# The Zika Virus Outbreak in Brazil: Knowledge Gaps and Challenges for Risk Reduction

We analyzed uncertainties and complexities of the Zika virus outbreak in Brazil, and we discuss risk reduction for future emergencies. We present the public health situation in Brazil and concurrent determinants of the epidemic and the knowledge gaps that persist despite building evidence from research, making public health decisions difficult.

Brazil has adopted active measures, but producing desired outcomes may be uncertain because of partial or unavailable information. Reducing population group vulnerabilities and acting on environmental issues are medium- to long-term measures.

Simultaneously dealing with information gaps, uncontrolled disease spread, and vulnerabilities is a new risk scenario and must be approached decisively to face emerging biothreats. (*Am J Public Health*. 2017;107:960–965. doi:10.2105/AJPH.2017.303705)

*Claudia Garcia Serpa Osorio-de-Castro, ScD, Elaine Silva Miranda, ScD, Carlos Machado de Freitas, ScD, Kenneth Rochel de Camargo Jr, ScD, and Hilarie Hartel Cranmer, MD, MPH*

**See also Rodrigues, p. 831.**

In November 2015, the Brazilian Ministry of Health declared the Zika virus (ZIKV) outbreak a national public health emergency.[1] The World Health Organization (WHO) established ZIKV as a public health emergency of international concern in February 2016. As of August 2016, there were 68 countries and territories reporting mosquito-borne transmission, with a very significant increase after 2015.[2]

Initially endemic in Africa and Asia, there were few records describing the clinical consequences of ZIKV infection. Over the years, cases were confirmed in Indonesia, Micronesia, and Polynesia where, in 2006, an outbreak was recorded. From Polynesia, ZIKV made its way to the Pacific coast of South and Central America. Several countries in the Americas have now registered cases. The virus has spread rapidly, and causal links to neurological abnormalities and Guillain–Barré syndrome, as well as birth defects such as microcephaly, have been established.[3–6]

We analyzed the uncertainties and complexities of the ZIKV infection outbreak in Brazil, and we have discussed risk reduction for emerging biothreats, thus contributing to awareness of the current situation and prevention of future crises.

## UNCERTAINTIES IN BRAZIL'S ZIKA VIRUS EMERGENCY

Zika is an arbovirus (genus *Flavivirus*) of the same family as dengue and yellow fever (*Flaviviridae*). Chikungunya is an *Alphavirus* of the family *Togaviridae*. Dengue, chikungunya, and Zika viruses are present and circulating in the Brazilian population.[7] Since 1981 and 1982, Brazil has suffered from recurrent dengue outbreaks, including hemorrhagic manifestations. Guillain–Barré syndrome was of interest in the early days of the epidemic, when the Brazilian population had no acquired immunity.[8] Yellow fever and dengue types DENV-1, DENV-2, DENV-3, and DENV-4 are endemic in rural Brazil.[7] In late 2014 chikungunya infections with moderate to severe clinical manifestations were reported in Feira de Santana, Bahia (northeastern Brazil).[9] It is unclear whether ZIKV was also present at that time. It was first hypothesized that the virus entered Brazil during the 2014 FIFA World Cup, but it is now thought to be most likely that it entered earlier, in 2013.[10]

### Consequences and Surveillance Confounders

Since May 2015, registered cases of microcephaly have increased 10-fold in Brazil, from a base rate of 5.6 per 100 000 live births[8] to 49.9 per 100 000 live births.[11] Although the northeastern region accounted for 38.5% of all probable ZIKV infections, it concentrated 71.2% of notifications and 85.1% of confirmed cases of microcephaly.[11,12] This concentration of cases has not been clearly explained, but possibilities for it include population susceptibility, coinfection with chikungunya, previous infection

**ABOUT THE AUTHORS**

*Claudia Garcia Serpa Osorio-de-Castro is with the Departamento de Política de Medicamentos e Assistência Farmacêutica, Escola Nacional de Saúde Pública Sergio Arouca, Rio de Janeiro, Brazil. Elaine Silva Miranda is with the Departamento de Farmácia e Administração Farmacêutica, Universidade Federal Fluminense, Niteroi, Brazil. Carlos Machado de Freitas is with the Centro de Estudos e Pesquisas em Emergências e Desastres em Saúde, Escola Nacional de Saúde Pública Sergio Arouca, Rio de Janeiro. Kenneth Rochel de Camargo Jr is with the Departamento de Planejamento e Administração em Saúde, Universidade do Estado do Rio de Janeiro, Rio de Janeiro. Hilarie H. Cranmer is with the Department of Global Health and Population, Massachusetts General Hospital, Boston, MA.*

