The Interplay Between Epigenetics, Vector Competence and Vaccine Immunodynamics as a Possible Explanation for Recent Yellow Fever Resurgence in Nigeria

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Summary

BACKGROUND

Yellow fever virus (YFV), a member of the genus *Flaviviridae* is the causative agent of YFD. The virus is classified as single-stranded RNA which is mostly transmitted by mosquitoes identified by Walter Reed in the year 1900 as *Aedes aegypti* [4].

In the past, Nigeria had been facing asporadic outbreaks of Yellow fever (YF), which began with the populous Northern region of the country. *Aedes* species of mosquitoes mainly transmit yellow fever virus (YFV) and vaccination is the only effective means of preventing it.

OBJECTIVES

This article presents a critical review and literature updates on the vector biology, YF vaccine immunodynamics and epigenetics of YFV, with the aim to understand the interplay of these factors in the re-emergence of YF and risk assessment of living or traveling to YF endemic areas. (in the year 2016-2018)

METHODOLOGY

The live, attenuated viral strain of the 17D vaccine was administered to tourists and inhabitants of endemic regions of Africa *(Figure: 2)* and South America. Those eligible for the vaccine were usually given through routes of administration either by single subcutaneous or intramuscular injection. The vaccine (17D-204 strain) could be given either to infants (pediatric dosage) above 9 months or adults (adult dosage) using one dose of subcutaneous injection (≥4.74 $\log^{10}$ plaque-forming units/0.5mL) not later than 10 days to regional migration

CONCLUSION

Vectorial migration, jungle-to-urban spillover, immunization failure (especially in persons with chronic immune-mediated inflammatory diseases) and perhaps, genetic modification of YFV could be reasons for the resurgence of YF in the country. The single dose of the vaccine was usually sufficient to confer prolonged immunity against the infection but booster

doses were often required based on endemic state of certain countries' Medical Laboratory Staff who frequently work on wild-type yellow fever virus. Based on regular exposure to this virus on routine basis, the neutralizing antibody titers against the virus are usually assessed every ten years to determine the necessity for booster doses of the 17D vaccine. Irrespective of the knowledge of neutralizing antibody titers for the virus, vaccination every 10 years is recommended especially for individuals frequently exposed to the vir

RECOMMENTATIONS

Increase vaccination coverage. Include YF vaccine in childhood vaccination programs. Make effort to maintain and control future outbreaks.

Keywords: Vaccination, Genetics, Yellow Fever, Re-emergence

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Introduction

In the year 1969 Yellow Fever disease (YFD) was first reported in Charleston, South Carolina, Philadelphia and Pennsylvania [1] while the most recent outbreak was reported in Brazil, Angola and DR of Congo from 2015 to 2018 [2,3].

Yellow fever virus (YFV), a member of the genus *Flaviviridae* is the causative agent of YFD. The virus is classified as single-stranded RNA which is mostly transmitted mainly by mosquitoes identified by Walter Reed in the year 1900 as *Aedes aegypti* [4]. Based on the virus genotype, Yellow fever Virus (YFV) was classified into East African, West African, South American No. I, and South American No. II [5].

The most common virus route of transmission was categorized into three, viz;

(a) *Sylvatic* cycle, involving non-human primates (NHPs) which are infected by tree-dwelling mosquito vectors such as *Haemagogus spp.* and *Sabethess pp.*

(b) Intermediate cycle, involving peridomestic *Aedes* species which act as a bridging point between humans and non-human primates.

(c) Urban cycle, involving humans are infected by *Aedes* spp. Mosquitoes that feed mostly on humans [6].

Despite the success of the vaccine developed against the virus, YFV remain a threat to the general populations of the world due to low coverage of the vaccine and exposure to mosquito vector common in African and South American countries. Hence, suggesting that the disease outbreak can effectively be controlled by a vaccine supply and minimizing vector population [7].

Recently 200,000 cases of YFD had been reported across African and South American region with 30,000 cases resulting in the death of the infected individuals. Yellow fever disease sudden re-emergence has been associated with travels of individuals to different parts of the world [1].

This article presents a critical review and literature updates on the vector biology, vaccination immunodynamics and *epigenetics* of YFV with the aim to understand the interplay of these factors in the re-emergence and risk assessment of living or travelling to YF endemic areas.

Global Distribution and Epidemiology of Yellow Fever

Tropical and sub-tropical areas of South America and Africa are known for Yellow fever outbreaks from time to time. Globally, an estimated 600 million people live in such endemic areas. About 200,000 cases of disease and 30,000 deaths are recorded annually[8].

As indicated by the World Health Organization (WHO) profile, Africa continent experience the vast majority of Yellow fever infection cases and deaths. In particular, Sub-Saharan Africa the disease is a major public health problem occurring in epidemic patterns. The periodic and yet unpredictable outbreaks of Yellow

fever experienced in Africa, with a population of 610 million people, among which more than 219 million reside in urban settings in 32 African countries were considered at risk of Yellow fever infection [8].

South, Central American countries were Yellow fever endemic, and several Caribbean Islands were considered at high risk as well. Although the disease usually causes only sporadic cases and small outbreaks, nearly all major urban centers in the American tropics have been re-infested with *Aedes aegypti* and most urban dwellers are vulnerable. Immunization coverage was low. The Latin American region was at that moment at greater risk of urban epidemics than within the past 50 years [8].

