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Did Zika virus attenuation or increased virulence lead to the emergence of congenital Zika syndrome?

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Teaser: The global emergence of Zika revealed the unprecedented ability of a mosquito-borne virus to cause severe congenital abnormalities. Recent studies indicate that the ability to harm fetuses is not a novel feature of Zika virus. Counter-intuitively, it may have in fact recently ‘attenuated’ from killing embryos to causing birth defects.

Zika virus (ZIKV) was once considered an innocuous member of mosquito-borne flaviviruses because documented human infections had remained sporadic and benign during several decades following its discovery. From the first isolation of ZIKV in 1947 in Uganda to the first documented human outbreak in 2007 in Micronesia, fewer than 20 human cases were reported and all were associated with mild and self-limiting symptoms.¹ The large-scale ZIKV epidemics that have occurred since 2007 and the unexpected link to neuropathologies and birth defects subsequently raised ZIKV to the status of global public health emergency.¹ The emergence of ZIKV culminated in 2016 in the Americas where thousands of babies were born with congenital Zika syndrome, a range of birth abnormalities including microcephaly, a smaller-than-normal head size. ZIKV typically circulates in sylvatic transmission cycles between non-human animals and forest-dwelling mosquitoes, but can occasionally spillover to humans and initiate a human transmission cycle primarily mediated by the domestic mosquito vector, *Aedes aegypti*.² Whereas this emergence mechanism is similar to that of yellow fever and dengue viruses, the ability for a mosquito-borne flavivirus to cause severe birth defects is unprecedented.

In the last few years, considerable research effort has been dedicated to understanding the factors that might have contributed to the explosive emergence of ZIKV, and the appearance of previously unobserved severe clinical manifestations.³ Proposed explanations generally fall

under two non-mutually exclusive hypotheses. On the one hand, ZIKV emergence could have simply resulted from fortuitous introduction of the virus into immunologically naïve human populations in the presence of high densities of *Ae. aegypti*. In this case, novel clinical manifestations would simply result from the increased ability to detect rare complications due to the sheer number of infections. On the other hand, the virus could have evolved and acquired new features facilitating its emergence in the human population, such as adaptation to the human transmission cycle. In particular, whether ZIKV recently acquired mutations increasing its fetal pathogenicity has been intensely debated^{4,5} and supported by some experimental evidence in mouse models. For instance, a single amino-acid substitution in the viral precursor membrane protein led to impaired embryonic brain development and increased mortality of neonatal mice after intracranial virus injection.⁶ Another substitution in the viral envelope protein increased neurovirulence in neonatal mice and produced higher viral loads in the placenta and fetal heads in pregnant mice.⁷ Both mutations arose just prior to the 2013 outbreak in French Polynesia and were maintained during subsequent spread to the Americas. However, the observations that ancestral viral variants can also result in microcephalic phenotypes and that reverse mutations in epidemic strains do not abolish neurovirulence or vertical transmission^{6,8} indicate that there are not the sole determinants of ZIKV fetal pathogenicity.

ZIKV consists of two phylogenetically distinct lineages, the African lineage and the Asian lineage (Figure 1). The two lineages presumably diverged about two centuries ago⁴ and they only share ~88% of their genome sequence, which translates into more than 100 different amino acids in the viral polyprotein. Strikingly, all documented human ZIKV outbreaks so far have been associated with strains belonging to the Asian lineage.³ For instance, epidemic ZIKV strains isolated during the American outbreak form a monophyletic subclade within the Asian lineage (Figure 1). However, neurotropism and vertical transmission are not exclusively associated with the American subclade or the epidemic strains from the Asian lineage. ZIKV strains from both lineages interfered with multiple aspects of neurodevelopment in organotypic brain slice cultures.⁹ Both historic and contemporary strains of ZIKV productively altered the outcome of pregnancy in an immunocompetent mouse model of transplacental transmission.¹⁰ In particular, intrauterine inoculation of an African ZIKV strain isolated in 1968 in Nigeria resulted in productive infection of placental and fetal tissues including the fetal

brain, and resulted in neuroinflammation and cortical thinning in neonatal brains.¹⁰ Similarly, an African ZIKV strain isolated in 1984 in Senegal infected and harmed fetuses to a greater extent than Asian ZIKV strains in an immunocompromised mouse model of vertical transmission.⁸ In the same mouse model, the ability to cause fetal harm was not associated with the viral precursor membrane mutation that emerged and spread during the American outbreak and was suggested to increase fetal pathogenicity.⁸ Finally, prenatal infection of immunocompetent mouse embryos with an African ZIKV strain isolated in 2011 in Senegal resulted in embryonic death whereas Asian ZIKV strains caused microcephaly.¹¹

