Dengue Infection: Burden in India

Kateryna Malkina
Department of Biology
Lake Forest College
Lake Forest, Illinois 60045

Introduction

Dengue is a rapidly expanding mosquito-borne virus that can be found in tropical and subtropical climates (Rodríguez-Barraquer et al., 2015). Across a human population, it is endemic in more than 100 countries and 400 million people are infected with it annually. Around 100 million shows symptoms and 40 thousand dies from severe dengue due to internal bleeding and organ damage (CDC, 2021a). There are four serotypes that cause the dengue disease – DENV-1, DENV-2, DENV-3, and DENV-4. They are spread by two vector species — mosquitos *Aedes aegypti* and *Aedes albopictus* — which survive well in both tropic and cooler regions (15-320C) (Reinhold et al, 2018). While mild symptoms of dengue cause fever, aches, and rash, the severe form of dengue — Dengue Hemorrhagic Fever (DHF) — can cause death within a few hours and requires hospital care (CDC, 2021a). Since dengue can be induced by four genetically related viruses, a single person does not develop immunity to all at once and is at risk of getting sick as many as four times in their lifetime. Although a new dengue vaccine has recently become available on the U.S. territories (CDC 2021b), there has not yet been developed a long-lasting, successful, and widely accessible vaccine (Rodríguez-Barraquer et al., 2015). The disease requires urgent and special attention to reduce high infection rates across the world.

India, a country of 1.42 billion people (World Population Review, 2023) with a tropical monsoon climate (Mutheneni et al., 2017), has had a continuous presence of dengue in endemic stage over two centuries. Recent studies suggest that there is a high probability of dengue occurrence in most of the Indian subcontinent while only a small fraction of cases is diagnosed and reported due to the insufficient testing rates (Rodríguez-Barraquer, 2015). Hence, a yearly average for mortality is 212, and for morbidity is 140 thousand people (NCVBDC, 2021). Currently, the only way to effectively decrease the number of active infections is to prevent mosquito bites (CDC, 2021a). This poses a challenge due to the current state of India's economy. As of 2021, 97 million people live in extreme poverty (The Global Statistics, 2021). Besides having housing in livable conditions, these people need to have access to window nets, repellent spray, or appropriate clothing for children to prevent the mosquito bites. Moreover, high poverty rates lead to earlier employment, which may significantly decrease the level of education. This can potentially lead to missing the important knowledge that helps prevent the mosquito development around one's household. For instance, these mosquitos breed and lay eggs in water, hence once a week one should clean or change items that hold water, such as tires, buckets, pools, and toys (Rodríguez-Barraquer et al., 2015).

Enviro-climatic factors

The mosquitos of the *Aedes* species are known to live in close association with humans and prefer them over other animals as a source of food. Therefore, they are mostly concentrated in urban and suburban areas where human hosts can be easily found. For the two dengue vector species, *Aedes aegypti* and *Aedes albopictus*, the lower temperature limit that allows them some activity is 10-150C, whereas the highest temperature they can still fly at is 350C (Reinhold et al., 2018). The optimum temperature that allows mosquitos to fly longer over greater distances is 210C. If there is a temperature increase, females are seen to eat faster (at 26-350C) and lay eggs withing just a few days (3.5 days). For example, at the temperature of 300C, the biggest number of reproducing cycles has been recorded as 3.9 cycles during a female's life.

A foreseeable climate change is predicted to gradually increase the global temperature. Hence, it is expected to have a major impact on the vector species distribution and potentially even expand their geographical range. Besides covering larger territorial range, mosquitos may infect a greater number of people with the virus. The time between the mosquito taking in infected blood to transmitting the disease to the next host is seen to decrease with higher temperatures (32–35 ◦C) by a few days. Hence, this may potentially facilitate faster transmission rates (Reinhold et al., 2018). Nevertheless, it is important to note that the average temperature in some areas of India is already approaching the critical temperatures for mosquitos. As a vivid example, the state of Punjab had the highest mean temperature in the entire country from 1998 to 2014. On average, 33.60C was its average maximum temperature. This is extremely close to the borderline of 36-400C at which mosquitos are unable to breed and even fly; past 400C they experience rapid death (Reinhold et al., 2018). Hence, high temperatures prevalent in the region could be the reason for the lower number of dengue cases reported. The study conducted by the Vector Control Research Centre in Pondicherry city found that dengue infections reported for the Punjab state in 2012 fell under the range of 201-700 cases (Figure 39(a), Palaniyandi, 2014).

