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Vaccination and Therapeutics: Responding to the Changing Epidemiology of Yellow Fever

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Abstract

At the turn of the nineteenth century, yellow fever (YF) was considered the most dangerous infectious disease with high case fatality. Subsequent, mass vaccination campaigns coupled with widespread elimination of the YF mosquito vector significantly decreased YF cases and reduced outbreaks to the tropical and subtropical forested regions of Africa and South America. However, recent (2016) large outbreaks in Angola, Democratic Republic of Congo (DRC), and South-Eastern Brazil, where previously had been demarcated as low-risk regions, have highlighted the possibility of a rapidly changing epidemiology and the potential re-emergence of yellow fever virus (YFV). Furthermore, the first-ever importation of YFV into Asia has highlighted the potential fear of YFV emerging as a global threat. In this review, we describe the changing epidemiology of YF outbreaks, and highlight the use of public health policies, therapeutics, and vaccination as tools to help eliminate future YFV outbreaks.

Introduction

Yellow fever (YF) is a re-emerging acute viral disease that less than a century ago was considered the most dangerous infectious disease in the world [1]. YF is caused by the etiological agent, yellow fever virus (YFV), which belongs to the *flavivirus* genus of arboviruses. YFV exists in circulation between humans, non-human primates

(NHPs), and several species of mosquito vectors [2]. The presence of epizootic transmission means that YFV cannot be eradicated from the world. However, preventative vaccination campaigns with live-attenuated YFV vaccines along with widespread mosquito elimination programs have proven to be efficient at substantially reducing YF cases and outbreaks [3]. Individuals infected with YFV can present with a wide spectrum of symptoms, ranging from asymptomatic infections to death, with severe cases displaying high fever, dysfunction of multiple organs (including the liver, kidneys, and heart), or hemorrhage [4]. The ratio of subclinical (i.e., asymptomatic to mild symptoms) to severe cases is estimated to be 1–70, indicating that severe cases represent only "the tip of the iceberg" [5]. Mathematical models have also predicted over 200,000 annual cases of YF in high risk areas, with case fatalities ranging from 20 to 80% [1, 6, 7]. However, due to the sporadic nature of YF outbreaks, the lack of rapid diagnostics, and the high serological cross-reactivity among co-circulating flaviviruses has meant that confirmed diagnosis is limited to reference laboratories where viral RNA can be detected using reverse transcription (RT)-PCR [8•, 9]. Therefore, quantifying the true global burden of YF disease and infections has been challenging.

The complex transmission pattern of YFV between humans, non-human primates, and its mosquito vector has shaped the epidemiology of YF. Genotypes and transmission patterns of YFV are highly divergent between Africa and South America [2]. In South America, YFV strains circulate in two different cycles (Fig. 1a), i.e., (1) a sylvatic cycle between non-human primates (NHP) and rainforest-dwelling mosquitoes of the *Haemagogus* and *Aedes* species, and (2) an urban cycle where in rare opportunistic forest mosquito-feeding events YFV infect humans and spreads through urban human populations via the urbanized mosquito, *Aedes aegypti*. Africa observes an additional YFV transmission cycles known as the intermediate cycle (Fig. 1b), where anthropophilic mosquitoes in the savannah regions feed on both NHPs and humans leading to constant transmission of YFV between mosquito, NHPs, and humans [10]. Interestingly, compared to NHP species from Africa, NHP species in South America are far more susceptible to YFV infection with high mortality [11, 12].

YFV exists as seven genotypes (or major lineages), with 5 circulating in Africa and 2 in South America. Phylogenetic studies show that the African lineages have a common ancestor that then spread to discrete geographical locations and further evolved to establish the five genotypes (1) West African I, (2) West African II, (3) East and Central African, (4) East African, and (5) Angola [1, 13]. The South American genotypes I and II are thought to have evolved from the West African strains during the time of the slave trade when YFV spreads to the Americas [14]. Unlike flaviviruses such as dengue virus (DENV), YFV is highly stable with slow epidemic and evolutionary rates [15, 16]. Due to slow evolutionary rates and constant spillover, the phylogeny of YFV isolates from NHP are genetically similar to isolates from human outbreaks [12, 17, 18]. Consequently, in South America, regular surveillance of YFV outbreaks in NHP populations can be used as an epidemic preparedness strategy [12, 19]. In addition to active surveillance, elimination of future YF outbreaks requires a comprehensive understanding of the current epidemiology and the influence of control and prevention methods, such as vaccination.

