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WHY IS YELLOW FEVER VIRUS STILL CAUSING OUTBREAKS IN SOUTH AMERICA AND AFRICA, DESPITE AN EFFECTIVE VACCINE?

ABSTRACT

The yellow fever virus (YFV) is a viral hemorrhagic fever transmitted by mosquito vectors to humans. In 1937, vaccine 17D was created causing most recipients to acquire life-long immunity. Despite this effective vaccine, YFV is responsible for 30,000 to 60,000 deaths annually in South America and Africa alone. In recent years, the global increase of temperature allows the vector *Aedes aegypti* to quicken its life cycle which directly enhances the YFV replication cycle and also allows the species to invade areas further from its native habitat around the equator. Analysis of Brazil's largest outbreak in 2016 revealed that the sylvatic cycle was the dominant mode of transmission, thus increasing urban cycle spread. Even though global vaccination has increased since the release of the vaccine, the largest outbreaks are seen in poverty-stricken high-risk areas of Africa and South America with inadequate population vaccination coverage. The CDC urges that high-risk countries achieve an 80% threshold of population vaccination coverage by means of conducting vaccination campaigns targeted on the most susceptible populations. Increased distribution of protective clothing and use of pesticides to kill potential vectors are additional preventative measures urged alongside the vaccine to further increase population immunity.

INTRODUCTION

Belfa was a healthy, active 14-year-old living in Angola as her family had just celebrated her birthday when suddenly she came down with a fever and extreme fatigue, so her mother rushed her to the local hospital (DW News 2016). There she tested positive for yellow fever but soon discovered that the hospital had no vaccines in stock. The doctor told her the only way to obtain this vaccine would be illegally through Angola's black market. Belfa searched the streets but found she could not afford the black-market prices, and returned home with no vaccine in hand. For the next week, all Belfa's mother could do was comfort her daughter and provide her fluids as her condition deteriorated and she suffered through the brutal yellow fever symptoms. The mother watched her pass away in pain in the home, leaving behind her empty room and a photograph that she carries along with her everywhere she goes (DW News 2016). Sadly, this is a common occurrence in poverty stricken areas of South America and Africa, as family members are left helpless due to the lack of vaccination affordability and availability, resulting in the deaths of anywhere from 30,000 to 60,000 people in Africa and South America alone (Faria et al. 2018).

Yellow fever virus (YFV) is a member of the flavivirus family along with Zika, Dengue, and West Nile virus, and is a single-stranded RNA genome wrapped in a protective protein covering. In some cases, people infected by YFV do not show any symptoms at all, but those with symptoms may experience a low-grade fever, chills, extreme headaches, muscular weakness, nausea, and vomiting (CDC 2020). Most people recover within a week, but in 1 out of 7 cases may experience a high fever, jaundice of the eyes and skin, internal bleeding, shock, and organ failure. It is known to have up to a 60% fatality in severe cases in Africa and South America, but in the western world the case fatality is much lower due to advances in medical treatment and technology (CDC 2020). This disease created horrific epidemics throughout all human existence wiping out small civilizations in the Caribbean and remote areas of Africa (Norrby 2007). The currently used yellow fever vaccine was initially developed in 1937 by Max Theiler when he was working to improve the "Asabi" strain, named after a South African citizen. This new strain, called 17D, was a mutation of the original Asabi strain and showed great promise in human trials and was quickly administered to one million people worldwide just two years later (Norrby 2007). This vaccine functioned by injecting a live attenuated strain that cannot cause disease in humans. Once in the body the virus is identified, and our immune system produces memory immune cells that can destroy the pathogen by producing antibodies following repeated exposure (Norrby 2007). Immunity is achieved in most people by about 10 days, and by one month 99% of recipients achieve lifelong immunity (Shearer et al. 2017). Despite having this extremely effective vaccine that provides long-term immunity, yellow fever outbreaks are still an issue killing thousands annually. Inadequate vaccination coverage in poverty-stricken high-risk areas, increasing global temperatures, and sylvatic cycle dominated transmission are all factors that explain how and why this virus is still spreading.

INCREASING GLOBAL TEMPERATURES FAVORING *AEDES AEGYPTI* YFV TRANSMISSION

The life cycle of *Aedes aegypti* plays an extremely important role in transmission of YFV as it benefits from increasing environmental temperatures and an expansion in territory, resulting in accelerated YFV replication and geographic spread of the virus. *Aedes aegypti* is the primary mosquito species involved in urban cycle transmission to humans and can become a vector after biting other infected mosquitoes or humans. *Aedes aegypti* feasts on human blood primarily because it has receptors that are extremely sensitive to detecting changes in air carbon dioxide concentrations and heat, which humans give off both in high amounts (Staughton 2019). Only female mosquitoes bite humans, and they can sense the local air carbon dioxide concentration change generated from human exhalation up to 50 meters away. Once females mature and are able to lay eggs, they require more nutrients than can be received from just sugar-rich nectar, so they feed on human blood to obtain necessary lipids and proteins for egg development (Staughton 2019). *Aedes aegypti* is also a poikilothermic ectotherm, meaning that its internal body temperature can fluctuate and is directly dependent on the temperature of its environment (Hamlet et al. 2018). Figure 1, from Hamlet et al. 2018, shows the impact of temperature on the biting rate of *Aedes aegypti*. The study found that as the environmental temperature increases, so does the number of times these mosquitoes are biting humans each day. Because these mosquitoes are ectotherms, their metabolism increases as environmental temperature increases, forcing the females to ingest more blood to maintain nutrients for their increased cellular activity and development of eggs (Hamlet et al. 2018). Increased metabolism also speeds up female development into adulthood since the immature forms of the mosquito are consuming high amounts of sugar to meet energy needs. This is problematic because a larger population that can feast on humans is generated, thus increasing the risks of contracting YFV for any humans who contact them.

YFV enters the mosquito when it bites an infected host, causing the virus to travel to the stomach where it invades the lining epithelial tissues. In the host epithelial cell, its viral RNA genome is replicated inside the rough endoplasmic reticulum and hundreds of copies are produced (Wikipedia, 2020; taken from Fontenille et al. 1997). The mature virions are then released by the host cell infecting neighboring cells or pouring into the mosquito's bloodstream. From there the virus makes its way to infect the mosquito saliva glands and is transmitted to the next host as it delivers infected saliva when it bites (Wikipedia, 2020; taken from Fontenille et al. 1997). With increased metabolism, cells are more actively using energy in order to quicken the rates of their respective function, so during this time the viral replication cycle is being expedited as well. This faster rate reduces the viral extrinsic incubation period, meaning that the time it takes for the mosquito to become infectious after ingesting the virus is significantly shortened (Hamlet et al. 2018). This is also problematic because mosquitoes' increased biting rates paired with a short extrinsic incubation period makes *Aedes aegypti* more effective at transmitting the virus between its hosts in short time frames.