The *Aedes aegypti* density and habitats had expanded in both urban and rural areas. The mosquito was once again infesting regions that it had been previously eradicated. This disease was reported to have originated from Africa and imported into the Americas, but became widely established there. Yellow fever has never been reported from many developed countries. Should it be accidentally imported, the potential for outbreaks exists because the appropriate mosquito vector is present [9].

It had been estimated that, 90% of the outbreaks of YFD occur on the African continent [9].

(a) In 2008, Togo recorded the largest number of cases.

(b) In 2016, Angola experienced a big outbreak and spread to neighbouring countries before the adoption of massive vaccination campaign that contained the disease.

(c) In March and April 2016, China recorded and reported 11 cases, which in history was the first appearance of the disease in Asia [8,10].

Seven genotypes of yellow fever viruses have been identified through *Phylogenetic* analysis, and they are assumed to be differently adapted to humans and to the vector *A. aegypti.* Five (5) genotypes (Angola, Central/East Africa, East Africa, West Africa *I,* and West Africa *II*) occur only in Africa. West Africa *Genotype I* is found in Nigeria and the surrounding areas [11].

This appears to be especially virulent or infectious, as this type was often associated with major outbreaks. However, the 3 genotypes in East and Central Africa occurred in areas where outbreaks were rare. Two previous outbreaks in Kenya (1992–1993) and Sudan (2003 and 2005) involved the East African genotype, which had remained unknown until these outbreaks occurred [12].

Two genotypes had been identified in South Africa (South American genotypes *I* and *II*) *Phylogenetic* analysis identified two genotypes that appear to have originated in West Africa, and were introduced into Brazil [13 - 15].

Year 1882 appears to be the date of introduction into South America (95% confidence interval 1701 to 1911). Between 1685 and 1690, historical record shows an outbreak of yellow fever in Recife, Brazil. Afterwards, the disease seems to have disappeared, until 1849 when the next outbreak occurred. The yellow fever virus was likely introduced with the importation of slaves from Africa through slave trade. *Genotype I* have been divided into five subclades, A through E [15, 16].

In the late 2016, a large outbreak began in Minas Gerais state of Brazil that was characterized as a *sylvan* or jungle *epizootic*. The outbreak was believed to have begun in brown howler monkeys which was a sentinel species for yellow fever, then later spread to men that worked in the jungle. No case had been reported suggesting transmission between humans by the *Aedes aegypti* mosquito, that can sustain urban outbreaks that can spread rapidly. [17, 18]

The *sylvan* outbreak continued spreading towards the Brazilian coast that, in April 2017, where the predominant people were unvaccinated (more than 3,000 suspected cases, 758 were confirmed and 264 deaths confirmed to be of yellow fever). The outbreak appeared to be declining by the end of May A vaccination campaign was launched by the Health Ministry and was concerned with the spread of the disease during the Carnival season in February and March. A level 2 alert was issued by the CDC(practice enhanced precautions) [19 - 22].

According to Bayesian analysis of *Genotypes I* and *II*, it was shown that *Genotype I* accounts for virtually all the current infections in Brazil, Colombia, Trinidad, Tobago, and Venezuela, while *Genotype II* accounted for all cases in Peru [23]. *Genotype I* has

been documented to have originated around the year 1908 in the Northern Brazilian region (95% Highest Posterior Density interval [HPD]; (1870–1936) while *Genotype II* in 1920 had originated in Peru (95% HPD: 1867–1958). Both (*Genotype I and II*) have an estimated rate of mutation of about 5×10^{-4} substitutions/site/year, similar to that of other RNA viruses [21].

The main vector (*Aedes aegypti)* is also found in tropical and sub-tropical regions of Asia, Australia and the Pacific, but yellow fever outbreak or case has never occurred there, until the recent 11 cases introduced by jet travel from the 2016 Angola and DR Congo yellow fever outbreak in Africa. Proposed explanations include;

(a) The fact that, the strains of the mosquito in the east were less able to transmit yellow fever virus
(b) That immunity was present in the populations because of other diseases caused by related viruses (for example, *dengue),*.
(c) That the disease was never introduced because the shipping trade was insufficient [24].

But none of the explanations was considered satisfactory. Another proposal was the absence of slave trade to Asia on the scale similar to that of the Americas. The trans-Atlantic slave trade probably introduced yellow fever into the Western Hemisphere from Africa [25].

Yellow Fever Transmission

a. The urban cycle is most clearly delineated by the human environment and, thus, primarily involves *A. aegypti* mosquitoes since these were some of the most anthropophilic mosquitoes known. Humans forms the reservoir for this cycle, but since mosquitoes can transmit the virus transovarially they may also serve as a reservoir [26, 27].

b. The sylvan cycle (i.e. jungle cycle) involves two genera of-mosquitoes: *Aedes* and *Haemagogus* [8]. These mosquitoes transmit the virus primarily to non-human primates, which serve as the reservoir. Other mammals may be infected in this cycle but are not likely to be important for the maintenance of the viral ecology [27].

These two cycles, the urban and the *sylvan*, occur in both South America and Africa and so are relevant transmission cycles in both macro-regions[28]. The *sylvan* cycle in Africa requires *A. africanus* to maintain the viral ecology. However, the *sylvan* cycle in South America is the only transmission cycle that does not involve *aedine* mosquitoes.

In the South American *sylvan* cycle, *Haemagogus* mosquitoes are the critical vectors of yellow fever. They were particularly tropical forest mosquitoes, typically living their lives in the forest canopy [8]. When adapted to a somewhat narrower ecologic niche, these mosquito's oviposition in tree holes, the crevices of tree bark, or within exposed bamboo stalks [27].

