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Zika Virus in Brazil

Introduction

In 1947, medical researchers Dick, Kitchen, and Haddow found something completely unusual in Uganda. What they found were not the cases of yellow fever but rather of a new unrecorded virus. It would be called Zika virus as it was discovered in a rhesus monkey in the Zika Forest and in a group of *A. africanus* a year later (Dick et al., 1952). Zika virus remained uneventful, staying in the native African region that it was first found in, until it made its way into Brazil in the beginning of 2015 and spread rapidly throughout the country. What worried people was not of the Zika Fever, a mild illness consisting mainly of a headache and rash, but rather its link to microcephaly, a birth defect where a baby's head is significantly smaller than expected. Due to this, much research has been done on the biology, epidemiology, and social/environmental causes of Zika. From this information, the future impact of Zika can be evaluated and assessed.

Biology of Zika

Zika virus, or ZIKV for short, is according to Dick et al., "a member of the family Flaviviridae, genus Flavivirus, and is transmitted among humans by Aedes mosquito species such as *A. aegypti*, *A. albopictus*, and *A. africanus*" (1952). A flavivirus is a viral genome that is composed of a single-stranded RNA molecule. Virologists Perera et al. would discover that these flaviviruses enter the host cells by, "binding nonspecifically to the cell surface, followed by internalization specifically through clathrin-mediated endocytosis in a viral glycoprotein E-dependent manner,"(2013). Essentially, what this internalization means is that E glycoprotein enables the combination of the viral genome with the host cell which releases the viral genome to the rest of the cell. Zika virus, also referred to as ZIKV, is thus very similar to other mosquito-borne flaviviruses such as West Nile Virus and yellow fever (Song, Yun, Wooley, &

Lee, 2017). This similarity would explain why ZIKV was identified in the first place due to the similar effects, locality, and vector.

However, going one step further in the process does the spread of ZIKV become severe. Doctors Barzon, Trevisan, Sinigaglia, Lavezzo, and Palù would describe the pathogenesis as, "[Zika virus infects] and efficiently replicate in the placenta and in the brain and induced foetal demise or neural damage"(2016). The description given is corroborated by the fact that researchers Zhang et al. found that infection led to reduced forebrain organoid size (2017). In addition, when ZIKV was injected into the cerebroventricular space/lateral ventricle (LV) of an embryo's brain, cell populations were found damaged (Li et al., 2016). Ultimately, Birth defects would come to no surprise as the brain damage caused would go unchecked and last for months until birth.

Despite being a mosquito-borne flavivirus, there are other methods of transmission. As implied by the above paragraph, the virus can manifest itself in babies through vertical transmission. In addition, unprotected intercourse can lead to the transmission through the semen of the male. Researchers Matheron et al. found that through RT-PCR that ZIKV tested positive in semen samples with high viral loads. They then found that, "ZIKV excretion in semen can last at least 80 days after onset of symptoms, known to occur 2–12 days after exposure" (Matheron et al., 2016). ZIKV can last a long time in semen so even when the Zika Fever itself is gone, sexual contact can still pose a risk for transmission.

Not all cases of Zika virus are the same though. Researchers Saiz et al. find that there are about three major lineages of ZIKV. These are, "the African lineage, the Asian lineage (that includes the American strains) and a neglected lineage circulating in Africa (designated African II)" (Saiz et al., 2017). This is supported by the work of Faria et al. who sequenced seven Brazilian ZIKV genomes to find that they, "form a robust monophyletic cluster (bootstrap score = 94%) within the Asian genotype" (2016). The main differences between the Asian and African Lineages are that the Asian one does not cause significant cell death early on after infection. Although this may seem to make the Asain lineage weaker, scientists Anfasa et al. have seen that, "the fact that Asian ZIKV strains infect only a minority of cells with a relatively low burst size together with the lack of early cell death induction might contribute to its ability to cause

chronic infections within the central nervous system" (2017). This suggests that high occurrence of microcephaly due to Zika virus can be due to the virus' way of staying hidden by keeping host cells alive.

