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REVIEW ARTCLE

The Perennial Threat of Yellow Fever

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Despite the availability of a safe and effective vaccine, yellow fever remains a major vaccine-preventable disease in endemic regions. Additionally, travelers risk acquiring yellow fever when visiting areas of endemic transmission or locations with ongoing outbreaks. Yellow fever is a viral hemorrhagic fever that has inflicted stigma, illness, and death among human societies. From the 17th to the 19th centuries, yellow fever remained a mysterious illness that predominantly affected tropical regions in Africa, the Caribbean and the Americas. The disease was as feared as cholera or smallpox, and played a significant geopolitical role in shaping modern societies. Epidemics of yellow fever brought out the best and the worst of human nature: the disease spread to new regions during the Atlantic slave trade; while the identification of its causative viral agent and mode of transmission, as well as the development of a vaccine, were made possible by the sacrifice of selfless scientists. Confirmation of the vector transmission of YF paved the way for the development of an effective vaccine in the first half of the 20th century. Encroachment of human settlements into locations with sylvatic transmission has blurred the distinction between the urban and sylvatic cycles. Introduction or expansion of routine immunization activities and reaching hard-to-reach populations consitute public health priorities toward ensuring vaccine equity in endemic areas. It is also critical to ensure the timely immunization of at-risk populations during outbreaks and to promote vaccination of international travelers. We conclude that the threat of YF will linger far into the 21st century as a leading public health emergency of global concern under the International Health Regulations.

Keywords: Yellow fever, Vaccine, Vaccine-preventable diseases, *Hemagogus*, *Aedes aegypti*, *Aedes albopictus*.

Introduction

Yellow fever (YF) is a mosquito-borne viral infection that has inflicted fear, stigma, disease, and death on human societies for centuries (1–3). The flavivirus family is named after the Latin root *'flavus'* for the yellowish coloration of the skin and mucosae (jaundice) that result from the cytotoxic injury of the yellow fever virus (YFV) in hepatocytes (1). YF has had a profound impact on the establishment of modern human societies (4–6). With the Atlantic slave trade, YF reached the New World (7–8). The Caribbean island of Barbados became an epicenter for transmission that spread further to other Caribbean islands and continental cities in the Americas (7). The expansion of commercial trading routes also played an important role in the spread of YF to new territories (2,7). More recently, the YFV has expanded its territorial reach through modern social and demographic forces, including population growth, global migration, deforestation and land use (9–10). Despite the availability of a safe and effective vaccine since the 1930s,

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YF remains a threat to millions of people residing in tropical and subtropical regions of Africa, South and Central America (11–15) and to international travelers who visit these at-risk regions (2).

The geographical spread of YFV transmission leading to epidemics is intimately linked to social, political, and economic forces (2,7,12). This narrative review presents an overview of the current epidemiologic trends of YF transmission and a discussion of the potential risk of introduction into new areas. It also explores the historical impact of YF in different regions and the development and deployment of the YF vaccine.

Current Epidemiology of Yellow Fever

During the past few centuries, there have been geographic expansions and retractions of areas at risk for YF transmission (16–21). At present, there are 44 countries in Sub-Saharan Africa and the Americas (South and Central America), which are considered by the World Health Organization (WHO) to have intermittent, sylvatic, epizootic, sporadic cases, and urban outbreaks of YF (22–24). Some countries are at an increased risk for experiencing YF outbreaks (27 in Africa and 13 in Central and South America) (22). Yellow fever is transmitted to humans by different and overlapping transmission cycles involving mosquito vectors and non-human primates. In Africa, outbreaks occur periodically, while in South America, these outbreaks appear sporadically (17,22–27). In Sub-Saharan Africa and South America, YF is maintained through enzootic cycles among certain species of non-human primates (i.e., *Alouatta palliata* in the Amazon region) (25–26). Unvaccinated travelers visiting at-risk areas in South America may acquire the infection through the bite of *Hemagogus* spp. that had previously fed on infected non-human primates (25–27). In some African regions, there is an *intermediate cycle (savannah)* in which infection is transmitted to humans via mosquitoes that bite infected monkeys or infected humans laboring or living in the areas bordering both the rainforest and the African savannah (28–30). The entomological inoculation rate in Africa is many times higher than in South America, where *Aedes africanus* is responsible for YF transmission in the sylvatic, intermediate, and urban cycles (31–33). Nonetheless, *Aedes albopictus* may play a role in bridging the sylvatic and urban cycles (22).

