asociado a anomalías cerebrales. Este hecho generó conmoción social, movilización de la comunidad académica y obligó al Ministerio de Salud a decretar la emergencia de salud pública nacional, seguida de la declaración de interés internacional de la Organización Mundial de la Salud. La hipótesis formulada para este fenómeno fue la infección congénita por el virus Zika (ZIKV), en base a la correlación espacio-temporal y a las características clínico-epidemiológicas de las dos epidemias. Se acumularon evidencias, y en el ámbito del raciocinio epidemiológico se cumplieron los criterios que dieron apoyo a la hipótesis. Su plausibilidad está anclada en el neurotropismo del ZIKV, demostrado en animales, alcanzando progenitores neuronales del cerebro en desarrollo, y en seres humanos, debido a las complicaciones neurológicas observadas en adultos tras la infección. El aislamiento del ARN y antígenos virales en el líquido amniótico de madres infectadas, en cerebros de neonatos y fetos con microcefalia, contribuyeron a demostrar la consistencia de la hipótesis. El criterio de temporalidad se contempló al identificarse desenlaces desfavorables en una cohorte de gestantes con exantema y positivas en ZIKV. Finalmente, el primer estudio caso-control realizado demostró que existía una fuerte asociación entre microcefalia e infección congénita por el ZIKV. El conocimiento construido en el ámbito del paradigma epidemiológico recibió la aprobación de la comunidad científica, existiendo consenso en cuanto a la relación causal entre el ZIKV y la epidemia de microcefalia.

Virus Zika; Microcefalia; Epidemias

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