While temperature greatly impacts the species growth and development, precipitation is also an essential factor of mosquito's density and dispersion. India receives 75% of its rainfall from June to September in southwest monsoon period. The rain is required to create and maintain mosquitos' breeding sites, and in this 4-month period more than sufficient precipitation is accumulated. Therefore, high vector densities are expected to occur across the tropical and humid subtropical regions of India (Mutheneni et al., 2017). Precisely, India's southern states are in the tropical range with warm weather conditions (Palaniyandi, 2014) and high precipitation rates. Moving up the coastline, southern-eastern coast states have more moderate rainfall. The southern-eastern state of Gujarat, for instance, reported the second largest precipitate level – an average of 688 mm (Table 1, Mutheneni et al., 2017) along with slightly larger number of dengue cases than in Punjab. Gujarat's cases were in the range of 701-1700 in 2012 (Figure 39(a), Palaniyandi, 2014). In terms of enviro-climatic factors discussed, the most suitable state for mosquitos' development in 1998-2014 was the state of Kerala, the most southern coastline state in the country (Figure 3, Mutheneni et al., 2017). It had the highest average annual rainfall indicator – 2375 mm of precipitation and an average temperature 28.30C (Table 1, Mutheneni et al., 2017). As expected, it reported the highest number of dengue cases (>3600) in the country in year 2012 (Figure 39(a), Palaniyandi, 2014).

Geographical distribution of dengue

Population mobility, geographical centrality, and population density in major cities in India have shown to impact the rates of dengue transmission. One of such metropolises, the city of Delhi (16.8 million people), is the most dengue-affected city in India (Telle et al., 2016). It has striking social and environmental disparities due to the underinvestment in urban infrastructure (water/waste management) and rapid demographic growth. The study conducted by an international group of researchers found an association between the abundance of cases and typology in the city between 2008 and 2010 (Figure 2, Telle et al., 2016). The dengue cases have shown to be decreasing in numbers as the distance from forest was increasing (Table 2, Telle et al., 2016), which could be linked to the substantial number of mosquitos seeking for shelter in vegetation.

The areas with different distribution of wealth and population densities have also exhibited infection patterns. Deprived areas with medium and high population densities that do not have acceptable living conditions reported the highest incidence of dengue in the study (Table 1, Telle et al., 2016). As for deprived areas with low population densities, they had similar demography to the rich areas in Delhi. The wealthy areas turned out to have higher infection rates than the low-density deprived areas (Table 1, Telle et al., 2016). The observation is counterintuitive since in preliminary entomological studies, rich areas showed fewer Aedes aegypti larvae. There are two possible reasons suggested to interpret this observation. First, population in wealthy areas may be more prone to detect infection cases, which is strengthened by the fact that the cases registered earliest in the epidemic season were detected in the central areas of the city which are inherently wealthier in Delhi. (Telle et al., 2016). These areas are characterized as such in regards of the daily mobility network of the city. Hence, the second reason – more people interact with each other on the daily basis and have a higher possibility of passing on the infection. (Telle et al., 2016).

Besides understanding the pathogen transmission routes within the specific cities, we need a thorough understanding of dengue epidemiology across the country (Mutheneni et al., 2018). There are specific areas that need to be considered to predict the future outbreaks and dengue infection rates which are rapidly increasing across India. Proper surveillance studies, analysis of epidemiological data, and hot spot analysis are critically important in creating a broad picture of where the prevalence of dengue cases in the country is located. For the state of Andhra Pradesh, for example, the distribution of dengue cases appeared to be significantly clustered (Mutheneni et al., 2018). It showed its most endemic areas to be along the borders with Tamilnadu, Karnataka, Orissa and Mahashtra states. Together, these hot spot areas can be treated as a single cluster of cases since the neighboring districts share similar economy, human behavior, social patterns, and lifestyles (Mutheneni et al., 2018). The share of these characteristics can bring about a positive (or, in other states, negative) association with the geographic distribution of dengue. Along with the human factor, the geographical characteristics of the territory turned out to largely contribute to the spread of dengue. The dengue hotspot areas in Andhra Pradesh are the forest regions. The population of these regions was shown to keep close contact with each other, frequently migrate, and rapidly urbanize. By year 2019, 25.56% of India's area is occupied by natural forests and trees in plantations (Forest survey of India, 2019). Having observed the pattern of emerging cases and their relationship with the region's location, future studies can examine whether this pattern is universal and can account for the rest of the communities next to the forest areas. Since the vegetation accounts for a quarter of India's territory, the control of mosquito vectors can substantially help prevent or reduce dengue virus transmission and even interrupt human-vector contact (Mutheneni et al., 2018).