In the Americas, most transmissions occur via urban cycles, involving only humans, driven by the urban-dwelling mosquito *Aedes aegyptii* (19,34–35). However, the sylvatic cycle is becoming an important form of transmission of YF in Latin American due to the growing incursion of human populations into forests for housing or work (mining, agriculture, oil extraction), where it is transmitted by mosquitoes such as *Hemagogus* spp. and *Sabethes* spp (6,22,25–26). This social and ecological phenomenon is best exemplified by the recent large outbreak of YF that appeared in Brazil from 2017–2019, characterized as an *urban cycle* of transmission but transmitted by *Hemagogus* spp., with cases identified in large urban centers in the coastal areas of the states of Sao Paulo, Minas Gerais, and Rio de Janeiro (there were more than 2000 cases and close to 700 deaths) (25–26). The spread of this outbreak was facilitated by the growing expansion of human settlements encroaching upon rainforest areas that were exclusive of the *sylvatic cycle. Hemagogus* spp. mosquitoes reside in the rainforest canopy where they feed upon non-human primates. However, due to a drought period that coincided with this outbreak, *Hemagogus* mosquitoes descended during their peak-biting time (around noon time) to feed on humans (25–26).

The clinical spectrum of YF ranges from a mild nonspecific viral syndrome to a severe biphasic, clinical course culminating with liver failure, coagulopathy, and death (1). Similarly to other arboviruses, the ratio of symptomatic to asymptomatic infection of YF is 1:7–12 (36). However, there are four times more human cases of YF in West Africa compared to South America, likely explained by an increased prevalence of underlying immunity (36). Outbreaks of YF are associated with elevated case-fatality rates reaching 40–60% in the Americas compared to 20% in West Africa (1,3,36). This lower fatality rate encountered in Africa is likely due to genetic factors selected by a longer co-evolution with the YFV (22–23,36). Most cases of YF are described in Africa, with an estimated 200,000 clinical cases of YF and 30,000 deaths reported every year (based on passive surveillance) (22–24).

Since the different YFV lineages emerged in the African forests, non-human primates in these locations have a high natural immunity to asymptomatic viremia (25–26,36). In the Americas, in contrast, epizootics among non-human primates frequently manifest symptoms with an elevated case-fatality rate (25). Monitoring fatalities among certain non-human-primate species is an epidemiological early-warning tool of potential spillover of YF transmission to humans.

Yellow Fever: The Good, the Bad, and the Ugly of the Human Condition

Recent studies conducted to elucidate the phylogenetic lineage have shown that the YFV arose in Africa within the last 1500 years (8). YFV arrived in the Western hemisphere during the Atlantic slave trade 300–400 years ago. Trade ships carrying enslaved people arriving at seaports or riverports of the Americas introduced infected mosquito vectors (7,37). Portuguese ships began arriving from Angola, bringing thousands of enslaved people to Brazilian territory in the early 17th century (7). The importance of the role played by infected enslaved people harboring or incubating the infection is unlikely to have been

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significant, given the short incubation period of the disease and the prolonged travel time of ships across the Atlantic during that period (7,37). The mode of spread was mosquitoes breeding in water barrels carried by the boats. By 1642, England and Portugal signed a pact allowing England to obtain enslaved people from the Portuguese dungeons in coastal Africa. From there, English vessels started shipping enslaved Africans to the Caribbean Island of Barbados (7). By 1647, Barbados, which had no running water, became an initial epicenter of YF transmission since they collected rainfall in water towers that became major breeding grounds for mosquitoes. English ships carried infected enslaved people and mosquitoes from Barbados to other Caribbean islands and coastal cities. The expansion of slave colonies introduced yellow fever into other Caribbean islands, including Cuba and Guadalupe (1647–1650). YFV also reached the coast of the continent, including Yucatan, México (1648) and cities such as New York, Philadelphia, Charleston, and Boston between 1668–1690. Additionally, the disease spread to Gibraltar and Cadiz in the Iberian Peninsula between 1649–1700 (7).