The *Haemogogus* mosquitoes lay their eggs directly on the surface where the eggs, similar to the *aedes* mosquitoes, will mature once they are immersed in water following the next raining season [8].

These mosquitoes transmit the virus primarily to non-human primates, especially those that occupy the canopy. Humans were at risk of infection in this transmission cycle when they come into contact with this forested habitat, particularly when that contact actually disrupts the habitat [29].

This scenario arises with deforestation and the development of natural habitat for agricultural or resource extraction purposes. Transmission to humans via this cycle was typically limited to workers in industries that encounter this forested habitat, where sporadic cases, or occasionally, small-scale outbreaks are the norm [29].

In the African *sylvan* cycle, the *Haemagogus* mosquitoes and *Aedes africanus* are analogues (***Figure 1***) [27].

This mosquito has a similar ecology to the South American *Haemagogus* species by living in the forest canopy and taking blood meals primarily from non-human primates, which are reservoirs for the yellow fever virus. The *A. africanus* also mimics the ovipositioning of the *Haemagogus* mosquitoes. Therefore, transmission to humans in the African *sylvan* cycle also affects workers involved in deforestation, but is not limited to this population [27].

Consequently, conflict in some regions of sub-Saharan Africa where the *sylvan* yellow fever was endemic exposed refugees and displaced communities to this cycle, ultimately resulting in more severe outbreaks in those setting than had been experienced in South America [30].

(c) The intermediate cycle (i.e. the savannah cycle, or the rural cycle) occurs only in Africa and involves several different species of *Aedes* mosquitoes in the transmission of the virus [31].

As the name suggests, this cycle occurs in the landscape between the strictly forest, or *sylvan* cycle and the strictly domestic, or urban cycle. As such, the *Aedes spp.* involved typically obtain blood meals from both humans and monkeys. It is essentially an ecotonal cycle, wherein the geography of transmission is determined by landscapes of transition from one habitat to the other [27, 31].

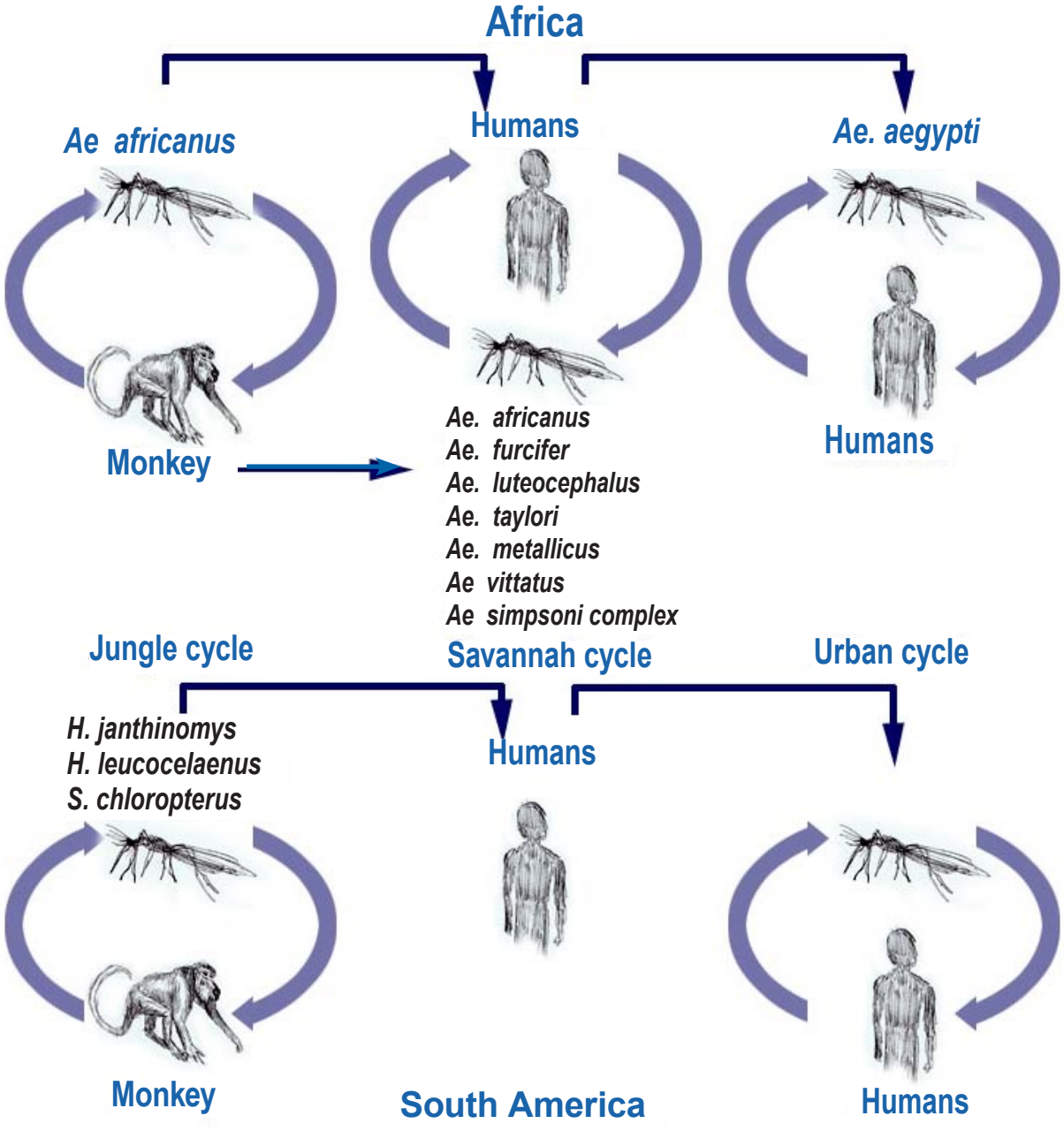

Figure 1: *Transmission Cycle Between Yellow Fever Virus and Its Vector Source: Walsh [27].*