*Correspondence should be sent to Claudia Garcia Serpa Osorio-de-Castro, Escola Nacional de Saúde Pública Sergio Arouca, Prédio Ernani Braga, Rua Leopoldo Bulhões 1480 sala 625, Manguinhos, 21040-210, Rio de Janeiro, RJ, Brazil (e-mail: claudiaosorio.soc@gmail.com). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.*

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with dengue, changing viral genetic characteristics, immunologic enhancement from preexposure to other flaviviruses, and social determinants related to poverty, poor sanitary and living conditions, and lack of education.

Additionally confounding the diagnosis of microcephaly are its case definitions. Fluctuations of head circumference thresholds, employed as the standard for diagnosing microcephaly, have led to oscillation in diagnostic accuracy. Before February 2016, the Brazilian Ministry of Health adopted a 30.0-centimeter head circumference limit; the limit was later increased to less than or equal to 33.0 centimeters.[13] This measure, however, which possessed high sensitivity, was not fully supported by evidence. In December 2015 the threshold was lowered to 32.0 centimeters.[13] In January 2016, the Pan American Health Organization suggested that the threshold be lowered again to less than 32.0 centimeters for boys and less than 31.6 centimeters for girls.[14,15]

Differences in measures may have caused over- and under-notification, depending on the timeline and on individual case management by the attending physician. Fixed values of head circumferences may not take into account children born before 40 weeks' gestation because of Brazil's high cesarean delivery rates.[13] Furthermore, WHO acknowledges that microcephaly is present only when other structural abnormalities of the brain are also present.[13] In fact, consequences of exposure to ZIKV may not be limited or characterized by microcephaly alone.[13] The full scope of neurological damage is not yet known. Reports of severe shrinkage and calcifications of brain tissue, hydrocephaly, and abnormal brain development demonstrate the need for image diagnostics at birth and several years after.[16]

Although legislation was passed that now makes notification of ZIKV infection and microcephaly mandatory,[15] lack of notification for infectious diseases has historically been a difficult problem to overcome in Brazil.[17] Because of public outcry and the seriousness of malformations, a veritable microcephaly notification spree has occurred since the beginning of the ZIKV crisis. From October 2015 to August 2016, parents were notified of 8801 suspected cases of microcephaly. Among 1773 confirmed cases, there were 275 laboratory-confirmed cases and 1498 cases linked to other congenital infections or to unspecified causes. A total of 3012 were still under investigation, and 4016 had been discarded.[11] Because of the benign nature of the disease (in most cases), difficulties in differential clinical diagnosis with dengue and chikungunya,[3,4] and the interference of yellow fever immunity (from vaccination) for laboratory-testing possibilities, Zika cases may be much more common. A large proportion of microcephaly cases lack laboratory confirmation when ZIKV involvement is suspected but cannot be proven.

Nearly all ZIKV infections in Brazil are diagnosed clinically, and laboratory testing (mainly using the polymerase chain reaction technique) is performed primarily in research environments.[10] Diagnosing microcephaly in infants, however, now that the standard is not fluctuating, is more accurate than is diagnosing actual ZIKV infections. Simple calculations of the risk of microcephaly (considering 3 million live births a year in Brazil), maintaining the proportion of cases in the first 11 months of the period (October 2015 through August 2016), would come to a rate of 9 per 100 000. With the same rationale, for other causes of microcephaly, such as those originating from any of the TORCHS diseases (toxoplasmosis, rubella, cytomegalovirus, herpes, syphilis),[13,16] the rate would be 49.9 per 100 000. Dealing with Zika-related microcephaly is urgent, but other underlying causes must also be dealt with.