Social and Environmental Causes

Mobility is a key factor in spreading disease. In an interview, Dr. Castellón of the World Health Organization stated that, "...traders, students, vacations, tourism, [and] a constant coming and going between Brazil and Cabo Verde [was] an important factor for the introduction of the "Asian" virus in Cabo Verde and triggered the outbreak in our country" (Dye & Castellón, 2017). As Cabo Verde is an island nation off the coast of Africa, it wouldn't be too hard to imagine that Zika eventually made its way there and then to Brazil. This coincides with the increase in air traffic to Brazil in late 2012-early 2013 from ZIKV endemic areas, including outbreaks in islands like Cabo Verde. Specifically, Faria et al. used air traffic data to find, "an increase in the number of travelers arriving in Brazil from these [ZIKV endemic] countries, rising from 3775 passengers per month in early 2013 to 5754 passengers per month a year later" (2016). In essence, the increase in movement between ZIKV endemic countries and Brazil would eventually lead the virus to Brazil as infected passengers would bring the disease to the local mosquito population.

Zika virus performs at its best in urban environments. Barzon et al. noted that part of the reason the virus emerged was due to, "the presence of...susceptible human hosts in urban areas"(2016). Urban areas provide mosquito vectors a dense population. In fact, cities were made to attract mosquitoes. This was because many of the cities in Brazil experienced severe poverty. Data from The Brazilian Institute of Geography and Statistics recorded that in 2010, "about 11.4 million people in Brazil lived in favelas (slums) on the outskirts of metropolitan areas" (2011). Life in favelas means life without infrastructure, sewage systems, portable water, and waste management. In addition to the *Aedes* mosquitoes that would be attracted to the favelas, there exist other spillover hosts. Ali et al. had found that spillover of ZIKV came from, "capuchin monkeys and common marmosets…[who] are highly adaptable and thrive near industrialized cities"(2017). Both *Aedes* mosquitoes and humans who came in contact with these primates

could thus be infected with the virus. All in all, due to a mix of poverty and density, Zika virus would be able to spread easily through urban areas.

Rainfall and humidity play an important role in the transmission of Zika virus. This is because of the mosquito life cycle, mainly the *Ae. aegypti* mosquitos which are common in Brazil, which is highly sensitive to these factors. Using dengue virus, which is again very similar to ZIKV, as a base, S. Wiwanitkit, and V. Wiwanitkit created a mathematical model of predicted incidence of Zika virus. They saw a "rapid increase in predicted incidence...in mid of the year during rainy season" (S. Wiwanitkit & V. Wiwanikit, 2017). In the same paper, they noted how it confirmed their previous report of increased prevalence of Zika in Thailand during the rainy season (2017). Since the lineage of the Thailand virus and the Brazil virus are the same, the behavior of Zika should be similar. Buathong et al. found that in Thailand that humidity was a proven determinant of Zika virus. Using data from 7 sites in Thailand that experienced Zika outbreaks, they saw that the average humidity level is, "equal to (66.14% ± 19.86%) with min = 33% and max = 94%. The estimated range of humidity is between 51.30% and 81.15%" (Buathong et al., 2015). These numbers indicate the humidity was moderate to severe in these areas. As humidity is linked to rainfall, it is fair to assume that during Brazil's rainy season there is a high amount of humidity as well. All in all, the environment of Brazil's tropical regions were prime for an extended Zika transmission season.