The observations that some African ZIKV strains and pre-epidemic Asian strains are neurotropic and possess the ability to cross the placenta and cause fetal harm⁸⁻¹¹ do not support the idea that ZIKV global emergence was associated with the recent evolution of more pathogenic virus variants from the Asian lineage. Based on the principle of maximum parsimony – an optimality criterion used in phylogenetics to minimize the total number of character-state changes – it is more likely that the ability to cause fetal harm was always present during ZIKV evolution rather than lost and subsequently reacquired or independently acquired multiple times. In other words, these studies support the hypothesis that neurotropism, vertical transmission and fetal pathogenicity are not new but ancestral features of ZIKV. Ancestral neurotropism is also consistent with the evolutionary hypothesis that ZIKV originates from a recombination event between an *Aedes*-borne flavivirus and a neurotropic *Culex*-borne flavivirus.¹² A recent study even put forward the idea that ZIKV ‘attenuation’ rather than increased virulence was in fact responsible for the outbreak of congenital Zika syndrome.¹¹ In this study, African ZIKV strains were associated with fetal death rather than birth defects in an immunocompetent mouse model.¹¹ Moreover, a non-epidemic Asian strain isolated in 2014 in Thailand was associated with more adverse fetal outcomes than an epidemic Asian strain isolated in 2013 in French Polynesia.¹¹ When ZIKV infection causes abortion rather than birth defects, it is arguably less likely to be detected by public health surveillance systems because spontaneous abortion is typically unnoticed and/or unreported. If these findings are confirmed in humans, they imply that ZIKV strains that are not lethal to fetuses but cause birth defects are more likely to emerge as a public health issue. Considering that microcephaly is less severe than abortion is obviously a virologically-oriented interpretation. ZIKV infection during pregnancy is clearly more medically and psychologically

impactful when the consequence is a severe birth defect instead of an early abortion. Therefore, using the term 'attenuated' to qualify ZIKV strains that are not lethal to the fetus is only appropriate from a purely virological and evolutionary viewpoint. From this perspective, it is possible that the evolution of ZIKV fetal lethality – from fetal death to fetal abnormalities – may have facilitated the recognition of ZIKV fetal pathogenicity.

The spectacular global emergence of ZIKV and the appearance of previously unobserved birth defects caused by infection during pregnancy may thus be due to a combination of extrinsic factors that triggered the human transmission cycle on a large scale, and the propensity of the Asian ZIKV strains to cause fetal abnormalities and not fetal loss. The extrinsic factors that allowed ZIKV emergence on a global scale are probably the same as for the emergence of yellow fever and dengue viruses, centuries and decades earlier, respectively. These extrinsic factors include high population densities of *Ae. aegypti* mosquitoes promoted by rampant urbanization and large-scale virus dispersal through intense globalization of exchanges. In turn, the large number of human ZIKV infections that occurred between 2013 and 2018 was a major contributing factor to the detection of rare congenital malformations.¹ Indeed, an estimated 20-30% of women who were infected during their pregnancy transmitted ZIKV to their fetuses, among which 4-6% developed microcephaly.¹ One cannot say with certainty if an equivalent increase of the incidence of fetal loss would have been detected by public health surveillance systems during an epidemic of the same magnitude, but it would have certainly changed the perception of the public health threat, the long-term consequences and the responses to the epidemic. Whether ZIKV 'attenuation' from fetal lethality to sub-lethality was adaptive or random is currently unknown. At first sight, there is no obvious evolutionary advantage for the virus to cause birth defects rather than abortion, but fetal sub-lethality could be an indirect consequence of the adaptive evolution of another trait influencing viral fitness such as increased potential for transmission. Correlated evolution of traits is expected for viruses with a compact genome because they typically rely on genetic pleiotropy. However, the observation that ZIKV strains from the African lineage combine high transmissibility and fetal lethality¹¹ indicate that these two phenotypes are not necessarily incompatible. Therefore, the evolution of ZIKV 'attenuation' could have been driven by genetic drift, which may have randomly captured attenuated variants through a founder effect when the Asian and African lineages diverged.¹³ Although the lack of longitudinal samples consistently