Not only is *Aedes aegypti* becoming more effective in its current warm climate, but a gradual increase in global climate allows the mosquito to expand its territory far beyond the equator. Figure 2, from Mordecai et al. 2017, used confirmed case data of mosquito-borne illnesses to show the areas in the Americas where *Aedes aegypti* and *Aedes albopictus* are most effective at transmitting YFV and other mosquito borne-illnesses to humans with a 97.5% efficacy rate for at least one month of the year. This percentage considers all the *Aedes* arborviruses (YFV, Dengue, CHIKV, ZIKA), so for a single bite there is a 97.5% chance that one of these viruses will be transmitted to unvaccinated humans. *Aedes albopictus* is included because it plays a very minor role in YFV transmission to humans, but it is capable of propagating YFV urban cycle spread (Mordecai et al. 2017). In areas along the equator such as Brazil, Ecuador, Venezuela, and countries of Central America, *Aedes aegypti* were found transmitting the disease for every single month of the year. At least one month of confirmed cases of YFV have been reported as far north as the southern provinces of Canada ranging south to Argentina (Mordecai et al. 2017). These areas have such a short time frame of warm temperature for *Aedes aegypti* that any outbreaks are likely to die off very quickly as these mosquitoes become significantly less metabolically active as it gets colder (Mordecai et. al 2017). As global temperatures continue to rise, areas farthest from the poles will soon reach temperatures that are suitable for *Aedes aegypti* to survive for more than a month, giving enough time for larger scale outbreaks to occur. Governments around the world enacting green policies to limit emissions or reduce any factors that contribute to global warming will be a valid option to slowing the transmission and effectiveness of these dangerous mosquitos.

SYLVATIC CYCLE DOMINATED TRANSMISSION

Figure 3 shows a diagram of the viral life cycle as it undergoes two modes of transmission that eventually lead to a human host. The sylvatic cycle is defined as the transmission of YFV between non-human primate reservoirs and female mosquito vector species in the jungle. Spread is facilitated by YFV the vector *Haemagogus spp.*, a jungle residing mosquito species who feeds primarily on primates and to a lesser amount, humans (Faria et al. 2018). Female *Haemagogus spp.* bites wild primates, injecting them with YFV, and the virus replicates in the primate reservoir and travels through its bloodstream. In turn, *Haemogogus* and other jungle dwelling species feed on infected primates, also becoming vectors themselves. A spillover event occurs when a human in the jungle is bitten by an infected *Haemagogus spp.* or other infected jungle species. This leads to the urban cycle, which is defined as the cycling of YFV between *Aedes aegypti* and human hosts in urban settings such as towns, cities, and farms. *Aedes aegypti* is a mosquito species known to only bite humans and other urban mosquito species. An uninfected female

Aedes aegypti bites an infected human that returns from the jungle, and in turn ingests the virus and becomes a vector. It can then transmit YFV by biting other humans or other urban dwelling mosquitoes.

From August 2016 to October 2017, Brazil experienced its largest YFV outbreak ever recorded, accumulating 777 confirmed cases and 261 deaths with a case fatality rate of 33.6% (Faria et al. 2018). Prior to the epidemiological analysis of Faria et al. 2018, it was known that YFV transmits through the urban and sylvatic cycles, but there were no prior studies to determine which mode of transmission is the driving force behind an outbreak. This is problematic because epidemiologists could not find the origin of outbreaks and protect the susceptible population who initiate these cycles in the jungle and spread it to others in cities. Faria et al. 2018 obtained blood samples from human and primate YFV cases, as well as human Chikungunya Virus (CHIKV), and modeled the proportions of cases based on factors including age, sex, and location of each confirmed case. Figure 4 shows the age and sex distribution of observed cases compared to urban models in the epicenter region of Minas Gerais, Brazil. The observed age and sex distribution were manipulated in two models that predict how an urban cycle dominated epidemic case trend should appear. This graph supports the notion of sylvatic transmission since the observed case trends do not follow the trends seen in the models. Adult men 35-54 were disproportionately infected by YFV and showed a higher proportion than any other age range in the two models, while women maintain a mostly uniform percentage, with the most cases being seen by ages 30 and older (Faria et al. 2018). If urban transmission were the driving force behind the epidemic, the urban cycle model calculations would be around the same distribution as the observed values because everyone, regardless of sex and gender, has generally equal exposure in urban transmission. This is different from sylvatic infection which is dependent upon an individual's likelihood to travel to forested areas, affecting mostly adult males who work in the forest labor industry (Faria et al. 2018). Figure 5 shows the infection timeline of YFV in humans compared to primates and CHIKV in humans from August 2016 to October 2017 in Minas Gerais. CHIKV is an RNA mosquito borne virus and is only spread through the urban cycle via the vector *Aedes aegypti*, so it is an excellent comparison for determining if the YFV outbreak is urban cycle dominated (Faria et al. 2018). The graph reveals that the spike in primate cases directly correlates to a spike in human cases shortly after, indicating a spillover event. During that time, an increased number of primates were infected, most likely resulting from or causing many *Haemagogus spp.* to be infected. This increases the risk of human transmission as adult males working in the jungle exposed to a larger population of infected mosquitoes. As the primate cases decline so do the human cases, indicating that the observed YFV data does not match the CHIKV trends, so it is assumed that the spike in cases is due to the sylvatic cycle, which in turn induced urban cycle spread in cities as the men returned from the jungles. This caused *Aedes aegypti* to continue infection in cities at a much lower magnitude.

Figure 6, from Faria et al. 2018, reinforces the notion of sylvatic spread by providing the geographical distribution of human YFV cases compared to human CHIKV and primate YFV cases. Primate cases are distributed in high concentration in jungle areas of Minas Gerais, and human YFV cases are concentrated in urban centers that are also near the jungle, allowing for the highest possible exposure and a higher chance of spillover. CHIKV cases are concentrated in similar urban centers as well, indicating that *Aedes aegypti* is present in those areas and is capable of being able to receive the spillover strain (Faria et al. 2018). For example, the jungle town of Teofilo Otoni is a hotspot for all three variables understudy and demonstrates how the virus easily hops from sylvatic cycle to urban cycle spread through *Aedes aegypti*. Faria et al. (2018) found that most of the males within the 35-54 age range of infected cases indeed had an occupation that involved significant jungle exposure and commuted home to at least one of the three hotspot urban centers (see Figure 6). These conclusions made by Faria et al. 2018 regarding sylvatic cycle dominance is extremely important because it is fueling outbreaks by constantly creating spilling over strains to humans, which explains why this virus has not been eradicated yet. Now that it has been shown who the most susceptible population is and the dominant mode of transmission, vaccination campaigns can be directed toward adult males 35-54 and prevent the spread of illness into urban centers. These men could also be equipped with protective clothing that covers all extremities and their faces to prevent jungle mosquitoes from biting exposed skin. Providing them with a pesticide or repellent could further decrease their chances of contracting YFV as these mosquitoes could be killed.