Epidemiology

Possible dates and locations on the emergence of Zika virus vary. Zanluca et al. identify the World Cup soccer tournament that was held in Brazil from June to July 2014 (2015). Musso puts this at a slightly later date, stating that ZIKV was introduced in the Va'a canoe event held in Rio de Janeiro between in August 2014 (2015). These studies place specific events as the main cause of introduction which ignores some of the other possible causes of introduction. As stated earlier, travel from Zika endemic countries had already been occurring in 2013. Zhang et al. use this kind of information to build a more robust estimate. Through a "data-driven global stochastic epidemic model" they analyzed the spread of Zika virus in Brazil (Zhang et al., 2017). Their estimates concluded that the first introduction of ZIKV, "occurred between August 2013 and April 2014 (90% credible interval)" (2017). The latest date provided in the estimate is still a

couple of months behind the soccer tournament and Va'a canoe event, suggesting that it could not have been these events that first introduced Zika virus. What likely happened is that these two events brought an upsurge in Zika cases which helped make this an epidemic. What these sources do have in common is their predicted location of emergence: Rio de Janeiro. Zhang et al. continue their analysis stating that, "The most likely locations of ZIKV introduction, in descending order, are Rio de Janeiro (southeast), Brasilia (central), Fortaleza (northeast), and Salvador (northeast)" (2017). They mention the "greatest passenger flow" as the main reason for choosing this city (2017). Indeed, Rio de Janeiro is one of the most populated municipalities in Brazil meaning there are plenty of people to start the spread. Being a top tourist attraction on the coast, a plane or a boat could have easily transported an infected mosquito or person. All in all, the data suggests that Zika emerged in Rio de Janeiro in mid-2014, prior to the world cup.

Brazil would experience its first epidemic of Zika in 2015. Zhang et al., using the same data from when they calculated emergence, identified two 'waves' of Zika virus. The first occurred between January and July 2015, initially hitting the northeast region of Brazil but later spreading to the rest (2017). This is consistent with data from the World Health Organization and the Brazilian Ministry of Health. Towards the end of 2015, the World Health Organization stressed that ZIKV activity had expanded to at least 14 Brazilian states with an estimated 440,000-1,300,000 suspected cases (2015). Using data from The Brazilian Ministry of Health, Faria et. al stated that, "Reported cases in Brazil indicate an epidemic peak in mid-July 2015 and most Brazilian ZIKV cases (93%) were reported in Bahia state" (2016). Indeed the Bahia State, and the northeast region of Brazil in general, were hit the hardest throughout both waves. Researchers De Góes Calvancati et al. saw in their analysis of ZIKV cases that, "a very rapid dispersion of ZIKV was identified, mainly in the Northeast region. This area has the lowest vaccine coverage for YF and notified 65.7% of all cases[of ZIKV in Brazil]" (2016). The reason why northeastern Brazil was affected so harshly remains unknown. Speculation suggests that the northeast portion of Brazil was home to a very warm, tropical, and humid environment that mosquitoes congregated. Like the rest of Brazil, the northeast region was not prepared.

The second wave occurred between January and May 2016 (Zhang et al.).Faria et al. also used the data collected from The Brazilian Ministry of Health to present that, "In Brazil, nearly

30,000 cases of ZIKV infection had been notified by 30th Jan 2016" (2016). The Pan American Health Organization and World Health Organization released a detailed report on weekly cases where, "At the national level during 2016, an increase in the numbers of weekly cases was observed since EW 1, with a peak being reported in EW 7. A decreasing trend was observed since." (2017). In addition to an overall number of cases, this report offers specific epidemiological rates. They saw from March to September 2016, "there was an incidence rate of ZIKV infections of 69.22 cases/100,000 newborns, a mortality coefficient of 5.37 deaths/100,000 newborns and a case fatality rate of 7,750 deaths/100,000 cases. The highest incidence and mortality were found in the Northeast region with 201 cases/100,000 newborns and 4 deaths/100,000 newborns, respectively" (2017). From these rates, it can be seen that death from Zika is rare but it had started affecting a considerable number of newborns. It also points out how the northeastern region of Brazil was hit the hardest, having the highest incidence and mortality rates.

From the PAHO and WHO data, Zika virus has subsided currently and no new waves are expected. As of epidemiological week 33 (Mid July), "the highest Zika virus incidence rate has been observed in the states located in the North and Central-West region of Brazil, with Mato Grosso state reporting the highest cumulative incidence rate (714 cases per 100,000 population)" (2017). Zika has seemed to move from the Northeast to these new regions, again for unknown reasons. Speculation is that after the first wave public awareness of the disease allowed people in the northeast region to avoid mosquitoes, causing a shift.