These congenital infections are alternate causes of microcephaly, which are also proven to cause brain malformations and impair brain development in human fetuses.[16] Congenital syphilis has been spreading and a high prevalence has been detected; higher rates have occurred in the Brazilian Northeast.[18] From 2014 to 2015, the country faced a serious benzylpenicillin stock shortage, the antibiotic used to treat syphilis,[18] and this may have been a factor influencing the high rates of congenitally acquired disease. Furthermore, a very serious measles outbreak happened in 2013 and 2014, affecting mainly the Brazilian Northeast.[19] At that time, the epidemic was controlled largely with the triple viral (measles, mumps and rubella) vaccine.[19] The impact of these factors has not been formally assessed, but it seems likely that they may have had an influence on the surge of cases of microcephaly.

The fact remains that the risks of neurological impairment and of fetal microcephaly have not been definitively established. In French Polynesia, microcephaly occurred in 1% of pregnancies exposed to ZIKV infection in the first trimester; in Brazil the measured overall rate in 1 study showed a 29% infection rate.[5,6] However, methods of measurement were not the same: the first study used serological data, whereas the second used clinical follow-up data. More uncertainties arise from the fact that malformations may occur at any time during the pregnancy,[6] modulating risk. Risk cannot be calculated without a precise estimate of exposure, which is still nonexistent. Work has been done to determine causation,[16] but relative and absolute risk have yet to be established, as do confounding factors, intervenient factors, and risk modulation owing to time when infection takes place.

Uncertainty about the safety of pregnancy in the wake of ZIKV has affected all women of reproductive age in Brazil. Until more is known about transmission and immunity, it is expected that this issue will continue to have a major impact on reproductive decisions. However, the part of the population that can effectively plan parenthood may be less prone to chance, but for less educated or disenfranchised women without access to family-planning resources, the risk may indeed be greater.[20]

## Transmission and Vector Control

ZIKV transmission by *Aedes* mosquitos, a vector that is widespread in much of the tropical Southern Hemisphere, has shown that countries of the Northern Hemisphere may be seasonally affected in lower latitudes and that the potential for spread of the disease is considerable.[3] Approximately 60% of the populations in Argentina, the United States, and Italy, for example, reside in areas that may be affected, and 22 to 30 million people, in Mexico, Colombia, and the United States may be continuously exposed to the virus.[2,21] Nevertheless, transmissibility of the infection (involving factors such as herd immunity, naïve population susceptibility, and viral evolution), geographic variations, climate variations, and vector characteristics may determine the epidemic characteristics of the emerging infection.[22] At this point, it is not possible to accurately predict the dynamics of the infection. Substantial risk may also stem from the fact that herd immunity will diminish eventually. If there are future epidemics, a younger nonimmune population will become exposed.[22]

It has been postulated that the ZIKV might also be present in other types of mosquitos, and research regarding possible transmission has reaffirmed that *Aedes aegypti* and *Aedes albopictus* are the main vectors. Researchers from the Oswaldo Cruz Foundation in Brazil have established that *Culex quinquefasciatus* mosquitos from the Rio de Janeiro area cannot transmit the disease, but researchers do not rule out possible transmission by this species in other environments.[23] Research has reported that Zika can also spread from sexual contact and blood transfusions, in addition to from a pregnant woman to her fetus,[2] rendering the presence of a mosquito as possibly unnecessary to establish risk.

The effectiveness of vector control is a further source of uncertainty. In Brazil, since the beginning of the dengue epidemic, health workers have been designated to carry out vector-control strategies in the community, mainly by insecticide spraying and the use of larvicides in water containers. In drought-ridden areas, water storage is common and larvicides are used in drinking water. It is common knowledge that health workers use larvicides without consistently estimating the concentration. This may also be a hazardous exposure.[23,24] However, in Singapore, where dengue is endemic and despite strict control measures, *Aedes* is a threat and dengue cases peaked in the summer of 2016.[25]

Other determinants of disease have been hypothesized as important factors in the ZIKV infection outbreak. The conjunction of a tropical climate, substandard housing and sanitation, poverty, and low levels of education and income may increase the risk.[24] Because of the estimated 1 500 000 ZIKV infection cases in Brazil to late 2016,[26] establishing countermeasures for control and management of the epidemic is paramount. However, gaps in knowledge about the disease must first be overcome.

The 2016 Olympic Games in Rio de Janeiro took place in the wake of the ZIKV emergency. The games were held in August, a winter month in the Southern Hemisphere, and a seasonal break in incidence of dengue, Zika, and chikungunya was registered. Researchers had hypothesized that ZIKV infection would be minimal.[27] Nevertheless, there was a great influx of international visitors and international teams, many from countries where these viruses have not been detected. Conversely, Brazil may be prone to new diseases brought in by visitors, as determined in the previous outbreak.

