Challenges in Efforts to Control Yellow Fever Outbreaks in Brazil Since 2016: A Literature Review

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Abstract

Yellow fever is a vector-borne disease transmitted to humans and non-human primates through the bite of an infected mosquito. The disease is preventable with a live-attenuated vaccine, which is considered safe, effective, and provides lifelong immunity. Since 2016, Brazil has experienced an influx of Yellow fever outbreaks throughout the country due to the expansion of the virus. This literature review examines factors contributing to the expansion of Yellow fever throughout Brazil and identifies challenges to Yellow fever prevention and control efforts ongoing throughout the country. A systematic literature search was conducted, and twenty-nine relevant articles were found to meet the selection criteria of Yellow fever, Brazil, challenges, and population health. This review of literature revealed lack of Yellow fever immunity, adverse effects of vaccination, deforestation, fractional dosing, and various vaccine supply chain challenges to be the leading challenges facing the Yellow fever control efforts in Brazil since 2016. In the interest of public health, these findings are significant because they have shown that initiating additional prevention methods and revising policies in turn could exceedingly end the Yellow fever epidemic in Brazil, while simultaneously reducing morbidity and mortality of this vaccine-preventable disease.

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Abbreviations

GAVI..Global Alliance for Vaccines and Immunizations

IHR..International Health Regulations

NHPs...Non-Human Primate

WHO..World Health Organization

YF...Yellow Fever

1.0 Introduction

Yellow fever (YF) is a vector-borne disease caused by a Flavivirus that is endemic throughout tropical and subtropical regions of Africa, Central America and South America. Throughout history, YF has caused numerous epidemics with high mortality. The World Health Organization (WHO) currently reports an average of 200,000 cases with 30,000 deaths per year (Staples, Gershman, Fischer, & Centers for Disease Control and Prevention, 2010). The official number of reported cases are far lower than projected numbers, due to the geographic spread of the disease and inadequate surveillance and reporting.

Brazil has been experienced many YF outbreaks in both endemic and non-endemic regions throughout the country. Over the course of the past two decades, the number of YF cases worldwide have increased, particularly within Brazil. Since 2016, the Brazilian Ministry of Health has confirmed 2,229 human cases of YF with 763 deaths ("WHO | Yellow fever – Brazil"). Current vaccination coverage in Brazil is less than the WHO recommendation of 80%, which puts greater risk for YF transmission throughout the country (Klitting, Gould, Paupy, & de Lamballerie, 2018). This literature review examines factors contributing to Yellow fever outbreaks and identifies challenges in YF prevention and control efforts in Brazil since 2016. Furthermore, this literature review offers strategies to help guide public health officials and government leaders on the necessary changes to address and control the YF epidemic in Brazil.

1.1 Fever Transmission

YF infects both humans and non-human primates (NHPs) through the bite of an infected female mosquito. Increased temperature, humidity, and rainfall lead to higher mosquito abundance and consequently an increase in YF circulation throughout Africa and South America (Staples, Gershman, Fischer, & Centers for Disease Control and Prevention, 2010). Specifically, in South America, YF follows a seasonal pattern with highest incidence rates and vector density from January to May (Monath & Cetron, 2002). These mosquito species live and breed in different habitats, thus producing three different types of YF transmission cycles.

The first cycle, known as sylvatic, transmits in jungles or tropical rainforests. Monkeys are the primary reservoir from infected *Haemogous* or *Sabethes* mosquitoes and the YF virus passes on to other monkeys and occasionally humans who work or travel to these remote locations. The second cycle, known as intermediate, encompasses semi-domestic mosquitoes that breed both in the wild and around households. Increased contact between people and infected mosquitoes create outbreaks amongst neighboring villages and communities. The third transmission cycle, known as domestic, occurs in urban settings by infected *Ae. aegypti* mosquitoes through person-to-person transmission. Urban settings are vulnerable to create endemic outbreaks, not only because of high population and mosquito density, but also due to the lack of vector control and low immunization rates (Cupertino et al., 2019).

1.2 Yellow Fever Clinical Presentation

YF is an acute, non-contagious viral hemorrhagic disease that can cause mild, severe, and fatal effects. The incubation period varies between three to six days from initial infection. Signs and symptoms include fever, muscle pain, headache, loss of appetite, nausea and vomiting. With no cure, the primary treatment is supportive care with intravenous hydration, fever reducers, and rest. About 15% of those infected progress to a more toxic phase from initial symptoms, effecting both the liver and kidneys and usually die within 7 to 10 days. Infected patients will develop yellowish coloring of the skin and eyes, known as jaundice, due to inflammation of the liver and dying liver cells that are unable to secrete bilirubin through the gallbladder (Cupertino et al., 2019). South America has a higher case-fatality ratio than Africa, due to enhanced diagnostic testing of persons from remote areas with fatal disease, rather than an indication of a more virulent strain of the disease (Possas et al., 2018). Moreover, YF is challenging for health providers to diagnose during early stages of infection because of asymptomatic symptoms or similar symptoms to other viral infections in South America like Zika, Dengue or Chikungunya.

1.3 Yellow Fever Prevention

Vector control is a crucial method to prevent the spread of the YF virus. Endemic populations should be properly trained on how to use insecticides or repellents, remove stagnant or infested water sources, and how to dispose garbage properly in order to help reduce YF transmission and other vector-borne illnesses. In addition, people living in high-risk areas should be aware of mosquito activity, especially during dawn and dusk periods of the day. Other behavioral initiatives include promoting physical barriers, like wearing light-colored clothes and long sleeves, or using bed netting, and household screens. Lastly, as a clinical prevention method, infected patients should be temporarily isolated indoors away from potential mosquito activity to reduce the possibility of spreading the virus to uninfected mosquitos with their lingering viremia (Tauil, 2010).

1.4 Yellow Fever Vaccination

With only supportive treatment, the most effective prevention method to reduce morbidity and mortality is through vaccination. In 1937, Max Theiler developed the 17D live attenuated YF vaccine and is now prepared by culturing the 17D-204 strain of the YF virus in living avian leukois virus-free chicken embryos (Cupertino et al., 2019). The vaccine contains sorbitol and gelatin as a stabilizer and is hermetically sealed under nitrogen. Its lyophilized makeup extends the shelf life and makes the vaccine more convenient for transport. Each vial of the vaccine is supplied with a separate vial of preservative free sterile diluent, which contains Sodium Chloride Injection USP. The YF vaccine is formulated to contain no less than 4.74 log10 plaque forming units (PFU) per 0.5 mL dose throughout the life of the product (World Health Organization, 2016).

To prevent further YF outbreaks, the WHO "End Yellow fever Epidemics" has advised Brazil to carry out catch-up vaccination campaigns to boost levels of immunity up to 80% among unprotected pockets of the population (World Health Organization, 2016). Both routine childhood immunization programs and mass vaccination campaigns are strategies to increase greater immunity. The YF vaccine is safe, affordable, and only requires a single dose. Vaccine recipients develop protective levels of neutralizing antibodies within 10 days and protective lifelong immunity within 30 days of vaccination (Staples, Gershman, Fischer, & Centers for Disease Control and Prevention, 2010). The vaccine is delivered subcutaneously to anyone 9 months of age and older, living in or traveling through high-risk areas. Contraindications for the YF vaccine include anyone less than 6 months old, immunocompromised, person with an egg allergy, and elderly persons over 60 years old. In addition, anyone who is pregnant, breastfeeding, or living with HIV should speak with their healthcare provider to discuss the risk of disease and potential adverse vaccine effects.

1.4.1 Yellow Fever Supply Chain

During immunization supply chain, YF vaccine must undergo proper storage and handling methods to stay in favorable conditions through all links of transit. Its lyophilized makeup requires it to be stored at 2° to 8°C (35° to 46°F) and can be safely stored for up to two years or more at -20° to 4°C (World Health Organization, 2016). In addition, this vaccine requires reconstitution by the provider who must restore it back to its original state with the addition of a diluent. Reconstituted vaccines are unstable, so it is important to keep them in ice baths and to never freeze before administering them. After the end of every six-hour immunization session, it is important to discard all opened vaccines and diluents to reduce the risk of contamination. Healthcare providers must persevere the potency for all unopened vaccines by storing and transporting them back to their stable temperature of 2° to 8°C.

1.5 Immunization Supply Chain

Immunization supply chain, also known as vaccine cold chain, is one of public health's most successful strategies for vaccine coverage in both urban and remote settings throughout the world. Vaccine supply chain was created separately from other medical distribution systems to assure timely access and control of vaccines (Lloyd & Cheyne, 2017). This systematic method is designed for products that are not naturally heat stable to remain their specified temperatures. As a temperature-control system, vaccines must be thermally maintained through every link of transit starting with the manufacturing plant, transport, delivery, facility, and lastly when administered by the provider.

