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REVIEWS

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Misperceived Risks of Zika-related Microcephaly in India

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After the discovery that Zika virus (ZIKV) could cause microcephaly and other birth defects, we have scrambled to understand how. Now, spreading along with the virus is misinformation that a ZIKV mutation is responsible for microcephaly. Putting too much onus on a single mutation could enhance a crisis in India.

A ZIKV epidemic in India, with a population exceeding one billion people, could represent a greater public health crisis than what was recently experienced during the pandemic in the Americas. Yet, following two recent ZIKV outbreaks in India, public health authorities sequenced virus isolates and have stated that they lack the 'known mutation linked to microcephaly'[i,ii,iii], a severe birth defect characterized by smaller than normal heads caused by exposure of the fetus to ZIKV during gestation. The ZIKV mutation they are referring to is an amino acid substitution (serine to asparagine, S139N) in the virus membrane that Yuan *et al*. found to enhance virulence in mouse brains and human neuronal cells [1]. Considering that the S139N mutation arose in ZIKV sometime in 2013, and was present in the virus introduced into Brazil, Yuan *et al.* concluded that the 'terrible sequelae of infection during pregnancy could thus be the result of a simple viral mutation' [1]. However, the authors did not provide evidence to support the relevance of these findings from *in vitro* and experimental animal studies to human infection. Furthermore, additional studies suggest that ZIKV strains without this mutation can cause birth defects [2–6]. Even though there are good reasons to be cautious about overinterpreting the Yuan *et al*. [1] study, it still appears to be misleading public health officials into believing that ZIKV in India is not dangerous to fetuses, thereby creating a situation where pregnant women may not be properly supported and educated on ways to protect themselves[i,ii,iii].

The next large ZIKV epidemic may be taking off in India. ZIKV transmission in India was first reported in the media during late 2016, when a few cases were detected from November 2016 to February 2017 (three cases in Gujarat, and one case in Tamil Nadu). Two outbreaks have subsequently been identified in September 2018, in northwest India (154 cases in Rajasthan) and central India (127 cases in Madhya Pradesh)[ii] [7]. Moreover, the outbreaks may be significantly larger than indicated by case numbers since the majority of exposures to ZIKV cause mild or inapparent infections. The looming threat is how much ZIKV will continue to spread in India. Most of the country has the climatic conditions conducive to year-round transmission of *Aedes aegypti* mosquito-borne viruses, such as dengue, chikungunya, and ZIKV [7,8]. Because these viruses have similar ecology, we can look at past epidemics to estimate the scale of a potential ZIKV epidemic. For example, a chikungunya epidemic in India resulted in more than one million reported cases from 2005 to 2006 [9]. The massive scale of the chikungunya epidemic was due, in part, to the fact that the virus had been absent from the region for over 30 years, meaning that there was little or no existing herd immunity. If there is also limited herd immunity to ZIKV, then a massive epidemic may ensue. One model projects that a ZIKV epidemic could cause more than 450 million infections in India [10]. However, the true scale of a potential ZIKV epidemic in India is difficult to predict because we do not know how much of the population has been previously exposed to the virus. Serological and phylogenetic data suggest that ZIKV has been circulating in Asia since the 1950s [7,11], indicating that ZIKV is endemic. If this were the case in India, it would limit future outbreaks.

As of December 2018, nearly 100 pregnant women were reported to be infected with ZIKV in India. With ~25 million births each year, an extensive ZIKV epidemic in India (assuming no pre-existing immunity) could result in 9–12 million infections among pregnant women across the country [10]. In an attempt to evaluate the risk for ZIKV-associated birth defects, the Indian public health authorities sequenced five isolates from Rajasthan and concluded that they cannot cause microcephaly unless the virus mutates[i,ii,iii]. In Madhya Pradesh, recent ZIKV sequencing results led the researchers to conclude that it 'is not a severe strain'[iv]. Indian officials also used these data to ask the US Centers for Disease Control and Prevention to withdraw or modify its Zika travel alert to India because the strain lacks the 'gene responsible for causing microcephaly'[v]. Despite these strong statements, and a World Health Organization policy statement on sharing pathogen-sequencing results during outbreaks[vi], no genetic or epidemiological data have been made available for anyone to corroborate their findings.

