Hiding in plain sight: an evolutionary approach to the South American Zika outbreak and its future consequences

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ABSTRACT. Emerging Infectious Diseases (EID) pose a world-wide health and socio-economic threat. Accelerating climate change and globalization are exposing unforeseen ways that pathogens cope with their surroundings. The 2015 Zika virus (ZIKV) outbreak was an example of expansion into previously inaccessible fitness spaces, causing a sudden epidemic. Recent studies indicating the subsequent decrease in symptomatic cases means the virus is in remission, currently poses little threat, and therefore can be ignored. We present an evolutionary scenario derived from the Stockholm Paradigm, of oscillating phases of expansion and isolation, accompanied by changes in transmission, persistence, virulence, and pathology. Chief among these is the likelihood that asymptomatic strains are constantly transmitted sexually. This suggests that the currently quiescent virus retains capacities to reemerge abruptly and spread rapidly in an arena of changing opportunity.

KEY WORDS. Emerging Infectious Disease, outbreaks, Stockholm Paradigm, Zika virus.
Guillain-Barré syndrome in the South-Pacific and in Colombia (Mendez et al. 2017). As expected, medical and epidemiological research scrambled to get a hold of the new virus, and studies initially focused on controlling the suspected vector A. aegypti. It is not completely without base to assume that the mosquito transfers Zika, since closely related viruses (chikungunya and dengue) have stable populations in South-America and are transmitted by A. aegypti. Nevertheless, although this mosquito is still a competent vector of the African strain, it transmits the American and Asian Zika strains much less efficiently (Roundy et al. 2017). Additionally, none of the widespread, related mosquito species seem capable of transmitting the virus (Dodson et al. 2018). Furthermore, the peak of Zika related cases appears to have been sustained outside of the mosquito-breeding season, which suggests the existence of an alternate transmission route underlying a vector-borne pathway (Ferdousi et al. 2019).

We must revisit previous cases and explore a neglected aspect of Zika biology. Along with the sudden change in virulence, the 2007 Zika outbreak in Yap produced one of the first documented cases of the sexual transmission of the virus (Foy et al. 2011, Sakkas et al. 2018). Little studied at the time, the number of documented cases of sexually acquired Zika has increased (Moreira et al. 2017). Furthermore, human male patients shed Zika RNA in the semen six months after the remission of their clinical symptoms (Barzon et al. 2016), and the virus increases the rate of spermiogenesis (Sakkas et al. 2018). With as many as 80% of infected adults reporting no symptoms, sexual contact could be an effective mode of transmission (Freour et al. 2016).

Phylogenetic studies show that Zika originated in Africa and dispersed to Asia, likely as a result of human migrations approximately 60 years ago (Smith et al. 2018). There is evidence that a sexually transmitted strain or genotype of Zika was present in the African lineage (Sakkas et al. 2018), along with the common vector-borne strain. When expanding its distribution to Asia, Zika faced new mosquito taxa, but the human host remained constant. The sexually-transmitted variant (Sakkas et al. 2018) had the advantage of not having to expand to new vectors and its prevalence seems to have been amplified by selection as a result. The Asian strain introduced to the New World thus already had an enhanced capacity for sexual transmission relative to the African strain. Zika must be seen as a virus that persists through an interconnected network of both vectored and sexual transmission, increasing and expanding the risk factors associated with potential pandemics (Ferdousi et al. 2019).