The basic reproduction number of Zika virus has been estimated thanks to its similarity in other regions. Villela et al. did an analysis on surveillance notifications in Rio de Janeiro to find that the basic reproduction number was, "2.33, 95% CI: 1.97–2.97" (2017). This is broadly consistent with the basic reproduction number found by researchers Nishiura, Kinoshita, Mizumoto, Yasuda, and Nah in the outbreak in French Polynesia which ranged from 2-5 (2016). However, their estimates were a bit smaller than what was seen in Colombia. Being from the same lineage, it is fair to compare the Zika outbreaks in all these various countries. Doctors Nishiura and Mizumoto worked with Infectious Diseases and Infection Control Research Group members Villamil-Gómez and Rodríguez-Morales to find the basic reproduction number of Zika

virus in Colombia. They saw that the "MLE range of R_0 in Colombia [is] (3.0–6.6)" (2016). It is possible that Colombia was hit harder with Zika virus, but this increased number was offered because the number was calculated during a severe wave of ZIKV. In 2017, the virus had died down in Brazil allowing for estimates to be lower. In essence, the most consistent number of R_0 appears to be 3 as it is close or inside all of the previous estimates listed. This number indicates that the virus would indeed spread from Rio de Janeiro but not at an extreme pace. This matches with the theory that since Zika did not spread so quickly, it would stay hidden for a whole year. Infections in pregnant women would indeed be more rare, making it harder to see the correlation between birth defects and Zika virus exposure.

A rise in microcephaly cases that coincided with the outbreak of Zika caused extended investigation on these links. Schuler-Faccini et al. noted very early on during the first wave of Zika virus that, "The association of ZIKV with the reported microcephaly case clusters in Brazil during 2015" (2015). This agrees with the findings of França et al. where they saw, "Brazil, which likely experienced its first ZIKV epidemic peak in March 2015, had a sharp rise in microcephaly cases in September 2015" (2016). This sharp rise drove the work for more elaborate studies during the second wave. Broutet et al. would compare ultrasound findings of various women in Brazil. They had found that, "Ultrasound findings were abnormal, including indications of microcephaly, in 12 of 42 women with Zika virus disease and were normal in all 16 women with no Zika virus disease" (2016). Although there was not a strong correlation, Zika only appearing in about 28.57% of abnormal cases, a more elaborate study around the same time would help confirm the public's suspicions. De Araújo et al. conducted a case-control study in eight public hospitals in Recife, Brazil. Newborns with microcephaly were cases while newborns without microcephaly were controls. Results indicated that "Between Jan 15, 2016, and May 2, 2016...24 (80%) of 30 mothers of cases had Zika virus infection compared with 39 (64%) of 61 mothers of controls (p=0.12). 13 (41%) of 32 cases and none of 62 controls had laboratory-confirmed Zika virus infection" (2016). Within the same time period, microcephaly had an increased appearance in newborns whose mothers had been infected. This created a strong association between the Zika virus and microcephaly.

After the second wave, Zika settled down but that did not mean the risk was gone. Researchers would begin to wonder just how long cases of birth defects would remain. Eggo and Kucharski decided to quantify APO risk from a study on 134 women with Zika virus infection. They used this data from 9 regions in Brazil to estimate how long birth defect cases would be elevated after the epidemic. Their results suggest that "if fetal injury from Zika virus infection can occur across a range of gestational ages, APOs after a Zika outbreak could occur for a long time after the outbreak subsided" (Eggo and Kurcheski, 2018). Extended surveillance efforts were encouraged and indeed followed. According to the Brazilian Ministry of Health, "... suspected cases of microcephaly and other congenital malformations of the central nervous system (CNS) have been reported…[in] 1,851 [people] during 2017" (WHO & PAHO, 2017). Using data from the United Nations Population Division, Worldometers approximates the population of Brazil to be about 210 million(2017). 1851 cases/210 million total population gives an estimated prevalence of about 8.8 cases/1000 population. Before Zika hit Brazil, Cragan et al. of the CDC found a "prevalence (2.86 per 1,000) from the three population-based birth defects surveillance programs during the pre-Zika years," (2017). This suggests that Zika still has an effect on birth defects even though the epidemic had subsided.