Protocols for immunization supply chain incorporate vaccine inventory management, storage and handling equipment, transport, delivery, preparation, and injection. These protocols are set into place through operating procedures conducted by staff members. Vaccine inventory management oversees the flow of vaccines, orders, and stock rotation. Storage and handling guidelines include specific labeling and storing procedures. Vaccine storage equipment includes electrical outlets, warning signs, and safety locks. These functions must keep the product cold with temperature monitoring devices. Vaccine delivery is the process of unpacking, recording, and thoroughly checking deliveries. Vaccine transport is dependent on final location. Transport equipment includes portable cold storage units used for long-distance transport, like day clinics in the field or during emergencies. The final step before vaccination is vaccine preparation. Healthcare providers must create a specific location to prepare and draw up vaccines to avoid cross contamination. It is important to only draw up and prepare a vaccine at the time of administration. Providers should follow a safety guard rule when administering a vaccine. For instance, the seven rights rule ensures effective vaccination by identifying the right patient, vaccine, time, dose, route, site, and documentation. Guidelines with immunization supply chain are imperative to public health as they continually assist with the prevention and eradication of vaccine-preventable diseases.

Unfortunately, each year storage and handling errors are the results of poorly trained staff or failures in the critical areas of vaccine inventory, unreliable storage or temperature monitoring equipment. As a result, these supply chain failures can create long term consequences like financial loss for manufactures, public and private partners, and the community. Potency reduction and/or inadequate immune response can result from cold chain failure and lead to additional consequences of revaccination for patients. This requires additional time and resources for patients and their providers. If patients refuse revaccination, this could further decrease coverage and heighten the risk of contracting a serious vaccine-preventable disease. Lastly, supply chain failure can damage the public confidence of vaccines towards the government and healthcare providers for routine immunizations or future vaccine campaigns.

2.0 Methods

A PubMed (NLM) search query on YF and Brazil was created prior to assistance, see Table 2 for detailed summary. Medline (Ovid) and SciELO (ScieELO Network) searches were with the assistance of a public health librarian. The date of the last search was October 16, 2019. Concepts that made up the searches were: Yellow fever, vaccination, Brazil/South America, mosquitoes, urban/rural, and supply chains. A combination of MeSH terms and title, abstract, and keywords were used to develop the initial Medline search which was checked against a known set of studies. The search in SciELO focused on Brazil and Yellow fever. Strategies and dates searched for each database can be found in Table 2. All articles were thoroughly screened for availability of full English text. Zotero (Corporation for Digital Scholarship) was used to store all citations found in the search process.

2.1 Inclusion Criteria

To be included in this review, articles focused on the ongoing challenges contributing to the recent YF outbreaks in Brazil from 2016 to today. The search was limited to full abstract and complete English text. No specific date range was conducted, instead I manually filtered through articles addressing the recent YF epidemic from 2016 to today. Studies examining deforestation, government policy, YF coverage immunity and other vaccine supply chain challenges regarding the recent YF outbreaks in Brazil were the targets in this search. See Table 2 for summaries of all database searches and Table 1 for detail search strategy.

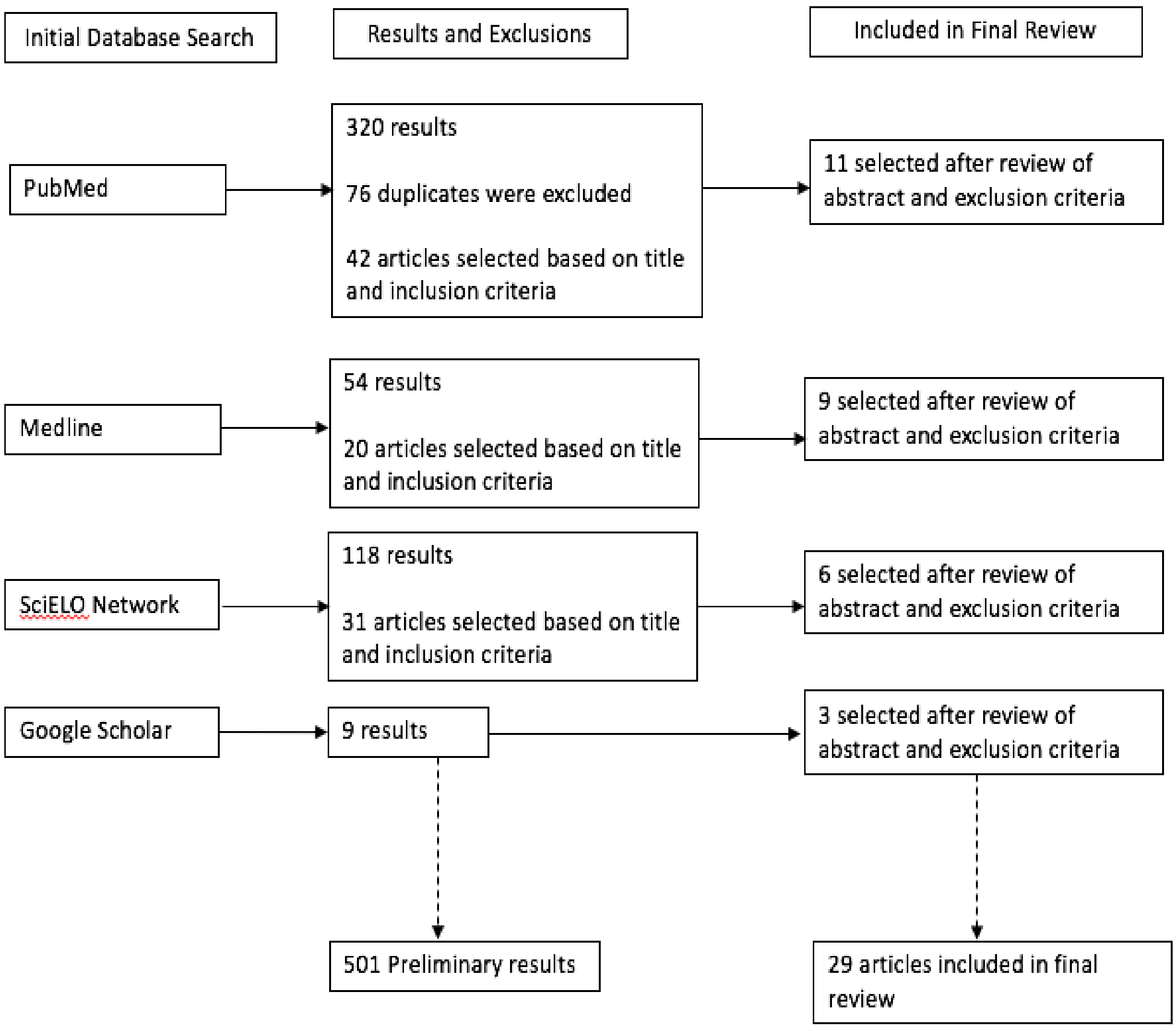

Figure 1. Condensed flowchart of literature included and excluded

2.2 Exclusion Criteria

Results were limited to causal factors contributing to the 2016 to 2019 YF outbreaks in Brazil; studies outside criteria were eliminated. Duplicated articles were removed during the screening process. Eligibility was based on title and abstract and studies not addressing the recent contributing effects of YF transmission or incomplete English text were eliminated.

3.0 Results

The methods, key findings and limitations from the 29 cited articles are outlined below in Table 1. The results section is arranged into: factors contributing to recent outbreaks in Brazil, challenges in YF prevention and control in Brazil, and strategies to address challenges of YF control in Brazil; the key findings of each article are categorized and expanded upon in sections 3.1 - 3.4 of this review.