The Vector and the Landscape

To begin, it must be emphasized that, this mosquito had a very particular preference for the water environment it selected for laying its eggs. It liked small containers that collect rainwater. The mechanics work as follows;

> That mosquito did not lay its eggs either in the water nor on the surface of the water, as most other species do [20]. Instead, *A. aegypti* lays its eggs above the water on the interior wall of the vessel containing water so that when the water vessel is refilled, from the water line at which the mosquito laid its eggs to the lip of the vessel, the eggs will have enough time to complete their developmental cycle to adulthood before evaporation depletes the water source. A truly incredible evolutionary adaptation [20].

That mosquito was originally adapted to a forest habitat wherein it would seek out holes in trees that could regularly collect rainwater[32]. Tree holes were much more ubiquitous than you could expect in a forest (think woodpeckers), and so that was quite an effective niche for that mosquito. As humans encroached more and more on forest habitat establishing agriculture, building increasingly dense communities and living conditions, *A. aegypti* readily adapted to the new circumstances [32].

The mosquitoes found an abundance of new and highly effective small containers strewn in and around households that could easily collect, or were intended to store water [33]. The mass production of plastics had been a major factor in the proliferation of potential water containers. Today *A. aegypti* is just as much an urban mosquito as it was a forest mosquito and probably more so. Likely, *A. aegypti* is now uniquely adapted to the human environment.

Unlike other mosquito species, they would often live in the household with humans and could complete their whole life cycle there. They also bite during the day, so they had unlimited access to humans for taking blood meals [33]. Finally, this mosquito's preferred host, as you might have already guessed, was humans. Since that mosquito was very effective at exploiting the human environment, it was also very effective at transmitting any viruses that it was capable of carrying and which were infective to humans.

Resurgence of Yellow Fever in Nigeria

In Nigeria, although YF was endemic in the Western regions, it had become epidemic outside this zone in the previuos last 2 years. The YF transmission cycle occasionally re-emerges and, in the last decade, an increase in viral circulation had been observed throughout the country.

From January 2019 to November 2019, 3009 suspected cases and 40 deaths. 10 laboratory confirmed cases an increase noticed in case fatality rate compared with 2018 (1.3% versus 0.0%) [34].

Out of the suspected YF cases in Nigeria, the most conspicuous was on 29th August 2019, when a suspected yellow fever case was reported from Kano state with a travel history to Yankari game reserve, Alkaleri Local Government Area (LGA), Bauchi state, Nigeria.

From 29th August through 22nd September 2019, Nigeria reported an outbreak of yellow fever with an epi-centre in the Yankari game reserve of Alkaleri LGA, Bauchi state [33].

According to Nigeria Centre for Disease Control (NCDC) [34], 231 suspected cases had been reported in four states including Bauchi (110), Borno (109), Gombe (10), and Kano (2), of which there had been 13 presumptive positive by IgM testing and 24 cases positive by reverse-transcriptase polymerase chain reaction (RT-PCR) at national laboratories.

Of the 24 cases confirmed by RT - PCR (20 cases in Bauchi, three in Gombe and one in Kano state), six deaths were reported, all from Alkaleri LGA, Bauchi state, resulting in a case fatality ratio of 25% among the confirmed cases. The vaccination history for the 231 suspected yellow fever cases was not known [34].

Vaccination was the only effective measure to prevent YF. The rapid recognition of the disease outbreaks in high - risk areas, followed by the vaccination of 60% to 80% of the population was crucial to prevent epidemics [35].

Generally, there were two vaccines available, derived from the same strain, with very similar and comparable response profiles and reactogenicity –

YFV 17DD (Biomanguinhos©) and 17D-204 (Sanofi Pasteur©) The current Nigerian immunization schedule recommends a single subcutaneous 0.5 ml dose at nine months of age and is contraindicated in some groups, as follows; [36-37].

(a) Infants younger than nine months for routine immunization or younger than six months during an epidemic;
(b) Pregnant women or breast feeding mothers, children under six months of age, except during YF outbreaks, when the risk of infection is high.
(c) Severe allergies to egg protein.
(d) History of severe adverse reactions to previous doses.
(e) Organ transplantation
(f) Previous history of *thymus* disease (*myastheniagravis, thymoma, thymus* absence or surgical removal).
(g) Severe immunodeficiency of any nature.