Current Epidemiology: Appearance of YF in Low or No Endemic Regions

In the eighteenth and 1nineteenth centuries, YFV led to high rates of mortality in Africa and the Americas [3, 20]. Fortunately, in the mid-1960s, Max Theiler and colleagues created the earliest versions of the live-attenuated yellow fever vaccine [3, 21]. Subsequently, widespread mass vaccination campaigns and mosquito control efforts significantly reduced YF outbreaks. Past public health successes led to a lax in maintaining local YF vaccination coverage leading to waning herd immunity and an eventual re-emergence of large outbreaks in West Africa in the 2000s [22••, 23]. This promoted a collaborative effort by the World health Organization (WHO), the United Nations Children's Fund (UNICEF), Global Alliance for Vaccines and Immunization (GAVI), and 47 YFV endemic countries to create the Yellow Fever Initiative (YFI) in 2006 [24]; an initiative that was primarily focused on mass YF vaccination campaigns and introduction of the vaccine into childhood immunization programs in high risk regions. In an emergency preparedness effort, the new initiative also set up a global stockpile of YF vaccines [25]. While implementation of YFI eliminated YF outbreaks, this was short-lived as the emergence of major YF outbreaks in 2016 in regions not previously characterized as high-risk for YF casted doubts on the YFI strategy [7].

In Africa prior to 2016, YFV outbreaks occurred predominantly in West and East Africa, with low or no endemicity in Central Africa (Fig. 1b). In 2013, highly
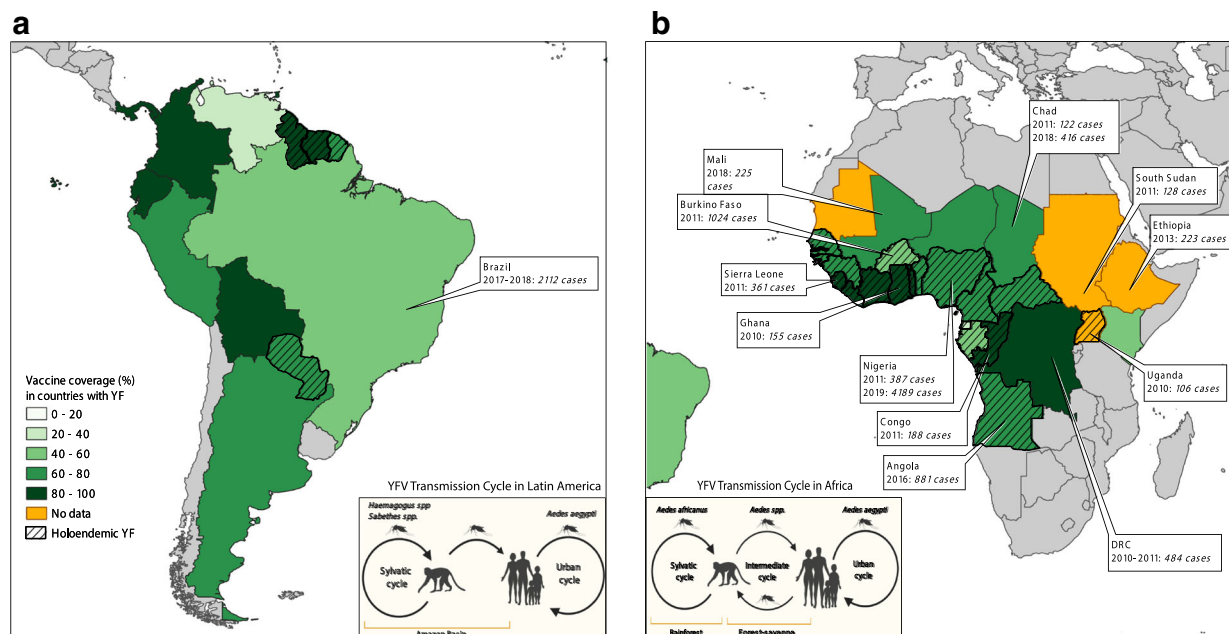
Fig. 1. Map displaying major outbreaks in the past decade and the vaccine coverage in countries reported as "high risk" for YFV by WHO. Major outbreaks are defined as greater than 100 cases of YF reported to WHO. All data for global YF cases and vaccine coverage were accessed from most current estimates on the WHO website (https://www.who.int/news-room/fact-sheets/detail/yellow-fever)

