



OPINION ARTICLE

Navigating the Zika panic [version 1; referees: 2 approved]

Nathan D. Grubaugh¹, Kristian G. Andersen¹⁻³

¹Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, CA, 92037, USA

²Scripps Translational Science Institute, La Jolla, CA, 92037, USA

³Broad Institute of MIT and Harvard, Cambridge, MA, 02142, USA

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Abstract

The epidemics of Ebola virus in West Africa and Zika virus in America highlight how viruses can explosively emerge into new territories. These epidemics also exposed how unprepared we are to handle infectious disease emergencies. This is also true when we consider hypothesized new clinical features of infection, such as the associations between Zika virus infection and severe neurological disease, including microcephaly and Guillain-Barré syndrome. On the surface, these pathologies appear to be new features of Zika virus infection, however, causal relationships have not yet been established. Decades of limited Zika virus research are making us scramble to determine the true drivers behind the epidemic, often at the expense of over-speculation without credible evidence. Here we review the literature and find no conclusive evidence at this time for significant biological differences between the American Zika virus strains and those circulating elsewhere. Rather, the epidemic scale in the Americas may be facilitated by an abnormally warm climate, dense human and mosquito populations, and previous exposure to other viruses. Severe disease associated with Zika virus may therefore not be a new trait for the virus, rather it may have been overlooked due to previously small outbreaks. Much of the recent panic regarding Zika virus has been about the Olympics in Brazil. We do not find any substantial evidence that the Olympics will result in a significant number of new Zika virus infections (~10 predicted) or that the Olympics will promote further epidemic spread over what is already expected. The Zika virus epidemic in the Americas is a serious situation and decisions based on solid scientific evidence - not hyped media speculations - are required for effective outbreak response.

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- 1 Eduardo Massad**, University of São Paulo Brazil, London School of Hygiene & Tropical Medicine UK, **Claudio J Struchiner**, Fundação Oswaldo Cruz (PROCC, FIOCRUZ) Brazil
- 2 Gonzalo Moratorio**, Pasteur Institute France, **Bryan.C Mounce**, Pasteur Institute France

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Corresponding authors: Nathan D. Grubaugh (nathan.grubaugh@yahoo.com), Kristian G. Andersen (kristian@andersen-lab.com)

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Zika's path from obscurity to severity

Zika virus, a name now synonymous with birth defects by many people, was not always a topic of public health debate. In fact, for 67 years, the virus was mostly ignored (89 publications from 1947 to 2014, compared to 850 over the last 19 months). That is because when Zika virus was discovered in 1947 it was not thought to cause severe enough disease in humans to warrant intense research¹. Fast forward to today and people are talking about canceling one of the world's most watched events, the Olympics, due to the Zika virus epidemic in Brazil^{2,3}. So, what happened? Did the virus change? Did we misinterpret its threat from the beginning? And will the Olympics this summer really exacerbate the current epidemic or provide new opportunities for Zika virus emergence? Zika virus research is now pouring in fast, but at times at the expense of fast-tracked studies and misinterpretation of results. As a result, there is significant confusion surrounding the Zika virus epidemic and many of the core questions need to be revisited.

It has been suggested that “*The Brazilian strain of Zika virus harms health in ways that science has not observed before*”³ and “[Africa and Asia] have mostly avoided the post-2013 neurotrophic strains of the virus that are ravaging Brazil”². Based on available evidence, however, it is too early to say whether this strain is in fact fundamentally different from other Zika virus strains. Only recently has Zika virus been associated with large outbreaks (since 2007 - Yap Island⁴) and severe disease such as microcephaly and Guillain-Barré syndrome (since 2013 - French Polynesia⁵). The epidemic in the Americas has proven to alarmingly increase these trends - 0.5 to 1.5 million suspected infections and ~4,000 cases of microcephaly in Brazil alone⁶. What are the real reasons behind the severity of this epidemic? We will explore aspects of 1) viral genetics that might alter transmission and pathogenicity in humans, 2) the ecological conditions in the Americas, 3) the potential impact of dengue virus on Zika virus-associated pathology, and 4) how small sample sizes and under reporting may have skewed our previous assumptions of Zika virus and the disease it can cause. Using this knowledge, we will discuss whether a global event like the Olympics would really impact further Zika virus emergence and the expansion of the epidemic.