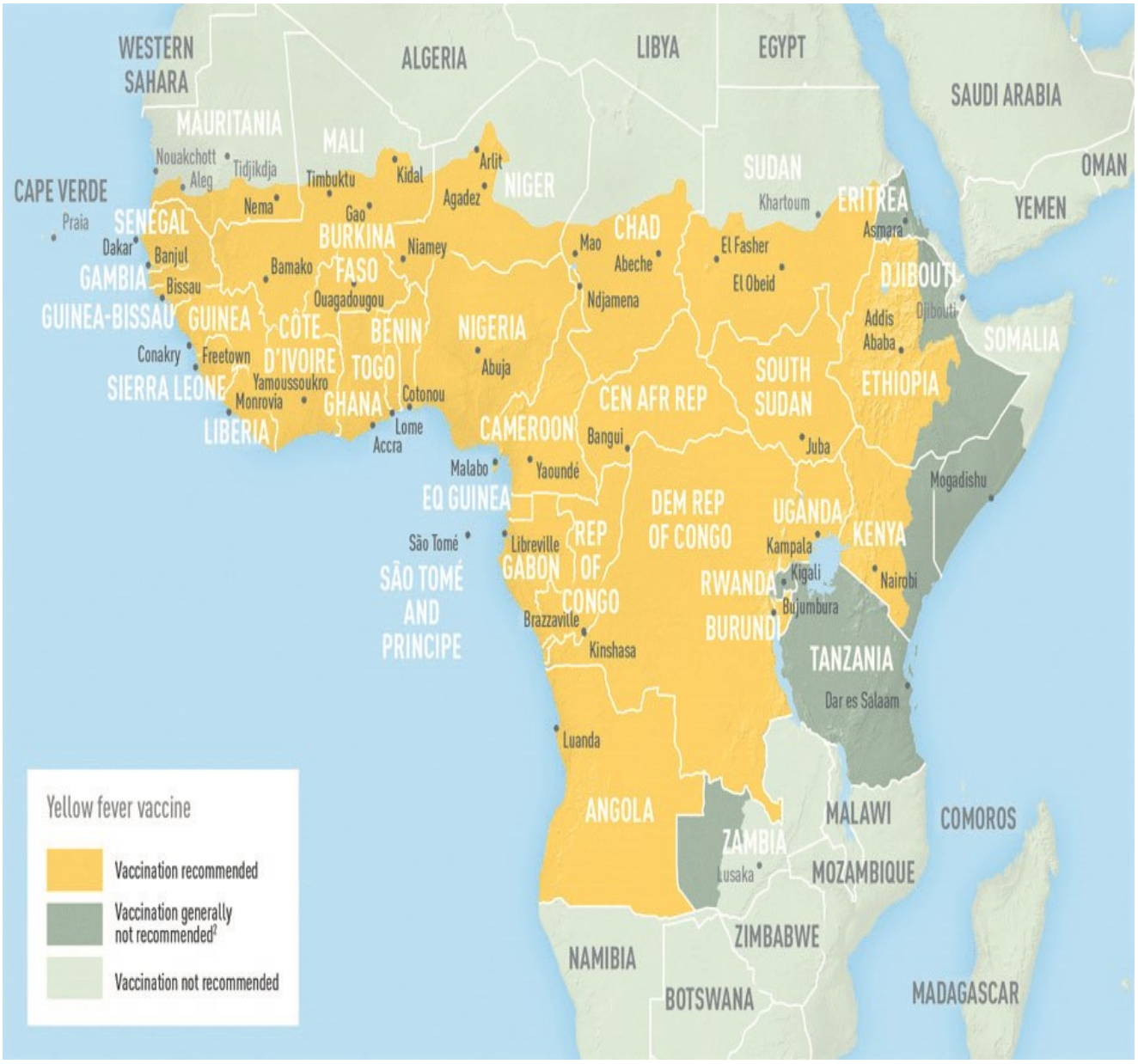

Figure 2: *Areas with Risk of Yellow Fever Virus Transmission in Africa. (Source:* ***CDC****) [39].*

Yellow Fever Vaccination Protocol

The live, attenuated viral strain of the 17D vaccine was available as the main commercially sourced yellow fever vaccine. It ensured highly effective and sustained immunity when administered to individuals with high risk of exposure to the wild-type Yellow Fever virus. Those were especially tourists and inhabitants of endemic regions of Africa ***(Figure 2)*** and South America.

Those eligible for the vaccine were usually given through routes of administration either by single subcutaneous or intramuscular injection. The administration of the vaccine (17D-204 strain) could be given either to infants (pediatric dosage) above 9 months or adults (adult dosage) using one dose of subcutaneous injection ($\geq$4.74 $\log^{10}$ plaque-forming units/0.5mL) not later than 10 days to regional migration [33,38].

The single dose of the vaccine was usually sufficient to confer prolonged immunity against yellow fever infection but booster doses were often required based on endemic state of certain countries and in the following circumstances:

i. Migrants who intend to spend prolonged durations in highly endemic rural regions of West Africa especially during outbreak or peak transmission period [37].

ii. Medical Laboratory Staff who frequently work on wild-type yellow virus. Based on regular exposure to this virus on routine basis, the neutralizing antibody titers against the yellow fever virus are usually assessed every ten years to determine the necessity for booster doses of the 17D vaccine.

iii. Irrespective of the knowledge of neutralizing antibody titers for the virus, vaccination every 10 years is recommended especially for individuals frequently exposed to the virus.

These recommendations aid in effectively controlling yellow fever re-emergence and transmission to regions of low risk for the infection [39].

Mechanisms of Action of D17 Vaccines

The successful reputation of the 17D vaccine has accredited it to serve a unique model in understanding responses of the human immune system during an acute phase of viral infection. The antibodies, generated on exposure to these viruses, play dominant effect or mechanistic roles in ensuring prolonged, vaccine-induced protective immunity. Several innate and cellular mechanisms as well as the helper (CD4+) and cytotoxic (CD8+) *T lymphocytes* are known to respond in ways that contribute to the provision of lifelong protective immunity [38 -43].