collected throughout ZIKV evolution prevents direct reconstruction of the evolutionary trajectory, future reverse genetic experiments using both Asian and African ZIKV strains could shed light on the viral genetic determinants of ZIKV fetal pathogenicity.

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Author contributions

LL wrote the paper.

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Conflicts of interest

The author has declared no conflicts of interest.

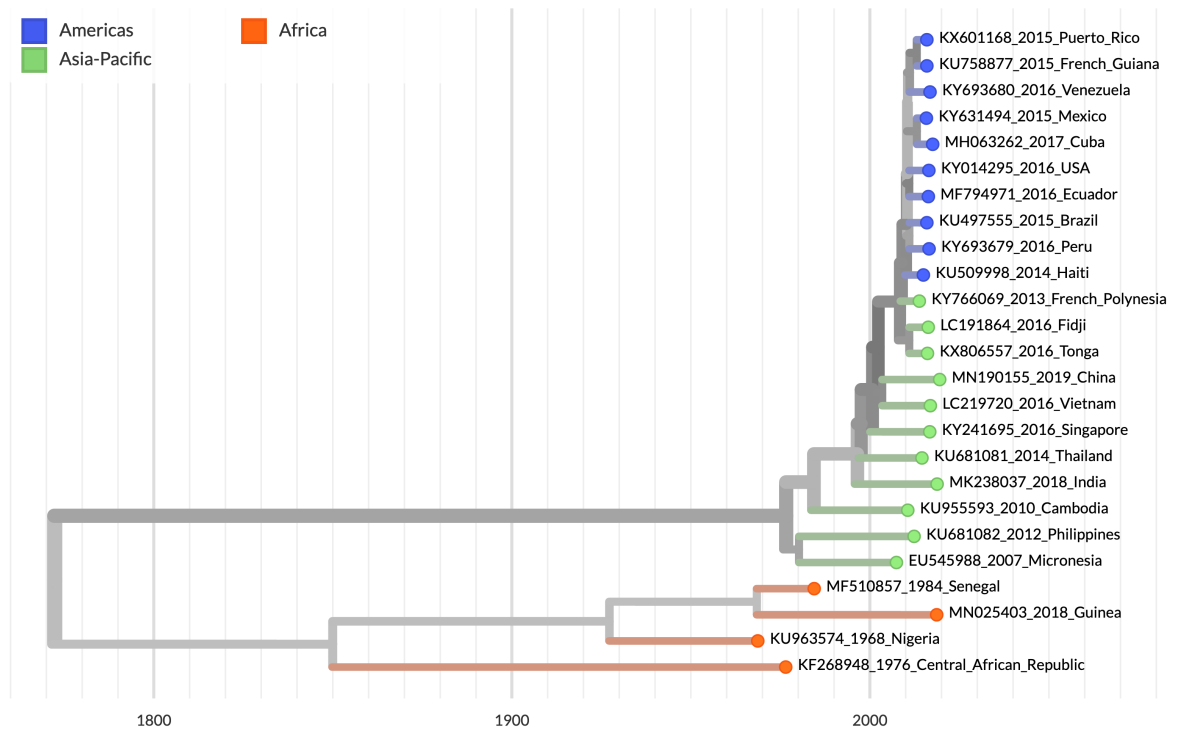


Figure 1. ZIKV phylogenetics. The tree represents the time-resolved phylogenetic relationships of selected ZIKV strains color-coded by their geographical region of origin. The 25 strains included in the tree are representative of the known worldwide genetic diversity and are labeled with the GenBank accession number of their genome sequence, date and location of collection. The tree was constructed using the Nextstrain build (<https://nextstrain.org/>) with Spondweni virus (GenBank accession number MN NC_029055) as the outgroup.