Pathogenicity and virulence

Pathogen-host associations do not always produce disease, even when the pathogen multiplies extensively in the host. As well, though in many pathogens (e.g. Influenza A and B virus) a high pathogen replication rate is associated with elevated pathogenicity (the potential of the pathogen to cause disease in a single host specimen), virulence (the measure of how much damage a pathogen causes to the host) is not necessarily associ-
and cause serious neural damage (Ahmad et al. 2018, Mladinich et al. 2017). This VNDT motif is polymorphic in both African and Asian strands, but American ZIKV isolates carry only the one VNDT morph (Mladinich et al. 2017), suggesting a recent change in the genome of the virus. Additionally, the abrupt loss of genetic variation in the newly emergent American strand corresponds with the founder effect (Provine 2004), when a small subset of the original population establishes a lineage, with different characteristics due to the decreased genetic variation. When applied to Zika, the Brazilian lineage is derived from the VNDT morph capable of neuro-invasion and represents a subset of the original ZIKV populations. Furthermore, recent studies showed that ZIKV is capable of causing long-term fetal developmental anomalies, including autism spectrum disorder, and other than neural damage, and poses a threat to pregnant mothers, regardless of the declining epidemic (Chakhtoura et al. 2018, Vianna et al. 2018, Walker et al. 2019).

A Specific Case of a General Principle

The Zika story highlights all the elements of the Stockholm Paradigm (Textbox 1). Beginning in Africa, where it is primarily a mosquito-transmitted pathogen, in keeping with the ancestral legacy of its closest relatives. African ZIKV also demonstrates plasticity in transmission, being capable of sexual transmission at a low level. When climate changes created hospitable connections out of Africa through the Arabian peninsula, ancestral ZIKV expanded geographically into Asia via ecological fitting. During this generalization in geographical fitness space, ZIKV was exposed to novel mosquitos but the same ancestral vertebrate hosts (including humans). That generalization in host fitness space led to decreased and diffuse selection focused on mosquito transmission with concomitant increased and focused selection on sexual transmission, produced an isolated, specialized form of ZIKV in Asia. The new specialized Asian form became what it is today, predominantly a sexually transmitted pathogen that

| Textbox 1. The Stockholm Paradigm. |
|-------------------------------------|
| For more than 60 years, pathogens and hosts have been envisioned as engaged in evolutionary arms races, each participant mutually modifying the other. The increasing specialization of a pathogen with respect to a given host should be accompanied by decreasing ability to survive in association with other hosts. In order to switch to a new host, therefore, a pathogen must first evolve novel host-use capacities and then colonize a suitable new host. Given the absence of a mechanism by which such mutations could emerge in response to the presence of any particular novel host, coevolution has been viewed as a kind of firewall against emerging disease; host switches should not be common (Thompson 1994, Wolfe et al. 2007). And yet, host switching happens often in real time and phylogenetic studies indicate that host switching has always been common (Brooks and Boeger 2019, Hoberg and Brooks 2008, 2015). This has been called the Parasite Paradox; how can ecologically specialized pathogens switch hosts easily? |
| The Stockholm Paradigm resolves the paradox by recognizing the influence of two fundamental but often overlooked aspects of Darwinian evolution. First, inherited traits of adaptive significance may be highly specialized but are also phylogenetically conservative (Brooks and McLennan 2002, Darwin 1872). The conservative nature of pre-existing specialized adaptations, aided by phenotypic plasticity and co-option produces ecological fitting (Agosta et al. 2010, Brooks and McLennan 2002, Janzen 1985), the ability of pathogens to take advantage of novel host opportunities based on pre-existing specializations. Entire pathogen communities ranging across a geographically expansive wide range of habitats, may be structured by ecological fitting (Brooks et al. 2006), suggesting that the potential for changing hosts through ecological fitting is large (fitness space is “sloppy”: Agosta 2006, Agosta and Klemens 2008). Second, strong coevolutionary arms race dynamics are intimate affairs, affecting a given pathogen and a given host at a given place. As a result, they have no impact on other potential pathogen-host associations in other places. The efficacy of a coevolutionary arms race is weakened in proportion to the number of different hosts occupied. Modelling efforts show that, as hosts are added, specialized coevolutionary arms race dynamics become generalized Red Queen dynamics in which the pathogen has all the advantages, because all hosts are focused on a single pathogen while the pathogen can take advantage of variation among multiple hosts (Araujo et al. 2015, Braga et al. 2018, Brooks et al. 2019). Environmental perturbations change the opportunity space for pathogens, altering trophic structures and geographic distributions. They increase the chances that a pathogen will encounter susceptible, but previously unexposed, hosts. Highly specialized pathogens become more generalized by virtue of occupying a larger proportion of susceptible hosts. Environmental stability reduces connectivity in fitness space, producing localized isolated pathogen-host associations in which novel specialized variants may arise and survive. Though arising in a localized context, such novel variants often have substantial potential for ecological fitting whenever the next perturbation creates new opportunities. Over long periods of time, pathogen diversity is thus shaped by increases and decreases in host range (the Oscillation Hypothesis: Janz and Nylin 2008, Janz et al. 2006) and expansions and isolations in geographic distribution (the Taxon Pulse: Erwin 1981, Halas et al. 2005). The Stockholm Paradigm thus identifies a critical, but simple role for climate change in the evolution of emerging diseases. Disease emergence occurs when pathogens are given the opportunity to explore more widely in fitness space based on pre-existing specific, yet phylogenetically conservative traits. In today’s world, such opportunities are being provided not only by the current episode of climate change, but also by increasing population density and hyper-connectivity of an increasing urbanized technological humanity. |
and public attention should be drawn to the elevated likelihood HIV, Chlamydia and many other STDs should also screen for ZIKV, screenings, identical to those applied for the diagnosis of Herpes, most recent reminder of the significance of protected sex. Regular introduction and spread). As an emergent STD, Zika is just the transmission; and (4) cause damage to fetuses and neurological transmission; and (4) cause damage to fetuses and neurological damage (in order of increasing cost) through unprotected sex; through screening both partners before conception; and by massive screening of all men and women, in countries where ZIKV is known to exist (to mitigate the next outbreak) and in countries where it is not yet known to exist (to mitigate its introduction and spread). As an emergent STD, Zika is just the most recent reminder of the significance of protected sex. Regular screenings, identical to those applied for the diagnosis of Herpes, HIV, Chlamydia and many other STDs should also screen for ZIKV, and public attention should be drawn to the elevated likelihood of acquiring Zika through intimate relationships.