During the 18th century, YF spread westward and throughout the Americas, causing major epidemics in North America (New York, Boston, Baltimore, Philadelphia and Veracruz) (7). In the rest of the continent, major outbreaks took place in Guyana, Venezuela, and Jamaica.(7) Sporadic epidemics appeared throughout the 19th century reaching Honduras and Nicaragua in Central America and Venezuela, Colombia, and Peru in South America. In Europe, outbreaks of YF arrived in the coastal towns of Barcelona, Dublin, Oporto, Swansea, Lisbon, and Alicante (7). Large-scale outbreaks of YF occurred in African territories including Senegal, Gambia, Angola, Sierra Leon, the Canary Islands, and Nigeria. In the US, major epidemics of YF affected more than 23 states (38–39). Some of these outbreaks spread via ships traveling up the Mississippi River, reaching the continental US through the Gulf of Mexico from Havana, Cuba (38–39). YF was a major cause of illness and mortality in the US during the 18th and 19th centuries. The epidemic of YF influenced major geopolitical events in the US: for example, in response to a major epidemic in Philadelphia 1793, the US capital was moved from Philadelphia to Washington, D.C. During the Napoleonic wars, French troops were decimated by epidemics of YF in Haiti, culminating in Napoleon selling the Louisiana territory to Thomas Jefferson in 1803 (40).

During the 20th century, new geographic expansions and retractions occurred in Africa and the Americas, coinciding with epidemics identified periodically in Africa and sporadically in the Americas (Brazil, Venezuela, Colombia, Panama, Honduras, and Costa Rica.) However, by the early 20th century, Europe and the United States succeeded in interrupting YFV transmission (2,7,38–39).

Figure 1. Cuban physician Carlos Finlay (1833–1915) whose theory on the mosquito-borne transmission of yellow fever led to the subsequent confirmation of the vector transmission by the team of scientists led by Walter Reed.

Historical Milestones in the Development of a Yellow Fever Vaccine

By the end of the 19th Century, YF was a widely feared plague that influenced international travel and the expansion of commercial trade routes (41). YF was then known as the "yellow jack" due to the yellow flag flown by ships to announce their quarantine period (7,40–41). The spread of YF coincided with the expansion of international commercial trading routes for goods such as sugar, cotton, and tobacco (7,40).

Different theories emerged to explain the mode of transmission of YF. For centuries, the predominant idea was that it originated from miasma – the noxious vapors or smells from decaying organic matter (1, 4). Then, the significant advancements made in bacteriology by the end of the 19th century led to speculations of a bacterial origin of YF (41). However, during a scientific session in August 1881, at the Royal Cuban Academy of Sciences, Physician Carlos Finlay (Figure 1) presented a paper titled *The mosquito hypothetically considered as a yellow fever transmission agent*, which shaped our future understanding of the origin of this infection (Table 1) (7). Finlay claimed

Table 1. Timeline of historical events in humankind's battle against yellow fever