Although a holistic event of the mechanism of protective immunity against Yellow Fever is not completely understood, *immunoglobulins* are considered to be the major contributors in conferring protective vaccine-induced mechanism and their presence have been associated with protective immunity [44].

Following a dose of immunization with the D17 vaccine, pre-existing non-cognate CD4+ *T-lymphocytes* are induced to enhance *immunoglobulin* response to the target antigens coated onto the Yellow Fever 17D (YF-17D) vaccine particles. These vaccine particles coated with target antigen also engage the B-cells with B-cell receptors (BCRs).

The B-cells internalize these antigen-coated vaccine particles within its *endosomes* with the release of *proteases* which disintegrate the antigens both on the vaccine surface and those entrapped within the vaccine particle to generate peptide fragments.

These fragments are presented on the major histocompatibility complex class II (MHC II) ***(Figure 3)*** to cognate CD4+ *T-lymphocytes* (i.e. those that recognize the same antigen as the rare or weak B-cell *epitomes*) and non-cognate CD4+ *T-lymphocytes* (i.e. those that identify the strong helper MHC II receptors) [45].

The pre-existing CD4+ *T-lymphocytes* that identify helper antigen generated either by Yellow Fever infection or pre-vaccination can induce co-stimulatory signals to B-cells which generates a *plethora* of neutralizing antibody titers, that is measurable in the vaccinated within 6-28 days after vaccination [45].

These signals drive the proliferation, differentiation, *immunoglobulin* synthesis, somatic hypermutation, and isotype switching of B-cells. Due to the determination of the specificity of *immunoglobulin* response at the point of BCR-induced antigen identification, the *immunoglobulins* generated

will be uniquely directed only against the target antigen on the YF-17D vaccine particle surface ***(figure 3***).

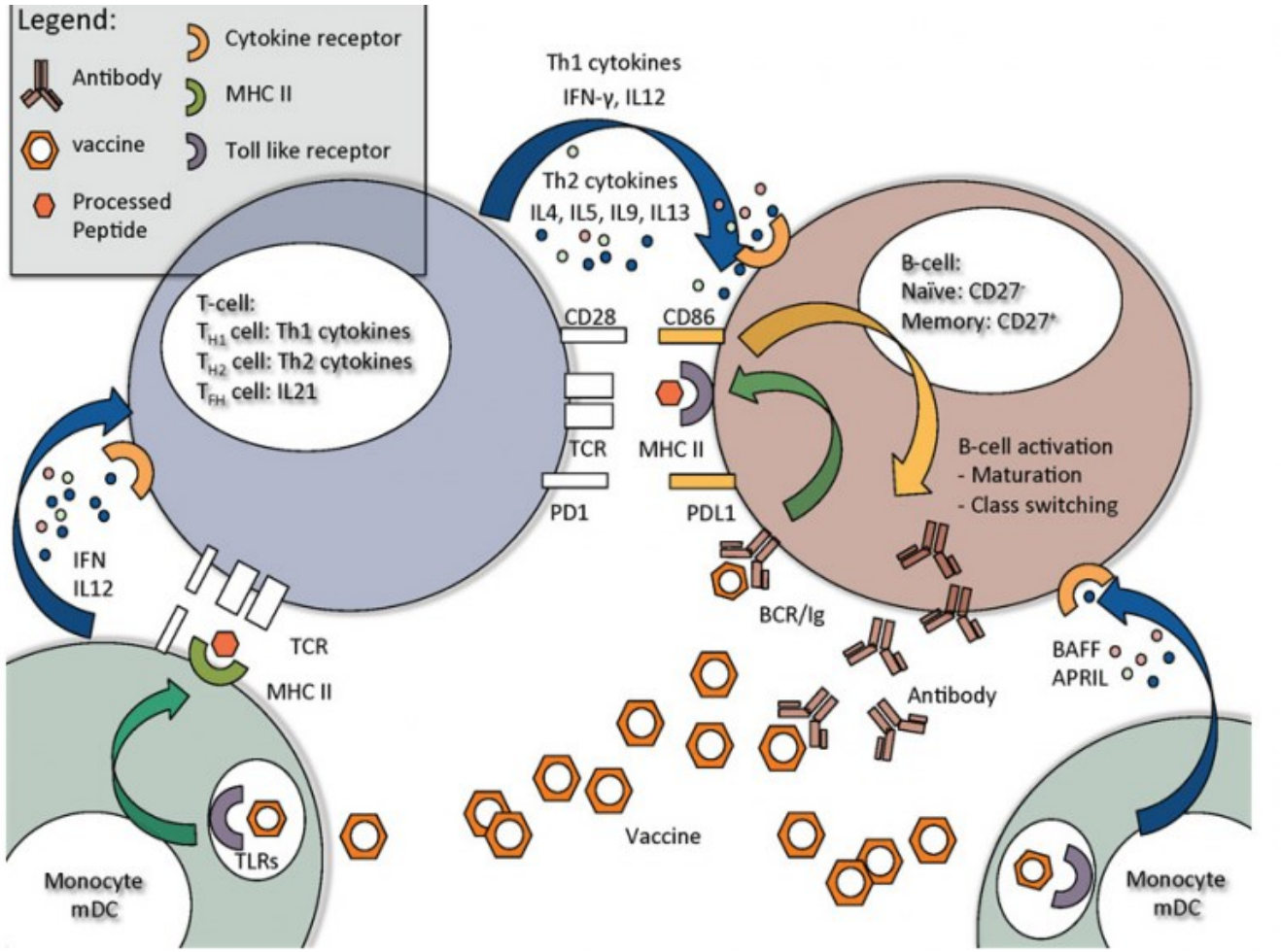

Figure 3: *Vaccine mechanism of action.* **Source:** Egliet al.[46].