These efforts will not eradicate the virus. They will help us buy time, postponing and mitigating the spread and impact of the next outbreak. During that time, we need to be assessing the possible connection between Zika and infertility. Viral infections are not considered major causes of such health problems, despite a large body of evidence of their capabilities in that regard. For example, immune reaction against trophoblasts can result in miscarriage or stillbirth. In line with these predictions, sexually transmitted viruses have already been demonstrated to terminate pregnancy at an early stage (Apari et al. 2014). Szaba et al (2018) found that ZIKV causes most developmental damage by inducing cross-immunity in the early stages of pregnancy. During embryonic development, the anti-tumor Type I interferon (IFN) is impaired to protect trophoblasts exhibiting tumor-like characteristics (Budhwani et al. 2018, Soundararajan and Jagannadha Rao 2004). Exposure to Zika reactivated IFN and triggered an immune reaction against the trophoblasts. As well, recent studies showed that the suppression of the interferon response also enables ZIKV to increase fibroblast growth factor expression, thereby enhancing spread of the virus to fetal glial cells and neurons (Limonta et al. 2019). Apart from causing neural damage, the virus has the potential to cause infertility. We suggest analyzing rates of miscarriages and stillbirths in affected areas before and after the outbreak. Female ZIKV patients should be monitored for spontaneous abortions or infertility issues.

The evolutionary story of ZIKV is fascinating, and the virus has become an important emergent pathogen. Strip away the unique details of this particular virus, however, and we find that ZIKV has been engaged in evolutionary business as usual for pathogens experiencing climate change events. That any pathogen can use climate change events to the extent allowed by their pre-existing capacities is a given. That those explorations of new connections in fitness space will lead to unanticipated innovations is also a given.