Timeline	Milestones
Within the last 1500 years	Circulating strains of YF arose in Africa
	First description of outbreaks consistent with YF in the early 17th century
17th–19th centuries	The Atlantic slave trade brought YF to colonial territories in the Caribbean and the Americas. The virus spread westward and throughout the Continent leading to enzootic cycles of transmission in South America. The disease reached Spain and Portugal and some islands in the Atlantic (e.g. the Canary Islands)
	International maritime trade commercial ships also plays a role in the spread of YF during this period and extending into the 20th century
1881	Carlos Juan Finlay Carrés (1833–1915) presented at the Royal Academy of Sciences in Havana, Cuba a new theory of the potential transmission of YF by mosquitoes
1898	The Spanish-American War culminated in the Treaty of Paris (December 1898) whereby the Spanish Empire transfers Cuba and other territories to the United States
	By the end of the 19th century, YF was prevalent in the Western hemisphere and Coastal West Africa
1901	The U.S. Surgeon General, George Sternberg appoints the army physician Walter Reed (1876–1902) to lead the team in Havana, Cuba that confirmed the vector transmission by mosquitoes of YF
	This was the first research study that implemented informed consent to recruit volunteers
1902	William C. Gorgas (1854–1920) designs and implements vector control interventions against YF in Cuba
1904	In Brazil, the "*Revolta da vacina*" was a civilian uprising in Rio de Janeiro stemming from the widespread objection to the mandatory smallpox vaccination policy.
	This civil unrest arose in part from the earlier unpopular sanitary campaign to control YF transmission that began in 1903 by Oswaldo Cruz, the chief sanitary officer. His sanitary policy to remove mosquito breeding sites to control YF demolished many dwellings in large segments of city primarily in low-income neighborhoods. This led to the establishment of housing settlements and unorganized urbanization in the hills surrounding Rio de Janeiro, creating the present-day *Favelas*
1905	William C. Gorgas is appointed to coordinate vector control activities that made possible the completion of the Panama Canal
1914	Opening of the Panama Canal
1918	The International Health Commission of the Rockefeller Foundation dispatched a group of researchers, including Hideyo Noguchi, with the goal of developing a YF vaccine. Noguchi's vaccine efforts failed after his vaccine was administered not only in the U.S., but also throughout Latin America and the French colonies
1920	The first West African Yellow Fever commission by the Rockefeller Foundation obtained minimal results
1925–1927	The Second West African Yellow Fever commission by the Rockefeller Foundation
1927	During this commission Henry Beeuwkes and Adam Stokes isolated the Asibi strain of YF from the blood of a Ghanaian man named Asibi
	Jean Laigret and Andrew Sellards led the team at the Pasteur Institute in Dakar, Senegal that isolated a second YF virus from a Lebanese-Syrian man named François Mayali
	Jean Laigret is transferred to the Pasteur Institute in Tunis where he continues working with Sellards and conducted studies similar to those of Max Theiler
1930s	Ernest Goodpasture and his team were the first to reproducibly grow pure viruses in culture by infecting fertilized chicken eggs
1930–1937	Using embryonated chicken eggs and the Asibi strain, Max Theiler and Hugh Smith described in 3 publications in the Journal of Experimental Medicine the development of the live attenuated 17-D YF vaccine. The 17-D vaccine was obtained after 176 passages in mouse embryonic tissue, non-human primate serum, and then in chicken embryos (without brain and spinal cord). Laigret and Sellards at the Pasteur Institute attenuated the Mayali strain using methodology similar to Theiler's
1938	The 17-D YF vaccine was licensed after demonstrating high immunogenicity and loss of neurotropism, viscerotropism, and competence inside mosquitoes without the use of human serum
	Large-scale deployment of the 17-D vaccine in the Western hemisphere and England, while the French vaccine was widely deployed in France and the French colonies
1951	Max Theiler is awarded the Nobel Prize in Medicine for the development of the YF vaccine
1982	The production of the French vaccine is discontinued due to persistent concerns regarding its neurotropism
2022	The 17-D yellow fever vaccine remains in use with more than 850 million doses of the 17-D YF vaccine administered globally
2017–2026	The EYE strategy by WHO is announced to improve immunization coverage in endemic settings and to produce sufficient doses to guarantee sufficient supplies for emergency responses to outbreaks

that it was the female *Stegomya* mosquito, currently known as *Aedes aegypti*.