Table 1. Characteristics of included publications

Author	Methods	Key Findings	Limitations
Ashok, A., et. al. 2017	Review	• Encourage upgrade of cold chain capacity gaps based on current and future needs • Current cold chain systems are struggling to support national immunization programs in Brazil	• Solutions should not be adopted in isolation, but as part of a broader transformation of cold chain performance management
Cândido, E. L., et. al. 2019	Field experiment	• First documentation of *Ae. fluviatilis* in Saboerio, Brazil • Experimentally able to transmit YF	• Uncertainty of urban YF transmission to NHPs and humans
Chen, L.H., et. al. 2019	Review	• Reemergence of YF outbreaks led to vaccine shortages	• Lack of solutions or alternatives provided to assist global stockpile if YF outbreaks are not contained
Chippaux, J., et. al. 2018	Review	• High deforestation increasing contact among human populations • Zika and dengue transmission diverting public health attention • Increase vector control and immunize high-risk populations for YF containment	• Lack of clinical diagnosis of YF index cases • Unknown flaws for YF transmission in Asia
Cupertino, M. do C., et. al. 2019	Review	• Spatial expansion of YF throughout previously considered nonendemic regions	• Insufficient diagnostic tests to detect YF earlier
de Paiva, C. A., et. al. 2019	Multicriteria analysis	• Proximity to Atlantic Forest domain increase vulnerability to YF among dense populations	• Sylvatic YF pattern may not represent actual distribution due to ability to fly long distances

Table 1 Continued

Ghedamu, T.B., et. al. 2019	Analysis of policy surveillance research on national immunization law	• Law and policies assist as tool to protect communities and prolong public health • Success of vaccination programs is only attainable with high rates of immunization coverage • Gaps in national immunization laws	• Mandatory vaccinations remain controversial • Unable to restrict human rights
Haidari, L.A., et. al. 2017	Simulation modeling study	• Solar refrigerators provide savings over electrical refrigerators for supply chain strategies	• WHO and GAVI guidelines may not capture all solar situations • This model is a simplified representation of reality thus cannot capture every feature
Jácome, R., et. al. 2019	Review	• Climate change from human activities initiate rapid spread of arboviruses • Concern for RNA viruses due to high mutation rates, absence of proofreading mechanisms, and ability to cross over species	• Asymptomatic or mild cases are underreported thus underreporting the actual burden of YF
Klitting, R., et. al. 2018	Review	• Transmission dynamics of YF virus • Possible spread of YF to Asia	• Need for more NHPs surveillance techniques • Limited data on genetic resistance to YF among Asian populations
Kristensen, D.D., et. al. 2016	Qualitative research study through semi-structured interviews	• Brazil's primary vaccine improvement demand was for better heat stability technology	• Brazil's lack of GAVI-eligibility • Surveyed small number of individuals, not representative sample • Biased opinions of stakeholders
Lloyd, J., et. al. 2017	Review	• Need to create reliable cold chain systems • Advance technologies shall reduce costs and management measures	• Continuous challenges to reach remote populations
Massad, E., et. al. 2003	Mathematical analysis of R0	• Great number of non-vaccinated people living in Ae. aegypti infested areas in São Paulo	• Assume Ae. Aegypti causes both Dengue and YF when estimating R0
Moeti, M., et. al. 2017	Editorial review	• Still places in the world where vaccines are not being delivered	• Strategies to overcome supply chain costs for low-income countries
Monath, T.P., et.al. 2002	Review	• YF stockpile shortage due to recent global outbreaks • Recommend fractional dosing to create greater immunity coverage • Need for stronger YF surveillance and vector control	• Lack of information regarding potential YF spread to Asia • Limited data on fractional dose immunity duration • Limited clinical testing on children with fractional doses

Table 1 Continued

Moussallem, T. M., et. al. 2019	Retrospective analysis on secondary data	• Highest intermediate incidence rates among forested areas during wet season in Espírito Santo, considered YF free until 2017 • Males more affected due to deforestation occupation	• Secondary data regarding limited epizootic details preceding human epidemic
Nava, A., et. al. 2017	Review	• Environmental changes impact the emergence and reemergence of infectious vector-borne diseases	• Lack of holistic approaches available to mitigate control of YF
Pagliusi, S., et. al. 2018	Review	• Improve supply chain tools and delivery methods of existing vaccines • Importance for partnerships developing countries in fostering innovations for public health	• Lack of innovative solutions to address declining vaccination coverage
Possas, C., et. al. 2018	Review	• Human behavior and ecological changes promote YF incidence in Brazil	• YF fractional dosing is not compliant with IHR • Ineffective NHPs immunization models and strategies
Romano, A. P., et. al. 2014	Retrospective analysis on secondary data	• Recent outbreaks resulted in revised vaccination guidelines in Brazil • Mass vaccination leads to increased detection of adverse effects	• Scare data on YF emergence in non-endemic areas
Saraiva, J. F., et. al. 2019	Field experiment	• First record of *Ae. albopictus* in Amapa, Brazil • Ability to transmit YF through laboratory tests	• Not considered a natural vector of YF
Shearer, F. M., et. al. 2017	Retrospective analysis on secondary data	• Increase in general vaccination coverage, but notable gaps in YF vaccine in Brazil • Brazil not meeting WHO immunization coverage recommendations	• Incomplete high-resolution data lacks certainty of vaccination coverage estimates
Silva, S.F., et. al. 2018	Prospective cohort	• Incomplete immunizations were higher with YF vaccine in Brazil • Immunization strategies should consider the vulnerability of older preschool age children and lower socioeconomic classes	• Lack of data from dates when vaccine doses were administered • Limited age group of 13 to 35 months • Only two cities represented in Brazil

Table 1 Continued

Staples, J. E., et. al. 2010	Review	• Revise recommendations for YF vaccine • At risk populations include unvaccinated foreign travelers visiting endemic regions and unvaccinated people living in endemic regions • Increase vector control and personal protective measures • Simultaneous vaccination with YF and inactivated vaccines is safe	• Need for more suspected risk factors for serious adverse effects • Lack of population and NHPs data on YF due to nature of YF transmission in rural settings • No drug treatments or clinical trials conducted • Limited data on regarding safety and immunogenicity of YF vaccine in pregnancy • Limited data on adverse effects or safety with breastfeeding • Limited data on suspected risk factors for serve adverse effects of YF vaccine
Tauil, P. L., 2010	Review	• Expand vaccination to reduce wild type YF in Brazil • Improve surveillance to enhance early detection of outbreaks	• Insufficient ecological and epidemiological assessment in forested areas
Veras, M. A. S. M., et. al. 2010	Survey on YF vaccine coverage	• Improvement on YF routine infant immunization is needed in endemic and non-endemic regions due to potential spread	• Survey only conducted in capital cities, not represented in rural areas • Non-endemic regions were not accounted for
WHO | Yellow fever – Brazil, 2019	Whitepaper	• Over 80% of recent cases are men • Highest outbreaks occurred with their last two seasonal periods • Brazil increased its immunization policies in more municipalities	• WHO recommendations may not be fulfilled by Brazil • Project further transmission in upcoming seasonal pattern
World Health Organization, 2016	Review	• Outbreaks are increasing the demand for YF vaccine • Fractional dose of YF provides dose-sparing option for recent outbreaks • Fractional dosing is not a long-term strategy nor be replaced with established routine immunization practices	• IHR lack of proof for YF entrance among travelers • Small non-representative sample sizes in fractional dose studies and narrow age range • Only short-term follow up with fractionally dosed subjects
World Health Organization, 2018	Whitepaper	• WHO advocates for YF vaccination requirement for foreign travelers entering at-risk countries for YF • Brazil is a country at risk for YF transmission	• Country requirement are subject to change at any time • Last update 11/05/2018

3.1 Yellow Fever in Brazil

YF has a long history in Brazil, it was first recorded after the Pernambuco epidemic in Recife and Olinda in 1685 (Chippaux & Chippaux, 2018). Historians believe the YF virus was transmitted by a boat carrying slaves from Cape Verde Islands that had stopped in Guadeloupe, where YF was endemic if not epidemic, before reaching the Brazilian coast. The prevalence of YF was greatly reduced, until the next outbreak occurring in 1849, which was attributed to importation of the slave trade from Africa (Chippaux & Chippaux, 2018). Since the invention of the YF vaccine, Brazil's efforts to control YF have included mass vaccine campaigns, which drastically reduced YF incidence rates through the 1930s. Since 1942, there has been no record of YF virus being transmitted by the domestic cycle in urban settings (Moussallem et al., 2019). This is primarily due to the combination of vector control efforts and higher levels of vaccination coverage in urban areas. In addition, low migration rates between urban centers and enzootic reservoirs are limited, but vaccination programs encourage those who travel to enzootic areas to be vaccinated at least 10 days before traveling.

Brazil's current YF epidemic is now drifting from its original epicenter to more populated southeastern states, see Figure 2. Due to the southeastern states landscape, YF transmission is crossing over the forested areas into nearby cities. When the YF virus reaches the edge of the forests it significantly increases contact between humans and the *Haemogous* or *Sabethes* mosquitoes. With little to no protection from infected mosquitoes, sylvatic YF transmission occurs mostly in unvaccinated young men on jobsites in forested areas in Brazil (Staples, Gershman, Fischer, & Centers for Disease Control and Prevention, 2010). In Brazil, where deforestation is in demand, occupations involving lumbering and forest clearing for building or road construction have been linked to human infection. Conversely, YF cases from *Ae. Aegypti* transmission have a higher prevalence infecting women and children due to greater breeding grounds near homes in urban areas; this is more prevalent in Africa. Overall, YF transmission varies based on graphic location with different mosquitoes targeting different populations among age and sex.