These measures could be administered during an outbreak to slow the spread of the pathogen to densely populated areas and save thousands of more people each year.

INADEQUATE VACCINATION COVERAGE IN HIGH RISK AREAS

Vaccine 17D has been available for over 80 years, prompting global governments to target infants and travelers, yet YFV still rampages through high risk zones. High risk zones include areas of Africa and South America that are near the equator in which YFV causes the most cases and largest scale outbreaks in the world. The high death rate in these areas is driven by the lack of adequate population coverage of the vaccine, primarily due to poverty and the shortage in the local or global stockpile. Figure 7 from Shearer et al. 2017 shows population vaccination coverage in Africa and South America from 2000 to 2016, largely based on data collected from the World Health Organization (WHO) and local governments. Vaccination rates have risen again in both continents since that time, but huge gaps remain in poor areas including Brazil's eastern coast. That is one of the driving forces as to why the outbreak of 2016 was so large in the Minas Gerais region of Brazil whose population vaccination coverage was only around 70% (Faria et al. 2018). Amazonia regions of Brazil and Ghana at one point had a 100% coverage, however a global stockpile shortage in the 1990s reduced vaccination coverage in these areas to around 60% and 50% respectively (Shearer et al. 2017).

Figure 8 is from a study that analyzed the impact of the 1990s shortage on the largest YFV outbreak ever observed in Guinea starting on September 4, 2001. By analyzing the timeline of cases and associated vaccine data, the researchers could see the course the virus takes when population immunity is decreased or increased by vaccines. Guinea is a small, impoverished nation in West Africa with a population vaccination coverage of under 25%, so the mosquito vectors could easily transmit the virus (Shearer et al. 2017). The country was blindsided by a YFV outbreak which in the end took 228 lives with some areas reporting over a 60% case fatality rate (Nathan et al. 2001). Guinea exhausted its stockpile of vaccines in the first few weeks of the outbreak, so they sent out an international appeal and received 630,000 doses which dramatically slowed the spread in affected regions. A second appeal was made shortly thereafter, but world leaders did not respond, leading to the huge spike seen at week 47 in which over 130 people were infected and 50 people died (Nathan et al. 2001). This indicates that most of these patients had no access to prevention due to the complete lack of available vaccines, allowing YFV to quickly spread from these humans to more mosquitoes and vice versa. Following the spike, an additional 900,000 vaccines were manufactured and sent to the country from the WHO, which ultimately ended the outbreak as no new cases were reported on January 7, 2001 (Nathan et al. 2001). The lesson learned from this experience is the timeliness of vaccines is key in stopping an outbreak. Each time Guinea received international aid in the form of vaccine doses, their cases declined, but when they had no available vaccines, cases skyrocketed. When vaccines become scarce, their price gets inflated, and those who could afford it previously may not be able to. This sends people to the black market YFV vaccine trade, which is even more expensive, and adds the extra risk of placebo injections (Shearer et al. 2017).

Unfortunately, not every country in Africa receives the same amount of international aid, so YFV creates its deadliest outbreaks in these countries that currently have under 10% vaccination coverage: South Sudan, Kenya, Uganda, Mauritania, and Ethiopia. Most of these nations are under civil unrest or civil war, so there are currently no YFV campaign efforts underway (Shearer et al. 2017). The CDC recommends that high risk countries should achieve an 80% threshold of population vaccination coverage through vaccination campaigns to target the most susceptible populations (Hamlet 2018). As of 2016, Bolivia is the only country in South America and Africa that has met the CDC guidelines, with Brazil nearing the threshold (Hamlet et al. 2018). To achieve immunity in high-risk countries, it is estimated that 361-396 million African and 32 – 77 million South American inhabitants still need to be vaccinated (Shearer et al 2017).

CONCLUSION

YFV transmission to humans is responsible for 60,000 deaths every year in Africa and South America even though vaccine 17D was released in 1939. Although vaccination coverage has increased overall, there is still a huge population living in poverty-stricken high-risk areas that remain unvaccinated, causing larger outbreaks. Rising global temperatures increase mosquito metabolism, which in turn accelerates YFV replication and allows the mosquitoes to invade areas further away from the equator. Sylvatic cycle transmission is the driving force behind outbreaks, as infected humans return to cities and induce urban cycle spread. Since this trend in transmission was observed, more measures are needed to protect the susceptible population of adult males 35-54 years old who contact the jungle vectors (Figure 9). There needs to be vaccination campaigns geared towards these men which allow them to build up immunity prior to jungle exposure to slow the spillover of the virus into urban centers. Also, exploring physical barriers such as providing protective clothing paired with pesticides, or providing screens for homes and workplaces would lessen the chances of an infected mosquito biting bare skin and transmitting infection. As global temperature continues to increase, the *Aedes aegypti* territory continues to expand, which is problematic because new areas will be exposed to YFV for longer periods of time and current affected areas will see larger infection as the mosquito metabolism and viral replication rates increase. In the 20th century, countries are enacting legislation that reduces global carbon footprint and emission, which could slow global warming (Hamlet et al. 2018). Finally, conducting mass vaccination campaigns to anyone at risk, specifically countries under the 80% population vaccination CDC threshold, is the most effective method to slow YFV. The cost of that is unknown, but it should be an international effort for countries to manufacture YFV vaccines and have them sent to struggling countries. It may take years, but any increase in vaccination coverage could potentially save thousands of lives annually. Epidemiologists are currently working to promote more preventative measures like those listed in order to protect areas being ravished by this deadly virus.

