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Vaccine Strategies for Yellow Fever: Current Status and Future Directions

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Abstract This study explores the current status and future directions of yellow fever vaccines. Despite the availability of an effective live attenuated vaccine, challenges such as vaccine shortages, rare adverse reactions, and insufficient vaccination coverage remain major obstacles to controlling yellow fever. This study reviews the advantages and disadvantages of live attenuated vaccines, inactivated vaccines, and emerging DNA and RNA vaccines, highlighting the potential of nanoparticle and Virus-Like Particle (VLP) platforms. An analysis of recent vaccination efforts in Nigeria and other yellow fever-endemic regions underscores the importance of integrating vaccination with vector control strategies. To address these challenges, the article suggests enhancing vaccine production capacity, developing safer next-generation vaccines, and improving vaccination rates through public education and policy support. This study also points out that future research should focus on the long-term efficacy of fractional-dose vaccines and the development of multivalent vaccines to address the threat of multiple arboviruses.

Keywords Yellow fever vaccine; Live attenuated vaccine; DNA vaccine; RNA vaccine; Nanoparticle vaccine

1 Introduction

Yellow Fever (YF) is a vector-borne viral disease that remains a significant threat in many parts of the world, particularly in Africa and South America. Despite the availability of an effective vaccine for over 70 years, YF outbreaks continue to occur, influenced by factors such as vaccine coverage, environmental conditions, and socio-political changes. Understanding the dynamics of YF and developing effective vaccination strategies are essential for controlling and ultimately eliminating this disease.

Yellow fever is caused by the Yellow Fever Virus (YFV), a flavivirus transmitted primarily by Aedes mosquitoes. It is endemic to tropical regions of Africa and South America, with recent outbreaks highlighting its re-emergence as a public health threat. The disease manifests as an acute febrile illness that can progress to severe forms with high mortality rates due to liver failure, hemorrhaging, and multi-organ dysfunction (Chen and Wilson, 2020). Recent studies have shown that the risk of YF outbreaks is closely tied to factors like mosquito population dynamics, human movement, and climate variability (Faria et al., 2018). Yellow fever has a significant public health impact, with estimates suggesting thousands of deaths annually due to outbreaks in areas with insufficient vaccination coverage. The World Health Organization's Eliminate Yellow Fever Epidemics (EYE) strategy, launched in 2017, aims to mitigate these risks through targeted vaccination campaigns, surveillance, and rapid response strategies (Jean et al., 2020).

The development of the YF vaccine represents a milestone in virology and vaccinology. The 17D live-attenuated vaccine, developed in the 1930s, remains one of the most effective vaccines, offering lifelong immunity with a single dose (Hansen and Barrett, 2021). Despite its efficacy, the availability of the vaccine has been a persistent issue, particularly during outbreaks when demand surges. The 2016-2018 outbreaks highlighted challenges in vaccine supply and led to the use of fractional dosing strategies to extend vaccine stocks, which have been shown to maintain immunogenicity (Nnaji et al., 2019).

This study seeks to explore and assess current strategies for yellow fever vaccination, including fractional dosing and mass vaccination campaigns, evaluate their effectiveness in different epidemiological contexts, review

challenges in vaccine supply and innovations in development, and identify future directions for optimizing global YF control efforts, with a particular focus on initiatives like the EYE strategy to mitigate outbreak risks and meet the needs of at-risk populations.

2 Current Vaccine Strategies for Yellow Fever

Yellow Fever (YF) remains a critical public health issue in many tropical regions, and vaccination is the primary method for preventing outbreaks. Various vaccination strategies, including live-attenuated, inactivated, recombinant, and vector-based approaches, have been developed and evaluated over the years. Each of these strategies has distinct mechanisms, benefits, and challenges. This section delves into these strategies and explores their role in current and future yellow fever control efforts.

2.1 Live-attenuated vaccines: mechanism and effectiveness

The 17D live-attenuated yellow fever vaccine is considered the gold standard for YF prevention and has been in use since its development in the 1930s. This vaccine is derived from an attenuated strain of the yellow fever virus, which has been modified to reduce its virulence while retaining its ability to elicit a robust immune response. The mechanism behind its effectiveness lies in its ability to mimic a natural infection, leading to the activation of both the humoral and cellular arms of the immune system. Upon administration, the vaccine stimulates the production of high titers of neutralizing antibodies, providing immunity that is often lifelong after a single dose (Beck and Barrett, 2015).

One of the primary advantages of the 17D vaccine is its long-term efficacy, which has been shown to last for decades in most vaccinated individuals. The World Health Organization (WHO) has recommended a single dose of the vaccine as sufficient for lifelong protection, a significant benefit for resource-limited settings where booster programs may be challenging to implement (Chen and Wilson, 2020). However, the 17D vaccine is not without risks. Rare but severe adverse events, such as Yellow Fever Vaccine-Associated Viscerotropic Disease (YEL-AVD) and Neurotropic Disease (YEL-AND), have been reported, particularly in older adults, immunocompromised individuals, and those with thymus disorders (Wang et al., 2022).