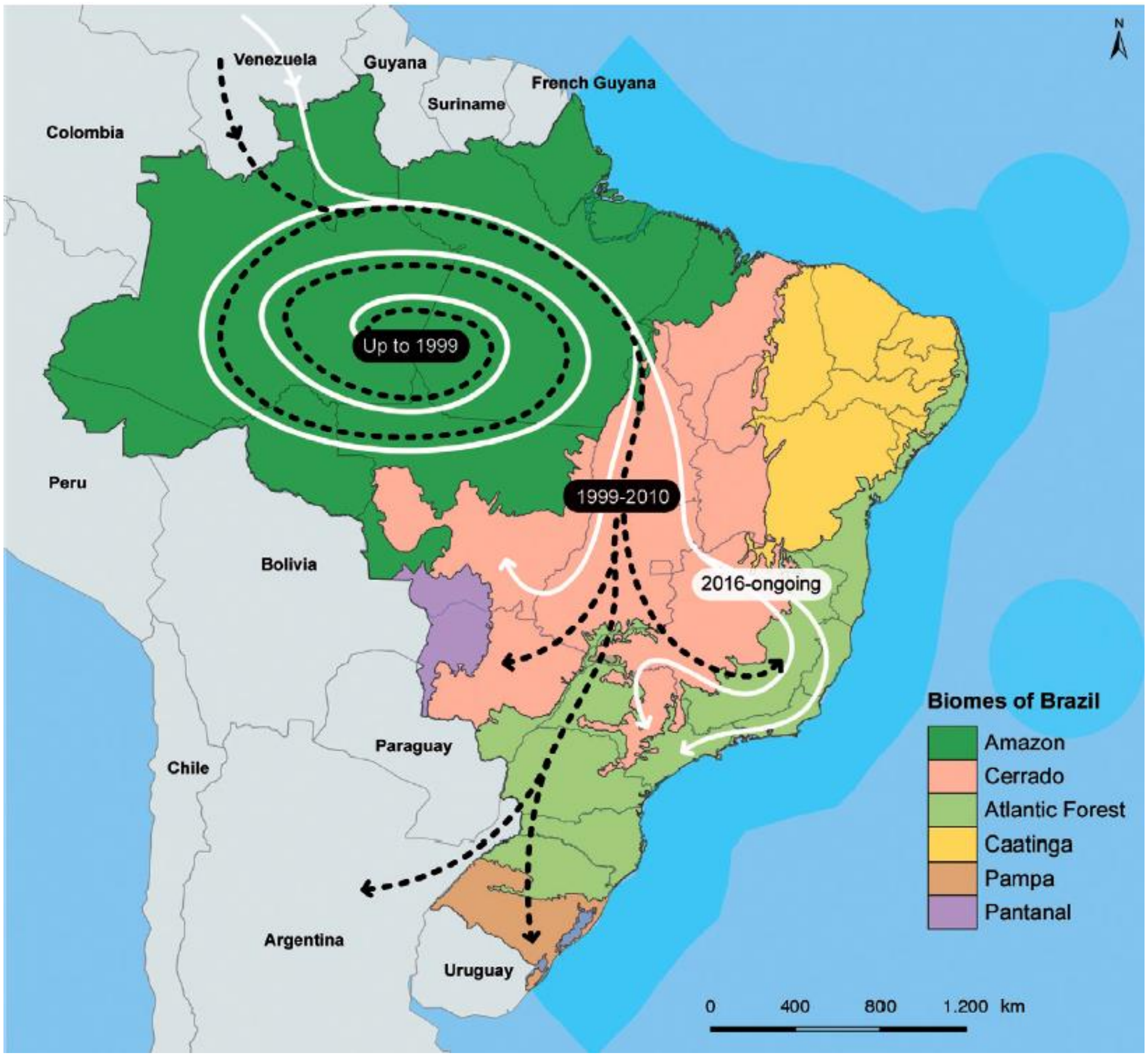

Figure 2. Ongoing Yellow fever viral spread from 1999

(Possas et al., 2018)

The majority of sylvatic YF transmission occurs within the Amazon region along with other outbreaks occurring around its border. Figure 2 highlights the vast geographic expansion of the YF virus throughout Brazil from 1999 to today. The pattern illustrates YF transmission migrating through various Brazilian biomes, thus causing the recent outbreaks into the Southeast and Atlantic Forest. The black dashed lines show YF viral spread from 1980' until 2010. The white lines show YF viral spread from 2016 to the current outbreaks in the Southeast regions of Brazil. Over the last decade, there have been numerous developmental factors contributing to YF transmission including climate, human behavior and economy changes. The reemergence of YF throughout Brazil is creating additional YF prevention and control methods, along with revisions for vaccination (Romano et al., 2014). These unwanted changes have assisted ideal vector transmission conditions for ongoing expansion of YF cases and case fatalities (Possas et al., 2018). In addition, what was previously considered risk-free and under-vaccinated zones are now contributing to the distribution of confirmed cases, due to the YF expansion.

Recent outbreaks of YF in Brazil have taken place largely in metropolitan regions around the country, putting 35.8 million people at risk for infection (Klitting, Gould, Paupy, & de Lamballerie, 2018). In May 2017, 130 cities were affected with 792 positive human cases and 274 confirmed fatalities (CFR – 35%) among eight Brazilian states to include most populated Rio de Janeiro, São Paulo, and the Distrito Federal (Jácome et al., 2019). These regions are susceptible to transmission because of their densities and proximity to the Atlantic forest region. The drastic incidence prompted Brazilian authorities to expand mass vaccination coverage with the use of fractional dosing and door-to-door visits. More than 26 million emergency vaccine doses were administered in 2017. Moreover, between July 2017 and May 2018 there were 1,266 cases with 415 deaths CFR 32.8% (Jácome et al., 2019). By the end of March 2018, this outreach covered 78.6% of the targeted population, equivalent to 17.8 million people (Jácome et al., 2019).

Fortunately, with surveillance initiatives from July 2018 to March 2019, there has been a reduction in YF human and NHPs cases compared to the last three years.

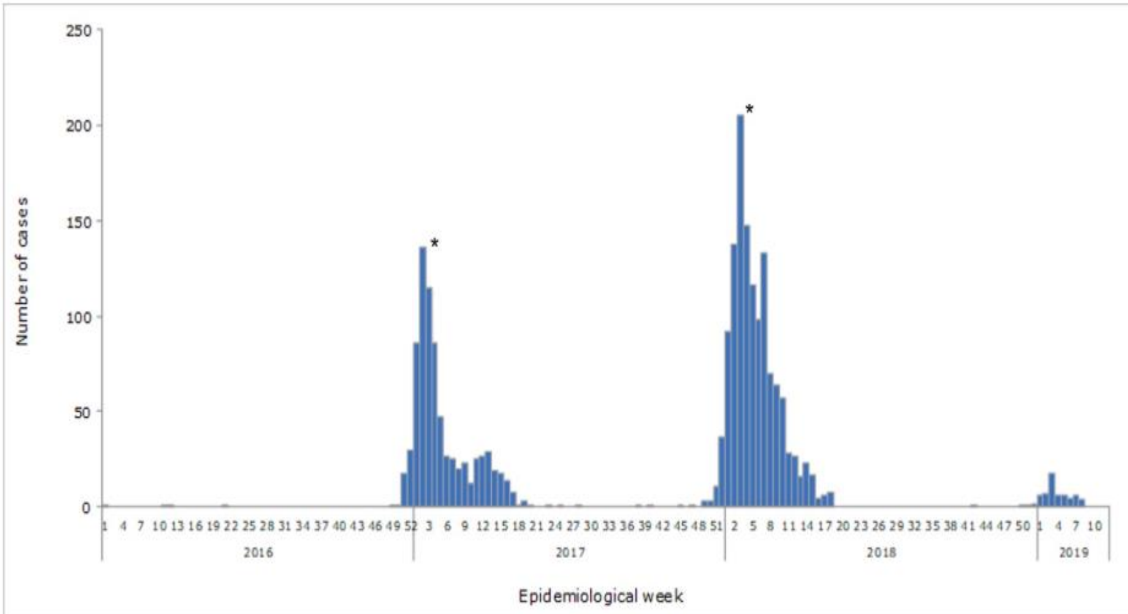

Figure 3. Distribution of confirmed human Yellow fever cases in Brazil, 2016 - 2019

("WHO | Yellow fever – Brazil").

