



BIOMEDICAL SCIENCES

The second coming of urban yellow fever in the Americas: looking the past to see the future

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Abstract: Yellow fever (YF) epizootics in South America during the 21st century have an unprecedented recorded magnitude and geographical dispersion. The YF spread progressively involved areas considered previously free of risk reaching the edge of cities with large unvaccinated populations, and urban outbreaks were frequently forecasted. We critically reviewed the initial stages and enhancing contexts of YF urban epidemics since the 17th century in the Americas, and the modeling attempts of YF epidemic risk by of *Aedes*-Human transmission, to find common factors that increase the probability of these events in the current scenarios. The YF urban outbreaks of the past showed as necessary conditions the multiple introduction by viremic carriers clustered in time and space, coincident with population peaks of *Aedes*. These conditions are not met in the current outbreaks in the Americas by sylvatic YF cycles, besides the protective impact of vector control campaigns, vaccination coverage, improved surveillance, and case management. Therefore, urban *Aedes*-Human YF outbreaks in the Americas are still possible but with low probability or very focal transmission, while the conditions reported in the past were avoided, and the surveillance and control measures sustained, including the vaccination of the population at risk.

Key words: *Aedes aegypti*, *Haemagogus*, epizootic disease, arbovirus, urban outbreak, sylvatic cycle.

INTRODUCTION

Yellow Fever Virus frame in the Americas

Yellow fever (YF) is an acute disease due to a Flavivirus with an estimated incidence of 200,000 cases/year, and 30,000 deaths along the tropical areas of Africa and Latin America. The Yellow Fever virus (YFV) is transmitted by the bite of an infected female mosquito, *Aedes aegypti* as the main vector of the urban cycle in the Americas, and mosquitoes of the genera *Sabethes* and *Haemagogus* in the “jungle” or sylvatic cycle that involves endemic or epizootic transmission between non-human primates, and incidentally to humans (Monath & Vasconcelos 2015). The history of epidemics and control of YF has several scientific milestones, but also

controversies related to hegemonic sanitary theories and geo-political and trade interests. Even the intervention of United States in the independence of Cuba from Spain was justified by YF risk (Benchimol 1994, Cirillo 2004, Headrick 2010, García 2019) (Figure 1).

The YFV outbreaks in the Americas up to the beginning of the 20th century were thought as urban events, with discussions about their imported or local origin. The involvement of mosquitoes was suggested in Venezuela by Louis Beauperthuy in 1853 due to the inoculation of septic juices sucked from dead fishes, and in Brazil in 1885 by Philogônio Utinguassú due to swamp mosquitoes contaminating the drinkable water. However, the role of *Aedes aegypti* (then *Stegomyia fasciata*) in YF outbreaks