There is no denying that a simple molecular test to determine the outcome of ZIKV infections in pregnant women would be game-changing, but at present, no such test exists. The Indian public health authorities were likely misled into thinking that a single mutation can predict the risk of ZIKV-associated microcephaly based

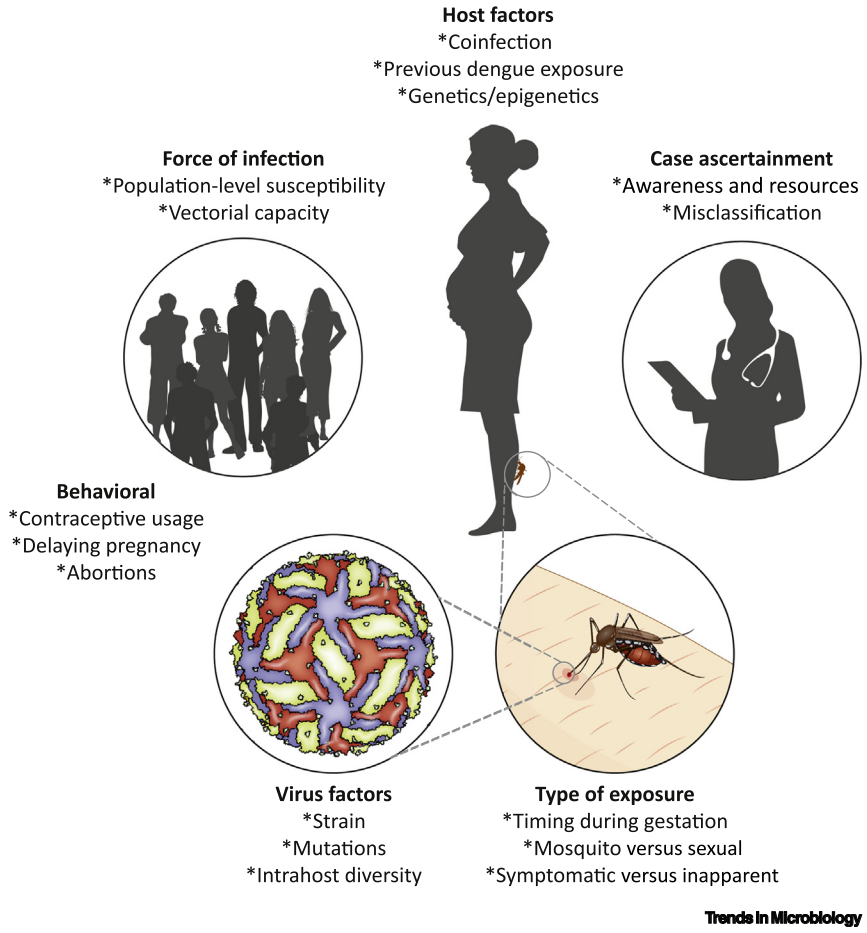

Figure 1. Potential Factors That Influence the Rates of Congenital Disease Caused by Zika Virus (ZIKV). A range of biological and nonbiological factors determine whether pregnant women will become infected by ZIKV (force of infection, behavior), the occurrence of congenital disease (type of exposure, host factors, virus factors), and whether congenital disease associated with ZIKV is reported (case ascertainment). The impact of these factors, especially host and virus factors, is mostly unknown.