Further detail of the recent YF transmission is shown in Figure 3. This graph highlights a wave pattern of the seasonal transmission among YF with greatest incidence rates between the months of December and May. The first epidemic curve in the 2016-2017 season confirmed 778 human cases to include 262 deaths. The second epidemic curve in the 2017-2018 season confirmed 1,376 human cases to include 483 deaths ("WHO | Yellow fever – Brazil"). The smallest epidemic curve, from July 2018 to March 2019, accounts for 75 confirmed human cases with 17 deaths.

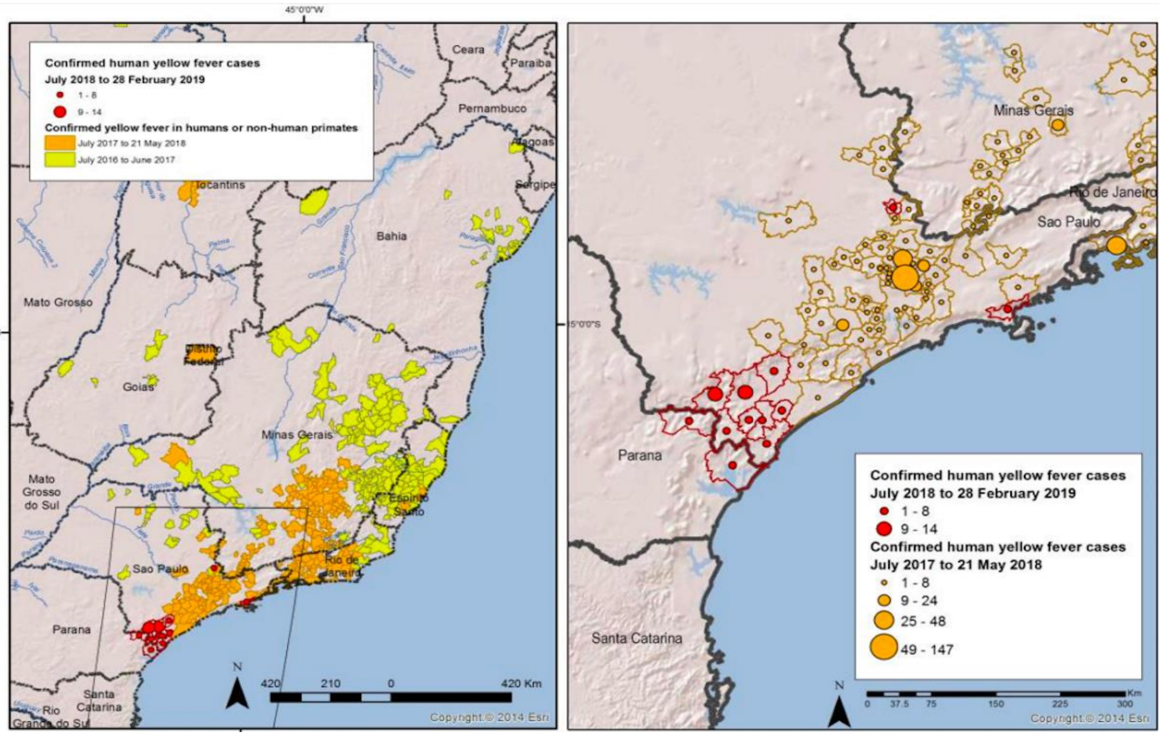

Figure 4. Distribution of both human and NHPs cases in Southeast region, 2018 - 2019

(“WHO | Yellow fever – Brazil”.).

Given the geographical expansion of YF cases in both human and non-human primate cases, the number of areas with recommended vaccination has increased from 3,526 municipalities in 2010 to 4,469 municipalities in 2018 (“WHO | Yellow fever – Brazil”). This public health response initiated the process of vaccinating unvaccinated residents within at-risk regions. Of the 2018–2019 cases, Figure 4 highlights YF incidence in the states of São Paulo (62), Paraná (12), and Santa Catarina (1). Significant findings report 88% (66/75) are males, median age is 43 years old, and 71% (53/75) are rural workers (“WHO | Yellow fever – Brazil”). This data further supports who is most at-risk due to the progression of deforestation and lack of vaccination policies. Moreover, these densely populated regions reside partially or fully within the Atlantic forest domain, which further contributes to the high prevalence of sylvatic YF cases in the states of Minas Gerias, Espírito Santo, Rio de Janiero, San Paulo, and Parana.

Another factor contributing to the recent YF outbreaks is the spread of uncontrolled epizootic cases. Epizootic is defined as a sudden die-off of NHPs in a small geographic area. Sightings of ill monkeys or carcasses are reported to local health departments, which conduct investigation and collect specimens for laboratory testing (Romano et al., 2014). NHPs are extremely susceptible to the virus and its infectious spread among the primate population cannot be stopped. Despite the reduction in the number of human YF cases after May 2017, there was a greater increase in the number of epizootics in Brazil. Reports show between July 2018 and May 2018, over 7,000 probable YF infections in NHPs were reported, with 752 confirmed in lab (Jácome et al., 2019). As a result, these outbreaks are putting endemic populations at greater risk, which is increasing the demand for the YF vaccine. Moreover, with the recommendation of vaccination and use of fractional doses it is exhausting both the national and global stockpiles; thus, it is imperative for their government to look for other sustainable solutions.

3.1.1 Brazilian Ministry of Health Response

In Brazil, YF is a notifiable disease due to its effects on morbidity and mortality among those infected. The Brazilian Ministry of Health's national surveillance system reviews reports of suspected YF cases and epizootic events from state and municipal health departments. Their mission is to reduce the number of sylvatic cases and continue zero YF incidence in urban areas (Tauil, 2010). Specified before, there have been no confirmed cases of YF in urban areas since 1942. This achievement is due to the multiple control programs to include an in-depth surveillance program of *Ae. Aegypti* and immunization campaigns that create a blocking belt of vaccinated individuals living in the transition zone between urbanized areas and enzootic regions (Massad, Burattini, Coutinho, & Lopez, 2003).

Due to the nature of YF, the epidemiology is difficult to capture because it relies on passive surveillance from both humans and NHPs (Klitting, Gould, Paupy, & de Lamballerie, 2018). Remains of NHPs serve as a surveillance tool and act as a warning signal for potential outbreaks or epidemics. Their remains allow researchers to account for incidence cases and additional specimen data. In addition, surveying mosquitos is as another tool used by researchers. Current practices on mosquito baiting and other capturing methods can identify specific species and test for positive YF infectivity. Other surveillance initiatives include raising YF awareness among healthcare workers, mandating notification of persons with hemorrhagic syndromes, and investigating unknown causes of human deaths (Romano et al., 2014). Increasing all forms of surveillance allows researchers and policy makers to access the magnitude of YF, evaluate control measures, and facilitate further planning.

3.2 Yellow Fever Vaccine in Brazil

The YF vaccine has been used in Brazil since the invention in 1937 through mass immunization campaigns. Mass immunization campaigns target at risk areas where there is a low vaccination coverage. Community outreach and education on vaccination campaigns can reach larger populations in short periods of time to prevent further exposure. Through the National Immunization Program access to vaccines are free in Brazil (Silva, Barbosa, Batalha, Riberio, & Simoes). As a part of the Brazilian national immunization program, Bio-Manguinhos Laboratory provides YF vaccines to public vaccination clinics (Tauil, 2010). In 1991, Brazil enacted routine vaccination schedules for infants in endemic regions to help reduce disease prevalence (Veras, Flannery, de Moraes, da Silva Teixeira, & Luna, 2010). Moreover, the YF vaccine is routinely administered at the same time as the measles-mumps-rubella (MMR) vaccine. This joint vaccination process assists with immunization convenience for health providers and families, while improving greater coverage among multiple infectious diseases.

Up until March 2017, the Brazilian Ministry of Health implemented the double-dose vaccine regimen for YF. This second dose was administered after 10 years of the initial vaccine to produce long-term immunity (Cupertino et al., 2019). Despite WHO guidelines declaring a single dose was enough to confirm full immunity, Brazil was the only country continuing the double-dose vaccine. However, due to the recent outbreaks and epidemiological situation in the country over the last three years, the Brazilian Ministry of Health adopted the WHO recommendations and started to recommend only one dose of the vaccine as of April 5th, 2017 (WHO | Yellow fever vaccination booster not needed). Individuals who had been vaccinated at any time in their life no longer need the second booster dose and are considered fully immunized.