Is Zika virus different today than it was when it was first discovered?

Undoubtedly, yes, Zika virus circulating today is genetically different from the Zika virus of the past. A key aspect of Zika virus is that it has an RNA genome. Central features of RNA virus biology is that these viruses replicate, produce large population sizes, but do so with lots of errors (mostly because their polymerases lack proofreading mechanisms, adding ~1 mutation per genome replication)⁷⁻⁹. Therefore, all RNA viruses have the ability to evolve fast relative to most DNA-based organisms¹⁰, and Zika virus has evolved into at least two distinct lineages: African and Asian¹¹. The viruses circulating in the Americas belong to the Asian lineage, which, to the best of our knowledge, originated in East Africa¹². Comparing the genetics of the first discovered Zika virus strain from 1947 (Uganda, strain MR766) to the strain currently circulating in the Americas (2015 Puerto Rico, strain PRVABC-59) reveals mutations in >1,100 nucleotide positions (~89% similarity), and confirms that yes, the viral genome is different. While the

genetic makeup has changed - as is expected - the more important question, however, is whether this means that the currently circulating strain of Zika virus has a fundamentally different “behavior” (*i.e.*, phenotype)?

Unfortunately, we are critically lacking comparative studies to directly address whether genetic changes in the virus are significantly contributing to the epidemic. For example, are there differences in mosquito vector competence (*i.e.*, ability of a population of mosquitoes to transmit the virus) between Zika virus strains in Africa and the Americas? While studies have shown that competence of the suspected Zika virus vectors in the Americas, *Aedes aegypti* and *Ae. albopictus*, can vary between mosquito populations¹³, the influence of Zika virus genetics has not been tested. There is, however, precedence for mosquito-borne viruses to adapt to local mosquitoes, increasing their epidemic potential. This happened with chikungunya virus during the Indian Ocean epidemic¹⁴ and West Nile virus during its invasion of the United States^{15,16}. Hence there could be some yet-to-be discovered Zika virus mutations that facilitate faster transmission and increased rates of mosquito infection. A lot of work needs to be directed towards lab and field mosquito studies to actually determine if this has occurred and whether Zika virus could have adapted to enhance local transmission. At this point, however, there is no evidence that the Zika viruses in the Americas have adapted to the local conditions or can be transmitted any more efficiently than previous strains.

Perhaps even more controversial and urgent are the questions: is the Brazilian strain of Zika virus more capable of 1) being transmitted during pregnancy or 2) causing neuropathogenesis leading to complications such as microcephaly¹⁷ and Guillain-Barré syndrome⁵ than strains from Africa or other Asian strains? Several recent laboratory studies have shown that Zika virus can infect placental cells¹⁸⁻²⁰, be vertically transmitted to offspring during pregnancy^{21,22}, target and replicate in neuronal cells^{20,23,24}, and cause birth defects²⁵ (*in vivo* in mice, *in vitro* with human cells, organoids, and organ explants). These studies, however, were conducted with a variety of Zika virus strains indicating that some of these phenotypes are common features of the virus, irrespective of the strain. In fact, the virus was first isolated in 1947 by injecting serum from a febrile rhesus macaque directly into a mouse brain¹ and a subsequent paper published in 1971 showed that the same Zika virus strain could cause neurological disease in mice²⁶. While these observations may not be that surprising - the mice were infected intracerebrally after all (as is common for these types of experiments) - these early experiments already demonstrated that Zika virus can replicate and cause pathology in neurons. Together, these studies suggest that vertical transmission and neuropathogenesis are not specific attributes of the Brazilian strain and perhaps Zika virus has always been capable of this.

So were those ancestral strains from the 1940's to 1970's in Africa reported to cause mild disease actually misunderstood? We know that people in some areas of Africa had high seroprevalence to Zika virus (*e.g.*, ~30% in Nigeria during the early 1970s²⁷). Perhaps disease associated with Zika virus was just overlooked in Africa because of the many other diseases such as malaria, acquired immune deficiency syndrome (AIDS), and tuberculosis that ravage

the continent. In the Americas, a large number of Zika virus-naïve people (*i.e.*, without previous immunity) are getting infected at the same time, which may reveal previously unknown clinical features of viral infection. Finally, genetic analysis of Zika virus strains has yet to discover any appreciable patterns associated with adaptation towards humans, vector species, or disease outcome²⁸. This is not to say that it has not occurred, only that at this point in time our sampling is too insufficient to make any conclusions. Therefore, more experimental evidence is required before we can say whether Zika virus genetics or phenotype has changed in any significant way.