on a study published by Yuan *et al*. [1]. The authors hypothesized that, because ZIKV transmission has occurred in Asia since at least the 1960s, and cases of ZIKV-associated microcephaly were not reported in the region, ZIKV had evolved to cause congenital disease just prior to its introduction into the Americas [1]. Yuan *et al*. evaluated different ZIKV mutations that arose between 2008 and 2013 and found that the S139N mutation enhanced neurovirulence in neonatal mice and *in vitro* viral replication in human neurons [1]. Critically, however, Yuan *et al*. did not assess whether the mutation enhances the ability of ZIKV to cross the placental barrier – the most important factor for congenital disease. Several studies indicate that ZIKV strains without the S139N mutation can still cross the placental barrier in animals and damage neurons (e.g., [2–4]). While S139N may enhance the risk of severe congenital disease once ZIKV is in the fetal brain in experimental animals, microcephaly in humans may not depend upon this single virus mutation. In fact, a microcephaly case recently diagnosed in Thailand was associated with a ZIKV strain that did not have the S139N mutation [5].

More than 1.6 million ZIKV cases and ~3000 microcephaly cases were reported during the 2015–2016 epidemic in Brazil[vii]. During this epidemic, and the subsequent spread of a single ZIKV strain in the Americas, it was estimated that, of the infants whose mothers were exposed to ZIKV during pregnancy, only a fraction (3–6%) developed microcephaly[vii] [12]. This indicates that other factors, in addition to ZIKV genetics, can influence the risk of severe outcomes of congenital ZIKV syndrome (Figure 1). For example, the timing of ZIKV infection during gestation impacts congenital disease, with higher rates observed when infection occurred during the first trimester [12], and individual fetuses may respond differently to ZIKV infection [13]. Furthermore, if an outbreak is unrecognized, or if there is a lack of clinical resources and expertise to diagnose both congenital disease and ZIKV infections, then identifying severe manifestations of congenital ZIKV syndrome, such as microcephaly, may go unrecognized [14]. This scenario may explain why microcephaly was not associated with ZIKV infections until after a large outbreak occurred in Brazil, a tropical country suitable for mosquito-borne transmission and home to a uniformly susceptible population [8]. It was only after the discovery in Brazil that researchers and clinicians began to look for and find associations between ZIKV exposure and birth defects in Africa [6] and Asia [5]. This suggests that a lack of previous evidence is not necessarily indicative that certain ZIKV strains cannot cause birth defects [15], but rather severe clinical manifestations associated with fetal ZIKV infection were not being diagnosed and reported. These issues with accurate reporting also make it difficult to distil which of the other biological and nonbiological factors contribute to the manifestation of severe birth defects caused by ZIKV, and in which context. Making progress requires a global effort to do large-scale epidemiological investigations and access to historical data to determine the baseline rates of microcephaly and other birth defects (which are currently not available in

India). Until new evidence suggests otherwise, all ZIKV strains should be considered to have the potential to cause birth defects, and many region-specific factors need to be taken into account when evaluating the population risks.

The misleading messaging about the risks of microcephaly during the ongoing ZIKV outbreaks in India stems from many failed processes: (i) the journal review process for allowing overextrapolated findings to be published, (ii) the process by which journals and researchers disseminate information to the public, (iii) the interpretation and fact-checking process by the press, leading to over-hyped and sensationalized stories (e.g.,[viii]), and (iv) the lack of robust scientific advisory committees for public health institutions. Not only should we be vigilant about the threat of future ZIKV spread, but also of the spread of misinformation that could put many vulnerable populations at risk. It is imperative that we stop trying to assign a phenotype to a virus based on its strain to diminish the perceived risks without strong epidemiological evidence. This messaging is a real disservice to control efforts. In the absence of licensed vaccines or prophylactic drugs, our most powerful weapons to combat ZIKV are mosquito control, education, and support from clinicians, community health workers, and social workers. Health policy towards ZIKV should be based on strong epidemiological evidence and open communication to empower the public.