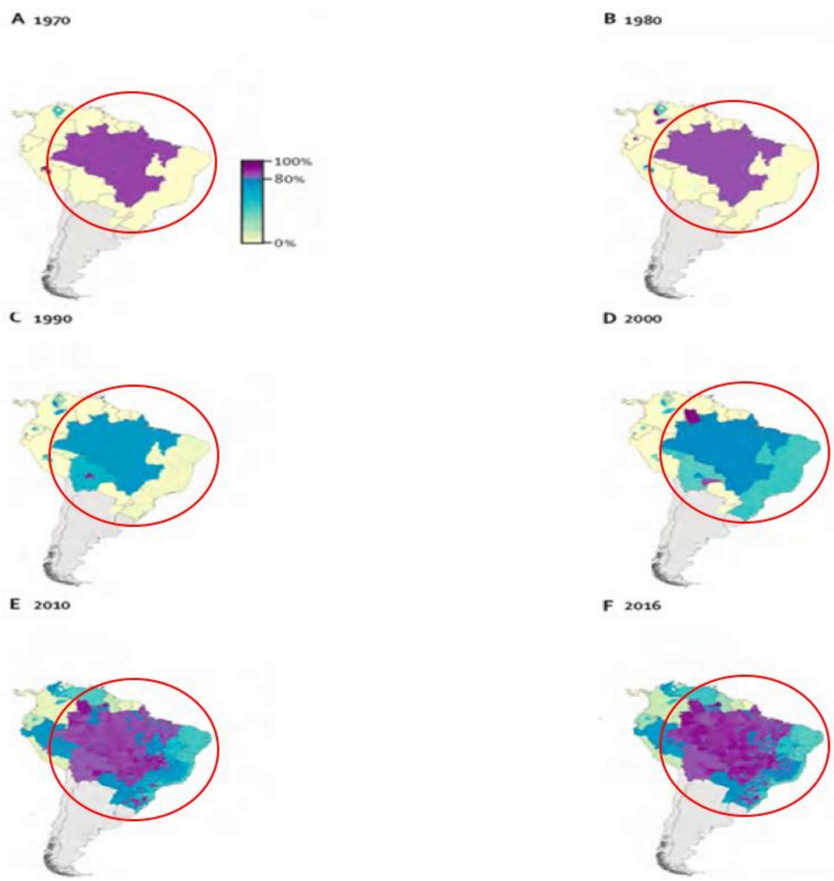

Figure 5. South America vaccination coverage, 1970 - 2016

(Shearer et al., 2017)

Figure 5 portrays YF vaccination coverage from 1970 to 2016 in South America. Throughout each decade, Brazil (circled in red) has consistently increased YF vaccination rates. During the 1970s, the enactment of routine immunization programs for children and young adults have contributed to YF vaccination coverage. YF vaccination is primarily delivered through three different vaccination models; routine childhood vaccination targets infants aged around 9 months in at-risk regions, mass vaccination campaigns are conducted with an outbreak response; and vaccination of people travelling to high-risk areas (Shearer et al., 2017). Unfortunately, from the 1990s until today, there have been numerous sylvatic YF outbreaks prompting further mass vaccination coverage campaigns. As a result, the 2016 vaccination coverage rates were estimated to be much greater for most parts of the country.

Furthermore, effective measures greatly reduce the risk of YF transmission. Enforcement of effective vector control, vaccination, and disease surveillance can all prevent further outbreaks. The results of the Shearer study highlight the progression of closing the immunization gap in high-risk regions, while identifying populations most susceptible to yellow fever infection (2017). Unfortunately, YF cannot be universally eradicated due to the presence of NHPs reservoirs, which maintain the ongoing sylvatic transmission cycle of the virus in remote forested or rural settings. According to the International Health Regulations from WHO, YF is the only infectious disease specified for which countries may require proof of vaccination from travelers as a condition of entry into their country (2016). The purpose of the IHR is to "prevent, protect against, control and provide health response to the international spread of disease in ways that are commensurate with and restricted to public health risk, and which avoid unnecessary interference with international traffic and trade" ("WHO | What are the International Health Regulations and Emergency Committees?"). The legality of the IHR is important as it protects international travel and transport when crossing borders. As of July 2016, the WHO announced Brazil to be considered at-risk for YF transmission. However, Brazil does not require YF vaccination for travelers arriving from neighboring or foreign countries. Similarly, Peru and Columbia are also at-risk countries for YF and do not require proof of YF vaccination. Whereas, other neighboring countries at-risk for YF include Bolivia, Suriname, French Guiana, Guyana, and Paraguay all require proof of vaccination for at least 9 months to 1 year of age (World Health Organization, 2018). Lack of vaccination security from foreign travelers or workers in Brazil create greater risk for further YF transmission. Moreover, the feasibility of implementing this measure at border crossings remain an additional challenge and may not be logistically feasible if legalized given the porous borders at crossings points (World Health Organization, 2016). Ultimately, to see greater vaccination improvements it is up to Brazilian policy makers and other government officials to extend proof of YF vaccination among travelers entering Brazil.

3.2.1 Fractional Dose of Yellow Fever

To add to the recent YF outbreaks in Angola, Brazil and the Democratic Republic of the Congo, the vaccine global stockpile is diminishing as the demand for the YF vaccine is increasing, thus putting greater risk for unimmunized populations in endemic areas (World Health Organization, 2016). The global stockpile is replenished every year to sustain ample supplies to rapidly respond when needed, but without proper vaccine inventory or funding for vaccination campaigns, countries not only face the effects of morbidity and mortality, but also social and economic disruption. Future stockpile concerns include densely populated areas like cities which could overwhelm the emergency response system and ultimately jeopardize global health security (Klitting, Gould, Paupy, & de Lamballerie, 2018). As a result, the Brazilian Ministry of Health initiated other vaccination alternatives to overturn the strained stockpile.

In January 2018, the Brazilian Ministry of Health, with the approval of the WHO, announced that it would initiate fractional dosing as an alternative to achieve maximum coverage. During a public health emergency, this immunization strategy is used to control an infectious outbreak when current vaccine supplies are limited, while assisting the increase of the current local or global stockpile (Pagliusi, Dennehy, Kim, & DCVMN AGM Organizing Committee, 2018). The fractional dose campaign occurred in 76 municipalities in the states of São Paulo, Rio de Janerio, and Bahia to expand vaccination coverage and prevent further outbreak. The Ministry of

Health focused on these municipalities because of the recent sylvatic YF cases nearby and their high population densities of unvaccinated residents. As one of the few countries that manufactures the YF vaccine, Brazil enlisted Bio-Manginhos to implement the fractional dose vaccines in efforts to vaccinate the entire population of 77 million people by April 2019 (Chen, Kozarsky, & Visser, 2019). The fractional dose applied was 0.1 mL, 20% of the standard 0.5mL amount, which allows five people to become partially vaccinated with the use of one standard vial (Cupertino et al., 2019). Contrarily, fractional doses of YF are not yet fully compliant with IHR and therefore should only be used in outbreak settings until more data is gathered.

Experts suggest that the most expedient approach to increase YF vaccine supply during a large outbreak or emergency would be to use a lower dose of the YF vaccine to immunize those at risk. Stretching the supply of the YF vaccine through fractional dosing can protect more people during a YF outbreak. From the Roukens study, researchers show that $1/5^{th}$ of the regular dose of YF can provide the same immunogenicity as the full dose against the disease for at least 12 months (World Health Organization, 2016). Another study by Martins, showed $1/46^{th}$ dilution of the full dose resulted in equivalent humoral response as full dose (World Health Organization, 2016). At 30 days these participants showed seroconversion in 97%. All fractional doses of YF vaccine must have a minimum dose administered, preferentially 3000 IU/dose, but no less than 1000 IU/dose and the minimum volume of administration should be not less than 0.1 ml (World Health Organization, 2016). To reiterate, fractional dosing is not a long-term solution, public health departments cannot replace it with established routine immunization practices and must revaccinate people with the full dose once available.

With fractional dosing only being used in emergent situation, many limitations can apply. Although studies have shown immediate immunity response, it only provides short-term immunity. Thus, it is imperative to let recipients know a fractional dose of YF will not cover lifelong immunity and recipients should return to their healthcare providers to get fully vaccinated once the situation normalizes. Another limitation includes these study populations who participated in fractional dose research are likely different from the effected populations living in YF endemic areas. People living in YF endemic regions may have a different biological makeup among the relationship with flavivirus exposure and genetic background (World Health Organization, 2016). In addition to study populations, the data only represented adults, which limits the entirety of an actual population. Therefore, more research needs to be conducted to further examine YF fractional dosing as a public health tool.