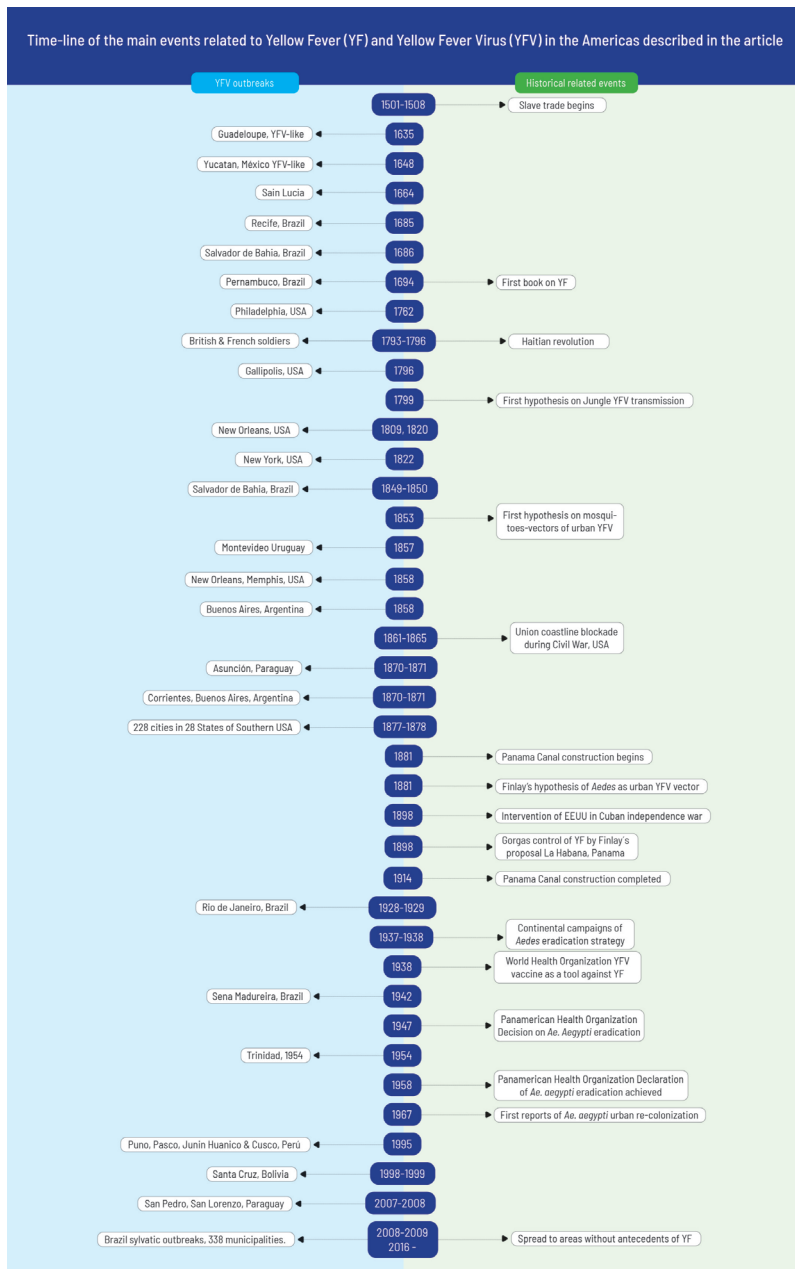


Figure 1. Time-line of the main events related to Yellow Fever (YF) and Yellow Fever Virus (YFV) in the Americas described in the article.

turned contrastable evidence with the research of Carlos Finlay in Cuba, and the acceptance of the scientific community through the reports of Walter Reed during 1881-1890. (Barbosa 1929, Franco 1969, Clements & Harbach 2017).

The Jungle transmission of YFV in America was suggested by Von Humboldt in Venezuela as early as 1799, and proposed by many local physicians along two centuries up to the 1930s.

During this period sylvan-related outbreaks were recorded by Colombian medical doctors as Roberto Franco, and the infection by YFV in other mosquitoes different from *Ae. aegypti* in America by Nelson Davis and Raymond Shannon. However, a sylvatic cycle of YFV involving non-human primates and non-urban mosquitoes was not accepted until the concept was proposed by

Soper (Soper 1967, Franco 1969, Quevedo et al. 2008).

The concept of a sylvatic YFV circulation, persistent and disperse, jeopardized the rationale behind the strategy of eradication of YF from the Americas focused on the control of *Ae. aegypti* urban breeding sites mainly with DDT, and afterward re-oriented to the control of *Aedes* in few source populations then called 'key centers' (Soper 1937, 1942). This urban-focused approach driven by health leaders as Oswaldo Cruz and William Gorgas was effective against the periodic outbreaks in the cities (Siconelli et al. 2019), and to support the continent-wide campaigns that achieved the *Ae. aegypti* reduction of populations in the Americas in 1938-1955, and the formal declaration of its eradication in 1958. Simultaneously, from 1937 to 1939 the YF vaccine based on the 17D attenuated strain of YFV was developed, field tested in Brazil, and then recommended for different scenarios of risk through the world (Frierson 2010, Staples et al. 2020).

However, *Ae. aegypti* reappeared sporadically in domestic habitats since 1967 and during the next decades colonized most of *Aedes*-free certified areas of the continent (Franco 1969, Lima 1985, Mondet et al. 1996). Meanwhile, despite the urban Dengue virus outbreaks that testifies the presence of *Ae. aegypti*, the different effectiveness of control programs between countries (Horstick et al. 2010, Bowman et al. 2016), the impact of the decentralization of the programs since 1980 (Schmunis & Dias 2000), the urban YF transmission remains in very low incidence and scattered in time and space. On the other hand, the epizootic cycles show a periodic pattern that ranges from 6 to 14 years related to the renewal periods of susceptible non-human primate populations (Vasconcelos 2010, Couto-Lima et al. 2017). This scenario changed in magnitude

with the great waves of sylvatic YF in 2008-2009, and 2016-2017 continued in 2018-2019 in the southeastern and northeastern Brazilian states, with a fatality rate among humans that could reach in some foci up to 43%, although this rate depends also in the active detection effort and case management quality (Couto-Lima et al. 2017, Possas et al. 2018, Mares-Guia et al. 2020).