Another notable sickness associated with Zika virus is Guillain-Barré syndrome (GBS). GBS is a disorder in which the body's immune system attacks part of its own nervous system.. The CDC states on their website that unlike microcephaly, this is not only a birth defect and can happen to any person(. In addition, CDC reports that, "Most people fully recover from GBS, though some people have permanent damage. Very few people die from GBS" (2017). This matches with current information on Zika as deaths are very uncommon but sickness can still occur. PAHO and WHO data indicate a peak around March in 2016 with an estimated 3000 cases(2017?). This corresponds with the PAHO and WHO data on Zika virus which had a peak around March 2016 also (2017). In addition with this correlation, researchers Cao-Loromeau et. al describe a case-control study in French Polynesia during the 2013-2014 outbreak where they saw, "that 41 of 42 patients with Guillain–Barré syndrome...(98%) were carrying Zika virus antibodies, as compared with 35 of 98 hospitalized controls" (2016). People with GBR typically had Zika virus in French Polynesia and the same effect was carried to Brazil. Not enough data

has been collected to show the Zika virus is a direct cause as of yet, but the association still remains.

Conclusion

Zika virus works in mysterious ways. Although preliminary work has been accomplished in showing that birth defects can be caused due to Zika entering the embryo and damaging the neural network of the child, it does not explain why Zika virus is associated with the rare Guillain-Barré syndrome. Even with knowledge of its close relatives like Spondweni virus and yellow fever, there are no current vaccinations against the virus. No one truly knows who was patient zero in Brazil but estimates indicate that a few months before the 2014 world cup that someone came to Rio de Janeiro and started the spread. What is known however are the known vectors and reservoirs for Zika in Brazil, those being Aedes mosquitoes and primates respectively. The warm urban cities that receive plenty of rainfall and humidity in Brazil make a great environment for mosquitoes to pass disease in an environment that suits them best. Two waves of Zika virus hit which lead to an increase in microcephaly cases and other birth defects. Ultimately, Zika virus has subsided but still remains an issue in Brazil. The long-term outlook for the disease carries dangerous implications if a vaccine is not developed or if people in Brazil forget about the virus. The same increase in urbanization and globalization that brought Zika virus to Brazil can easily cause an epidemic in other countries due to Zika's subtle nature. What is needed for future research is a complete understanding of how Zika interacts with the cells in a fetus and in the central nervous system. Methods of identification would also need to be improved on so Zika does not get mistaken for any of the other flaviviruses and to make surveillance easier.

References

Ali, S., Gugliemini, O., Harber, S., Harrison, A., Houle, L., Ivory, J., . . . Mordecai, E. A. (2017). Environmental and social change drive the explosive emergence of zika virus in the americas. *PLOS Neglected Tropical Diseases, 11*(2), e0005135.

Anfasa, F., Siegers, J. Y., van, d. K., Mumtaz, N., Stalin Raj, V., de Vrij, F.,M.S., . . . van Riel, D. (2017). Phenotypic differences between asian and african lineage zika viruses in human neural progenitor cells. *Msphere, 2*(4), e00292-17. doi:10.1128/mSphere.00292-17

Barzon, L., Trevisan, M., Sinigaglia, A., Lavezzo, E., & PalÃ¹, G. (2016). Zika virus: From pathogenesis to disease control. *FEMS Microbiology Letters, 363*(18), fnw202-fnw202.