The alarming rise in microcephaly cases attracted international attention, because the symptoms of early neural-damage were easily noticeable. But other aspects of the pathogen’s pathology are far less conspicuous. Zika continues to exist in areas where it has been reported previously and has increased its geographic range since the 2015 outbreak in South America. With the recognition that Zika is a significant STD risk, with more than 80% of infected humans being asymptomatic, and with non-human vertebrate hosts being added to ZIKA’s host range, we must use this as a teachable moment about the potential impacts of business as usual for pathogen evolution during periods of climate change perturbations (Brooks et al. 2019).

ACKNOWLEDGEMENTS

We thank Eörs Szathmáry for his support and valuable contributions to the study. We also thank the Economic Development and Innovation Operational Programme (GINOP 2.3.2-15-2016-00057) for providing funding for the study. Funder website: https://www.palyazat.gov.hu/evaluation
Future implications of the emergent Zika virus

LITERATURE CITED

Agosta SJ (2006) On ecological fitting, plant-insect associations, herbivore host shifts, and host plant selection. Oikos 114: 556–565. https://doi.org/10.1111/j.2006.0303-1299.15025.x

Agosta SJ, Janz N, Brooks DR (2010) How specialists can be generalists: resolving the “parasite paradox” and implications for emerging infectious disease. Zoologia 27: 151–162. https://doi.org/10.1590/s1984-46702010000200001

Agosta SJ, Klemens JA (2008) Ecological fitting by phenotypically flexible genotypes: implications for species associations, community assembly and evolution. Ecology Letters 11: 1123–1134. https://doi.org/10.1111/j.1461-0248.2008.01237.x

Ahmad F, Siddiqui A, Kamal MA, Sohrab SS (2018) Inhibition of Neurogenesis by Zika Virus Infection. Cns & Neurological Disorders-Drug Targets 17: 78–86. https://doi.org/10.2174/187152731766180202115114

Anderson RM, May RM (1982) Coevolution of hosts and parasites. Parasitology 85: 411–426. https://doi.org/10.1017/s0031182000055360

Annamalai AS, Pattnaik A, Sahoo BR, Muthukrishnan E, Natarajan SK, Steffen D, Vu HLX, Delhon G, Osorio FA, Petros TM, Xiang SH, Pattnaik AK (2017) Zika Virus Encoding Nonglycosylated Envelope Protein Is Attenuated and Defective in Neuroinvasion. Journal of Virology 91: 16. https://doi.org/10.1128/jvi.01348-17

Apari P, de Sousa JD, Muller V (2014) Why Sexually Transmitted Infections Tend to Cause Infertility: An Evolutionary Hypothesis. Plos Pathogens 10: 5. https://doi.org/10.1371/journal.ppat.1004111

Araujo SBL, Braga MP, Brooks DR, Agosta SJ, Hoherb EP, von Hartenthal FW, Boeger WA (2015) Understanding Host-Switching by Ecological Fitting. Plos One 10: 17. https://doi.org/10.1371/journal.pone.0139225

Audy JR (1958) The localization of disease with special reference to the zooneses. Transactions of the Royal Society of Tropical Medicine and Hygiene 52: 309–328. https://doi.org/10.1016/0035-9203(58)90145-2

Barzon L, Pacenti M, Franchin E, Lavezzo E, Trevisan M, Sgarbiotto D, Palu G (2016) Infection dynamics in a traveller with persistent shedding of Zika virus RNA in semen for six months after returning from Haiti to Italy, January 2016. Eurosurveillance 21: 2–5. https://doi.org/10.2807/1560-7917.es.2016.21.32.30316

Beaver JT, Lelutiu N, Habib R, Skountzou I (2018) Evolution of Two Major Zika Virus Lineages: Implications for Pathology, Immune Response, and Vaccine Development. Frontiers in Immunology 9: 17. https://doi.org/10.3389/fimmu.2018.01640

Braga MP, Araujo SBL, Agosta S, Brooks D, Hoberg E, Nylin S, Janz N, Boeger WA (2018) Host use dynamics in a heteroge-neous fitness landscape generates oscillations in host range and diversification. Evolution 72: 1773–1783. https://doi.org/10.1111/evo.13557

Brooks DR, Boeger WA (2019) Climate change and emerging infectious diseases: Evolutionary complexity in action. Current Opinion in Systems Biology 13: 75–81. https://doi.org/10.1016/j.coisb.2018.11.001

Brooks DR, Hoberg EP, Boeger WA (2019) The Stockholm Paradigm: Climate Change and Emerging Disease. University of Chicago Press, Chicago.