Commercial interests in Cuba after the Spanish-American War in 1898 drove public health efforts to control YF (2,7). The brief war had caused 968 combat casualties among US troops, however, yellow fever caused more than 5,000 fatalities (7). As doubt persisted as to whether YF was produced by a germ or an intermediate host, George Sternberg, - the US Surgeon General - appointed the army physician Walter Reed in 1900 to lead a team of researchers to conduct studies in Havana, Cuba. The mission of this team was to identify the causative agent of yellow fever and its mode of transmission (*Yellow Fever Commission*, 1900–1902) (41). Inoculation studies using mosquitoes to bite human volunteers demonstrated the vectorial transmission of YF by mosquitoes (41). This

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was also the first time that the use of informed consent appeared in the process of recruiting volunteers for a research study (42). The "YF Commission" accepted the contributions of a by-then elderly Finlay, resulting in a collegial accomplishment of identifying the mosquito-borne mode of transmission of YF.

After the confirmation of the vector-borne transmission of YF, William Crawford Gorgas demonstrated the beneficial effect of vector control in reducing the incidence of YF in Havana. In 1905, Gorgas was appointed as the chief health officer for construction activities of the Panama Canal (43–44). After a 10 year effort to build the Panama Canal, the French commission supervised by Ferdinand de Lesseps failed to complete the task (Lesseps led the construction of the Suez Canal) (43–44). Epidemics of YF and malaria led to thousands of workers falling ill, with many of them dying, which prevented the completion of the canal project. In 1904, the US obtained the concession to continue building the canal (43). Gorgas orchestrated, from the Ancon hospital in Panama (45), the use of pesticides and larvicidal oil to control mosquito-breeding sites. The implementation of these sanitary measures ultimately let to the Panama Canal's opening in August of 1914 (43–45).

By 1918, the Rockefeller Foundation's International Health Commission resolved to assist in controlling YF in the Americas and deployed a team of researchers to Guayaquil, Ecuador, to develop a yellow fever vaccine (41). Hideyo Noguchi, one of the leaders of this commission, pursued the idea that the spirochete *Leptospira icteroides* caused YF, which he thought was a newly identified *Leptospira* species different from *L. icterohemorrhagiae*, the etiologic agent of leptospirosis. He produced a vaccine using this spirochete that failed to provide any protection despite its wide deployment in Latin America, the US, and some French colonies. Noguchi remained convinced that the vaccine afforded significant protection (41).

After the First World War, the Rockefeller Foundation established a second yellow fever commission in 1925 that traveled to Lagos, Nigeria, in an attempt to isolate the causative virus (7,41). By 1927, Henry Beeuwkes and Adam Stokes isolated the causative virus of YF from the blood of a Ghanaian man named Asibi (hence the Asibi strain of YF). Around the same time, a team led by Jean Laigret and Andrew Sellards at the Pasteur Institute in Dakar, Senegal, isolated a second YF virus from a Lebanese-Syrian man named François Mayali (hence the Mayali strain of YF) (7,41,46).

In 1930, Max Theiler joined the Rockefeller Foundation, whose research goal was attenuating the Asibi strain's virulence (47). By 1937, the Asibi strain eventually became the 17-D vaccine after the 176th passage in subcultures leading to this strain losing its viscerotropism and, to some degree, its neurotropism. The French also developed a YF vaccine using the Mayali strain, but this vaccine was demonstrated over the years to maintain significant neurotropism leading to severe neurological adverse events (41). By 1983, the production of the French vaccine was discontinued due to sufficient evidence of severe neurological adverse events (2,48–55). The 17-D vaccine was manufactured from the original Asibi strain and used a defined number of seed lots. The 17-D vaccine remains in use today. Two sub-strains were developed from the 17D vaccine: the 17DD vaccine obtained from passage number 195 in subcultures, and the 17D-204 vaccine from passage 204 (48–49). Both yellow fever vaccines are highly immunogenic by inducing potent cellular responses (56–58). The development of the 17D vaccine would earn Theiler the Nobel Prize in Medicine and Physiology in 1951, the only time that the discovery of a vaccine has been awarded this honor (Figure 2) (4,59).

Figure 2. South African physician Max Theiler (1899–1972) who was awarded the Nobel Prize in Physiology and Medicine in 1951.