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FIGURES

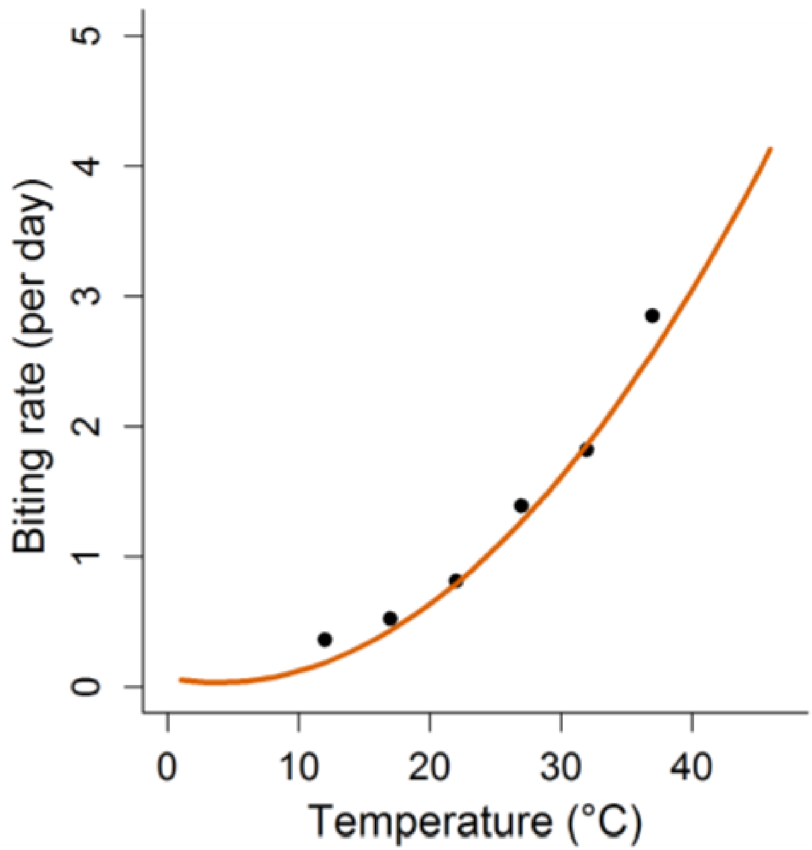

Figure 1. The effect of increasing environmental temperatures on *Aedes aegypti* biting rate. Study conducted on female *Aedes aegypti* because males do not bite humans. As external temperatures rise, mosquitoes' metabolism rises causing them to need to bite more to obtain sustainable energy. At lower temperatures, female mosquitoes are less metabolically active, so there is less of a need for nutrients from human blood. From (Hamlet et al. 2018)

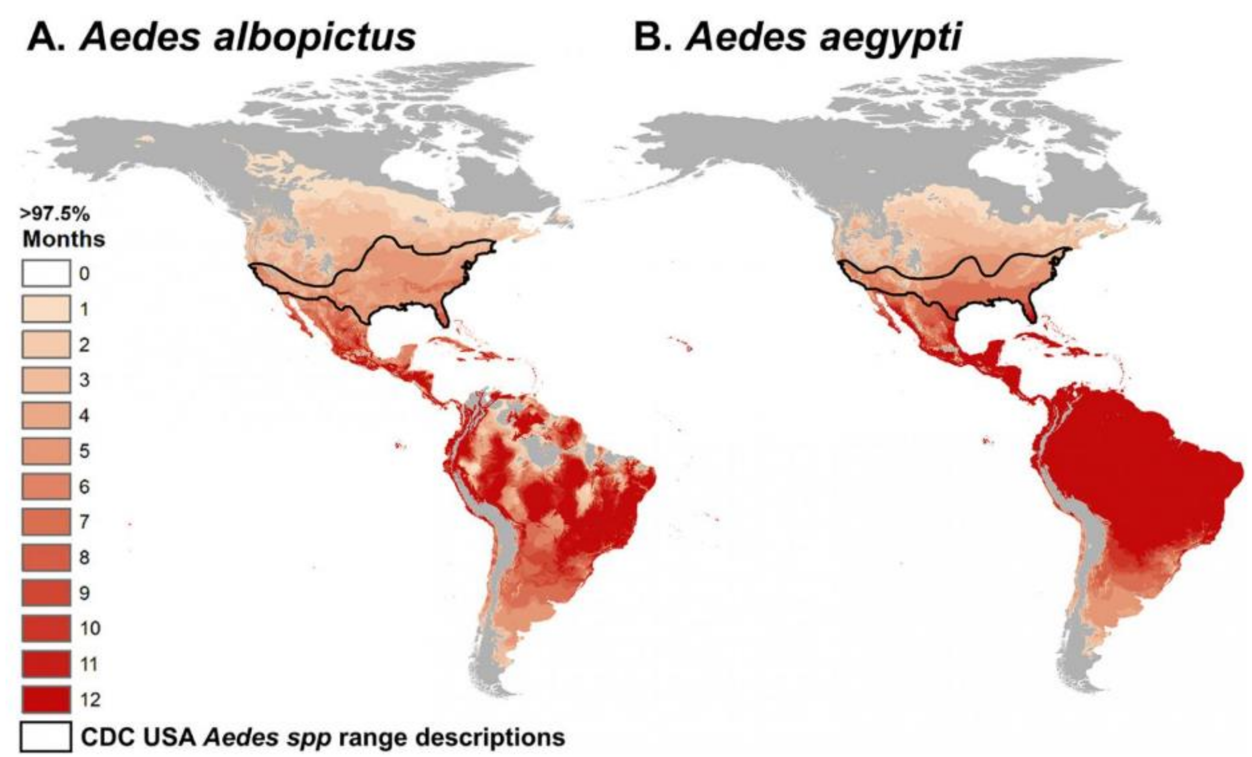

Figure 2. The number of months in which there is a greater than 97.5% chance of disease transmission by *Aedes aegypti* and *Aedes albopictus*. The darker the red shade of an area, the more months per year that these species are known to have a 97.5% chance of transmitting any arboviruses (YFV, Dengue, CHIKV, ZIKA) to humans per bite. Image A displays where *Aedes albopictus* was reported to be found, which is a species that is known to bite YFV infected humans and become a minor impact vector during an urban transmission cycle. This species was reported transmitting disease as far north as the Canadian provinces of Yukon and Northwest Territories, and as far south as Argentina. Image B displays where *Aedes aegypti* is reported to be found, which is the dominant vector of urban cycle transmission. *Aedes aegypti* were reported transmitting disease as far north as the southern provinces of Canada, ranging south to Argentina. The outlined region in black is the Centers for Disease Control and Prevention (CDC) precise ranges of both mosquito species as of 2017. From https://eurekalert.org/pub_releases/2017-05/uosf-mvl050817.php