Brooks DR, Hoberg EP, Boeger WA, Gardner SL, Galbreath KE, Herczeg D, Mejia-Madrid HH, Racz SE, Dursahnihan AT (2014) Finding Them Before They Find Us: Informatics, Parasites, and Environments in Accelerating Climate Change. Comparative Parasitology 81: 155–164. https://doi.org/10.1654/4724b.1

Brooks DR, McLennan DA (2002) The nature of diversity: an evolutionary voyage of discovery. University of Chicago Press, Chicago, Illinois.

Budhwni M, Mazzieri R, Dolcetti R (2018) Plasticity of Type I Interferon-Mediated Responses in Cancer Therapy: From Anti-tumor Immunity to Resistance. Frontiers in Oncology 8: 16. https://doi.org/10.3389/fonc.2018.00322

Chakhtoura N, Hazra R, Spong CY (2018) Zika virus: a public health perspective. Current Opinion in Obstetrics & Gynecology 30: 116–122. https://doi.org/10.1097/gco.0000000000000440

Cohen J (2018) Infectious disease steep drop in Zika cases undermines vaccine trial. Science 361: 1055–1056. https://doi.org/10.1126/science.361.6407.1055

Darwin C (1872) The origin of species. Murray, London.

Dick GWA (1952) Zika virus (II). Pathogenicity and physical properties. Transactions of the Royal Society of Tropical Medicine and Hygiene 46: 521–534. https://doi.org/10.1016/0035-9203(52)90043-6

Dodson BL, Pujhari S, Rasgon JL (2018) Vector competence of selected North American Anopheles and Culex mosquitoes for Zika virus. PeerJ 6: 10. https://doi.org/10.7717/peerj.4324

Dudley DM, Aliota MT, Mohr EL, Weiler AM, Lehrer-Brey G, Weisgrau KL, Mohns MS, Breitbach ME, Rasheed MN, Newman CM, Gellerup DD, Moncla LH, Post J, Schultz-Darken N, Schotzk ML, Hayes JM, Eudailey JA, Moody MA, Permar SR, O’Connor SL, Rakas E, Simmons HA, Capuano S, Golos TG, Osorio JE, Friedrich TC, O’Connor DH (2016) A rhesus macaque model of Asian-lineage Zika virus infection. Nature Communications 7: 9. https://doi.org/10.1038/ncomms12204

ZOOLOGIA 36: e36272 | https://doi.org/10.3897/zooologia.36.e36272 | November 26, 2019 5/7
Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, Pretrick M, Marfel M, Holzbauer S, Dubray C, Guillaumot L, Griggs A, Bel M, Lambert AJ, Laven J, Kosoy O, Panella A, Biggerstaff BJ, Fischer M, Hayes EB (2009) Zika Virus Outbreak on Yap Island, Federated States of Micronesia. New England Journal of Medicine 360: 2536–2543. https://doi.org/10.1056/NEJMoa0805715

Erwin TL (1981) Taxon Pulses, Vicariance, and Dispersal: An Evolutionary Synthesis illustrated by Carabid Beetles. In: Gareth NaDER (Ed) Vicariance Biogeography: A Critique. Columbia University Press, New York, 159–196.