endemic regions in Africa were estimated to have a YF burden of 130,000 cases per year, which accounted for greater than 90% of the global burden [7]. It had also been observed that ambient or environmental temperatures and rainfall patterns could sustain mosquito vectors and promote the spread of YFV to regions of low endemicity [26]. In December 2016, YF cases were detected in Luanda, the capital city of Angola, which was previously categorized as a low-risk region for YF. The epidemic rapidly spread from Luanda to other urban populations in Angola and crossed into the neighboring country, Democratic republic of Congo (DRC) [27]. Modeling studies predict that YFV transmission was continued for longer than usual due to the rain patterns affected by the 2016 EL Niño phenomenon [28]. Emergency vaccines were deployed to affected regions, but by the mid-2016, the entire global stockpile of YF vaccine doses was exhausted, and fractional dosing of the YF vaccine was implemented as an emergency measure [29]. By November 2016, the WHO had confirmed 962 cases and 393 deaths related to this YFV outbreak. Since Angola and DRC were previously classified as low-risk for YFV transmission, these countries had not qualified for the previous vaccination campaigns within the YFI [24]. Low herd immunity, due to low YF vaccination

coverage, facilitated the large 2016 outbreak in Angola and DRC. As a response, the WHO revised its YFI program and implemented the new "EYE" strategy, with the goal of eliminating all global YF epidemics by 2026 [30••]. Since 2016, there have been outbreaks of 100 or more cases reported to WHO from Mali and Chad (2018) and Nigeria (2019). As a step towards eliminating future YF outbreaks, mass vaccination campaigns are currently being carried out in YF endemic regions where previously vaccine coverage had been poor [22••].

In South America, case fatality rates from YFV infections are more than double that in Africa (40–60% versus 20%) [1]. Therefore, under the YFI program, preventative vaccination campaigns in high risk YF regions significantly reduced YFV outbreaks in humans until no major outbreak (i.e., greater than 100 cases) was detected between 2010 and 2015 in Latin America. Nevertheless, in 2016, a large YF outbreak occurred in regions of Brazil that had previously had low or no risk of YF infections and therefore, low vaccination coverage [17]. Phylogenetic tracking of the epidemic strains identified the originating dissemination event to have occurred in "Central-West" region in the Brazilian state of Goiás about 2 years prior to the

outbreak [31, 32]. The epidemic then moved into the state of Minas Gerais, from where it moved along two different routes (route 1 towards the east and route 2 towards the south-east) into peri-urban regions of the Brazilian megapolis, São Paulo and Rio de Janeiro [31]. This led to an exponential increase in transmission leading to over 2000 confirmed cases and over 600 deaths. Molecular analysis confirmed that the 2016–2017 epidemic strain was within the South American (SA) 1 genotype and that the epidemic resulted from direct sylvatic spillover to humans with the absence of sustained YFV transmission within the urban cycle [19, 32, 33]. Some studies have attributed the 2016 YF epidemic in YF non-endemic regions of Brazil to increased virulence of the new virus strain [31, 32, 34]; others have blamed changing aspects of population and ecology, such as the rise in population density [34], the geographical expansion of the peri-urban mosquito *Aedes albopictus* [35], human encroachment into NHP habitats [36], and global warming [37]. Since the factors that promote emergence of YFV in low or non-endemic regions are not well understood, currently, we are unable to predict the next YFV outbreak in these regions.