Socio-economic factors

Geographic distribution of dengue and socio-economic factors are closely related to the difference in economic burden in the population. Deprived areas across India are known to lack public health initiatives and have disengagement on outbreak control measures (Rodríguez-Barraquer et al., 2015). Due to the differences in applied public measures for disease control across different areas, infection rates vary for people of different age, education background, and social status. A study conducted by a group of researchers in Chennai, the city on the southern-eastern coast of India, demonstrated that there is evidence for high undertesting rates of dengue in densely populated areas. As many as 228-thousand possible infections are estimated to be missing from India's official annual reports (Rodríguez-Barraquer et al., 2015). It accounts only for 23% of the susceptible-to-dengue population in India. The predicted transmission intensity is significantly higher than the known infection statistics in Southeast Asia and Americas. Such large number of unreported cases is suggested to be due to the difference in educational levels and testing accessibility (Rodríguez-Barraquer et al., 2015). The population sample of the study in Chennai included 1010 people, 5-40 years old, from randomly chosen households. It turned to have a specific gender ratio: for each 2.5 male there was 1 female. In the previously mentioned research in the district of Andhra Pradesh, the male to female ratio was also uneven. The number of cases infected with dengue demonstrated to be higher among males. It was mentioned that the pattern is similar in many other studies (Mutheneni et al., 2018). There are several social factors that might explain this observation. Males might be more frequently exposed to mosquito bites than females due to the gendered behavioral and lifestyle patterns in India. They might also not take sufficient precautionary measures, such as applying repellents or wearing protective clothing at the time of mosquito bite.

In the research conducted in Chennai, all the participants were unaware of contracting dengue in the past. To determine if they had previously been infected and recovered from dengue without their knowledge, each person had a venous blood sample taken along with answering the survey. The results suggested that 93% of the population sample have been exposed to dengue virus without prior knowledge (Rodríguez-Barraquer et al., 2015). Dengue seroprevalence showed evidence of age-specificity in this population: the seroprevalence increased with age, from 70% in children 5-8 years old to 99% among adults 25 years of age or older. This pattern suggests the endemic circulation of dengue over an extended period. With age, a person is exposed to bigger and dense communities, such as in educational institutions and workplaces. People with high school education showed twice the probability of having dengue in the past and 4 times the probability of recently getting sick with dengue than people with illiterate level of education (Table 4, Rodríguez-Barraquer et al., 2015).

Due to the high undertesting rates, a study in Maduri district predicts the economic and disease burden of dengue in India to be hundreds of times greater than the estimates based on official reports (Shepard et al., 2014). Considering that it takes 2 weeks on average to be treated for dengue in a hospital, its medical cost is estimated to be $6.77 and $94.85 for the 14 days. The additional costs per person that cannot be accounted for are non-medical costs such as traveling and indirect costs of the value of time lost from morbidity and premature death (Shepard et al., 2014). Dengue hospital treatment is twice as expensive as treatment for tuberculosis. Considering the widely estimated undertesting rates, one other potential reason for the under-reported statistics could be the medical costs. With the emerging pandemic of COVID-19 disease, we have observed certain hesitancy towards testing. People are more reluctant to test for a disease or refer to medical facilities if they know that they either cannot financially afford it, or if it would put them in financial debt (Tolbert, 2020). The Maduri district study suggests that direct medical costs from dengue might represent 49% of overall illness costs and increase annual economic burden as high as $1.11 billion. However, even greater economic burden is anticipated if all dengue patients were tested and provided the necessary care (Shepard et al., 2014).