Ewald PW (2004) Evolution of virulence. Infectious Disease Clinics of North America 18: 1–15. https://doi.org/10.1016/S0891-5520(03)00099-0

Ferrous T, Cohnstaedt LW, McVey DS, Scoglio CM (2019) Understanding the survival of Zika virus in a vector interconnected sexual contact network. Scientific Reports 9: 7253. https://doi.org/10.1038/s41598-019-43651-3

Foy BD, Kobylinski KC, Foy JLC, Blitvich BJ, da Rosa AT, Haddow AD, Lanciotti RS, Tesh RB (2011) Probable Non-Vectorborne Transmission of Zika Virus, Colorado, USA. Emerging Infectious Diseases 17: 880–882. https://doi.org/10.3201/eid1705.101939

Freour T, Mirallié S, Hubert B, Splingart C, Barriere P, Maquart M, Leparc-Goffart I (2016) Sexual transmission of Zika virus in an entirely asymptomatic couple returning from a Zika epidemic area, France, April 2016. Eurosurveillance 21: 10–12. https://doi.org/10.2807/1560-7917.es.2016.21.23.30254

Halas D, Zamparo D, Brooks DR (2005) A historical biogeographical protocol for studying host diversification by taxon pulses. Journal of Biogeography 32: 249–260. https://doi.org/10.1111/j.1365-2699.2004.01147.x

Hoberg EP, Brooks DR (2008) A macroevolutionary mosaic: episodic host-switching, geographical colonization and diversification in complex host-parasite systems. Journal of Biogeography 35: 1533–1550. https://doi.org/10.1111/j.1365-2699.2008.01951.x

Hoberg EP, Brooks DR (2015) Evolution in action: climate change, biodiversity dynamics and emerging infectious disease. Philosophical Transactions of the Royal Society B-Biological Sciences 370: 7. https://doi.org/10.1098/rstb.2013.0553

Janz N, Nylin S (2008) The Oscillation Hypothesis of Host-Plant Range and Speciation. In: Tilmon KJ (Ed) Specialization, Speciation, and Radiation: The Evolutionary Biology of Herbivorous Insects. Berkeley, University of California Press, 203–215.

Janz N, Nylin S, Wahlberg N (2006) Diversity begets diversity: host expansions and the diversification of plant-feeding insects. BMC Evolutionary Biology 6: 10. https://doi.org/10.1186/1471-2148-6-4

Janzen DH (1985) On ecological fitting. Oikos 45: 308–310. https://doi.org/10.2307/3565565

Limonta D, Jovel J, Kumar A, Lu J, Hou S, Airo AM, Lopez-Orozco J, Wong CP, Saito I, Branton W, Wong GK, Mason A, Power C, Hobman TC (2019) Fibroblast growth factor 2 enhances Zika virus infection in human fetal brain. Journal of Infectious Diseases. https://doi.org/10.1093/infdis/jiz073

May RM, Anderson RM (1983) Epidemiology and genetics in the coevolution of parasites and hosts. Proceedings of the Royal Society Series B-Biological Sciences 219: 281–313. https://doi.org/10.1098/rspb.1983.0075

Mendez N, Oviedo-Pastrana M, Mattar S, Caicedo-Castro I, Arrieta G (2017) Zika virus disease, microcephaly and Guillain-Barre syndrome in Colombia: epidemiological situation during 21 months of the Zika virus outbreak, 2015–2017. Archives of Public Health 75: 11. https://doi.org/10.1186/s13690-017-0233-5

Mladinich MC, Schwedes J, Mackow ER (2017) Zika Virus Persistently Infects and Is Basolaterally Released from Primary Human Brain Microvascular Endothelial Cells. Mbio 8: 17. https://doi.org/10.1128/mBio.00952-17

Moreira J, Peixoto TM, Siqueira AM, Lamas CC (2017) Sexually acquired Zika virus: a systematic review. Clinical Microbiology and Infection 23: 296–305. https://doi.org/10.1016/j.cmi.2016.12.027

Petersen LR, Jamieson DJ, Powers AM, Honein MA (2016) Zika Virus. New England Journal of Medicine 374: 1552–1563. https://doi.org/10.1056/NEJMra1602113

Provine WB (2004) Ernst Mayr: genetics and speciation. Genetics 167: 1041–1046.