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Resources

[i]www.pib.nic.in/PressReleseDetail.aspx?PRID=1551803

[ii]www.thehindu.com/sci-tech/health/stopping-the-virus/article25580955.ece

[iii]www.thehindu.com/opinion/op-ed/cause-to-remain-alert/article25457709.ece

[iv]https://timesofindia.indiatimes.com/city/bhopal/uganda-strain-of-zika-virus-found-in-madhya-pradesh-aiims-report/articleshow/67414003.cms

[v]https://indianexpress.com/article/india/not-so-alarming-revise-zika-alert-india-to-cdc-5514459/

[vi]http://apps.who.int/iris/handle/10665/254440

[vii]www.paho.org/hq/dmdocuments/2017/2017-phe-zika-situation-report-bra.pdf

[viii]www.latimes.com/science/sciencenow/la-sci-sn-zika-mutation-microcephaly-20170928-story.html

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References

1. Yuan, L. *et al.* (2017) A single mutation in the prM protein of Zika virus contributes to fetal microcephaly. *Science* 358, 933–936.
2. Rosenfeld, A.B. *et al.* (2017) Replication of early and recent Zika virus isolates throughout mouse brain development. *Proc. Natl. Acad. Sci. U. S. A.* 114, 12273–12278.
3. Jaeger, A. *et al.* (2018) Zika viruses of both African and Asian lineages cause fetal harm in a vertical transmission model. *bioRxiv* Published online August 7, 2018, https://doi.org/10.1101/387118.
4. Setoh, Y.X. *et al.* (2018) Fetal brain infection is not a unique characteristic of Brazilian Zika viruses. *Viruses* 10, 541.
5. Wongsurawat, T. *et al.* (2018) Case of microcephaly after congenital infection with Asian lineage Zika virus, Thailand. *Emerg. Infect. Dis.* 24, 1758.
6. Rosenstierne, M.W. *et al.* (2018) Zika virus IgG in Infants with microcephaly, Guinea-Bissau, 2016. *Emerg. Infect. Dis.* 24, 948.
7. Ishtiaq, F. (2018) A call to introduce structured Zika surveillance in India. *Trends Parasitol.* 34, 92–95.
8. Messina, J.P. *et al.* (2016) Mapping global environmental suitability for Zika virus. *eLife* 5, e15272.
9. Mavalankar, D. *et al.* (2007) Chikungunya epidemic in India: a major public-health disaster. *Lancet Infect. Dis.* 7, 306–307.
10. Siraj, A.S. and Perkins, T.A. (2017) Assessing the population at risk of Zika virus in Asia – is the emergency really over? *BMJ Glob. Health* 2, e000309.
11. Haddow, A.D. *et al.* (2012) Genetic characterization of Zika virus strains: geographic expansion of the Asian lineage. *PLoS Negl. Trop. Dis.* 6, e1477.
12. Johansson, M.A. *et al.* (2016) Zika and the risk of microcephaly. *N. Engl. J. Med.* 375, 1–4.
13. McGrath, E.L. *et al.* (2017) Differential responses of human fetal brain neural stem cells to Zika virus infection. *Stem Cell Rep.* 8, 715–727.
14. Costa, F. *et al.* (2016) Emergence of congenital Zika syndrome: viewpoint from the front lines. *Ann. Intern. Med.* 164, 689–691.
15. Nutt, C. and Adams, P. (2017) Zika in Africa – the invisible epidemic? *Lancet* 389, 1595–1596.

Spotlight

Influenza and *Staphylococcus aureus* Coinfection: TLR9 at Play

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Bacterial lung infections are frequent causes of mortality following influenza infection, but the fundamental mechanisms remain largely unknown. A new study by Martínez-Colón *et al.* (*PLoS Pathog*. 2019;15:e1007560) now suggests that influenza-induced immune suppression of *Staphylococcus aureus* is mediated by TLR9 signaling.

Secondary bacterial pneumonia, particularly with *Streptococcus pneumoniae* and *S. aureus*, is a frequent cause of severe morbidity and mortality associated with influenza infection. Likely due to difficulties in modeling *S. aureus* infection in mice, previous *in vivo* studies were often performed with secondary *S. pneumoniae* infection. However, in recent years, the increasing incidence of fatal methicillin-resistant *S. aureus* (MRSA) pneumonia has promoted a need for direct investigations of influenza and *S. aureus* coinfection pathogenesis.

In both influenza/*S. pneumoniae* and influenza/*S. aureus* coinfection models, a