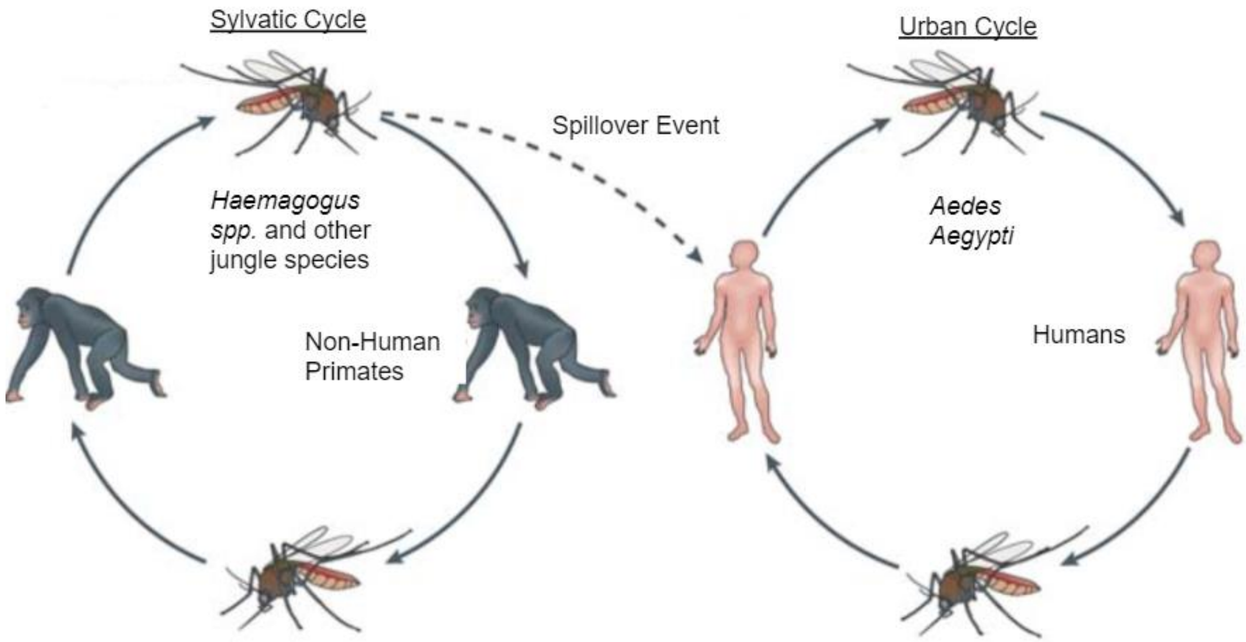

Figure 3. Urban cycle and sylvatic cycle roles in YFV transmission to humans. Arrows display the movement of YFV between the different reservoirs and vectors. The Sylvatic cycle is defined as the transmission of YFV between non-human primate reservoirs and mosquito vector species in the jungle. Spread is facilitated by YFV the vector *Haemagogus spp.* who feeds primarily on non-human primates and infects them with YFV. In turn, *Haemogogus* and other jungle dwelling species feed on infected primates, also becoming vectors themselves. A spillover event occurs when a human in the jungle is bitten by an infected *Haemagogus spp.* or other jungle species. Urban cycle is defined as the cycling of YFV between *Aedes aegypti* and human hosts in urban settings including towns, cities, and farms. *Aedes aegypti* bites an infected human that returns from the jungle, and in turn ingests the virus and becomes a vector. It can then transmit YFV by biting other humans or other urban dwelling mosquitoes. From http://www.southsudanmedicaljournal.com/archive/february-2012/dengue-fever.html