Therefore, in the 21st century, without a significant urban outbreaks since 1939, but with YFV spreading out to reach the borders of the biggest cities of Brazil, the new question is about the probability to an urban YF outbreak due to the spill back from *Primate-Heamagogus/Sabethes* forest-mosquitoes to human/*Aedes aegypti* urban cycles (Figueiredo 2019). Hence, the second coming of urban YFV was warned by many authors due to the abundance of *Ae. aegypti*, *Ae. albopictus* or both in the cities besieged by the YFV epizootics and human cases due to the sylvatic YF cycle, and so the risk was estimated by different modeling attempts (Mondet et al. 1996, Codeço et al. 2004, Johansson et al. 2012, Massad et al. 2018). However, despite the so foretold event the YFV did not encroach the surrounded cities, *Aedes* mosquitoes were not found naturally infected up to now, and so actually many authors wonder about why this urban transmission did not happen yet (Lima 1985, Possas et al. 2018, Sacchetto et al. 2020). To try to answer this question, in the following sections we will review the triggering steps in the Americas of the huge urban YFV epidemics of the past, the urban outbreaks after the *Aedes* control campaigns, and the current urban scenario and risk of YFV introductions.

THE PERIODIC VISITATION OF YELLOW JACK

The introduction of YFV and its vector *Ae. aegypti* to the Americas and the YF spread

from the United States to Argentina was usually associated with the slave trade from Africa, consistent with the timing of phylogenetic analysis without apparently recent introductions in post-vaccine times (Bryant et al. 2007). The “Tratado Único da Constituição Pestilencial de Pernambuco” by Ferreira da Rosa, published in 1694, was probably the earliest book on YF, as the first report of YF in Africa was in 1778 (Franco 1969). After this theoretical introduction or multiple introductions since the 17th century, many urban outbreaks were recorded in the following three hundred years in the new growing cities and even become so frequent that were naturalized as the ‘Visitations of Yellow Jack’ or ‘of His Saffron Majesty’ (Carrigan 1962).

The first epidemic that resembles YFV in America was reported in 1635 among French migrants in Guadalupe, and in mainland an outbreak highly compatible with YF happen in Yucatan during 1648 with numerous infections among the Spaniards within the forts. The former event led French colonies to apply quarantine on ships coming from Africa during the rainy season; the second one was thought by Mayan chroniclers as a divine punishment due to the colonization, so a previously unknown disease (Barbosa 1929, Goodyear 1978). This high susceptibility among Europeans was observed again in the 1790s wars between English and French armies and the success of the revolution in Haiti (Patterson 1992).

The factors associated with the first epidemics were repeated through America during the next centuries up to the major anti-*Aedes* campaigns, constituting so the pattern of the main urban outbreaks: a) the punctual introduction of YFV by aliens as soldiers or migrants; b) the role in the spread of YFV of ships and ports, and sequentially to the sea-fluvial-ports introduction the role of the new railroads in the following dispersion; c) the

susceptibility of the foreigners to YF that allowed xenophobia and stigmatization. These factors had particularities according to physical variables as the latitude-seasonality, but also cultural ones regarding policy, the pressure of the trade-related sectors, and denial of the actual risk by the authorities.

The pestilence is introduced by people from another place

Usually, the people signaled to carry the disease from outside were sailors, soldiers, or migrants. The individualization of a pretended patient zero is more related with a need to blame an individual than to the epidemic actual events. This is the case of the 1858 Memphis outbreak attributed to a pursuer that evaded the quarantine landing from a ship arrived from Liverpool via Havana and then died in the city, but with previous six fatal cases of YF on board (Keating 1879). However, many officials and wealthy passengers are exempted from the quarantine or even entire floats due to merchant pressures. Besides, once no more people died on board the crew were allowed to disembark, and the maritime traffic is so intense that many ships are coming simultaneously crowding in the port side by side, quarantined and non-quarantined, and then many asymptomatic infected sailors and passengers land at the same time or sequentially. In this sense, regarding the preclinical, subclinical and infectious people with no symptoms, even currently the severe cases are just 10% of the total infected people, while 55% are asymptomatic and 33% experienced a mild disease (Johansson et al. 2014), thus even today with more sensitive diagnostic tools, in the early stages of an epidemic the transit of viremic people is unrecorded.