Broutet, N., Krauer, F., Riesen, M., Khalakdina, A., Almiron, M., Aldighieri, S., . . . Dye, C. (2016). Zika virus as a cause of neurologic disorders. *N Engl J Med, 374*(16), 1506-1509. doi:10.1056/NEJMp1602708

Buathong, R., Hermann, L., Thaisomboonsuk, B., Rutvisuttinunt, W., Klungthong, C., Chinnawirotpisan, P., . . . Plipat, T. (2015). Detection of zika virus infection in thailand, 2012â€“2014. *The American Journal of Tropical Medicine and Hygiene, 93*(2), 380-383. doi:10.4269/ajtmh.15-0022

Cao-Lormeau, V., Blake, A., Mons, S., LastÃ¨re, S., Roche, C., Vanhomwegen, J., . . . GhawchÃ©, F. (2016). Guillain-barré syndrome outbreak associated with zika virus infection in french polynesia: A case-control study. *The Lancet, 387*(10027), 1531-1539. doi:10.1016/S0140-6736(16)00562-6

Centers for Disease Control and Prevention. (2017). Guillain-barré syndrome. Retrieved from https://www.cdc.gov/campylobacter/guillain-barre.html

Chris, D., & Mariano, C. (2017). Zika epidemiology. Retrieved from http://www.who.int/mediacentre/multimedia/podcasts/2017/mysteries-zika-transmission/en/

Cragan, J., Mai, C., Peterson, E., Liberman, R., Forestieri, N., Stevens, A., & Honein, M. (2017). *Baseline prevalence of birth defects associated with congenital zika virus infection — massachusetts, north carolina, and atlanta, georgia, 2013–2014.* (Morbidity and Mortality Weekly Report No. 66).Centers for Disease Control and Prevention.

de Araújo, T. V. B., Rodrigues, L. C., de Alencar Ximenes, R. A., de Barros Miranda-Filho, D., Montarroyos, U. R., de Melo, A. P. L., . . . Martelli, C. M. T. (2016). *Association between zika virus infection and microcephaly in brazil, january to may, 2016: Preliminary report of a case-control study* doi:https://doi.org/10.1016/S1473-3099(16)30318-8

de Góes Cavalcanti, L., Tauil, P., Alencar, C., Oliveira, W., Teixeira, M., & Heukelbach, J. (2016). Zika virus infection, associated microcephaly, and low yellow fever vaccination coverage in brazil: Is there any causal link? *The Journal of Infection in Developing Countries, 10*(6), 563-566. doi:https://doi.org/10.3855/jidc.8575

Dick, G. W. A., Kitchen, S. F., & Haddow, A. J. (1952). Zika virus (I). isolations and serological specificity. *Transactions of the Royal Society of Tropical Medicine and Hygiene, 46*(5), 509-520.

Eggo, R. M., & Kucharski, A. J. (2018). Expected duration of adverse pregnancy outcomes after zika epidemic. *Emerging Infectious Disease Journal, 24*(1) doi:10.3201/eid2401.170482

Faria, N. R., Azevedo,Raimunda do Socorro da Silva, Kraemer, M. U. G., Souza, R., Cunha, M. S., Hill, S. C., . . . Vasconcelos, P. F. C. (2016). Zika virus in the americas: Early epidemiological and genetic findings. *Science (New York, N.Y.), 352*(6283), 345-349. doi:10.1126/science.aaf5036

França, G. V. A., Schuler-Faccini, L., Oliveira, W. K., Henriques, C. M. P., Carmo, E. H., Pedi, V. D., . . . Victora, C. G. (2016). *Congenital zika virus syndrome in brazil: A case series of the first 1501 livebirths with complete investigation* doi:https://doi.org/10.1016/S0140-6736(16)30902-3

Li, C., Xu, D., Ye, Q., Hong, S., Jiang, Y., Liu, X., . . . Xu, Z. (2016). *Zika virus disrupts neural progenitor development and leads to microcephaly in mice* doi:https://doi.org/10.1016/j.stem.2016.04.017

Matheron, S., d'Ortenzio, E., Leparc-Goffart, I., Hubert, B., de Lamballerie, X., & Yazdanpanah, Y. (2016). Long-lasting persistence of zika virus in semen. *Clinical Infectious Diseases, 63*(9), 1264-1264.