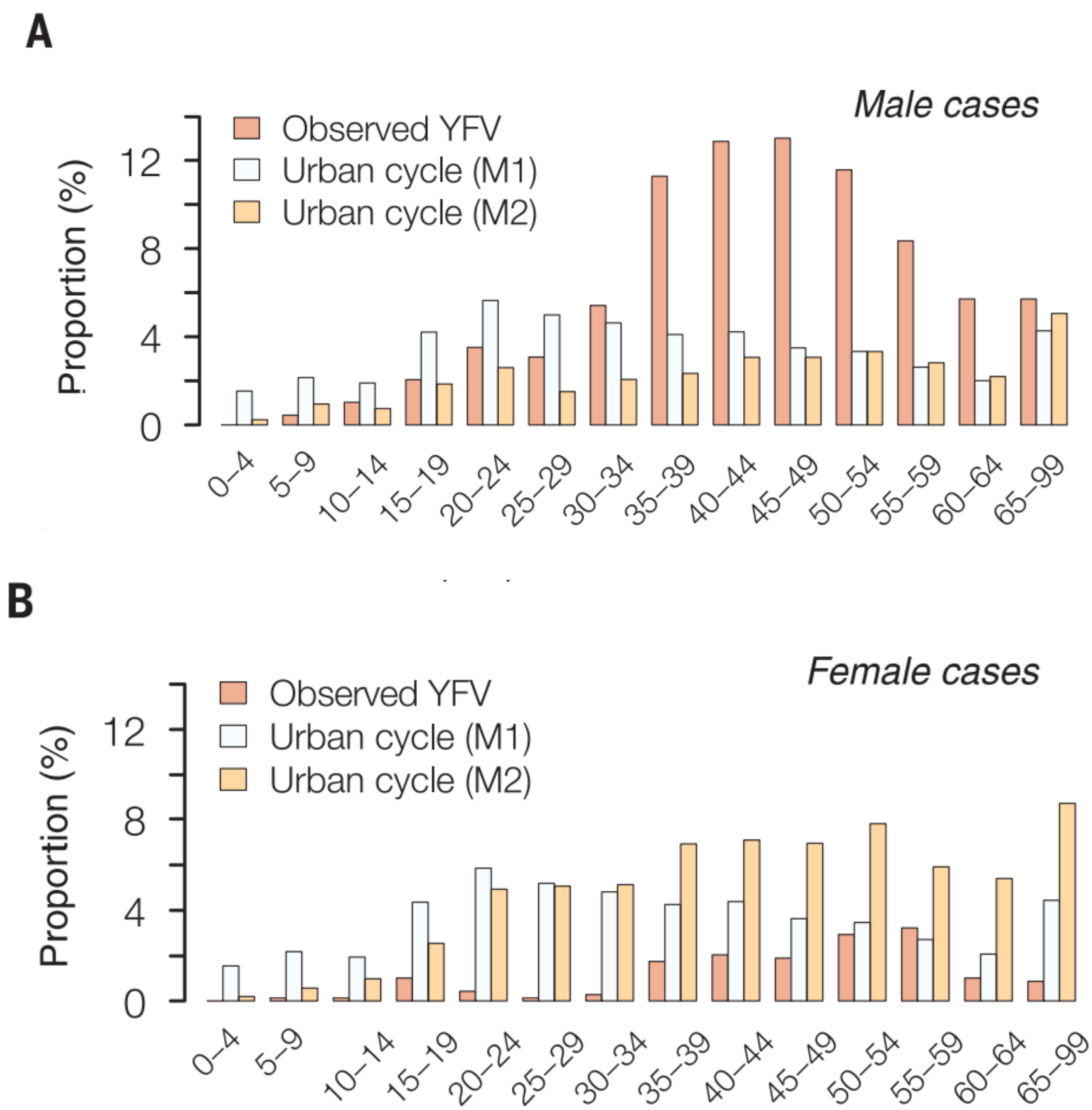

Figure 4. Age and sex distribution of YFV confirmed cases observed during the Brazil epidemic of 2016-2017, compared to two models predicting urban transmission trends. The Y-axis is the proportion of cases in comparison to all cases and the X-axis is the age ranges under study (0-99 in groups of 5). These age ranges were selected because they imply similar roles in society. For example, 20-year-old males travel to go to work while 10-year-old males stay at the house. Red bars are the observed case statistics that occurred in each age group for both (A) males and (B) females. M1 and M2 models are calculations that display what the observed dataset should look like if this epidemic were dominated by urban spread. White bars represent the M1 model, in which the observed dataset is run through calculations that make exposure to YFV independent from age and sex. Yellow bars represent the M2 model, in which the observed dataset is run through calculations assuming that exposure based on age and sex is directly proportional to trends seen by CHIKV in the same region. From (Faria et al. 2018)

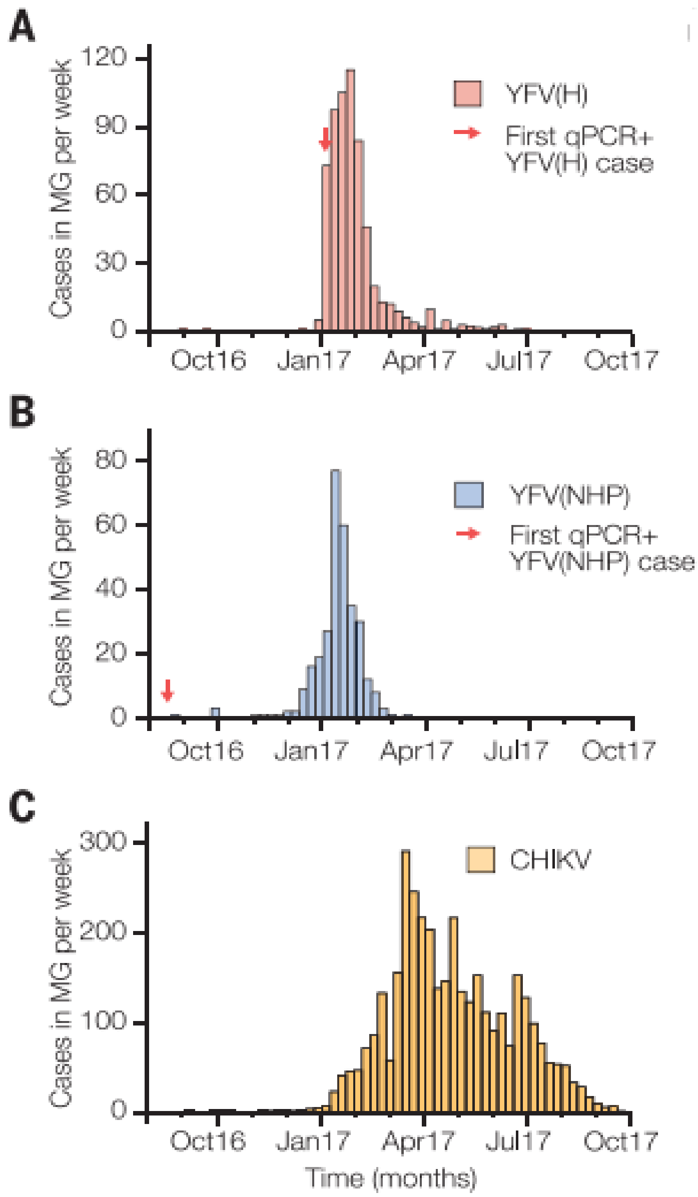

Figure 5. Timeline of YFV human, YFV primate, and CHIKV human cases confirmed per week in Minas Gerais, Brazil from August 2016 to October 2017. The bars are displaying the number of confirmed RT-PCR cases per week in Minas Gerais, Brazil. Graph A shows the timeline of YFV human (H) cases per week in Minas Gerais confirmed through RT-qPCR. Graph B shows non-human primate (NHP) YFV cases, and Graph C shows Chikungunya (CHIKV) confirmed cases. This method was used to obtain a visual representation of the course the virus took during the outbreak. The red arrow indicates the date of the first confirmed case of YFV through RT-qPCR confirmation. CHIKV metadata was used as the urban transmission dataset because it displays the infection characteristics of that cycle. Non-human primate data was used as a comparative dataset to represent sylvatic transmission. By doing this, YFV human case trends should resemble the style of infection cycle it uses, and qualitative observations can be used to determine mode of transmission. From (Faria et al. 2018)

