Chikungunya in Southeast Asia

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Chikungunya is an ancient infectious disease that is currently endemic in both tropical and subtropical regions of Southeast Asia (Silva and Dermody 2017). The disease is predominantly spread by the mosquito species, *Aedes aegypti*; however, it can also be spread by the mosquito species *Aedes albopictus* as well as maternally or via blood transfusions (Bettis et al. 2022). After entering the blood stream, the virus will often enter and replicate in lymphoid organs (lymph nodes and spleen), as well as the skin, joints, and tendons (Silva and Dermody 2017). Currently, the receptor that the virus binds to is unknown; however, research has shown that after the virus binds and enters the host cell, it will form granule formations at the affected areas and limit apoptosis (Silva and Dermody 2017). While research has shown that Chikungunya originated in Africa approximately 500 years ago, the virus has reemerged across the world beginning in the early 20th century and spreading to temperate regions such as the United States and Europe (Silva and Dermody 2017). Since the emergence of the ECSA strain in 2004, Chikungunya has affected over 110 countries and has resulted in over 10 million cases worldwide (Mourad et al. 2022). In Southeast Asia, there have been 53 sporadic outbreaks since 2004; however, only 12 out of the 53 outbreaks had incidence data in their reports (Bettis et al. 2022). Therefore, it is imperative that more research and data is collected in Southeast Asia to potentially prevent further spread of Chikungunya. While these sporadic outbreaks have caused high rates of morbidity across the globe, mortality rates remain under .1%; however, those who obtain Chikungunya are at risk of acute and/or chronic disability, leaving infected patients with life-long consequences (Silva and Dermody 2017). Therefore, Chikungunya is a re-emerging disease that has affected many populations across the globe, especially those living in Southeast Asia. Since the disease has become a worldwide public health issue, no anti-viral/antibiotic treatment or vaccine has been fully developed (Silva and Dermody 2017). Consequently, Chikungunya remains highly prevalent in Southeast Asia due to a rising climate, overuse of insecticides and inability to do blood screening tests before transfusion. Therefore, it is crucial that funding towards preventing further spread and creating a vaccine or treatment is placed.

Chikungunya remains highly prevalent in Southeast Asia due to its rising climate. Southeast Asia's climate is predominantly tropical, consisting of hot temperatures and large amounts of rainfall nearly year-round. Chikungunya outbreaks are caused by the mosquito species *Aedes aegypti*; consequently, hot and humid environments result in human populations having a high risk of getting bitten, which creates outbreaks within the region. In a study conducted by Servadio et al (2017), temperatures around 34˚C have the highest probability of Chikungunya outbreaks in Southeast Asia. Currently, the temperature ranges from 21˚C to 28˚C, with warmer temperatures from April to August and cooler temperatures from September to March (Supharatid et al. 2022). However, temperatures are projected to increase 1.88˚C by 2050 and as far as 3.6˚C by 2080, (Supharatid et al 2022). While an increase of 1.88˚C does not seem significant, any increase in temperature will cause a larger number of Chikungunya outbreaks to occur in the region. Therefore, stopping or delaying climate change is critical in preventing an increase of Chikungunya outbreaks in Southeast Asia. In addition to an increase in temperature causing a larger number of outbreaks, an increase of temperature will result in the mosquito species being able to reproduce and lay eggs throughout the year, increasing the mosquito population as well as prolonging the exposure humans have to them. In a study conducted by Ryan et al. (2019), Southeast Asia is most likely to allow year-round reproduction and transmission for *Aedes aegypti* and *Aedes albopictus* (Figure 2). However, if temperatures increase too much, *Aedes albopictus* may be unable to survive and reproduce. In conclusion, populations in Southeast Asia are expected to stay at risk for infection year-round as well have a higher risk of infection due to optimal temporal conditions. Overall, climate change in Southeast Asia has caused an increase in temperature, therefore prolonging and intensifying the risk of getting infected. To prevent larger numbers of outbreaks in Southeast Asia, funding must be placed in delaying or stopping climate change, at least until a vaccine or treatment is made.

In addition to an increase in temperature, climate change will result in an increase in precipitation. According to Servadio et al. (2017), 650 mm of precipitation in Southeast Asia will bring the highest probability of Chikungunya outbreaks. However, the p-value was found not significant (p=0.7871), therefore questioning whether the predicted maximum precipitation is reliable or not. Currently, past research regarding precipitation to Chikungunya has had correlations in which it was and was not significant to the outbreaks, making it unclear whether precipitation is a factor towards spreading Chikungunya. In Southeast Asia, the current maximum precipitation is around 250 mm (Supharatid et al. 2022). However, due to climate change, the maximum projected increase of precipitation is approximately 8.09% and 15.58% (Supharatid et al. 2022). Therefore, a drastic increase of precipitation will happen if climate change continues to occur, resulting in a possible increase of outbreaks. While Servadio et al. (2017) shows that precipitation may not be significant to Chikungunya outbreaks in Southeast Asia, it is a factor that must be taken into consideration, as climate change will bring larger amounts of rainfall to the region. Therefore, funding must be invested into further research clarifying whether precipitation is a factor towards Chikungunya outbreaks in Southeast Asia. In conclusion, if funding is not invested into delaying or stopping climate change, an increase of temperature and precipitation will take place in Southeast Asia, causing further transmission and possible increases of outbreaks.