3.2.2 Adverse Effects of Vaccine

Adverse effects from the YF vaccine is one of the leading challenges related to successfully vaccinating the entire country. The YF vaccine has been used for decades and side effects are generally mild, but there are continuous cases of adverse events. There have been reports of rare life-threatening allergic reactions, alters to the nervous system and/or internal organs (Kaiser, 2018). In Brazil, it is estimated that 1 and 21 cases per million doses are fatal (Massad, Burattini, Coutinho, & Lopez, 2003). Studies have also shown that vaccination of adults without prior immunity may increase rates of severe events, because risk is greatest with first vaccination and appears to increase with age (Romano et al., 2014). Therefore, healthcare providers caution vaccination in adults who are older than 60 years of age.

Mass vaccinations have shown an increase in adverse side effects, which may be better detected and addressed through improved surveillance. Studies suggest there is an association with lower socioeconomic and demographic factors to incomplete childhood immunizations due to limited access and fear of adverse effects (Silva, Barbosa, Batalha, Ribeiro, & Simões). To reduce the stigma against the YF vaccine, public health officials and healthcare providers need to educate and discuss all indications for vaccination, including contraindications and precautions for persons who might be at increased risk of severe adverse events (Romano et al., 2014). Open communication from trusting health professionals may reduce associated stigma of vaccines for patients who may have concerns with personal or religious beliefs regarding YF vaccination. Likewise, nonclinical adverse effects like human suffering, economic loss due to infeasibility to work, treatment costs, and reduction of tourism and exports can lead to additional consequences of the morbidity and mortality of YF (de Paiva et al., 2019).

3.3 Vaccine Supply Chain Challenges

With today's technology and sources of mobility, it is a shame that vaccines are still not able to reach all people around the world. This is largely due to the complexity of vaccine supply chain systems. Vaccines can become lost, damaged, or expired before they reach local health clinics or points of use, thus hindering efforts to cover greater immunity (Moeti, Nandy, Berkley, Davis, & Levine, 2017). An additional challenge to the vaccine supply chain is the ability to reach healthcare providers in remote communities who need more supplies. This requires meticulous control of temperature during storage and transport, specialized cooling equipment, and logistical expertise to avoid breakdowns in delivery systems of cold chain equipment (Moeti, Nandy, Berkley, Davis, & Levine, 2017). Thus, it is imperative to establish a renewed focus on next-generation supply chains that can safely and reliably manage, store, transport, and deliver vaccines.

The point of use is vital to closing the immunization gap for not only YF, but for all vaccine-preventable diseases.

Although improving supply chain equipment can expand vaccination coverage, an additional challenge is reaching unvaccinated people in remote locations. Remote populations include people living off rivers, in mountains, on islands, and as nomadic tribes. Logistically reaching out to these communities costs up to five times more than in urban areas to fully immunize someone (Lloyd & Cheyne, 2017). Yet the cost-effectiveness of investments is compelling: recent research suggests that for every dollar invested in childhood immunization, there is a return on investment of US $16 through savings in health care cost, wages, and productivity due to illness in low and middle-income countries (Moeti, Nandy, Berkley, Davis, & Levine, 2017). Furthermore, cold chain systems are struggling to support national immunization programs due to vast coverage demands, inadequate equipment and cold chain capacity (Ashok, Brison, & LeTallec, 2017). WHO and Global Alliance for Vaccines and Immunizations (GAVI) both recommend solar refrigerators for regions with limited time of electricity (Haidari et al., 2017). Solar refrigerators are less costly than on-grid refrigerators and are only used when electric supplies are unpredictable and can help overcome these challenges.

3.4 Deforestation in Brazil

Deforestation is the process of permanently clear cutting or burning away forests in order to make land more available for agriculture, cattle ranching, or harvesting timber. In 2019, the State of Amazons in Brazil declared a state of emergency over the wildfires and deforestation (Cereceda, 2019). As a result, sylvatic YF transmission has become the leading cause of infection to NHPs and unvaccinated people in these once forested areas. With deforestation, *Haemogous* or *Sabethes* mosquitoes are no longer enclosed in their forest reservoir and open to migrate outwards. What was once a barrier containing sylvatic transmission, is now a vulnerable area where infected mosquitoes can infect the edges of vegetation where forests and cities intermix (Moussallem et al., 2019). This especially increases sylvatic YF transmission among workers with forest-related occupations and people living in nearby villages or cities.

In 2016, Brazil lost almost 8,000 square kilometers of forest through deforestation, according to NGO Observatório do Clima, this was a 29% increase to 2015 (Veiga, 2017). Notoriously known as one of the highest deforestation contributors, Brazil does not seem to be slowing down. As a result, the WHO has warned neighboring countries with similar ecosystems to Brazil of the possible increase of YF transmission and the importance of vaccination to avoid sylvatic YF outbreaks. It is important to remember that deforestation is a public health threat, not only to the effects of climate change and biodiversity, but also to animal reservoirs and human inhabitants.

4.0 Discussion

4.1 Recommendations

4.1.1 Increase Yellow Fever Vaccination Coverage

Routine vaccination to all unvaccinated people living in Brazil should be highly recommended because of Brazil's YF history, prevalence of other vector-borne diseases, and the ongoing YF outbreaks. This would strengthen adherence to routine vaccinations and avoid unnecessary future mass vaccination campaigns. Moreover, this is a more cost-effective plan in the sense that it optimizes allocation of limited resources and prevents unwanted healthcare costs (Massad, Burattini, Coutinho, & Lopez, 2003). Additionally, reducing the stigma associated with the YF vaccine and its adverse effects is fundamental when proposing greater vaccine coverage. The Brazilian Ministry of Health and healthcare providers should continue to advocate YF vaccination and educate at-risk populations who reject immunization for religious or personal belief.

Equally important, with the increase of NHPs being exposed to more open and public surroundings, the Brazilian Ministry of Health should create a policy to reduce potential YF circulation with methods to vaccinate NHPs. Vaccinating NHPs in confined parks and forests reserves contiguous to urban areas as well as animals maintained in zoos is already underway (Possas et al., 2018). Since NHPs live and hide in forested areas, it would be near impossible to physically vaccinate all of them with an injection. More research needs to be conducted to develop other strategic delivery strategies to vaccinate NHPs. Examples could include food containing the recombinant YF vaccine, transgenic fruit, or other technological alternatives (Possas et al., 2018). It should be noted, vaccinating NHPs protects immunity for both animal and human populations, while preserving greater biodiversity.

Another suggestion to increase YF vaccination is to promote simultaneous vaccinations. YF vaccine can be administered simultaneously or 30 days apart from other live viral vaccines to limit the impaired effects (Staples, Gershman, Fischer, & Centers for Disease Control and Prevention, 2010). There has been no evidence the YF vaccine interfering with the immune response when paired simultaneously with the Bacillus Calmette–Guérin, human papillomavirus, meningococcal, pertussis, smallpox, tetanus, typhoid or rabies vaccine. In addition, during infant routine vaccinations, the YF vaccine can be administered in conjunction with other vaccines to include diphtheria, hepatitis A, hepatitis B, influenza, measles-mumps-rubella (MMR), polio, and varicella (Veras, Flannery, de Moraes, da Silva Teixeira, & Luna, 2010). Advantages to simultaneous vaccinations reduce appointment time for the provider and patient, cut cost of transportation, and vaccinate against multiple diseases in less increments. Moreover, studies show routine immunization services in fixed facilities, along with consistent outreach services carried into the field help increase vaccine coverage (Lloyd & Cheyne, 2017). This allows the public to be more familiar with vaccination schedules and longer lasting healthcare resources.

Furthermore, the need for collective work among all stakeholders is imperative to end the YF epidemic in Brazil. A study involving Brazilian stakeholders was captured and analyzed among other middle to low-income countries with vaccine challenges. Brazil's main concerns on how to understand and improve vaccine products include decreasing vaccine waste, preventing heat damage, and simplifying delivery methods (Kristensen, Bartholomew, Villadiego, & Lorenson, 2016). By collaborating with YF stakeholders to include manufacturers, researchers, and international organizations like WHO, GAVI and National Immunization Program, there is hope to advance this shared goal of increasing YF vaccination coverage in Brazil (Pagliusi, Che, & Dong, 2019).

In contrast to the WHO and other neighboring countries, the Brazilian government does not require the YF vaccine for foreign travelers or workers coming into country. Recommending documentation of the YF vaccine will reduce infectivity and stop the ongoing cycle of outbreaks among unvaccinated people. In addition, the Brazilian Ministry of Health needs to further emphasize that newly vaccinated people traveling to endemic regions must be vaccinated at least 10 days prior to travel. This proposed mandatory requirement ties into the idea by Ghedamu and Meier, which is to create a national public health law to prevent further infectious disease outbreaks. Creating vaccine travel restrictions helps sustain global health security. Furthermore, national public health laws could provide requirement around licensure and legal obligation to those who want to travel to foreign countries (Ghedamu & Meier, 2019). Not only would this be used as a public health tool, but it would allow researchers to better understand the impacts of regulated public health outcomes and/or propose new law reforms.