Vaccines and available treatment

The greatest challenge on the way of creating the dengue vaccine is the number of serotypes of the dengue virus that can trigger the disease. Dengue is known to be caused by the total of four different serotypes of the same virus. Once a person has had dengue, they have a long-lasting immunity to the infected serotype and a short-lasting immunity to other, unexposed serotypes (Soo et al., 2016). This signifies that some time needs to pass first before the individual can be infected with dengue for the second time. For secondary infection with different serotypes, the antibodies produced are unable to neutralize the virus, but instead they form immune complexes with the virus. This is primarily the reason why the secondary infection can lead to more severe symptoms and a higher chance of developing the severe dengue hemorrhagic fever (Soo et al., 2016).

When creating the vaccine, it needs to protect an individual from all four serotypes at once. Dengvaxia (R), a live attenuated dengue vaccine, has been successfully approved by 11 countries, including the United States, Mexico, Brazil, Thailand. It was also approved in the European Union. It is currently under evaluation in phase 3 clinical trials in most Asia and Latin America (Mutheneni et al., 2017). The vaccine is strictly recommended to the individuals who have a history of dengue infection. After the clinical trials, it is expected to be introduced to the places where a great portion of the population has been previously infected with the virus. Common side effects of the vaccine include headache, pain at the site of injection, and general muscle pains, hence the benefits outweigh the concerns about the vaccine.

The protective efficacy of Dengvaxia (R), meaning how likely a vaccinated person is to contract the disease after exposure, was in the range between 50.2% and 76.6% for different ages and serotypes. Dengvaxia (R) has not yet been approved by the Ministry of Health and Family Welfare, Government of India, because more clinical trials are expected to be conducted in India with the local people (Mutheneni et al., 2017). In addition, Indian pharmaceutical companies have recently reported that they are developing a new, indigenous dengue vaccine that protects against all four strains in clinical trials.

Dengue and COVID-19

The currently ongoing COVID-19 pandemic created another issue of rapid diagnosis of dengue. The similarities between the early symptoms of the two infectious diseases make it hard to diagnose without doing the blood test. For both the symptoms begin 3-14 days after the infection. They can show as fever, nausea, vomiting, and headache. Moreover, patients may show rapid clinical deterioration within 48 hours after fever onset. Both infections have a higher likelihood of causing complications in people with underlying chronic conditions, such as diabetes and heart disease.

It is also known that a person can simultaneously be infected with both viruses – dengue and SARS-CoV-19 (CDC, 2021a). Most people with dengue and COVID-19 demonstrate mild illness development and recover at home without hospitalization. The symptoms usually last for a few days and the pace for recovery is seen after a week since the first day of showing the symptoms. Despite the general trend, both dengue and COVID-19 are known to cause severe illness that can result in death. Any individual of any age can develop severe illness with either COVID-19 or dengue. While COVID cases are rapidly rising across the world, the diseases are worth being studied alongside each other. It is unknown whether the antibodies to one can have an impact on the other or if they have an effect on the relative recovery rates of the patients (CDC, 2021).

Recently India's hospitals were overwhelmed with the second deadly wave of COVID-19. After challenging all the available health resources to fight the pandemic, India is now facing the worsening of the dengue epidemiological profile in the country (Phadke et al., 2021). Due to the similarities between the nonspecific symptoms of the disease, patients are a subject to misdiagnosis. Improper treatment given to the patient because of misdiagnosis can be fatal for the patient. One drug used to prevent thrombosis in COVID patients, LMWH, substantially increases the risk of internal bleeding if given to a dengue patient (Phadke et al., 2021).

Conclusion

The epidemic of dengue has been present in India over the centuries, overlapping and worsening with the currently ongoing COVID-19 pandemic. The greatest challenge posed to the public health system in fighting the disease is the lack of exact data on morbidity and mortality of the disease. Knowing where the cases are least spotted in the country may indicate insufficient data collection rather than low infection rates. Further research can help estimate the key transmission parameters and aid in exploring the factors associated with dengue seroprevalence. It may help to predict the areas of future outbreaks and localize the most affected groups due to the cultural, economic, and social factors. One of the ways to decrease the gender ratio disparity in dengue cases is to target specific groups with education about the issue.