It is unclear why Asia has never reported endemic YFV transmission, despite similar flaviviruses (such as DENV and zika virus) circulating in this region. However, Asia is the home to over 4 billion individuals, contains widespread prevalence of the YF mosquito vector (*Aedes aegypti*), and has no heard immunity against YFV (due to lack of natural circulation and vaccination) [38]. Therefore, increased movement of individuals between Asia and Africa and/or South America pose a real fear that YFV might spread to Asia [39]. In 2016, eleven Chinese working in Angola returned to China and imported YFV for the first time into Asia [40, 41]. Despite mandatory YF immunization requirements at least 10 days prior to travel to YFV-endemic regions outlined by the International health regulations (IHR), 5/11 of the Chinese workers had no YF vaccination record, while 4/11 had been vaccinated < 14 days of acquiring symptoms [42, 43]. As links between Asia and Africa and/or South America increase, the threat of YFV spreading to Asia becomes real. Therefore, there is an urgent need to invest in research for new YFV rapid diagnostics, therapeutics, and vaccines. Furthermore, as part of YFV epidemic preparedness, it is essential that Asian countries also strengthen YFV surveillance, implement mosquito elimination programs, and put in place measures to rapidly manufacture and deploy vaccines.

YF Vaccine: Our Imperfect but the Strongest Control Strategy

In the live-attenuated YF vaccine, 17D remains the single best control measure against YFV infection and is widely regarded as one of the most successful vaccines ever developed. The 17D strain was developed in 1936 through the tedious process of serial passaging in chicken tissue of the wildtype YFV Asibi strain isolated from a patient in Ghana. There are currently three sub-strains (17D-204, 17D-213, and 17DD) licensed for use in individuals aged 9 months to 60 years old, residing in or traveling to YF-endemic regions. For all substrains of YF vaccines, antibodies against YFV are currently the gold standard when examining correlates of protection against future infection [44, 45]. Protective titers were originally determined by passive immune transfer and subsequent challenge with YFV in monkeys [46]. A log neutralization index (LNI) of 0.7 or higher is protective. However, calculating LNI requires pre- and post-vaccine serum, which is not always feasible in the context of natural infection or mass vaccination. Consequently, plaque reduction neutralizing titer (PRNT) assays have replaced LNI measurements, where an 80 or 90% PRNT (i.e., $PRNT_{80}$ $PRNT_{90}$) is used to indicate protection [47]. However, both YFV LNI and PRNT are slow, tedious, not standardizable, require experienced laboratory staff, and are limited to biosafety level-3 containment facilities [48]. Therefore, currently, we are urgently in need of new rapid, high-throughput, easy-to-use techniques that can be used to accurately assess protective antibodies following vaccination.