Reducing the impact of YF requires that populations living in endemic areas be immunized, through the implementation of routine childhood immunization protocols activities and mass vaccination campaigns to control outbreaks (22–24). Pre-travel consultations of international travelers to ensure the provision of the YF virus vaccine constitute an important preventive measure before visiting an area at risk of YF transmission (2). The current official recommendation by the Scientific Advisory Group of Experts

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(SAGE) of the WHO is that a single dose of the YFV is sufficient to provide life-long protection in most individuals (58–60). However, certain populations may require a subsequent booster dose, including young children who received their initial dose at a young age, women who received the vaccine during pregnancy, those with HIV infection, and persons with cellular immune deficiencies (2,60–61).

The Continuous Threat of Yellow Fever in the 21st Century

YF remains a major public health threat with the risk of regional geographic expansions (1,20). A comparison of the geographic distribution of YF in the Americas and Africa between 2005 and 2022 shows that areas at risk of YF transmission in Africa have shrunk, while those in South America have significantly expanded. For example, the risk of YF in Brazil has expanded to coastal areas that had not experienced urban outbreaks in many decades. In addition, YF re-emerged in Venezuela in 2019 (62–63). Understanding the geographic distribution of YF is important in designing and implementing vaccination strategies in endemic regions and for travelers visiting areas at risk for YF. Indeed, every year, an increasing number of travelers visit remote tropical locations where there is a risk of contracting yellow fever (64), and many of them are not vaccinated. The risk of unvaccinated travelers of contracting yellow fever during a 2 week stay in a YF endemic area is fifty cases per 100,000 population (2). The rate in South America is lower: five per 100,000 population (2). Not only is the infection potentially life-threatening for the traveler, but this event also carries the risk of introducing YF into new areas by viremic travelers returning home to locations with suitable ecological conditions for YF transmission, including high population density, environmental factors, and vector prevalence and competence (20).

The number of confirmed cases of YF among travelers has increased over the last decade (29,60,65). The recent urban outbreak of YF in Luanda, Angola, in 2015 spread to neighboring countries, including the Democratic Republic of Congo and Uganda (60). During this outbreak, 11 Chinese nationals became infected with YF at the time of their return to China (60). During the recent large-scale outbreak in Brazil, ten cases of YF occurred in travelers from France, Denmark, Romania, Switzerland, Germany, Argentina, and Chile (2,29).

In summary, YF remains a major public health threat to millions of individuals in tropical South America and many locations in Sub-Saharan Africa. In addition, there is a continuous risk of yellow fever being introduced into new areas given the ease of international travel and increasing global migration to and from at-risk areas (20). Dispersion of YF by travelers into new locations may lead to a public health emergency of international concern with the potential disruption of economies, social development, and health systems.(20,22–24)

Understanding the Social Origin of Yellow Fever Transmission and the Future of Public Health Interventions

Science, public health, and medical practice have all experienced major achievements in the late 19th century and 20th centuries. In the case of YF, there have been fundamental successes, including the identification of the causative pathogen, understanding its mode of transmission, providing supportive medical care to those with symptomatic infection, and developing and deploying a safe and effective vaccine (41).

The profound impact of YF on humankind reminds us that our treatment of the vulnerable has profound consequences (40). Also, the damage inflicted on the natural world in the form of deforestation for agriculture and farming, uncontrolled urbanization resulting from population growth, as well as global warming, all facilitate the geographic spread of insect vectors and have direct consequences on the transmission of YF and other arboviral infections (9–10).

European colonial powers irresponsibly extracted resources from their colonies through the exploitation and oppression of enslaved people and indigenous groups. These practices reveal how human lives are often valued differently depending on an individual's skin color and/or cultural and religious beliefs. Epidemics of YF have played a significant role in shaping the history of the modern world (64). Moreover, the impact of these epidemics on human societies has revealed that this pestilence stems fro social inequalities (37,66). Yellow fever and a spectrum of neglected infections in the tropics represent the biological expression of long-standing social inequality in the Americas and Africa (66–68).