The probability of multiple YFV introductions is higher when a collective was traced from its previous itinerary through endemic areas

or epidemic places, as in the New Orleans outbreak of 1809 that could be introduced by French refugees from Cuba, Jamaica, and other West Indian islands (Carrigan 1962). Similarly, at the end of 1870 Asunción, Paraguay was impoverished after a war against Argentina, Brazil and Uruguay coalition, then the city had a YF outbreak presumably associated with the Paraguayan soldiers that come back released from prison camps located in endemic foci of Brazil (Ruiz Moreno 1949). The Argentinean troops stationed in front of Asunción had the first 15 dead cases of YF, and so were ordered to move to the Argentinean city of Corrientes, a command node during the war with soldiers of the three allied countries, and then in Corrientes died 18% of the population by YF. These soldiers move again and discharged in the poorest neighbors of Buenos Aires, Argentina, where in 1871 the town suffered the worst YF outburst of his history (Navarro 1894, Ruiz Moreno 1949, Scenna 1967, 2009).

Therefore, despite the anecdotal narratives that identified just one person that carried the disease and initiate an epidemic, the urban YFV outbreaks of the past in the Americas seems to be originated by multiple virus-carriers and even massive introduction of human viremic cases rather than an individual inoculum, reinforced by the facts described in the following sections.

The death travels in ships and trains

In the United States, the initial source of YF outbreaks was associated with the introduction of germs or effluvium or 'seeds' from Latin America due to the intense maritime trade exchange, for instance with the vessels arrived from Santa Lucia where the disease decimated troops and crews since 1664. Consequently, New Orleans learned to wait for local 'visitations' of YF when news came about YF epidemics in the islands of the gulf. Still, in 1820 the

Physico-Medical Society of New Orleans committee reported that the former and last cases of this year YF epidemic had appeared on board of ships and at the wharves (Keating 1879, Carrigan 1962). Conversely, in the 1840-1850 YF outbreak in Salvador de Bahia, Brazil, the ship signaled as the source of the epidemic come from New Orleans, but the vessels that arrive in this period to South American and North American sea-ports had both resupply stops in the Caribbean islands.

Furthermore, the first known outbreak in Brazil, in Recife during 1685, was traced to ships that arrive from the African Islands of São Tomé or Cabo Verde but also with stopovers in the Caribe; although the first symptomatic cases were among the cargo handling workers, as it was due by infected imported mosquitoes (Barbosa 1929, Franco 1969). The Brazilian ships were also an ineludible resupply port for the journey to the American South Cone ports, then following the Brazilian outbreaks, Montevideo, Uruguay, had the first outbreak in the summer of 1857 with almost 900 YF deaths out of 15,000 inhabitants (Galeano 2009), and in 1858 Buenos Aires, Argentina, on the other shore of the Rio de la Plata was visited by the YF first epidemic (Scenna 1967).

The importance of trade by sea in the epidemiology of YF is evident when observing the low incidence in previously epidemic ports of the United States during the maritime blockade of the Civil War despite the deteriorated quality of life of the troops and civil population (Patterson 1992). Besides, other facts had an impact on the YFV transmission in the continent since the first outbreaks related to the demand of the 'nouveau riche' creoles, and the related industry and goods traffic as the sugar cane monoculture. The changes in the ecology of the Caribbean island due to this sugar commercial boom were suggested to favor the breeding

of *Ae. aegypti*, even before the slave trade intensification, and so probably before the YFV massive arrival to the continent. Furthermore, the richness of carbohydrate sources in the cultures, in the decantation-milling molasses storing containers, in the ship-cargo and port warehouses was also propitious for *Ae. aegypti* population amplification. In Philadelphia, the 1762 epidemic was traced to a ship and the Sugar House Wharf, and in New York City in 1822 four sugar-loaded ships arrived from Havana was suggested as the origin of the YFV outbreak (Goodyear 1978, McNeill 2004).

The YF ship-source has another implicit component, the influence exerted by the commercial sector on the political authorities. The legislature of New Orleans in March of 1858 reduced the detention period of vessels coming from infected ports which presented a clean 'bill of health' on arrival emitted by civil officials without the intervention of the board of health, and so this year the city had 4,855 deaths of YF out of 166,000 inhabitants (Carrigan 1962). Similarly in Salvador de Bahia, Brazil, although 1686 had a toll of 900 dead and 25,000 YF cases, the inspection of ships ordered in 1691 was soon replaced by a 'passaporte da saúde' (Health passport) signed by bureaucrats (Barbosa 1929, Franco 1969). In Buenos Aires the President canceled the quarantine ordered by health officials to ships coming with goods from epidemic ports of Brazil, even jailing the doctor who issued the order. The same authorities, 'to avoid the panic and promote the 'general happiness' allowed the Carnival festivities in the neighborhoods that concentrate the first YF cases, and today we know these celebrations took place also where *Aedes* were in high densities and during the hours of *Aedes* higher activity. Consequently, in Easter week Buenos Aires city reached the YF epidemic peak with more than 500 casualties/day when usually are

less than 20, and so became the time to blame the foreign migrants (Scenna 1967, 2009).