Recent epidemiological studies have expanded our understanding of factors that affect YF vaccination-induced human antibody responses (Fig. 2). Historically, YF vaccine studies conducted in health adults demonstrated that a single subcutaneous dose elicits a remarkably high seroconversion (nearly 100%) [49–51]. However, recent studies show that age has a large influence on seroconversion rates, as observed by the high rates of vaccine failure in infants (9–12 months) and the elderly (> 60 years) [52••, 53]. In particular, seroconversion rates of children who received the YF vaccine in conjunction with the routine childhood vaccines for measles-mumps-rubella (MMR) had a lower seroconversion rates (69%) compared to children who received the YF vaccine alone (~ 85%) [54, 55]. Additionally, seroconversion rates in non-endemic countries
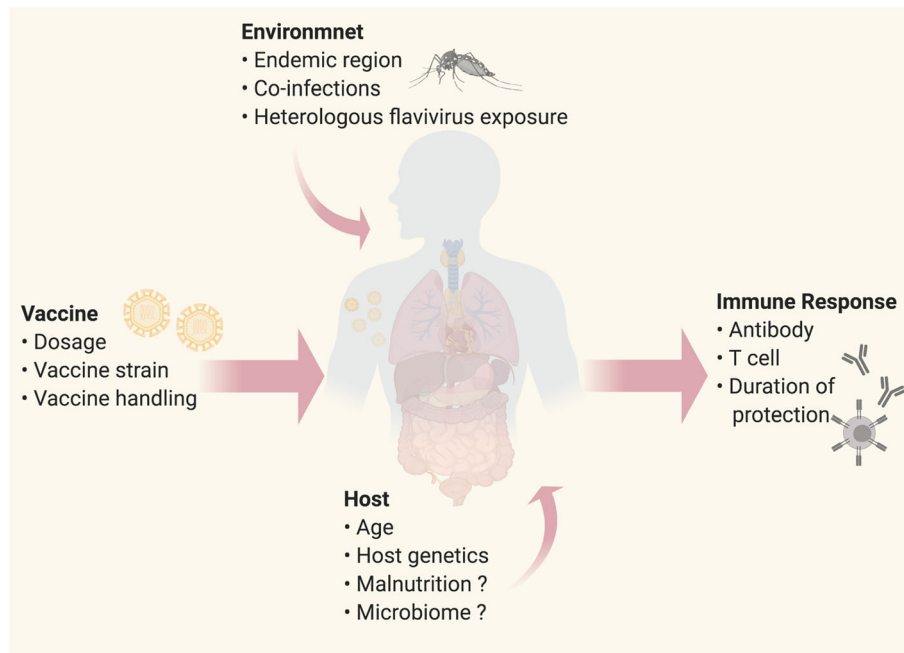
Fig. 2. Determinants of yellow fever live-attenuated vaccine immunity. Schematic diagram illustrating different elements of the YF vaccine (dosage, vaccine strain, vaccine handling, i.e., cold chain), environment (endemic vs non-endemic regions, co-infection, heterologous flavivirus exposure), and host (age, genetics, microbiome) that could influence host immune response outcome to YF vaccination. Created with BioRender.com

(98.9%) tend to exceed seroconversion rates in endemic countries (94.2%) [50]. Whether the observed difference in seroconversion rates between endemic versus non-endemic countries is due to host genetics [56], exposure to other circulating flaviviruses [1], microbiome, and additional co-infections that alter host immune response [57, 58] or host nutritional status remains to be elucidated.

Duration of immunity and the need for a booster has been highly debated in past years, with arguments for [59] and against a YF booster vaccination [60]. In controversial studies carried out in non-endemic countries, it had been reported that 17D offer long-term sero-protection lasting up to 30–40 years post vaccination [61, 62]. Therefore, in 2012, the WHO Strategic Advisory Group of Experts on immunization declared that a single dose of YF vaccine was sufficient for long-term protection in 2012 [63]. However, more recently, a substantial number of studies have highlighted that neutralizing antibody titers and cellular immunity wane with time [59, 64]. In adults, sero-positivity decreases at just 5–9 years post vaccination from 100 down to 82% [59]. This trend of waning immunity is further exaggerated at around 10-year post-vaccination with sero-protection

dropping under 80% in both endemic [59, 65] and non-endemic cohorts [64]. Furthermore, waning immunity in children vaccinated between 9 to 12 months of age is more severe with only ∼ 40% retaining long-term sero-protection (∼ 6 years post vaccination) in Brazil [54, 55] and Ghana [52••]. Surprisingly, a retrospective study in Brazil between 1973 and 2008 noted that the number of hospitalized YF cases with and without records of past YF vaccination (52% vs 45%, respectively) was not significantly different [47]. In fact, vaccination coverage of up to 95% maybe required for high risk regions to eliminate yellow fever outbreaks [66]. These disturbing observations are further evidence of waning YF vaccine immunity over time, and thus provide strong support that a YF booster vaccination is needed (i.e., a 10-year vaccination booster for travelers [67] and a 4–5 year booster for children vaccinated during their first year of life).