Neutralizing antibody titers was known to persist in those vaccinated up to 45-60 years after immunization [47]. Kongsgaard and colleagues demonstrated that an average neutralizing (Plaque Reduction Neutralization Test) antibody titer of 1 : 1280 (within 1 : 160 to 1:20,480) in those immunized after 9-40 days following vaccination with YF-17D vaccine. That finding corroborated with an animal study involving either *immunoglobulin* transfers or genetical induction of immune deficiencies [47-49].

In YF-17D vaccinated mice, protection was demonstrated around 5 - 7 days evident with the influx of specific cytotoxic (CD8+) T-cells. Reduction in CD8+ T-cell population correlated with reduced protective immunity and elevated organ viral load [49]. These selected studies synergistically reveal the efficiency of YF-17D vaccine in providing protective immunity in immunized individuals.

Demerits of Yellow Fever Vaccines

Despite the successes of the YF-17D, limitations and side effects were associated with the use of this vaccine. This vaccine was contra-indicated in infants less than 8 months of age except during the peak of yellow fever transmission. Other limitations associated with this vaccine include history of severe allergic response to egg or to any component of the vaccine, hypersensitivity to earlier dose of the vaccine, history of *thymectomy*, medication-induced immunodeficiency and HIV infection [50].

Adverse effects associated with YF-17D vaccine included the *Neurotropic* and v*iscerotropic* disorders but the YF-17D vaccine-associated *Viscerotropic* disease (YEL-AVD) was observed to be more lethal [38].

Two unique patterns of YEL - AVD risk existence include:

i. Risk in younger individuals which mainly involve females with innate immunity defects in whom mortality rate is higher.

ii. Risk in the elderly especially in males with age-associated immune deterioration and relatively lower mortality rate.

Viscerotropic disease related to YF - 17D vaccine was rarely observed after first immunization with the vaccine. Within 10 days following vaccination, severe multi-organ failure resulted with a mortality rate in excess of 60%. Risk factors involved a history of *thymectomy* of *thymoma* and greater or equal to 60 years of age.

Hence, *Neurotropic* disease related to YF - 17D vaccine, which involved *meningoencephalitis,* acute disseminated *encephalomyelitis* and Guillain – Barré syndrome, have been reported in infants less than 6 months of age and in individuals who were 60 and above years of age [50].

Risk for Travelers

A traveler is at the risk for acquiring YF by various factors, including immunization status, travel location, season, duration of exposure, recreational and occupational activities while traveling, and local rate of virus transmission at the time of travel [34].

Although reported cases of human disease were the principal indicator of disease risk, case reports might be absent because of a low level of transmission, failure of local surveillance systems to detect cases or a high level of immunity in the population (because of vaccination, for example) [51].

Since "*epidemiologic* silence" does not mean risk absence, travelers are advised not go into endemic areas without vaccination or taking other protective measures [34].

YF virus transmission was seasonal in rural West Africa, with an increased risk during the end of the rainy season and also the beginning of the dry season (usually July – October) [34].

However, *Ae. aegypti* mosquito may transmit YF virus periodically, including dry season, in both rural and densely settled urban areas. During the rainy season (January – May, with a peak incidence in February and March), the risk for infection by *sylvatic* vectors in South America was highest [34]. From 1970 through 2015, 11 cases of YF were reported in people who travelled to:

i. Risk West Africa (6 cases)

ii. South America (5 cases) from the United States and Europe,

Where 8 (73%) out of 11 infected travelers died. Only traveler who survived, had a history of YF vaccination documented.

From the year 2016, there was an increase in the number of travel-associated YF cases, primarily as a result of outbreaks in Angola and Brazil. Starting from 2016 through mid - 2018, more than 35 travel - associated cases were reported in unvaccinated travelers who were residents of non - endemic areas or countries. That included at least 13 European travelers and 1 American traveler to Peru [34].

It is difficult to predict the risk of acquiring YF during travel because of variations in ecologic determinants of virus transmission. For a 2 - weeks stay, the risk for illness and death due to YF for an unvaccinated traveler visiting an endemic area was estimated as follows:

a. In West Africa, 50 out of 100,000 and 10 out of 100,000, respectively.
b. In South America, 5 out of 100,000 and 1 out of 100,000, respectively [34].

These estimations are based on the risk to native populations, often during the peak transmission season. These might not accurately reflect the risk to travellers with different immunity profiles, have less outdoor exposure and take precautions against mosquito bites. However, during an outbreak, there is a higher risk of infection for travellers, as demonstrated with recent outbreaks in Angola and Brazil [52].

Novel Control Measures against Yellow Fever: Prospects and Drawback

Mosquito - borne viruses - such as *Zika, Dengue Fever*, *chikungunya,* and Yellow Fever, among others are of global concern. Although a vaccine development for the prevention of mosquito-borne *arbovirus* infections had been a focus, mitigation

strategies continue to rely on vector control. Failure to prevent recent epidemics and arrest expanding geographic spread of key *Arboviruses,* such as *Dengue*, had consequently increased the necessity to further improve current strategies within integrated approaches and advance development of innovative, and alternative strategies for the control of mosquito-borne *Arboviruses* [53].