Roundy CM, Azar SR, Rossi SL, Huang JH, Leal G, Yun R, Fernandez-Salas I, Vitek CJ, Papsloski IAD, Kitron U, Ribeiro GS, Hanley KA, Weaver SC, Vasilakis N (2017) Variation in Aedes aegypti Mosquito Competence for Zika Virus Transmission. Emerging Infectious Diseases 23: 625–632. https://doi.org/10.3201/ed2304.161484

Sakkas H, Bozidis P, Giannakopoulos X, Sofikitis N, Papadopoulou C (2018) An Update on Sexual Transmission of Zika Virus. Pathogens 7: 14. https://doi.org/10.3390/pathogens7030066

Silva JVV, Lopes TRR, de Oliveira EF, Oliveira RAD, Gil L (2017) Perspectives on the Zika outbreak: herd immunity, antibodydependent enhancement and vaccine. Revista do Instituto de Medicina Tropical de São Paulo 59: 2. https://doi.org/10.1590/s1679-9946201759021

Simonin Y, van Riel J, van der Velden S, Salinas S (2017) Differential virulence between Asian and African lineages of Zika virus. Plos Neglected Tropical Diseases 11: 8. https://doi.org/10.1371/journal.pntd.0005821

Smith DR, Sprague TR, Hollidays B, Valdez SM, Padilla SL, Bellanca SA, Golden JW, Coyne SR, Kulesh DA, Miller LJ, Haddow AD, Koehler JW, Gromowski GD, Jarman RG, Alera MTP, Yoon IK, Brathon R, Lowen RG, Kane CD, Minogue MD, Leparc-Goffart I (2016) Sexual transmission of Zika virus. New England Journal of Medicine 374: 1552–1563. https://doi.org/10.1056/NEJMra1602113
Phenotypic Differences Both In Vitro and In Vivo. American Journal of Tropical Medicine and Hygiene 98: 432–444. https://doi.org/10.4269/ajtmh.17-0685

Soundararajan R, Jagannadha Rao A (2004) Trophoblast ‘pseudo-tumorigenesis’: Significance and contributory factors. Reproductive Biology and Endocrinology 2: PMC407853. https://doi.org/10.1186/1477-7827-2-15

Szaba FM, Tighe M, Kummer LW, Lanzer KG, Ward JM, Lanther P, Kim IJ, Kuki A, Blackman MA, Thomas SJ, Lin JS (2018) Zika virus infection in immunocompetent pregnant mice causes fetal damage and placental pathology in the absence of fetal infection. Plos Pathogens 14: 26. https://doi.org/10.1371/journal.ppat.1006994

Thompson JN (1994) The coevolutionary process. University of Chicago, Chicago.

Vianna P, Gomes JD, Boquett JA, Fraga LR, Schuch JB, Vianna FSL, Schuler-Faccini L (2018) Zika Virus as a Possible Risk Factor for Autism Spectrum Disorder: Neuroimmunological Aspects. Neuroimmunomodulation 25: 320–327. https://doi.org/10.1159/000495660

Walker CL, Little MTE, Roby JA, Armistead B, Gale M, Rajagopal L, Nelson BR, Ehinger N, Mason B, Nayeri U, Curry CL, Waldorf KMA (2019) Zika virus and the nonmicrocephalic fetus: why we should still worry. American Journal of Obstetrics and Gynecology 220: 45–56. https://doi.org/10.1016/j.ajog.2018.08.035

Wolfe ND, Dunavan CP, Diamond J (2007) Origins of major human infectious diseases. Nature 447: 279–283. https://doi.org/10.1038/nature05775

Submitted: May 25, 2019
Accepted: June 28, 2019
Available online: November 26, 2019
Editorial responsibility: Sionei R. Bonatto

Author Contributions: PA KB and OM designed the study; PA OM and DRB collected data; PA KB DRB and OM analyzed the data; PA KB DRB and OM wrote the paper
Competing Interests: The authors have declared that no competing interests exist.
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