Following the global shortage of YF vaccine supplies in 2016, in an effort to maximize vaccination coverage and to curtail the epidemics in Angola and DRC, public health officials proceeded to conduct fractional dosing of the remaining YF vaccines [68]. Studies in *Rhesus macaques* showed fractional dosing of 17D to be effective

in protecting against wildtype Asibi in a challenge model [46]. In humans, a 10-fold lower dose of YF17D provoked a similar cytokine profile, viremia, and PRNT response as a standard dose [69]. Compared to full dose, fractional dosing of YF17D stimulated similar seroconversion rates [70] that persisted for 10 months to 1 year post-vaccination [71, 72]. Long-term protection was observed in 98% of patients receiving a fractional dose in a non-endemic setting [73], while only 85% of recipients in an endemic region maintained lasting immunity [74]. Overall, the decision to use a fractional dosing in an outbreak setting was supported by the prediction that during the 2016 YF epidemic in Angola, a lack of fractional dosing would have led to a 5.1-fold increase in mortality due to YF [28]. However, our understanding of the effect of fractional dosing on waning immunity, on vaccine shelf-life, on the antibody responses in different age groups and genetic backgrounds, is limited [68]. Hence, it is imperative that we continue to improve our evidence base to understand the effect of YF vaccine dose-fractionation on protection against YFV infections.

The role of T cell immunity in yellow fever vaccination remains unclear. Not surprisingly, YF vaccination induces strong CD4$^+$ and CD8$^+$ T cell responses, which persists for several years following vaccination [55, 75]. CD4$^+$ T cell expansion occurs earlier and with a greater magnitude after vaccination than CD8$^+$ T cells [62, 75–77]. Epidemiological evidence show that seroconversion rates drop and immunity wanes rapidly following YF vaccination of HIV-positive patients, whose CD4$^+$ T cell response is impaired [78]. While these studies suggest that T cells contribute to maintenance of seroprotection and flaviviral clearance, it is likely that T cell immunity alone is insufficient to confer protection [47]. Furthermore, immunization with the chimeric flavivirus vaccine on a YF17D backbone of non-structural proteins did not offer protection when challenged with YFV [79]. On the other hand, passive transfer of antibodies was sufficient for protection against wildtype infection [44, 46].

Therefore, it is likely that although both B and T cells play a role in establishing viral clearance, antibody responses play a more dominant role in eliciting YF vaccine-induced protection.

In terms of vaccine safety, YF vaccination has been associated with several rare but related adverse events (AEs) particularly in the elderly (≥ 60 years old) [80–82]. Vaccine-associated neurotropic disease (YFV-AND) causes neurological complications that are typically not fatal. However, vaccine-associated viscerotropic disease (YFV-AVD) results in infection that resembles natural YF disease accompanied by a high fatality rate. Virus isolated from YFV-AVD patients does not have any mutations in the 17D genome [83, 84]; thus, the driver of YFV-AVD remains unknown. AEs tend to be reported more frequently in non-endemic countries, possibly as result of under-reporting in endemic countries [47]. Additionally, host genetics [56], egg allergies (due to the manufacturing process) [80], and an active immune environment [58] have been linked with disease outcome and could contribute to frequency of adverse events experience by different populations. At the same time, YF vaccines unknowingly administered to pregnant women were immunogenic and elicited varying degrees of sero-protection without harming or transplacentally infecting the fetus, illustrating the safety profile of YF vaccines during pregnancy [85, 86]. Therefore, given the low incidence of AEs in high risk areas, and the large risk of mortality associated with YF infections, the threat from wildtype YFV infections outweighs that from YF vaccine-associated AEs [80].