Despite growing awareness of the disease and its possible aftermath, the situation is plagued by uncertainty. The research community has not adequately approached alternative explanations for outcomes incidence or the lack of information that may cause confounding. Risk communication has been confusing, causing speculation and fear.

## RISK MANAGEMENT OF THE ZIKA HEALTH EMERGENCY

The ZIKV outbreak is a challenge in the global context, where borders are ever weaker, impeding effective sanitary prevention strategies. In fact, 51 countries have experienced a first outbreak of ZIKV since 2015, with no previous evidence of circulation and with ongoing transmission by mosquitos. In addition, 13 countries or territories (Gabon; Isla de Pascua, Chile; Bangladesh; Maldives; Cambodia; Cook Islands; French Polynesia; Lao People's Democratic Republic; Malaysia; New Caledonia; Papua New Guinea; Solomon Islands; Vanuatu) reported evidence of ZIKV transmission in or before 2015, without recorded ongoing transmission.[2] As of August 2016, 68 countries have reported mosquito-borne ZIKV transmission and 11 have reported person-to-person transmission.[2] Microcephaly, and other fetal malformations associated with ZIKV infection or suggestive of congenital infection, have been reported in 14 countries. In the context of ZIKV circulation, 15 countries and territories have reported an increased incidence of Guillain–Barré syndrome.[2]

Both the number of affected or dead and perceptions regarding risk, morbidity, and mortality characterize the declaration of an emergency. The Ebola crisis gave rise to the "global health security" concept, which was promoted by several unilateral initiatives beginning in 2014. The global health security agenda has adopted the view that any health issue may be socially construed as a security problem.[28] In the case of the ZIKV outbreak in Brazil, 3 main aspects are related to securitization: (1) public panic, mainly spread by the media, which was evident in the first months of the outbreak; (2) difficulties in fighting the epidemic because of a lack of awareness of alternative causes and lack of government transparency with regard to data; and (3) stigma, which can be duly illustrated by the debacle over the Olympic Games in Rio de Janeiro.

After an article condemned the games in a renowned public health journal,[29] more than 200 scientists signed a letter asking the games to be cancelled.[30] Nevertheless, evidence argued that the cooler climate and very low transmission rates during winter in Rio de Janeiro would considerably lessen risk and suggested that the greater risk to athletes and travelers would be in the warmer areas of North America.[27]

In the wake of disaster mitigation and public health emergencies, international organizations have worked to establish standards and guidelines that focus on early warnings and comprehensive approaches to locally identified threats. Examples are the Pan American Health Organization document that establishes essential public health functions,[31] the WHO strategy for risk reduction and emergency preparedness,[32] the International Health Regulations,[33] and, most recently, the Bangkok Principles for the Implementation of the Health Aspects of the Sendai Framework for Disaster Risk Reduction 2015–2030.[34]

The Pan American Health Organization defined a list of 11 essential health functions. The 11th deals specifically with the reduction of the impact of health emergencies and disasters.[31] The WHO strategy emphasizes multisector collaboration and promotion of a comprehensive standpoint in respect to damages and etiology of health emergencies and disasters.[32] This view is in line with the "all hazards–whole health" approach, which proposes aggregated preparedness measures for diverse identified threats. The approach also recommends that emergency preparedness plans include addressing a series of aspects, some of which are in the forefront of the ZIKV crisis: environmental health (including water, sanitation, and hygiene); maternal, newborn, and child health; communicable diseases control; and health care delivery services (including health infrastructure).

The International Health Regulations of 2005 emphasize providing technical support—surveillance, epidemiology, and laboratory and other core capacities, including monitoring and evaluation strategies for public health and risk and damage control—to low-income countries by high-income countries. In essence, the International Health Regulations are intended to build capacity to survey and respond to outbreaks and to establish a detailed international benchmark.[33] The Bangkok Principles connects measures to prevent hazard exposure and vulnerability to disasters with several initiatives related to health emergency and disaster risk management, such as the global health security agenda, climate change, the sustainable development goals, and universal health coverage.[34]