The distribution of dengue in the cities and villages highlights the importance to have a better understanding of another factor – mobility, to localize where the intervention can be most successful. From the geographical perspective, the special environmental and climatic factors make India a critical area for dengue. Temperature and precipitation are key enviro-climatic factors in estimating mosquito's population development and disease transmission dynamics (Reinhold et al., 2018). High temperatures (up to 35 0C) and high humidity have shown to directly impact the development and range of mosquitos, as well as the incubation period of the dengue viruses themselves. Under high temperatures, the lifespan of adult Aedes mosquito species and the number of their reproductive cycles increases. They also spend less time on blood-feeding, which in combination with shorter viral incubation time leads to faster virus replication and increased transmission intensity. While global warming is expected to increase the average temperatures in all parts of the world, the burden of dengue in India might vary in each region. Some states, like Punjab, Gujarat and Kenala, known for its high temperature and humidity levels, may experience a decrease in dengue cases due to the temperatures being too high for the mosquitos to survive. Hence, the species distribution in the country may change and expose more people to the vector-borne infection (Malkina, 2021).

References

Centers for Disease Control and Prevention. (2021a). *Dengue vaccine*. Centers for Disease Control and Prevention.

Centers for Disease Control and Prevention. (2021b). About dengue: What you need to know. Centers for Disease Control and Prevention.

Forest survey of India. (2019).

India population (live, 2023). (World Population Review). Retrieved February 18, 2023, from https://worldpopulationreview.com/countries/india-population

Malkina K. (2021). Lake Forest College.

Mutheneni, S. R., Morse, A. P., Caminade C., Upadhyayula S. M. (2017). Dengue burden in India: recent trends and importance of climatic parameters. Emerging Microbes & Infections, 6:1, 1-10.

Mutheneni S. R., Mopuri R., Naish S., Gunti D., Upadhyayula S. M. (2018). Spatial distribution and cluster analysis of dengue using self organizing maps in Andhra Pradesh, India, 2011–2013, Parasite Epidemiology and Control, Volume 3, Issue 1, 2018, Pages 52-61,ISSN 2405-6731

Ministry of Health & Family Welfare-Government of India. (n.d.). *Dengue/DHF situation in India*. National Center for Vector Borne Diseases Control (NCVBDC).

Palaniyandi, M. (2014). The environmental aspects of dengue and chikungunya outbreaks in India: GIS for epidemic control. International Journal of Mosquito Research, 1, 35-40.

Poverty rate in India 2021. The Global Statistics. (2021).

Phadke, R., Mohan, A., Çavdaroğlu, S., Dapke, K., Costa, A. C. dos S., Riaz, M. M. A., Hashim, H. T., Essar, M. Y., & Ahmad, S. (2021). *Dengue amidst COVID-19 in India*: *The mystery of plummeting cases.* Wiley Online Library.

Reinhold, J. M., Lazzari, C. R., & Lahondère, C. (2018). Effects of the Environmental Temperature on *Aedes aegypti* and *Aedes albopictus* Mosquitoes: A Review. *Insects*, 9(4), 158.

Rodríguez-Barraquer I, Solomon SS, Kuganantham P, Srikrishnan AK, Vasudevan CK, Iqbal SH, et al. (2015) The Hidden Burden of Dengue and Chikungunya in Chennai, India. PLoS Negl Trop Dis 9(7): e0003906.

Shepard, D. S., Halasa, Y. A., Tyagi, B. K., Adhish, S. V., Nandan, D., Karthiga, K. S., Chellaswamy, V., Gaba, M., Arora, N. K., & Group, the I. N. C. L. E. N. S. (2014). *Economic and disease burden of dengue illness in India.* AJTMH.

Soo, K.-M., Khalid, B., Ching, S.-M., & Chee, H.-Y. (2016). *Meta-Analysis of dengue severity DURING infection by Different dengue Virus serotypes in primary and secondary infections*. Plos One.

Telle O, Vaguet A, Yadav NK, Lefebvre B, Daudé E, et al. (2016) The Spread of Dengue in an Endemic Urban Milieu–The Case of Delhi, India. PLOS ONE 11(1): e0146539.

Tolbert J. (2020). *What issues will uninsured people face with testing and treatment for covid-19?* KFF.