The events in Rio de Janeiro in 1904 leading to a civilian uprising known as the *Revolta da vacina* (The revolt against mandatory smallpox vaccination) highlight the role of structural vulnerability in facilitating the spread of YF and other infectious diseases. In 1903, Brazilian President Rodrigues Alves, a coffee trade oligarch, was determined to control the outbreaks of YF, smallpox, and plague in Rio de Janeiro. His primary goal was reinstating the international prestige previously enjoyed by the port of Rio de Janeiro and hence expanding commercial trade routes. For over two decades, commercial ships had refused to dock at this port due to the frequent outbreaks of YF, plague, and smallpox among their crew. In 1895, the Italian ship *Lombardia* lost 234 of its 337 crewmembers to an outbreak of YF immediately after the ship docked in Rio de Janeiro. The second political goal of President Alves was to modernize the city's infrastructure to attract international travelers to the city. He modeled the renovation of

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Rio de Janeiro based on the renovation conducted in Paris from 1853–1870 and supervised by the prefect of Seine, France, Georges-Eugene Haussman, under the mandate of Napoleon III. For this formidable and expensive task, Rodrigues Alves appointed the major of Rio, Pereira Passos. The renovation of Paris under Haussmann's direction included the demolition of "unhealthy" and overcrowded neighborhoods of Paris.

By the time Oswaldo Cruz became the Brazilian chief sanitary officer in 1903, he had started a program to eliminate mosquito-breeding sites. Like Haussman's plans, the YF sanitary initiative required demolishing the city's poorly constructed and overcrowded dwellings. This policy caused major discontent among impoverished city-dwellers who lost their homes. Oswaldo Cruz imposed mandatory vaccination against smallpox on all citizens, to which a large sector of the population objected, given the prevailing unpopularity of the YF campaign of the previous year. The resulting civil unrest of 1904, (*Revolta da vacina*) resulted in many civilians killed and many more injured (37). Structurally marginalized people who lost their homes settled in poorly constructed houses in the hills surrounding Rio de Janeiro, and which are now known as *Favelas* (37).

The civil uprising of 1904 highlights the association between social forces and the spread and impact of epidemics. It also exposed the harm to society inflicted by vertically-designed health policies to control YF and other infectious pathogens. These policies ignored the voices and needs of the community, and instead, opted for demagogic power exercises that only perpetuated underlying social injustices that continue to prevail today in Brazil.

Conclusion

The rapid urbanization across Africa and South America would produce further large-scale outbreaks of YF (64). The increasing demand for the YF vaccine would frequently exceed the supply and have important policy implications. It is not uncommon for emergency stockpiles to rapidly run out during mass reactive vaccination campaigns to control large-scale outbreaks, and there and insufficient stockpiles to assist national immunization programs in administering the childhood YF vaccine. The World Health Organization's EYE (Eliminating Yellow Fever Epidemics) strategy was implemented in 2017 to respond to these increasing challenges. EYE is a three-pronged strategy that aims to protect populations at risk, prevent international spread, and rapidly contain YF outbreaks by increasing vaccine production to 1.4 billion doses in a 10 year period (2017–2026) (23–24).

Medical science and public health alone cannot solve the many challenges humanity faces in the 21st century, including the continuous threat of emerging and re-emerging infectious diseases such as yellow fever. We no longer live in a world where the idea of inevitable progress carries much conviction. We continue to rely on vertical approaches for disease control even though these have been shown to have limited impact and fail in the long run.

West Africa was often referred to as the "white man's grave" since the prevailing perception during the 19th century was that only black Africans could live and work there due to the risk of diseases such as malaria and yellow fever (69). This prejudice surrounding yellow fever is a clear indication of the intricate relation that exists between social forces and the development and spread of disease. Therefore, given that social factors influence the occurrence of epidemics of YF, any horizontal approaches that are implemented to control this disease need to take into consideration community participation and strategies for social development. To be successful, these aproaches need to include activities to reduce structural vulnerability and offer large-scale, sustainable improvements to reduce the disease burden of YF as well as of other, often-neglected, tropical infections. In the meantime, there is an urgent need to foster vaccine equality by ensuring not only the availability of the YF vaccine for international travelers but to prioritize its availability for routine administration by national immunization programs in endemic regions as well as increasing stockpiles to contain outbreaks rapidly.

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