However, as in the ZIKV outbreak, these international and organizational efforts and regulations have done little to curb the transportation of persons and merchandise during this disease emergence. Under the International Health Regulations of 2005, the declaration of a public health emergency of international concern is a tool that is available to help stop epidemics with global effect; only the WHO director-general can make this declaration. Although this is a central component of the obligations that countries bear for collective health security, capacity-building support to low-income countries that need it most critically has long been underfunded.[33]

The WHO director-general Margaret Chan has declared, "The world is not prepared to cope with . . . a dramatic increase in new and reemerging infectious disease threats."[35] Moreover, aspects of the epidemic show how these regulations fall short in problems that the media has publicized, creating alarm. ZIKV and other international health emergencies (e.g., SARS, H5N1, H1N1, H7N9, Ebola, West Nile, wild polio, yellow fever) may indicate that although restrictions do not resolve the problem, preventive and risk-reduction measures may help.

Efforts must be made to adequately analyze causes and determinants, reduce vulnerabilities of population groups, and act on environmental issues. Risks of ZIKV infection are truly not known because widespread diagnostic capability is not yet available. The development of diagnostic tests for acute and past infection is paramount. Vaccine development may encounter difficulties because of the unpredictability of outbreaks and limited time to initiate studies. Furthermore, safety profiles among pregnant women—a priority group in this case—are notoriously difficult to establish.[22]

Epidemiological surveillance may not be working as it should. The base rate of microcephaly in Brazil has never been well established. If surveillance had been robust enough to detect rapidly increasing rates, the health services organizations would have been able to understand the percentage of cases attributable to ZIKV alone, not just other concomitant infections and failed prevention strategies. The concentration of cases in the Brazilian Northeast also leads to questions concerning other health determinants and environmental issues, as they may relate to overusing pesticides and larvicides, drought and water shortage, water contamination, poverty, and lack of sanitation. It is very difficult to mitigate these determinants, as may be needed during a health emergency. Long-term initiatives should be implemented but will not have immediate results. This will always happen when an epidemic or emerging disease hits a developing country. No measure to be taken after the epidemic's onset will have an immediate effect on risk reduction.

The public health system is facing structural difficulties in many Brazilian states. The Brazilian public health system has not prepared itself to deal with the apparent challenges of the ZIKV epidemic,[13,24] which involves comprehensive social support in addition to comprehensive health care.[6] Needed services include early physical therapy for newborns, family counseling, and support for mothers who have limited access to resources.[20]

Nevertheless, Brazil has adopted active measures in 3 distinct areas: (1) mitigation of microcephaly, (2) social mobilization and vector control, and (3) technological development, education, and research. Brazil has established several initiatives to support families stricken by the consequences of the disease and to establish coordination and control of microcephaly.[15] Brazil has also developed some environmental measures to curb infestation. National research institutions have proposed vector-control strategies, such as liberating into the environment genetically modified mosquitos or mosquitos infected with bacteria that make them unable to reproduce. Social mobilization and outreach campaigns to combat infestation by *Aedes* have been widespread. Federal and state funding agencies had provided a surge of research funding for ZIKV and related issues. More importantly, other possible causes of microcephaly, overlooked at the beginning of the epidemic, are now being investigated, and the examination of several alternative diseases are now included in the protocol.[15]

Whether these countermeasures will actually produce the desired outcomes is open to speculation. The ZIKV outbreak has again signaled how unprepared we can be when dealing with emerging diseases and their consequences. Although clinical and epidemiological research is being carried out and many studies have been published in the wake of the ZIKV emergency, it is apparent how little is actually known about this disease. The same vector transmits various diseases and the same virus causes multiple effects. Moreover, in the case of emerging diseases, the world is dealing with novelty. Genuine novelty is rare; it is characterized by complexity and is very difficult to explain in terms of traditional science. In complex situations, no single viewpoint should be hegemonic; anomalies and surprises will always be present and challenge our established preconceptions. In this scenario, a new way of thinking may be necessary, broadening the scope of those involved and adopting consensus as a means of producing knowledge.[36]

We perceive the products of this outbreak (fetal microcephaly, neurological abnormalities, Guillain–Barré syndrome) in

### FACTORS LEADING TO UNCERTAINTIES, SUGGESTIONS FOR RISK-REDUCTION STRATEGIES, AND SUGGESTIONS FOR PREVENTION STRATEGIES FOR BRAZIL'S ZIKA EPIDEMIC