The EYE's initiative aims to eliminate YF through vaccination of 1 billion people living in at-risk areas by 2026. Unfortunately, these efforts have been thwarted by vaccine shortages. The ambitious EYEs initiative assumes that a single dose confers life-long immunity, yet as discussed above, this is likely not the case. It is estimated that 90 million doses of the 17D vaccine are needed every year. Due to the slow, tedious, and low-yielding process of manufacturing YF vaccine doses in chicken embryos [1], the production capability is limited and unable to meet increased demands during an outbreak or booster vaccination campaigns. Efforts are being made to develop new vaccines with higher yields and increased safety profiles [87–90]. The most promising is a cell culture (Vero cell)-based production of an inactivated YFV vaccine [91]. The inactivated vaccine showed promising results in clinical trials [91], but was less immunogenic than the live-attenuated YF vaccines and required a two-dose schedule with an adjuvant. Ideally, a new cell culture method for YF17D that

increases yields and cuts production time, while maintaining efficacy, genomic stability, and safety, would be required to meet the world's growing demands for the vaccine.

Possible Role for Therapeutics in YF Control?

There are no approved therapeutics against YFV infections and treatment of YF disease is reliant on supportive care to alleviate disease symptoms. Although its initial clinical presentation may be benign, 15% of symptomatic patients can rapidly progress to severe yellow fever that requires intensive care support [92]. This includes the prophylactic use of anti-convulsant drugs to reduce the frequency of seizures, and use of intravenous proton pump inhibitors to treat gastric bleeding [93]. While there are licensed YF vaccines, as discussed above, mass immunization programs have been hampered by global vaccine shortages. Against this backdrop, an effective antiviral against YFV could be used as a treatment (to significantly improve the clinical outlook for patients with severe YF) and also as an outbreak control strategy (i.e., as a prophylaxis when YF vaccine is in short supply).

Drug repurposing has been adopted as a strategy for identifying de-risked compounds that have demonstrated safety profile in preclinical models or humans, with potential time saved for drug development [94]. Although there are currently no approved antivirals for the treatment or prevention of YF, there are several repurposed candidates in the drug development pipeline. Galidesivir and Sofosbuvir are both nucleoside analogue antivirals originally used to treat chronic hepatitis C infections, which have emerged as promising antivirals for the treatment of YF [95, 96]. Both Galidesivir and Sofosbuvir were found to inhibit YF replication in vitro and in vivo in rodent animal models [97, 98]. Interestingly, therapeutic administration of Galidesivir allowed development of neutralizing antibodies against YFV that completely protected against secondary YFV challenge, highlighting that the use of these drugs will not hamper development of adaptive immunity [97]. Following completion of Phase IA clinical trial to evaluate safety and tolerability of intravenous Galidesivir in healthy volunteers, a Phase IB study that aims to evaluate antiviral effects of intravenous Galidesivir in YF patients is currently ongoing (clinicaltrials. gov NCT03891420). Recently, two YFV-infected patients presenting with acute liver failure were treated off-label with Sofosbuvir for a week as compassionate use and displayed marked reduction in viremia and improved liver function [99]. Furthermore, in recent years, virus-neutralizing monoclonal antibodies (mAbs) have also been recognized as a treatment modality for YF [100]. The candidate that is most advanced in clinical development is TY014, which has currently completed Phase 1A/1B safety trials (clinicaltrials.gov NCT03776786). As antivirals against YFV become licensed for use in patients and travelers, it is hoped that these will contribute to both treatment of YF disease and the control of YF outbreaks.

Concluding Remarks

The re-emergence of outbreaks in low-risk areas and importation of cases to Asia indicate the rapidly changing epidemiology of YF. As part of epidemic preparedness, efforts should be directed at enhancing YF surveillance, diagnostic capabilities of laboratories and improving vaccine coverage, even in low endemic regions. While the live-attenuated YF vaccine is highly efficacious, vaccine supply shortfalls due to limited production suggest that the development of new vaccines and improved manufacturing technologies will be urgently needed to meet increased worldwide demand. Lastly, a two-pronged approach that combines vaccination and therapeutic interventions will be paramount to prevent the re-emergence of future YF outbreaks.

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