The quarantine by itself could increase the number of viremic carriers, as the ships have many porous containers where *Aedes* can breed and replicate, for instance of drinkable water (Christophers 1960, Honigsbaum 2019). Therefore, during the quarantine, the passengers infected and not infected were forced to live together amplifying the number of symptomatic but also of asymptomatic virus transmitters that are allowed to land after the restriction time. The on-board transmission was also observed in a vessel that departed from Pernambuco to Lisboa during YFV active transmission in the Brazilian city, and then healthy crew became ill and dye of YF in open sea with symptoms that started much later than the expected for the intrinsic incubation period (Barbosa 1929, Franco 1969).

After the sea-ports, YFV traveled through river ports. During the deadliest 1877-1878 summer in the United States with a toll of 90,000 casualties in 228 cities of 28 States, following the 'wave' initiated in Atlantic main ports, the steam-tug 'Join D Porter' moved for two months on the Mississippi and Ohio rivers "carrying death and destruction to nearly all to who had anything to do with her" (Keating 1879). Then, after the sea and river-ports the YFV travel inland by train both in the United States and Brazil, as the new railroads expanded the internal frontiers of the countries. The train was also the preferred means of transport to the massive fled from the affected cities to previously un-affected villages, and also a replicative step by step colonization way of *Aedes* due to the regular containers on railroads in the water stops for steam engines. Besides, the train also created the possibility and defined the location of new towns, with migrant waves, as we will discuss in the next section.

Therefore, the introduction of viremic cases that produced urban YFV outbreaks, due to the ship-train traveling, policy denial, quarantine and, trade trends were not only generated by multiple introductions as we already stated, but also these transmitters were clustered in time during seasons with a flourishing population of *Aedes*.

The disease of newcomers

The susceptibility due to the immunological naivete of migrants arriving in a YFV active transmission area was explained up to the twentieth-century in terms of lack of acclimatization, in contrast with the locals and even the slaves carried to America that probably acquired the immunity during childhood (Keating 1879, Patterson 1992). Undoubtedly this is one of the main factors, but in the case of European migrants, additional factors were the undernourishment, and the crowding in unhealthy houses clustered by nationality in the more unhealthy quarters, close to the ports plenty of *Aedes*.

In Buenos Aires, Argentina, a lowland city without natural draining of the rainfall, the YF outbreaks were located in the same area close to the docks both in the smaller 1858 epidemics and for the first reports of the deadly 1871 epidemics. These neighborhoods are crowded with impoverished migrants, Afro-Argentinean families and discharged militia from the Paraguayan foci as was mentioned above. Furthermore, the first case and the last YF death of 1871 was 500 m apart one from each other, the former an Italian migrant and the last a Spanish newcomer. This 1871 epidemic in Buenos Aires killed almost 7% of the population but 75% of the casualties were European migrants, while 30% of the remaining inhabitants fled to small towns that replicate the outbreak (Navarro 1894, Ruiz Moreno 1949, Scenna 1967, 2009).

Similarly, the recently created towns with massive migration, unplanned urbanization with overcrowding and poor water management providing breeding sites for the vector were also signaled as a cause of the outbreaks. That is the case of recent established Gallipolis, Ohio, in 1796 where half of the army died in ten days, and Galveston in 1839 just two years after the foundation. The Memphis YFV epidemics of 1858, when 10% of their 50,000 inhabitants were killed by the virus, happen in a city that grew explosively first as a slave trade center, then during the Civil War with 15,000 Afro-American refugees clustered with Irish fled from the Great Famine and German immigrants looking for the American dream, all together crowding along the bayou where the latrines were drained and all the people also had accumulated water containers after a severe drought period (Keating 1879).