Why is the epidemic in the Americas so bad?

Zika virus is not the first, nor likely the last mosquito-borne virus, to explosively emerge in the Americas. In 1999, West Nile virus was introduced into the New York area and quickly spread across the continent, killing thousands of people and millions of birds (reviewed by 29). Even more recently, in 2013, chikungunya virus emerged throughout the Caribbean and much of the tropical regions in the Americas (reviewed by 30). By 2015, there were already more than one million suspected cases³¹. Since chikungunya and Zika viruses share similar ecologies (humans and *Ae. aegypti*), the current Zika virus outbreak should not be so surprising, given recent histories. Even the 2007 Yap Island outbreak gave us some indication of its potential - it is estimated that 73% of the population became infected with Zika virus⁴. A large outbreak in the Americas almost seemed inevitable, but why?

Well, likely because the Americas are home to large and dense populations of hosts (humans) without previous Zika virus immunity, and vectors (mosquitoes) capable of transmission. The climate may also have contributed to the scale and intensity of the epidemic; 2015 was the warmest year on record in the Americas³², which could have enhanced Zika virus transmission. Warmer temperatures can increase mosquito abundance, survival, blood feeding rates, and vector competence^{33–36}. Therefore, the extreme circumstances caused by *El Niño* and global climate change may have contributed to a higher density of mosquitoes³⁷. Together, these factors represent an ideal recipe for an infectious disease epidemic.

The unfortunate surprise was the discovery of an association between severe neurological complications and Zika virus infection, especially among newborns³⁸. This, however, could just be a consequence of numbers and reporting. Previous outbreaks may have missed these links because they were too small. In Brazil, the current estimate is that between 1–13% of pregnant women who become infected with Zika virus in their first trimester will deliver babies with microcephaly^{17,39}. That is 8-650× the baseline microcephaly rate of 0.02–0.12% per live birth^{17,39}. The largest previous Zika outbreak - which occurred in French Polynesia - had an estimated size of 30,000 infections based on serological evidence (11% of the 270,000 people)⁴⁰. Retrospective analysis of first trimester pregnancies indicated that about 1% of Zika virus infections resulted in babies born with microcephaly - a total of eight cases⁴¹. During the Yap Island outbreak, researchers estimated that about 5,000 of the 7,000 inhabitants over the age of three became infected⁴. Based on Yap State census reports⁴², roughly 200–300 women may have been pregnant during the outbreak, and only

about $\frac{1}{3}$ would have been in the first trimester. If the previous estimates were accurate during the Yap Island outbreak, then it may be possible that no babies were born with microcephaly just because there were not enough infected pregnant women for the chance occurrence. The current epidemic in the Americas, including Brazil, may therefore just seem more severe because there are more infected people to detect rare pathological complications such as microcephaly.

Discovering new disease associated with a particular virus only after a large outbreak is not unique to Zika virus. In fact, we can learn from previous epidemics with different viruses, such as West Nile virus. Prior to the 1990's, West Nile virus was only known to cause sporadic outbreaks with a few cases of severe neurological disease. An outbreak in Romania⁴³, however, redefined our perception of the virus. From 1996–1997, there were more than 500 clinical West Nile cases with a fatality rate approaching 10%, representing the largest mosquito-borne virus outbreak in Europe in more than a decade. Other outbreaks in urban areas soon followed, occurring in Russia⁴⁴, Israel⁴⁵, and the United States⁴⁶, all of which included neurological disease in about 1% of the cases²⁹. While genetic changes to the virus may account for some of the increase in severity⁴⁷, most of it can be attributed to previously underestimating its severity due to small sample sizes. Many parallels can be made between what happened with West Nile virus and the sudden increase in Zika virus associated disease during its current emergence.