Aside from climate change increasing the number of Chikungunya outbreaks in Southeast Asia, the overuse of insecticides has resulted in insecticide resistance in the mosquito species *Aedes aegypti*. Because there is no current vaccine or treatment available, Southeast Asia has routinely used insecticides to prevent transmission of the disease (Marcombe et al. 2019). During outbreaks, insecticides will often be sprayed upon clothing, shoes and/or any surfaces that mosquitoes land on (WHO 2022). As insecticides continued to be used as the only preventive measure for Chikungunya, insecticide resistance began to develop. In a study conducted by Marcombe et al. (2019), all wild groups of *Aedes aegypti* that were collected around different areas of Southeast Asia were found to have significant levels of detoxification enzymes used against insecticides. In addition, those same groups all had low mortality rates to current insecticides, such as permethrin, DDT, and malathion. Because insecticides have been overused in Southeast Asia as the only way to prevent transmission of Chikungunya, insecticide resistance has developed in the *Aedes aegypti,* resulting in low mortality rates when used. Therefore, continuous utilization of ineffective insecticides will ultimately leave populations at risk for infection. Overall, if the insecticides being used continue to be the only preventive measure against Chikungunya, insecticide resistance will continue to grow and leave citizens at risk for infection.

In addition to the overuse of insecticides in Southeast Asia, there are alternative bio-insecticides that have high mortality and emergence inhibition rates. In another study conducted by Marcombe et al. (2018), alternative bio-insecticides were found to be effective against wild populations of *Aedes aegypti*, as well as maintain emergence inhibition rates above the WHO requirement (<80%). In other words, alternative bio-insecticides were found to be highly effective against *Aedes aegypti* larvae over a period of 200 days. Therefore, if these bio-insecticides could be developed, manufactured, and used on *Aedes aegypti* larvae, then those populations would be significantly less at risk, as less mosquitoes would be resistant to the alternative bio-insecticides. To prevent insecticide resistance, they must be alternatively used with either existing ones that still have high emergence inhibition rates and/or routinely used in a schedule that would delay insecticide resistance from developing. However, these bio-insecticides are still undergoing testing, with some remaining in development for 4 years (Marcombe et al. 2018). Therefore, funding must be placed into speeding up the development of these bio-insecticides, as they are currently the only way to prevent transmission of Chikungunya. Ultimately, until a vaccine and/or treatment is developed, funding must be put into developing alternative insecticides for individuals to use for protection as well as pushing governments to implement strategies into alternating insecticides being used, therefore delaying development of insecticide resistance.

Aside from the overuse of insecticides in Southeast Asia, a lack of blood screening has been a factor in various outbreaks within the region. In Thailand in 2009, companies often required a seven day "screening" period, in which the donor was isolated and observed for any Chikungunya symptoms before donating blood (Appassakij 2016). In addition to being observed and isolated, the donor would often have to go through a series of questions to determine whether they were at risk for Chikungunya infection or not, such as their occupation, family history, and if they were in contact with anyone that was recently infected (Appassakij 2016). While this strategy did reveal that 2.3% of the potential donors were at risk, with 11 of the 299 potential donors developing symptoms of Chikungunya during the isolation period, the quarantine period was only implemented 85% of the time (Appassakij 2016). Consequently, this strategy was only 78.8-81.6% effective, resulting in individuals receiving blood transfusions becoming at risk for infection (Appassakij 2016). During the 2009 Thailand outbreak, 9440 Chikungunya suspected cases were reported after blood transfusions, with approximately 1170 suspected cases by week 16 (Appassakij 2016). Because the observation strategy was not fully implemented and was only at most 81.6% effective (due to asymptomatic donors), blood screening was a clear factor in spreading Chikungunya in Thailand. In another outbreak in Myanmar in 2019, all donors that were positive for Chikungunya were asymptomatic (Kyaw et al. 2019). In a study conducted by Kyaw et al. (2019), 14 of the 500 blood samples collected from donors were positive with Chikungunya. Consequently, the lack of blood screening resulted in 3.2% of blood donors and 20.5% of children (patients) being positive for Chikungunya (Kyaw et al. 2019). Because blood banks in Myanmar utilized observation-based strategies, asymptomatic donors were able to donate blood, therefore leaving patients at risk of obtaining Chikungunya via blood transfusions. In both Thailand and Myanmar, both countries did not utilize an RNA-based screening strategy, in which blood samples from the donor were taken and tested for Chikungunya RNA (Appassakij 2016). If both the seven-day screening and RNA-based screening strategy were used, both symptomatic and asymptomatic donors would have been discovered and therefore unable to donate blood. As a result, the risk for Chikungunya transmission would have been significantly lower, leaving those receiving blood transfusions at a much lower risk. In conclusion, utilizing both the RNA-based and seven-day screening strategy is essential in preventing asymptomatic donors from donating blood. Overall, funding towards providing blood banks and hospitals with the proper equipment to test blood before transfusion is critical in preventing transmission of Chikungunya, especially to those that are immunosuppressant, hemophiliacs, and/or in need of blood.