Another clustering effect was observed when the crews quarantined or not quarantined disembark from the ships, and usually goes to the same few lodgings. In Salvador de Bahia during 1849 the first case of the following outbreak was reported in a captain from a ship that had two sailors dead with YF in the open sea, but arrived at the port with an asymptomatic crew. After the captain death of YF many symptomatic sailors was clustered in a 'sanitary house' by a physician with the result that 20 sailors died together with the doctor wife. Afterward, from Bahia arrived a ship to Rio de Janeiro and nine sailors sleeping in the same hostel got sick with YF, followed by cases in sailors from other ships in contiguous lodges, fueling a Brazilian epidemic wave with a toll of 2,800 casualties and a total dead in the endemic period until 1902 of almost 59,000 people (Barbosa 1929, Franco 1969).

As it was mentioned above, the susceptibility of the 19th century European migrants, together with the local competition for jobs, the imported ideologies and civil unrest resulted

in xenophobic ‘science sustained’ discourses, with the stigmatization of these collectives as filthy, alcoholic, and prone to illness. In 1850 a physician of New Orleans denounces the spending of millions of the public money, that devouring the commerce of the city for the “strange pretense for all the extravagant systems of disinfection, quarantines, and Quixotic schemes of drainage” when it is “emphatically a German and Irish disease”, so he proposed that a stop to immigration will remove the fever combustible (Carrigan 1962). In São Paulo, Brazil, the public health measures that punish the migrants previously attracted by coffee planters and railroad constructors, and the actual risk of YF for these European newcomers was replicated specularly by an Italian government ban on the migration of their citizens during 1890-1891 (Lima 1985, Telarolli Jr 1996). This scenario was worsened when the migrants do not understand the rough orders of the police due to language barriers, they were evicted, and their scarce belongings and mattresses burned in purifying bonfires (Franco 1969, Navarro 1894, Ruiz Moreno 1949, Scenna 1967, 2009, Galeano 2009).

Therefore, the YFV urban outbreaks in America in the past were generated by multiple virus inputs, they were clustered in time, but also they were clustered in space as the most susceptible people are crowded in *Aedes* infested neighborhoods.

URBAN OUTBREAK AFTER THE *Aedes* CONTROL CAMPAIGNS

Despite the rural persistent foci, the urban YF re-appear as an urban event in Rio de Janeiro, Brazil during 1928-1929, after an explosive demographic growth and so with half of million inhabitants without YFV contact for more than 20 years. Meanwhile, the city probably has also an explosive population growth of *Aedes* as the

control teams were disengaged and the summer when the outbreak happens was too hot. The first two cases were quartering soldiers, followed by 738 cases scattered through the city, but many related with discharged soldiers that come from northern States where they were sent due to rural riots. The death toll reached 478 people along 17 months, but still, in the first decades of the 20th century, 64% of the dead were foreigners (Barbosa 1929, Silva & Gonçalves 2019).

Urban YFV transmission was also reported in three human cases in Sena Madureira, Acre State, Brazil in 1942 (Figueiredo 2000) and, 15 cases in 1954 in Trinidad, island with enzootic sustained cycles besides virus inputs from South American foci (Auguste et al. 2010). While the outbreak that involves Puno, Pasco, Junin, San Martin/Huanuco and Cusco departments in Peru in 1995, was related to massive susceptible human migration infected while clearing sylvatic-enzootic areas through the Amazon Basin, to colonize a new agricultural frontier (Bryant et al. 2003, Couto-Lima et al. 2017).

In Santa Cruz de la Sierra city, Bolivia, six YF cases were described in 1998-1999 after an active detection search. The cases were clustered in the outskirts of the city recently urbanized and in sites highly infested by *Aedes*. The vaccine coverage in the Santa Cruz urban population was then estimated in 35-40%, with a sylvatic YF foci less than 10 km, places from where the first case came and two other cases visited frequently (Van der Stuyft et al. 1999, Baronti et al. 2011).

Regarding the more recent YF outbreak described as urban, in 2007, in San Pedro, Paraguay, six individuals became infected during Christmas after hunting on platforms within the canopy of the forest, where non-human primates are clustered in fragmented habitats. These cases were followed with active YF transmission in humans in the rural villages of the hunters

and closer towns, where *Sabethes sp.* and *Ae. aegypti* were reported. In early 2008 in Laurenty neighborhood in the suburban county of San Lorenzo, 12 km from Asunción the capital city of Paraguay, 8 people became infected, 5 of them women, 3 deceased, all living in the same block with 26% of infestation of *Ae. aegypti*, the only known YF vector found. The main hypotheses were that the virus was introduced by infected people or mosquitoes by the weekly visits to sell charcoal and ornamental plants from San Pedro to Laurenty, and amplified in Laurenty during the funeral wake in the house of the first local case, with an additional case that lived eight blocks away from the focus but also attended the wake. From January to March 2008 the Paraguayan Ministry of Health and Social Welfare reported 24 cases of YFV, including the 9 urban ones, an alarm that triggered the vaccination of 1,5 million people and vector intense intervention measures over 25,000 households (Johansson et al. 2012, PAHO 2008, E. Vázquez-Fernández, pers. comm.).