4.1.2 Increase Yellow Fever Surveillance

Currently, the primary surveillance systems for YF are passive models that look at previous YF diagnoses and remains of infected NHPs. Unfortunately, this data contributes to underreporting and incompleteness. Although resource intensive, active surveillance is recommended due to the nature of YF disease and high-risk populations in endemic regions of Brazil. Ensuring more complete YF reports allows researchers and public health officials to monitor trends, patterns, and risk factors. This allows further detection of sudden changes in the disease transmission, progression, and distribution. With the collection of data, public health officials and epidemiologists can provide information to assist government programs, policies, and priorities. This further allows better evaluation on public health programs regarding prevention and control measures.

Apart from this, vector surveillance is imperative due to the rise of other vector-borne diseases and pathways. Recent findings of two potential vector-borne mosquitoes for YF are being researched. *Aedes fluviatilis* and *Aedes albopictus* are both arboviruses prevalent in Brazil and can share the same breeding grounds with *Ae. Aegypti*. Within experimental models, *Ae, fluviatilis* has demonstrated positive transmission of YF (Cândido, Silva, & Cavalcanti, 2019). Both mosquito species are well adapted in rural and urban environments. Although they are not yet classified as natural vectors for YF, this raises a public health concern that they could potentially act as an infestation bridge between rural and urban environments (Saraiva et al., 2019). Overall, the Brazilian Ministry of Health and other agencies must continue all types of surveillance methods to reduce the spread of YF across their county.

4.1.3 Increase Vector Control Measures

Another recommendation necessary to reduce further YF exposure in rural and urban settings is to continue vector control measures at all levels of government. For example, local prevention methods could include community practices of eliminating potential breeding grounds like removing stagnant water and using netting or screens as a physical barrier. State prevention methods include regular garbage pickup and spraying insecticides or repellents to prevent potential breeding grounds. Lastly, as a national prevention measure, immunization is the primary method to reduce YF morbidity and mortality. Ongoing research is underway to develop innovative vector control strategies. A promising study is the use of transgenic male mosquitoes carrying a dominant lethal copy gene, causing their offspring to die at the pupation stage (Jácome et al., 2019). Most importantly, all control measures must be accompanied with current vector-borne education, so the general public is aware of how to safely protect themselves and their families.

4.1.4 Restrict Deforestation

The recent outbreaks of YF were most likely driven by human enforced deforestation and forest fragmentation for extended transportation and agriculture use, that led to isolated and stressed reservoirs of NHPs while indirectly altering the vector expansion. Protection laws against industries in urbanization and agriculture are recommended to prohibit or reduce deforestation to further prevent vector-borne outbreaks and climate change. Despite, the Brazilian government signing the United Nations Framework Convention on Climate Change in 2016, their concerns when it comes to deforestation is superficial and can be connected to adverse political and economic interests (Nava, Shimabukuro, Chmura, & Luz, 2017).

Furthermore, there is an interconnecting relationship among deforestation, climate change, and infectious diseases. Climate change initiates increased temperature and higher rainfall, thus creating more breeding grounds for mosquito vectors. These effects may affect the survival, reproduction, and distribution of disease and their hosts (Nava, Shimabukuro, Chmura, & Luz, 2017). Global warming is leading to proliferation and dislocation of mosquito vectors from tropical to more temperate zones around the world. With government policies and public health initiatives to restrict deforestation, the spread of vector-borne diseases should subside.

4.2 Limitations

This review was limited by the methodology in choosing to build specific database search queries around MeSH terms. Relevant, published articles that have not been indexed may have not been captured by all database searches. In addition, this review may not be representative to all factors contributing to the recent YF outbreak in Brazil that were not published in academic journals. Lastly, my inability to read Spanish or Portuguese limited my article findings, thus narrowing my search of potentially relevant sources pertaining to my review.

5.0 Conclusion

When considering other infectious diseases, society is fortuitous in the sense there is an effective YF vaccine available and it only requires a single dose. Not having to worry about multiple doses or reaching people again allows greater accessibility to immunize more people, thus increasing coverage. With the reemergence of YF in Brazil, this literature review analyzes the contributing challenges in efforts to end the ongoing epidemic in Brazil and points to the need for government policy changes regarding vaccinations and deforestation, along with additional vector control measures and increased surveillance coverage. As a significant public health concern, this poses an unwanted threat to the Brazilian population and wildlife. The Brazilian Ministry of Health’s mission is to maintain zero YF incidence cases in urban areas and reduce sylvatic incidence in remote areas; however, they are neglecting indirect factors contributing to the spread of YF. Efforts to end the epidemic include restricting deforestation, mandating a YF vaccine policy for foreign travelers, increasing YF surveillance and vector control measures will in turn assist the elimination of YF in Brazil. Based on the YF seasonal pattern, increased infectivity is expected to occur in the next coming months, thus these proposed ideas can be organized into action to avoid the development of disease by containing the remaining outbreaks, protecting at-risk populations, and preventing further transmission.

Appendix: Search Queries

Table 2. Summary of databases searched

Table	Vendor/ Interface	Database	Date searched	Database update	Searcher(s)
2a	National Library of Medicine	PubMed	September 20, 2019	October 15, 2019	Elizabeth Owens
2b	Ovid	Medline®	October 16, 2019	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to October 7, 2019	Elizabeth Owens; Helena M. VonVille
2c	SciELO Network	SciELO	October 16, 2019	October 16, 2019	Elizabeth Owens; Helena M. VonVille

Table 2 a. National Library of Medicine search stratgegy

Provider/Interface	National Library of Medicine
Database	PubMed
Date searched	September 20, 2019
Database update	October 15, 2019
Search developer(s)	Elizabeth Owens
Limit to English	Yes
Date Range	No limits used
Publication Types	No publication types specified
Search filter source	No search filter used

1	Yellow fever and brazil
	Limits: English

Table 2 b. Medline® search strategy

Provider/Interface	Ovid
Database	Medline®
Date searched	October 16, 2019
Database update	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to October 7, 2019

Table 2b Continued

Search developer(s)	Elizabeth Owens; Helena M. VonVille
Limit to English	Yes
Date Range	No limits used
Publication Types	No publication types specified
Search filter source	No search filter used

1.	vaccines/ or viral vaccines/ or immunization/ or immunization schedule/ or immunization, secondary/ or immunotherapy/ or immunotherapy, active/ or vaccination/ or mass vaccination/ or immunization programs/ or (vaccin* or immuniz* or immunis*).ti,ab,kw.
2.	Yellow Fever/
3.	Yellow Fever*.ti,ab,kw.
4.	Yellow fever virus/
5.	2 or 3 or 4
6.	1 and 5
7.	yellow fever vaccine/
8.	6 or 7
9.	supply chain*.ti,ab,kw. and 8
10.	supply chain*.ti,ab,kw. and 1
11.	limit 10 to english language
12.	south america/ or argentina/ or bolivia/ or brazil/ or chile/ or colombia/ or ecuador/ or french guiana/ or guyana/ or paraguay/ or peru/ or suriname/ or uruguay/ or venezuela/
13.	(south america or argentina or bolivia or brazil or chile or colombia or ecuador or french guiana or guyana or paraguay or peru or suriname or uruguay or venezuela).ti,ab,kw.
14.	12 or 13
15.	11 and 14
16.	11 not 15
17.	(barrier* or challenge* or facillitat*).ti,ab,kw.
18.	1 and 17
19.	14 and 18
20.	limit 19 to english language
21.	8 and 20
22.	Mosquito Control/
23.	culicidae/ or aedes/ or anopheles/
24.	(culicidae or aedes or mosquito*).ti,ab,kw.
25.	22 or 23 or 24
26.	14 and 25
27.	17 and 26
28.	limit 27 to english language
29.	8 and 28
30.	Population Density/
31.	Urban Health/ or Urban Population/ or Urban Health Services/
32.	Rural Health/ or Rural Population/ or Rural Health Services/
33.	(rural or urban or population density).ti,ab,kw.

Table 2b Continued

34.	
35.	8 and 25 and 34
36.	35 and (brazil/ or brazil*.ti,ab,kw.)

Table 2 c. SciELO searach strategy

Provider/Interface	SciELO Network
Database	SciELO
Date searched	October 16, 2019
Database update	October 16, 2019
Search developer(s)	Elizabeth Owens; Helena M. VonVille
Limit to English	Yes
Date Range	No limits used
Publication Types	No publication types specified
Search filter source	No search filter used

1	yellow fever and brazil
	Limits: English

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