The main approach for *Arbovirus* outbreak control (such as *Dengue*) was the use of synthetic chemicals with quick-action killing of adult vectors using space spraying. The majority of recommended insecticides are of the *pyrethroid* chemical class, creating challenges to preventing selection pressure on susceptible mosquito populations as well as the control of *pyrethroid*-resistant vectors [54].

In the management of *arbovirus* vector population, precisely of *Ae. aegypti*, larval control had long been proposed and implemented as a principal strategy, including applications of chemical and microbial larvicides, bacterial toxins and insect growth regulators (IGRs) [55-56].

Biological agents used against immatures include predatory copepods, fish, and *Toxorhynchites larvae.* Arguably, the dependency to detect, access, and eliminate or treat domiciliary- often - cryptic - breeding sites, has been the greatest obstacle to *Ae. aegypti* larval control success, a challenging and costly task that often leads to low coverage.

In addition, their widespread adoption is limited due to reduced efficiency in some occasions [57].

Epigenetic Basis of Yellow Fever Resurgence

The resurgence of Yellow Fever Virus (YFV) infection in recent times (in the year 2016-2018) had been attributed to low vaccination coverage. There was need to reconsider YFV as a serious threat to human health due to its re-emergence in non-endemic and endemic areas with a history of low vaccination coverage [58].

Besides low vaccination coverage, other drivers existed that could result to YFV re-emergence in endemic and non-endemic areas such as:

a. Risky global warming.
b. Increased temperatures.
c. Increased rainfall intensity.
d. Expansion of human activities to YFV-endemic areas.
e. Increase in human YFV circulation locally and cosmic rays particles [58].
f. Solar particles and electrically charged cometary dust particles including *virions* [59].

The *sylvatic* (*Haemaghogus Leucocelaenus* and *Sabethesalbiprivus*) and urban (*Aedes aegyti*) transmission cycles are also important and crucial to the outbreaks [5, 60]. Therefore, there is need for further research elucidating the ecological connections between YFV, its vector, and its environmental niche so as to easily predict, anticipate and prevent future epidemics.

This presented the opportunity to eradicate the disease from human population but not the non-human primate host of the virus. Children aged nine months and older were administered the YF 17D vaccine. Thus enjoying the life long immunity of the vaccine and reputation of being one of the safest and most effective live attenuated vaccine [61].

YFV incidence reduced drastically and there were relatively few cases within 25 years span, with outbreaks limited to countries that did not administer the vaccines. As the sense of complacency and feeling that YF was beaten begins to set in, the effort to maintain and control future outbreaks was abandoned.

The YF vaccine was also not included in the childhood vaccination programs and therefore, individuals born after the vaccination programs were not vaccinated with young individuals who enter the jungle areas for employment were vulnerable to the infection.

In the late 1950s and early 1960s, there were several outbreaks in Africa, with the highest incidences in the Western region The number of cases continue to increase as a result of replacement of the routine vaccination campaigns with the emergency vaccination campaigns once an outbreak has been identified. Once the outbreak ceases, so does the vaccination.

This is clearly not a cost - effective mechanism to control a vaccine-preventable disease. As for the YF resurgence in the Americas, the YF vector (*Aedes aegypti*) returned to the South American countries after elimination in the 1930s and 1940s as a result of abandoned control measures [61].

Today, the vector mosquito infests a larger area of the Americas more than before its temporary elimination as a result of global warming and political decisions not to continue with mosquito-control programs[13]. Densely populated coastal regions of Brazil have become re-infested with *Aedes aegypti* leading to concerns about the resurgence of Urban YF. The South East region of Brazil has experienced the largest YF outbreak in Latin America in decades, which began in 2016 and it was spreading eastwards of the country.

Although poor hygiene and climate change were cited as the causes, other fundamental risk factors coexist such as cosmic rays, solar particles and electrically charged cometary dust particles including *virions* [59].

Cosmic rays have been well documented to cause genetic changes. In recent times, it has been discovered that there was a decrease in the Earth's magnetic fields in the Southern Hemisphere, straddling land masses in South America and Africa. European Space Agency (ESA) have recently released a new data that reveals that, our geomagnetic field was weakening by around 5% a year, which is ten times faster than it was previously estimated [59]. The vector mosquito responsible for these viral diseases is sensitive to the geomagnetic field, and a weakening in the field can increase the mosquitoes reproductive speed and density.

In January 2015, Mexico recorded a sudden increase of cosmic rays, as revealed by the World Data Centre for Cosmic Rays (WDCCR) and continued throughout the year and that was probably the cause of the ZIKV and YF outbreaks [61].

Conclusion

An ongoing sporadic outbreak of yellow fever in Nigeria began in 2018. The outbreak has now spread throughout the country. The Nigerian Ministry of Health had reported cases of the disease in all 36 states and the Federal Capital Territory. The large disparity in yellow fever incidence and mortality that currently exist between Africa and the Americas is largely due to the massive vaccination campaigns that have been undertaken in many countries in South America, which had thus, eliminated the urban cycle of disease in the western hemisphere.

In many endemic African countries, the same resources have not been available to mobilize widespread vaccination. This inadequate vaccination coverage, coupled with added intermediate transmission cycle, have been significant contributors to the much higher YF disease burden in Africa.

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