There may also be immunological explanations for pathology associated with Zika virus infection in the Americas. Zika and dengue viruses co-occur in many parts of the world. The fastest growing numbers of dengue cases occur in Latin America and the Caribbean with more than 10 million apparent infections a year⁴⁸, a ~250% increase since 1990⁴⁹. One interesting hypothesis is that antibodies produced from a previous dengue virus infection may enhance subsequent Zika virus infection^{50–53}. The proposed mechanism is that antibodies targeting dengue virus can bind to Zika virus during an active infection, but cannot always neutralize it. Instead, the bound antibodies can actually help Zika virus infect monocytes by attaching to the cell surface receptors (Fc gamma) and mediating efficient entry. This process of antibody-dependent enhancement is also known to occur between different serotypes of dengue virus and is a risk factor for severe dengue disease (reviewed by 54). Since 2010, between 600,000 and 1.6 million annual dengue virus cases in Brazil have been reported⁵⁵. Therefore the high incidence of dengue virus infection may be increasing the observed pathogenicity of Zika virus in the Americas. On the other hand, dengue and Zika viruses co-occur elsewhere, so the Americas may not be so unique. Indeed, further research is urgently needed to determine if dengue virus is not only exacerbating the Zika virus epidemic in the Americas, but also anywhere the two viruses co-circulate.

How many visitors will become infected with Zika virus during the Olympics?

Now turning our attention from the biology and genetics of Zika virus, to the different risks associated with Zika virus and the Olympics. There are two main risks to consider: 1) the risk of further spread and 2) personal risk to visitors. These are two very

different questions, but often they get blurred together. Here we will discuss them separately. First, how many of the expected half a million visitors to Rio de Janeiro during the summer Olympics this August will become infected with Zika virus? Massad *et al.* predict that the numbers of individuals acquiring Zika virus during the Games is low - 1 in ~30,000 to 100,000 people⁵⁶. This translates to only 5 to 15 visitors during the 3-week games will locally acquire Zika virus. The same model was used to predict that 3 to 59 visitors would become infected with dengue virus during the 2014 World Cup⁵⁷. The actual reported number was three, suggesting that such estimates are relatively accurate⁵⁸. Another group estimated that 3 to 80 visitors will become infected with Zika virus during the Games⁵⁹. Based on previous experience and scientific evidence, we might therefore only expect that about 10 people traveling to Brazil for the Games will get infected with Zika virus. Compared to the overall number of cases, that is an astonishingly low number.

One main reason behind the few predicted Zika infections of visitors is that August is winter in Brazil, so mosquito densities will have declined^{60,61}. That alone will severely decrease the likelihood of exposure to Zika virus through fewer mosquito “bites”. The remaining risk is dependent upon the 1) mosquito species, 2) proportion of infected mosquitoes, and 3) transmission rates upon blood feeding. A recent report helped to validate our assumption that *Ae. aegypti* is vectoring Zika virus in at least some parts of the Americas⁶², though other species may be involved⁶³. The proportion of *Ae. aegypti* that are infected with Zika virus at any given time, however, is unclear. *Ae. aegypti* infection rates range from extremely low (unpublished data suggesting only a few Zika virus RNA-positive mosquitoes among thousands tested) to very high (5–17% near homes of suspected Zika patients⁶²). If the infection rates are similar to chikungunya or dengue viruses, then we can expect that 1–2% of *Ae. aegypti* are infected with Zika virus^{64,65}. Moreover, only a small portion (5–50%) of infected mosquitoes can actually transmit the virus¹³. So even if you get fed upon by hundreds of mosquitoes, odds are that you will not get exposed to Zika virus.

Will the Olympics enhance the further spread of Zika virus?

The world is interconnected. Zika virus and many other mosquito-borne viruses have already utilized this interconnectivity to travel great distances. Does a global event like the Olympics really enhance this problem? One estimate indicates that 100 to 400 people infected with Zika virus will enter Europe in 2016 due to normal travel from endemic regions⁶⁶. That is already 7–80× greater than the number of people predicted to become infected during the Games (~10 - see above). In reality, not enough people will get infected with Zika virus while visiting Brazil for three weeks to have a significant impact on the already expected viral spread. Unfortunately, Zika virus will spread, just as dengue, chikungunya, and West Nile viruses have done before. Holding the Olympic Games in Brazil will have no, or extremely limited, effect on this process.