THE CURRENT WAVE OF EPIZOOTIC YFV IN THE AMERICAS

Finally, during the 21st century while the sylvatic YF still produces sporadic outbreaks in many countries of South America, the YFV re-emerged in Brazil with recovered strength as epizootic waves which in the period from December 2016 to June 2019 reported 2,251 YF human cases, 772 deaths and 15,000 epizootic events, in 338 municipalities (Couto-Lima et al. 2017, Possas et al. 2018, PAHO 2003-2019). However, despite the speed and extension of the YFV spread the transmission encircle but not intruded the cities once it reaches the urban-periurban edges, as there are no evidence up to now of urban cycles involving *Aedes*-humans.

Consistently, the males in labor-related ages are the more exposed and affected due to occupational or ecotourism activities, but female and younger age groups incidence has trend also to increase (Cunha et al. 2019, Abreu et al. 2020, Silva et al. 2020). Furthermore, *Cebus spp.* is present in 82% and *Alouatta spp.* in 79% of the counties with YF reports, and seven out of eight genera of American non-human primates were statistically associated with the YF areas (Hamrick et al. 2017).

In Santa Leopoldina, in the State of Espírito Santo involved in transmission cycles since 2017 without previous antecedents of YF, the greatest incidence rate was reported from the city but the human infections were still time-space closely related to epizootics. Furthermore, the gender-age pattern of human cases remains again associated with rural and forest-related activities. The cases were also spatially related to highlands with protected native forests, and ecotones between forest and anthropized environments, places with records of *Haemagogus* but not *Ae. aegypti*. An 'intermediate' cycle was proposed for foci as those of Spirito Santo associated with unvaccinated population where *Ae. albopictus* is present, similar to the African intermediate cycles (Moussallem et al. 2019). However, these scenarios are very different from those of Africa during the same YF epidemic periods where the urban transmission by *Aedes* mosquitoes was reported (Kamgang et al. 2019). On the other hand, *Ae. albopictus* and *Ae. scapularius* were the more frequent mosquitoes biting at ground level in Rio de Janeiro State YF focus, the former trying unsuccessfully to bite a dead monkey so it is possible that they try to bite descending agonizing monkeys, although no *Aedes* mosquito was found infected there, but neither *Haemagogus janthinomys*, *Hg.*

leucocelaenus, or *Sabethes albiprivus* (Abreu et al. 2019a).

Contributing factors proposed for the recent American YFV transmission waves were the conservationism, reforestation, 'green corridors', unplanned urbanization, change in land use and irrigation systems, and return to nature trends after the second half of the past century and the consequent global and local climate changes. These preserved and re-created landscapes increased suitable habitats for sylvatic mosquitoes species competent for YFV coexisting with non-human primates social groups, while increasing the exposure of humans on forest-urban borders and also during transit through primary forest due to legal activities or illegal traffic (Vasconcelos 2010, Douam & Ploss 2018, Possas et al. 2018, Abreu et al. 2019a).

Therefore, many attempts were made to estimate the probability of YF urban resurgence in the Americas by modeling approaches, after the introduction in an urban area of one viremic case. Probabilistic stochastic models were applied to Rio de Janeiro and Asunción scenarios. The former was based on the travelers that arrive in the city from each other endemic states of Brazil, and concludes that the probability to establish the disease by one imported infected case is 0-11%, but by a latent mosquito is 0-63% as they remain infective for a longer period than humans. Furthermore, the probability of an urban YF emergence during epizootic years is 0-29%, with a distribution skewed toward the lower limit, and so the authors stated that the lack of urban outbreaks up to now is just probabilistic (Codeço et al. 2004).

The modeling based on the Asunción outbreak of 2008 and meta-population assumptions found that local incidence, travel rates, basic reproductive number parameters, and vaccination coverage when it is pertinent explain the risk of YF spread within and outside

the focus. From the three tested scenarios the low transmissibility one resulted in local transmission in 2.3% of the simulations. The moderate scenario, presented by the authors as the more biologically plausible, leading to local transmission in 12.8% of the simulations, in 8.4% affecting 1-981 individuals, while in the remaining 15.6% the outbreak involves 450,000 to 500,000 cases in Asunción, figure that would involve the whole current population of the city and, this scenario even could produce international spread and pandemic potential (Johansson et al. 2012). However, the actual outbreak in Asunción involved just nine cases as it was mentioned above.