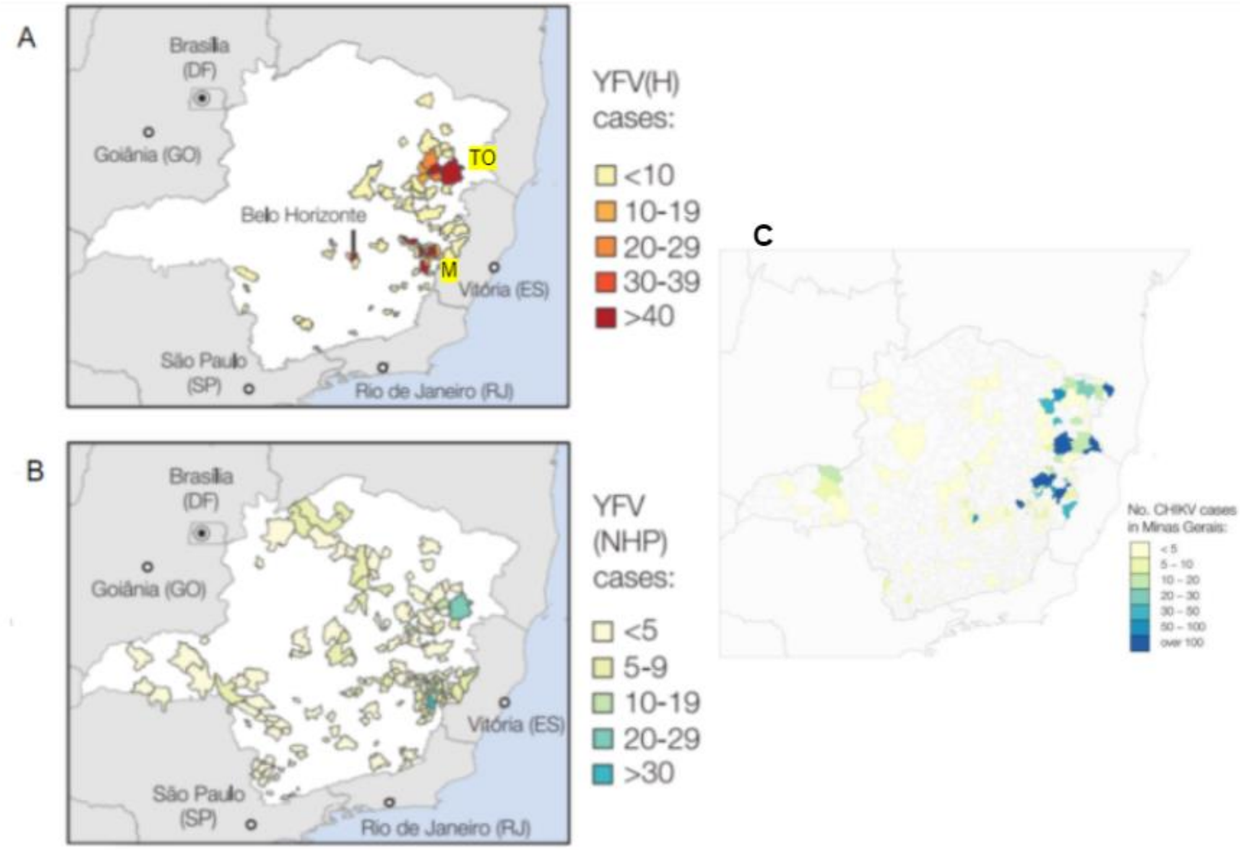

Figure 6. Geographical distribution of confirmed cases of YFV in humans and primates compared to confirmed human CHIKV cases in Minas Gerais, Brazil 2016-2017. Image A shows the geographic distribution of YFV RT-qPCR confirmed cases of humans in Minas Gerais from 2016-2017. A darker shade of red indicates a greater amount of cases seen in a district. Three hotspot cities are displayed by having the darkest shade of red on the map: the northernmost city is Teofilo Otoni (TO), Belo Horizonte is labeled, and directly east of Belo Horizonte is Manhuaçu (M). Image B displays geographic distribution of non-human primate (NHP) YFV cases. A darker shade of blue indicates a greater amount of cases seen in a district. Image C displays the geographic distribution of confirmed cases of CHIKV in humans. A darker shade of blue indicates a higher concentration of confirmed cases in each district. CHIKV metadata was used as the urban transmission dataset since it displays the infection characteristics of that cycle. It also gives the location of *Aedes aegypti* in Minas Gerais Non-human primate data was used as a comparative dataset to represent sylvatic transmission. From (Faria et al. 2018)

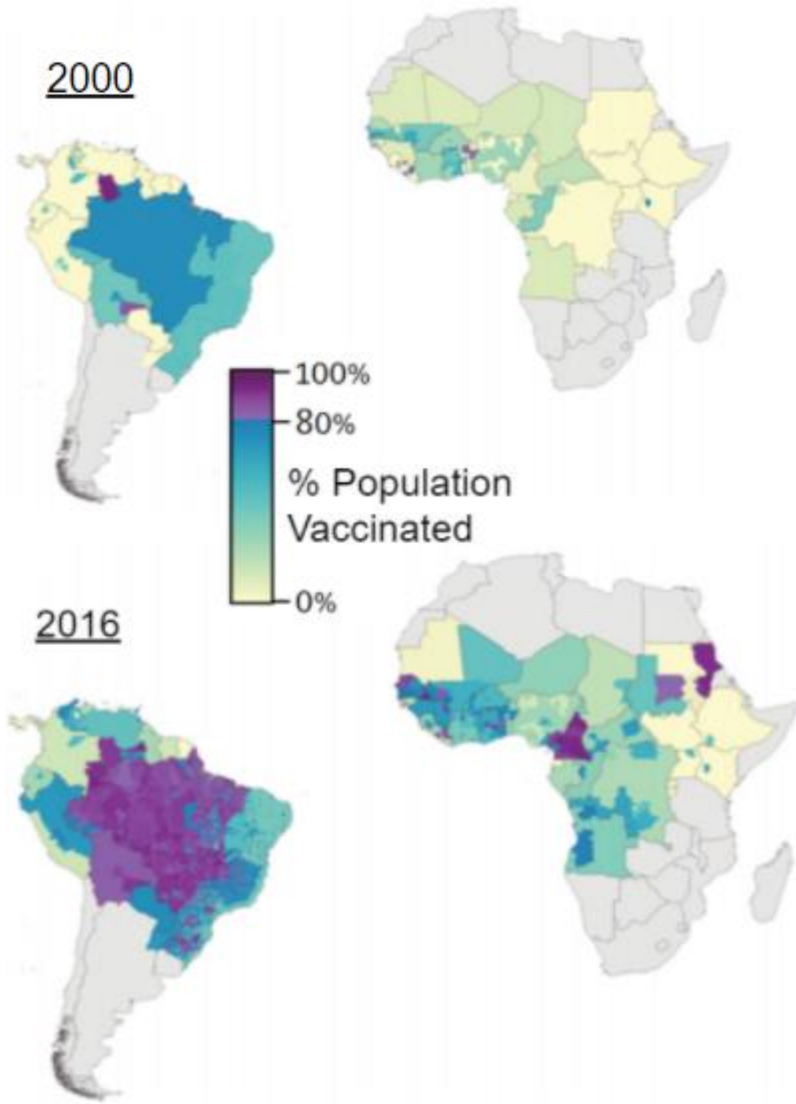

Figure 7. Yellow fever vaccination coverage in South America and Africa in 2000 compared to in 2016. South America and Africa report the highest confirmed case and death rates due to YFV in the world. Purple indicates areas containing over 80% of its population vaccinated, which is the threshold recommended by the CDC to prevent outbreaks. The lighter the shade of yellow indicates an area containing most of its population unvaccinated. The darker the shade of blue indicates areas whose percentage of people vaccinated is closest to the 80% threshold. Countries in grey were not involved in this study since data was unobtainable, or YFV is not a major risk to its population. From (Shearer et al. 2017)