To really understand the risks, let's use an example. If a person is infected with Zika virus and returns to their home country, what are the real chances that the infected person could initiate local mosquito-borne transmission? The answer is largely dependent

on the local conditions. Specifically, does the environment support enough competent mosquitoes that feed on humans to facilitate transmission? And will such transmission be sustained? Most of Europe, the United States, and other temperate regions cannot support local Zika virus transmission because they either 1) have an environment that is inhospitable to *Ae. aegypti* (or other susceptible mosquitoes) or 2) have infrastructure to minimize the risks of mosquito exposure (*e.g.*, air-conditioned homes and mosquito management programs)⁶⁷. Much of the tropical and subtropical regions of the world, however, have suitable environmental conditions to support Zika virus transmission⁶⁷. Spread to many of these places is not concerning, because they already have autochthonous (local) transmission of Zika virus. The Centers for Disease Control and prevention (CDC) recently conducted an assessment of countries that could be at risk of Zika virus importation following the Olympics⁶⁸. They suggest that Angola and China (among other countries) could be at risk because 1) they are currently not reporting autochthonous Zika virus transmission, 2) they likely have conditions to support transmission (*i.e.*, dense human populations and *Ae. aegypti*), and 3) there is a high amount of expected air travel from Brazil. In short, it really depends on the home country of the traveler, what season it is, their economic status, whether they can protect themselves from mosquitoes, and many other variables. While a single traveler could be responsible for a new outbreak (as suggested for the Zika virus introduction into Brazil²⁸), in all likelihood these events are extremely rare.

The ‘single introduction’ hypothesis put forward by Faria *et al.*²⁸ has often (wrongly) been used to suggest that it only takes one infected traveler to start an outbreak (*i.e.*, giving the sense that this could happen anytime)². That is not correct and was also not suggested by the authors. Instead, what the Faria *et al.* data show, is that the chance of starting an outbreak is extremely low. If it had been high, we would have seen multiple introductions of Zika virus into Brazil (and elsewhere), due to travelers arriving from Zika endemic countries. We don't see that, hence it likely takes many - not just one - infected travelers for the chance occurrence to start an outbreak.

Direct human-to-human transmission is another possible route of Zika virus infection. These routes notably include transmission from mother to child during pregnancy and sexual transmission from a man to a woman⁶⁹. Other forms of human-to-human transmission scenarios also appear to exist⁷⁰. Therefore, could sustained Zika virus transmission occur without mosquitoes and should this be a concern for further spread of the epidemic? Again, let's use an example: an infected man returns home from the Games and has sex with his partner. There are numerous reports of Zika virus infection associated with sex with a man (or woman⁷¹) returning from an endemic region⁷²⁻⁷⁴. Therefore, in this scenario, there is immediate risk to his partner. Importantly, however, in each of these reports, Zika virus spread was limited to just those single contacts. Thus, sex and other modes of direct contact with an infectious individual is highly unlikely to lead to sustained transmission in a new population. It has also been estimated that the role of sexual transmission in Brazil is minimal compared to mosquitoes⁷⁵, and without mosquitoes, transmission would dissipate. The single most compelling piece of evidence to support that Zika virus is primarily mosquito-borne is that it is only known to occur in regions with

*Ae. aegypti*⁶⁷. Therefore, Zika virus is still considered to be primarily transmitted by mosquitoes and sexual transmission (or other yet-to-be-discovered human-to-human means of transmission) will likely not expand the expected range of the Zika virus epidemic.

Take-home message

Our rapidly expanding knowledge about Zika virus is starting to reveal important information about the current epidemic and suggests that we may have misjudged its epidemic potential for decades. We explored four key areas to demonstrate how the epidemic severity may be more related to the conditions in the Americas rather than new disease caused by Zika virus. 1) There is currently no definitive evidence that the strain of Zika virus in Brazil has altered potential for transmission or pathogenicity in humans compared to the strains circulating in Africa and Asia (although this does not mean that the Brazilian strain does not have an altered phenotype compared to other strains, only that no good evidence is currently available to suggest that is the case). 2) Major factors for the scope of the epidemic were likely large urban settings housing people without immunity and an abnormally warm climate leading to a large population of mosquitoes. 3) Previous exposure to dengue virus could increase Zika virus disease severity, though such a connection is yet to be demonstrated as an important risk factor. 4) The recent associations of some Zika virus infections with severe neurological conditions, such as microcephaly and Guillain-Barré syndrome, may be simply a reflection of sample sizes - large numbers of infections are often required to discover rare pathologies.