Another model indicates that the risk of introduction and spread of YFV by one infectious individual to a city with un-vaccinated population is mainly modulated by the size of urban *Aedes* populations and the season, but requires a competence threshold in the vector at least of 70% to have a positive Basic Reproductive Number. Therefore, the authors conclude that the YF urban risk in these conditions is low but no-negligible (Massad et al. 2018).

The current risk of urban outbreaks is enhanced by: a) the YFV virus persistence in the forest without new introductions (Rezende et al. 2018); b) the synanthropic troops of non-human primates that increased the contact with humans due to the degradation of their habitat and trend to explore periurban/urban green patches (Cunha et al. 2020); c) *Hg. leucocelaenus* habits to bite and shelter frequently at the forest ground level (Abreu et al. 2019b); d) the closeness of the forest edge to human unvaccinated populations involving the larger cities of Brazil; and e) the high densities of urban *Ae. aegypti* and *Ae. albopictus* mosquitoes highly susceptible to American and African YFV strains (Couto-Lima et al. 2017, Possas et al. 2018, Douam & Ploss 2018, Abreu et al. 2019a, b). Furthermore, there are

not evident dissimilarities of epizootic spatial spread patterns between the outbreaks up to 1949 and those of 2016-2018, both with multiple pathways, but the historic ones with lower intensity and velocity (Vasconcelos 2010, Possas et al. 2018).

On the other hand, many explanations besides the herd immunity among vaccinated humans was proposed to explain the lack of an urban YFV outbreak yet, as the required degree of contact between infectious people and all the present *Ae. aegypti* supposed by some models, genetic changes in *Ae. aegypti* of Yellow Fever virus post-eradication strains after so long time elapsed (Prata 2000, Collins et al. 2018), given the high cross-reactivity between flavivirus the potential cross-protection provided by Dengue or other arbovirus infections (Rathore & St. John 2020, Schultz et al. 2020) as it was observed in *Rhesus* monkeys (Theiler & Anderson 1975), but many explanations were challenged by the facts as the *Ae. aegypti* and *Ae. albopictus* conserved competence for YFV infection (Couto-Lima et al. 2017).

CONCLUSIONS

The major outbreaks of urban YF in the Americas from the 17th to the 19th centuries were originated by the virus introduction in a city by multiple human viremic carriers, clustered where and when *Aedes aegypti* thrives. These three necessary conditions of massive and time-space concentrated virus inoculums were enhanced by the trends of trade exchange, huge European migration of susceptible fragilized people, and the growth of the urban unhealthy habitats. The miasmatic theory of transmission through “bad air” stated by Hippocrates was prevalent in this period (Shannon 1981), so the physician could not explain the time-space segregation of YF and its seasonality consistent with the habits of *Aedes*.

Once the campaigns against *Aedes* were settled in the continent, the foci with urban transmission of YF were reduced to events with few cases, promptly extinguished. Furthermore, during the 20th century better case and mosquito surveillance systems were developed, the YFV-vaccine were applied to the people at risk and, the molecular diagnosis increased the sensibility of the reporting.

During the current epizootic events of the 21st century, the viremic individual that comes to the city is usually not clustered either in space or time, although the concentration of patients from the wild cycle in reference hospitals of large cities without sufficient herd immunity, if no vector isolation measures are taken, may imply a risk similar to that of historical outbreaks. On the other hand, the tourist or the isolated un-vaccinated patient than arrives in the city during a period of YFV outbreak warning is usually diagnosed and, the transmission by vectors blocked around the potential virus carrier. In the same sense, the modeling indicates the low risk for sustained urban YFV transmission originated by one single isolated virus introduction. Conversely, to other infectious diseases, the current speed of travel avoids also the amplificatory effect of YF cycles on board, except for cruises.

In conclusion, the probability of an urban YFV outbreak during the present epizootic waves involving *Aedes*-Humans is low if the three conditions that produced the outbreaks of the past are still avoided, and the people at actual risk vaccinated. This low probability could explain that the urban event not happen up to now, but to be unlikely it is not to be impossible, although reduces also the probability of extensive urban outbreaks. On the other hand, the entomovirological monitoring in the forest-urban borders, and the control of urban *Aedes* due to other arbovirus risks still requires public health strategic interventions.

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