In order to decrease the affect climate change, insecticide resistance, and blood transfusions have on spreading Chikungunya, government implementations must be placed as well as funding towards speeding up the process of developing bio-insecticides, vaccines, antivirals, or antibiotics for the public to use. According to Soo-Chen and McCoy (2022), Southeast Asia is capable of rapidly reducing 43% of greenhouse gases, gases in the atmosphere that retain heat. Therefore, it is crucial that governments and organizations in Southeast Asia implement policies to reduce CO2 emissions throughout the region, as doing so would prevent rising temperatures and precipitation. As a result, climate change would be delayed, allowing more time for a vaccine and/or treatment to be developed. By pushing for an increase in energy efficiency, CO2 emissions would go down, therefore delaying climate change. Therefore, Southeast Asian governments must push to reduce CO2 emissions by utilizing energy efficient strategies to prevent optimal conditions for *Aedes aegypti.* In addition, Southeast Asian governments and organizations must implement a routine in which various insecticides are routinely used, therefore delaying development of insecticide resistance in mosquitoes. As a result, vector control would be significantly more effective than it is currently. Lastly, policies towards requiring blood screening and/or testing (not observation based) before transfusions are critical to preventing those receiving blood transfusions from obtaining Chikungunya. Overall, policies must be implemented throughout Southeast Asian governments to delay and/or prevent further spread via mosquito and/or blood transfusions. In addition to vector control, funding must be provided to speed up development of the alternative bio-insecticides tested in Marcombe et al. (2019), as they had an emergence inhibition rate above the WHO requirement throughout the duration of the trial. Because these bio-insecticides are still undergoing various stages of development, funding must be used to speed up the process, therefore allowing the public to use them and decrease the risk of getting infected.

Most importantly, funding towards development of vaccines, antivirals and antibiotics must be invested, as there is currently no vaccine or treatment available. At this moment, there are only treatments to manage the pain and inflammation using non-steroid and anti-inflammatory drugs (Tharmarajah and Mahalingam 2017). Currently, various broad-spectrum antivirals have been found to be effective in stopping replication; however, further testing is needed to determine whether these compounds are safe and/or highly effective. In addition, various treatments using monoclonal antibodies have been found to be highly effective in neutralizing Chikungunya in infected areas and reducing inflammation; however, these antibiotics are expensive to develop and require multiple boosters (Tharmarajah and Mahalingam 2017). Therefore, in order to provide possible antivirals and/or antibiotics for those that are infected or at risk of infection, funding must be invested in speeding up the development and manufacturing of these treatments. Lastly, there are currently two vaccines that have completed phase one of development (Tharmarajah and Mahalingam 2017). While they have shown to have strong immune responses and are relatively safe for human use, high manufacturing costs and potential risks to hypersensitivity of the vaccine, immunosuppression and possible infections leaves the vaccine in testing (Tharmarajah and Mahalingam 2017). Therefore, funding must be invested into speeding up development of these vaccines, making sure that it is safe and effective. Overall, it is critical to develop some sort of vaccine or treatment for citizens in Southeast Asia to use, as a heavy dependence on current insecticides has left their only use of protection as ineffective, leaving them at high risk for obtaining a disease that currently has no treatment available. In sum, government policies and funding towards the development and manufacturing of possible treatments and vaccines are critical in preventing future outbreaks in Southeast Asia.

Chikungunya is an arbo-virus that has become endemic in Southeast Asia, as well as becoming a public health concern across the world. Currently, new cases are arising in more temperate regions, such as the United States or Europe due to international travel (Silva and Dermody 2017). As Chikungunya continues to spread across Southeast Asia and new regions, climate change will continue to rise, providing optimal conditions in areas that were originally not ideal for *Aedes aegypti.* In addition, continuous use of insecticides will leave all populations at high risk for obtaining Chikungunya. Lastly, continuous blood transfusions without taking effective preventive measures will leave those who are immunosuppressant and/or hemophiliacs at risk. Consequently, those who are not healthy are more likely to suffer far worse, especially when there are no current treatments available. Therefore, funding must be invested into developing a treatment and/or vaccine for public use. Until then, governments and organizations must work together in preventing climate change, insecticide resistance by implementing policies and investing time and money into preventing further spread of Chikungunya.

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