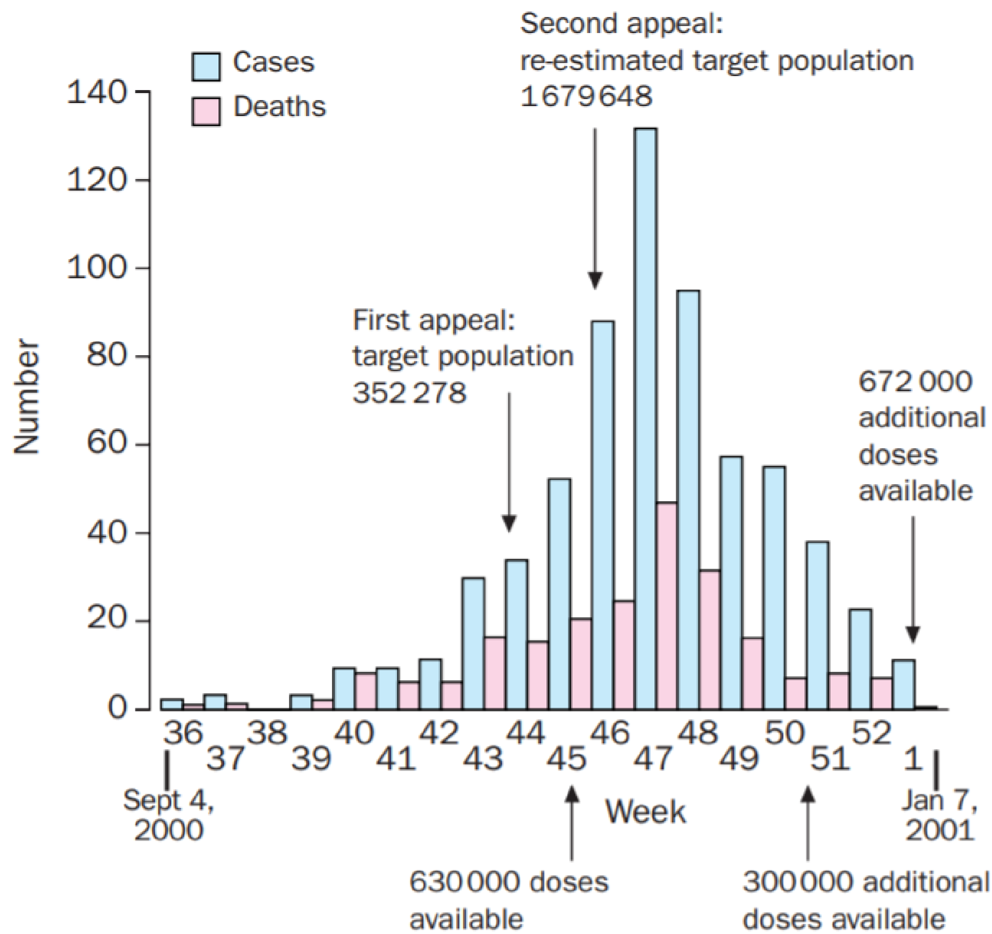

Figure 8. Number of YFV confirmed cases and deaths of humans per week, overlapping with the timeline of vaccination usage during the YFV outbreak in Guinea from September 4, 2000 to January 7, 2001. The week number is listed on the X axis and the number of confirmed cases of YFV is on the Y axis. Blue bars indicate confirmed cases, and pink bars indicate confirmed deaths per week from YFV. The vaccination timeline is represented with arrows pointing to specific dates at which certain doses of vaccines were made available to the country from the international stockpile. Guinean Ministry of Health appeals are shown with arrows pointing to specific dates in which they calculated the estimated amount of people they urgently need vaccinated to slow the outbreak. From (Nathan et al. 2001)

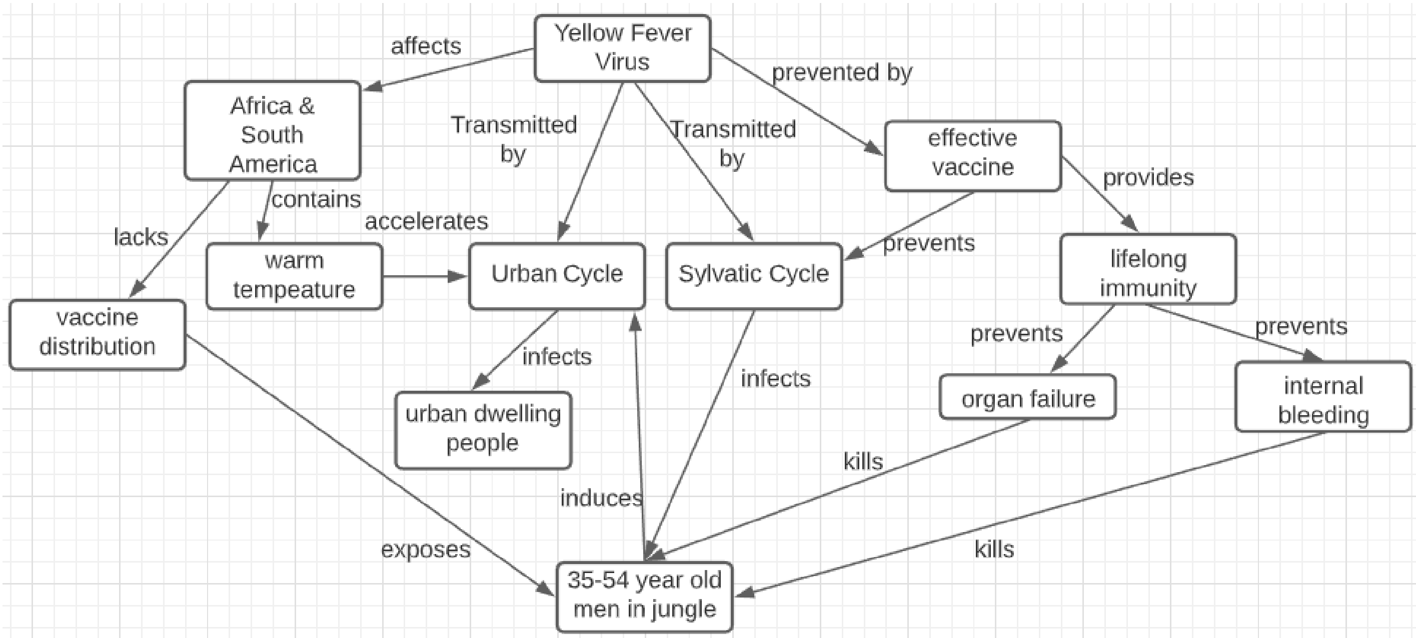

Figure 9. Summary concept map of YFV transmission. YFV affects primarily Africa and South America which have warm climates that benefit *Aedes aegypti* who can accelerate urban cycle transmission. These continents lack adequate vaccination coverage, which in turn exposes adult males working in the jungle. YFV is prevented by an effective vaccine which prevents the sylvatic cycle as well as provides lifelong immunity. Lifelong immunity prevents the fatal symptoms of YFV which would normally kill humans. YFV is transmitted by the urban and sylvatic cycles. The sylvatic cycle disproportionately infects adult men 35-54 working in the jungle. Those infected men induce the urban cycle spread which kills people living in urban centers.