The risks regarding Zika virus and the Olympic Games in Brazil are 1) whether it will enhance the epidemic spread and 2) personally

to people attending the games. The numbers of Olympic visitors expected to get infected with Zika virus in Brazil and travel home is far lower than the total numbers of these occurrences already expected to happen throughout the year. Therefore, the Olympics will not be a significant conduit for further epidemic spread. There is a personal risk of infection, though it is also predicted to be low. Obviously, pregnant women have the greatest risk as they could pass the virus to their developing fetus, with the possibility of causing severe neurological complications. Therefore each family needs to evaluate the consequences and likelihood of Zika virus infection to determine if they should travel to any region of the world with active Zika virus transmission. The Zika virus epidemic is a severe problem, but decisions should be based on scientific evidence^{78,79} and not fear-mongering². These should be lessons to keep in mind when we argue about some other relatively unknown virus before the start of Tokyo Olympics in 2020.

Author contributions

NDG and KGA conceived the ideas and wrote the manuscript.

Competing interests

All authors declare that they have no competing interests.

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Gonzalo Moratorio, Bryan.C Mounce

Vignuzzi Lab (Viral Populations and Pathogenesis Unit), Pasteur Institute, Paris, France

In this interesting and well-executed review, Grubauch and Andersen 'navigate' the literature to provide a clean, well-driven and totally enjoyable text about the current situation generated for the Zika outbreak in the Americas. Based on the bibliography, they conclude there is no scientific evidence that the Brazilian Zika strain presents a higher pathogenicity compared to others circulating elsewhere. In addition, as was discussed in previous reports, they agreed with the role played by urban and weather factors to particularly enhance this outbreak. The authors also believe that is totally necessary to confirm the connection between Dengue and Zika as a risk factor in disease severity. Finally, given the sample size of the recent outbreak, we could have under estimated rare diseases associated to this virus in the past.

The article itself is very nicely written and provides a very balanced viewpoint of Zika virus, which is something that has been lacking from several media sources. The authors have put significant thought into the attributes that affect the severity of the outbreak, but perhaps the most important statements concerning the evolution of the virus and the neurological phenotypes recently observed. With their calculations for the number of microcephaly cases that could have been detected on Yap Island (quite possibly none due to the size of the outbreak), they suggest that statistics and surveillance, rather than genetic differences, affect disease severity. Of course, additional research is necessary into understanding the severity of the Zika virus outbreak and its connections to microcephaly and Guillain-Barre syndrome and whether the genetic differences between the strains of Zika virus are or are not responsible for these newly observed phenotypes.

The authors also expand on the details on how Zika virus could infect a traveler in Brazil and then induce an outbreak in their home country, which they estimate to have a much lower probability than popular media sources might suggest. Though the commentary surrounding the possibility of the Olympics enhancing Zika virus comes after the games, the thoughtful consideration of the risks supplies rational thinking that has been lacking, especially when juxtaposed with the hysteria prior to the games. The review superbly quells the hyperbole that has surrounded the Zika outbreak in the Americas. Regardless of this low possibility of traveler-associated transmission of Zika virus in new locales, regions with the proper conditions for Zika virus transmission should remain vigilant, and continued campaigns of mosquito control, especially given the breadth of viruses spread by mosquitoes (including dengue, chikungunya and West Nile viruses).

We would like to highlight that the authors didn't cite any of their previous works, which surprised us in a positive way, showing the author's will to deliver a clean and not biased opinion about the topic.

Minor comments:

The article is written for any kind of reader, which we found excellent, but in that case would be nice to clarify what is *El Niño*. Even if wouldn't be necessary for most of the readers.

The paragraph that starts with "One main reason behind ...August is winter in Brazil..."

Brazil is huge, is the he largest country in South America and in the Southern Hemisphere. Is placed 5th in the list sovereign states and dependencies by area in the world. Particularly, the weather in Rio, still in august, can be warm enough for mosquitos. Last August the lower temperature registered was 71 F and the higher 78 F.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

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Eduardo Massad^{1,2}, Claudio J Struchiner³

¹ School of Medicine, University of São Paulo, São Paulo, Brazil

² London School of Hygiene & Tropical Medicine, London, UK

³ Program of Scientific Computing, Fundação Oswaldo Cruz (PROCC, FIOCRUZ), Rio de Janeiro, Brazil

In an attempt to justify the disastrous Iraq invasion in 2002, the then 13th Secretary of Defense of the USA, Donald Rumsfeld, stunned reporters when he uttered his (in)famous reflection on "known knowns", "known unknowns" and "unknown unknowns" (Rumsfeld, 2011).