**Factors Leading to Uncertainties**

- Possible effects of different and simultaneous arbovirus infections in Brazil
- When Zika virus arrived in Brazil
- Why the Zika virus outbreak occurred in Brazil
- Specific determinants in Brazil and in the Brazilian Northeast not known
- Population immunity and occurrence of disease over time
- Alternate causes for microcephaly and unknown exposure to these causes
- No certainty of exposed numbers or exposure rates
- Risk of microcephaly not determined
- Lack of accurate and universally available differential laboratory diagnosis for Zika virus, dengue virus, and Chikungunya
- Different hazardous effects on fetal brain at different periods of pregnancy
- Characterization of other types of transmission other than vector transmission
- Inaccurate notification
- Unknown exposure to larvicides in drinking and stored water
- Unknown risks related to larvicide and insecticide exposure

**Suggestions for Government and Organizations' Risk Reduction Strategies for Populations and Communities**

- Approach to Zika with an "all hazards–whole health" outlook
- Improvement of living and sanitary conditions
- Adequate water supply and piped water
- Sewage systems
- Laboratory diagnosis confirmation for all probable cases of Zika
- Differential diagnosis for Zika virus, dengue virus, and Chikungunya
- Screening blood for transfusions
- Adequate surveillance and notification
- Counseling for pregnant women and women of reproductive age
- Better vector-control strategies
- Enhanced risk communication strategies
- Improvement of health literacy
- Seroprevalence studies and investigations into alternate causes of microcephaly and nervous system abnormalities
- Comprehensive health care for women, children with Zika sequelae, and families

**Suggestions for Individuals' Prevention Strategies**

- Individual care and responsibility for the environment
- Planned pregnancy and planned parenthood
- Use of condoms
- Pregnant women's rational use of repellents and care to avoid mosquito bites

a much clearer way than we can understand the process, so we act on the product and not on the determinants. In a special report on climate change, the authors state,

> Disaster is real, palpable and visible and for ethical, moral, social and political reasons demands an immediate response. Risk is latent, accumulative, obscure and, in many ways, unpredictable in terms of when it will be 'actualized' and transformed into a real disaster context. As such, risk reduction is, in many cases, postponable or simply ignored as an option.[37(p7)]

Strategies and countermeasures in emergencies are always determined by partial or available information. Traditional science conceptualizes science-related problems to be solely resolved by accredited expertise.[38] The adoption of the preventive paradigm also obliges science to propose that it constantly be in charge of the consequences, always one step ahead. Therefore, decision-making may well be trial and error, more so in complex situations. Conversely, uncertainty and ignorance may also be sources of risk. For lack of sufficient information or understanding of the phenomenon, policy may reduce risk to probabilities and calculations, a much more comfortable terrain but open to error and manipulation.[39]

It has been recognized that the movement of persons around the globe, for commercial reasons or because of forced displacement, is becoming much more frequent, and as a consequence, health emergencies such as the ZIKV outbreak will be repeated. The establishment of health surveillance systems that can scan population movements while shunning discrimination and segregation and respecting fundamental rights are critically necessary despite a lack of resources to do so.

We must determine what types of prevention, preparedness, and response initiatives are technically sound, globally inclusive, morally acceptable, and ethically responsible. Dealing with information gaps, lessening disease spread, and recognizing vulnerabilities can be postulated as the Zika triad. The box on page 965 summarizes the possible factors in uncertainties, risk-reduction strategies (pertaining to government and organizations for the benefit of populations and communities), and prevention strategies (pertaining to individuals) stemming from the Zika epidemic in Brazil.

We must learn quickly for the next round of this epidemic. This new risk scenario must be approached decisively to impede what Wynne calls "natural validation" and "closure" by the research community, a comfortable "way out."[39] Simplification must be avoided, and boundary definitions should be constantly renegotiated to produce a comprehensive approach to face emerging biothreats. AJPH

## CONTRIBUTORS

C. G. S. Osorio-de-Castro conceptualized the study and led the data analyses, writing, and revision. E. S. Miranda contributed to design, data analyses, and writing. C. M. de Freitas contributed to data interpretation. K. R. de Camargo Jr assisted with the study analyses. H. H. Cranmer contributed to the writing of the article. All authors helped revise the article.

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No protocol approval was necessary because no human participants were involved in this study.

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