Musso, D. (2015). Zika virus transmission from french polynesia to brazil. *Emerging Infectious Disease Journal, 21*(10), 1887. doi:10.3201/eid2110.151125

Nishiura, H., Kinoshita, R., Mizumoto, K., Yasuda, Y., & Nah, K. (2016). *Transmission potential of zika virus infection in the south pacific* doi:https://doi.org/10.1016/j.ijid.2016.02.017

Nishiura, H., Mizumoto, K., Villamil-GÃ³mez, W. E., & RodrÃguez-Morales, A. J.Preliminary estimation of the basic reproduction number of zika virus infection during colombia epidemic, 2015–2016. *Travel Medicine and Infectious Disease, 14*(3), 274-276. doi:10.1016/j.tmaid.2016.03.016

Pan American Health Organization, & World Health Organization. (2017). *Zika - epidemiological report brazil.* (Epidemiological Report). Washington D.C.:

Perera-Lecoin, M., Meertens, L., Carnec, X., & Amara, A. (2013). Flavivirus entry receptors: An update. *Viruses, 6*(1), 69-88. doi:10.3390/v6010069

Saiz, J., MartÃn-Acebes, M.,A., Bueno-MarÃ, R., SalomÃ³n, O.,D., Villamil-JimÃ©nez, L.,C., Heukelbach, J., . . . Pimentel-Coelho, P. (2017). Zika virus: What have we learnt since the start of the recent epidemic? *Frontiers in Microbiology, 8*, 1554. doi:10.3389/fmicb.2017.01554

Schuler-Faccini, L., Ribeiro, E., Feitosa, I., Horovitz, D., Cavalcanti, D., Pessoa, A., . . . Sanservino, M. (2016). *Possible association between zika virus infection and microcephaly — brazil, 2015.* (Morbidity and Mortality Weekly Report No. 65).Centers for Disease Control and Prevention.

Song, B., Yun, S., Woolley, M., & Lee, Y. (2017). *Zika virus: History, epidemiology, transmission, and clinical presentation* doi:https://doi.org/10.1016/j.jneuroim.2017.03.001

The Brazilian Institute of Geography and Statistics. (2011). 2010 census: 11.4 million brazillians (6.0%) live in subnormal aggolmerates. Retrieved from https://censo2010.ibge.gov.br/en/noticias-censo.html?view=noticia&id=1&idnoticia=2057&busca=1&t=2010-census-11-4-million-brazilians-6-0-live-in-subnormal-agglomerates

VILLELA, D. A. M., BASTOS, L. S., DE CARVALHO, ,L.M., CRUZ, O. G., GOMES, M. F. C., DUROVNI, B., . . . CODEÃ‡O, C. T. (2017). Zika in rio de janeiro: Assessment of basic reproduction number and comparison with dengue outbreaks. *Epidemiology and Infection, 145*(8), 1649-1657. doi:DOI: 10.1017/S0950268817000358

Worldometers. (2017). Brazil population. Retrieved from http://www.worldometers.info/world-population/brazil-population/

Zanluca, C., de Melo, V.,Campos Andrade, Mosimann, A. L. P., dos Santos, G.,Igor Viana, dos Santos, C.,Nunes Duarte, & Luz, K. (2015). First report of autochthonous transmission of zika virus in brazil. *MemÃ³rias do Instituto Oswaldo Cruz, 110*(4), 569-572. doi:10.1590/0074-02760150192

Zhang, Q., Sun, K., Chinazzi, M., Pastore y Piontti, A., Dean, N. E., Rojas, D. P., . . . Vespignani, A. (2017). Spread of zika virus in the americas. *Proceedings of the National Academy of Sciences, 114*(22), E4334-E4343. doi:10.1073/pnas.1620161114

Zika virus outbreaks in the americas. (2015). (Weekly Epidemiological Record No. 90).World Health Organization.