In their interesting review on Zika epidemics, Grubauch and Andersen address the panic ensued by the overwhelmed number of cases in Latin America and elsewhere. They call the attention to several "known knowns" and "known unknowns" of the current Zika epidemics, although they do not shy away of pointing to possible "unknown unknowns".

Grubauch and Andersen find no conclusive evidence in the literature for significant biological differences between the Latin American Zika virus strain and those circulating elsewhere. They argue that the epidemic scale in the Americas has been influenced by climate, humans and mosquitoes population densities and local prevalence of other viruses, in particular flaviviruses, like dengue and yellow fever. The severe neurological abnormalities associated with Zika virus would not be a new trait of the Latin America strain, but rather may have been overlooked due to previously small outbreaks.

Every time the world is hit by an emergent or re-emergent pathogen with pandemic potential, panic ensues (Amaku et al., 2016). This is understandable due to previous history of recurrent pandemics, like the medieval Black Death or the 1918 Spanish Flu, which killed millions of people in Europe and around the world (Massad et al., 2007; Burattini, Coutinho & Massad, 2009). After the Pasteur-Koch germ theory was proposed, the previously "unknown unknowns" could explain the panic. The recent panic observed when SARS, H5N1 and more recently MERS-CoV emergence, or the current Zika, should not be justified

due to the prompt discovery of the ultimate cause and the possible control mechanisms. Unlike Londoners of the XVII century (Bell, 2001), who burnt witches and culled thousands of cats (by the way, both excellent rat killers), we have the scientific tools and mechanisms to face the threat with the necessary rationality.

In the case of Zika virus, however, many "known unknowns" still remain, like the true phenotypic repercussion of genotypic differences between the strains circulating in different parts of the world, differences in mosquito competences, the actual number of people that has already been infected, the competition by the vector of different viruses transmitted by the same aedes mosquitoes, vertical transmission of the virus in hosts and vectors, neuropathogenic potential of different strains, cross-immunity, antibody-enhancement by previous infection, just to mention a few. In addition, it is not well known the actual role of sexual transmission of Zika in triggering or maintaining an outbreak. As for the "unknown unknowns", just time will disclose.

One important unknown currently being discussed in the literature is whether Zika will disappear from the affected regions and whether and when it will recur. Mathematical models, very useful in the understanding and control of previous epidemics, have been widely applied in an attempt to describe and make prediction about the current Zika outbreak (Massad et al., 2016)). We now know that the Basic Reproduction Number, R_0 , of Zika is around 3, slightly higher than that of Dengue (Coelho et al., 2008) and it is even possible to predict the likelihood of Zika being exported to unaffected regions of the world, either causing a single and self limited outbreak or establishing itself, depending on whether localis lesser or greater than 1.

For the sake of completeness, two additional speculative unknowns are worth mentioning. The circulation of Zika virus and its potential interaction with dengue raises new concerns regarding vaccination strategies against the latter. The subtle trade-off justifying the recommendation of the vaccine might no longer hold. On the other hand, the patchy distribution of serious outcomes due to Zika has not been satisfactorily explained. Our navigation map cannot overlook the apparent clustering of cases of microcephaly reported in northeastern Brazilian states so far.

We think that the many "known unknowns" related to Zika epidemic explored in this paper are worthwhile being published and we are sure that Grubauch and Andersen reflections could help bring science and rationality to the fore, soothing the perhaps unjustifiable panic. Although Grubauch and Anderson do not cross all the t's nor dot all the i's, they at least show us all the uncrossed t's and undotted i's of the current Zika "unknowns" epidemic. This definitively qualify their paper for publication.

Finally, for the record: the World Health Organization officially declared - zero cases of Zika during the Olympic Games!

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We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Author Response 12 Sep 2016

Nathan Grubaugh, Scripps Research Institute, La Jolla, USA

Fantastic review! Thank you for taking the time and pointing out some of the issues that we did not get into, mainly because we were already >4000 words! There are so many unknowns of many varieties, we just ask for over-speculation to be tempered until the science can catch up.

No new Zika virus infections during the Olympics is amazing news!

Competing Interests: No competing interests were disclosed.