The need to mitigate these risks has spurred research into alternative formulations and delivery methods, such as fractional dosing, which has been employed during vaccine shortages. Fractional doses, which are smaller than the standard dose, have been shown to elicit similar immune responses, thus providing a temporary solution during periods of high demand (Nnaji et al., 2019). Nevertheless, the live-attenuated 17D vaccine remains the cornerstone of YF prevention, with ongoing efforts to enhance its safety profile and ensure adequate supply.

2.2 Inactivated vaccines: development and limitations

Inactivated yellow fever vaccines present an alternative approach aimed at overcoming the limitations associated with live-attenuated vaccines, particularly concerning safety. These vaccines use a killed form of the virus, which means they cannot replicate in the host, making them safer for use in immunocompromised individuals and those with contraindications to live vaccines. The development process involves cultivating the yellow fever virus in Vero cells, followed by inactivation using agents such as β-propiolactone. This approach ensures that the vaccine retains its immunogenic components while eliminating its ability to cause disease (Yang, 2024).

Recent studies have demonstrated that inactivated vaccines can induce robust immune responses, with high levels of neutralizing antibodies in animal models, comparable to those elicited by live-attenuated vaccines (Bassi et al., 2016). For instance, research using inactivated YF vaccines in mice has shown promising results, suggesting that these vaccines could provide an effective alternative to the 17D vaccine in populations where live vaccines pose a higher risk.

However, inactivated vaccines also have their limitations. They often require multiple doses or booster shots to achieve and maintain sufficient immunity, which can be challenging in regions with limited access to healthcare services. Additionally, the production process for inactivated vaccines can be more complex and expensive, which may hinder their widespread use, especially in low-income countries where yellow fever is endemic. Despite these

challenges, ongoing research is focused on optimizing inactivation methods and adjuvant formulations to enhance the efficacy and durability of the immune response, making inactivated vaccines a viable option for future yellow fever control efforts.

2.3 Recombinant and subunit vaccines: emerging approaches

Recombinant and subunit vaccines represent a newer generation of vaccines that offer several advantages over traditional methods, particularly in terms of safety and production scalability. These vaccines utilize specific proteins or antigens from the yellow fever virus to stimulate an immune response without the need for a live virus. A notable example is the use of the yellow fever virus envelope protein (YFE), which has been expressed in plant systems like Nicotiana benthamiana. This approach has shown the potential to induce strong virus-neutralizing antibody responses in preclinical studies involving mice and non-human primates (Tottey et al., 2017; Shou and Cai, 2024).

One key advantage of recombinant and subunit vaccines is their safety profile, as they do not contain live components and thus eliminate the risk of vaccine-induced disease. This makes them particularly suitable for use in populations that are more vulnerable to the adverse effects of live vaccines, such as the elderly, pregnant women, and immunocompromised individuals. Additionally, production using recombinant technology can be scaled more easily than traditional egg-based methods, making it a promising solution for meeting global demand during outbreaks.

Despite these benefits, recombinant and subunit vaccines for yellow fever are still largely in the experimental stage, and their immunogenicity tends to be lower compared to live-attenuated vaccines. This often necessitates the use of adjuvants to boost the immune response, which can add complexity to vaccine formulations. Moreover, ensuring that these vaccines elicit a balanced immune response capable of providing durable protection remains a critical challenge. Ongoing research aims to address these issues, with a focus on improving the stability and potency of recombinant vaccines, making them a potential candidate for widespread use in the future.

2.4 Vector-based vaccines: novel concepts and preclinical research

Vector-based vaccines use a viral or bacterial vector to deliver yellow fever antigens into the host cells, where they stimulate an immune response. This strategy is particularly appealing because it can combine the strong immunogenicity of live vaccines with the safety profile of non-replicating systems. Modified vaccinia virus Ankara (MVA) and replication-deficient adenoviruses are among the most promising platforms for vector-based yellow fever vaccines. These vectors can be engineered to express yellow fever virus antigens, leading to the production of neutralizing antibodies and T-cell responses similar to those seen with live-attenuated vaccines (Bassi et al., 2016).

The MVA-based yellow fever vaccine, for example, has been shown to generate a protective immune response in animal models, with levels of neutralizing antibodies comparable to those induced by the 17D vaccine. This vector-based vaccine also demonstrated improved safety, with no replication in the host, making it a potentially safer alternative for those at higher risk of adverse reactions to live vaccines (Julander et al., 2018).

Additionally, vector-based vaccines allow for rapid development and production, which is crucial during sudden outbreaks when time is of the essence. The flexibility of vector-based systems also opens up possibilities for creating combination vaccines that protect against multiple pathogens, potentially providing a broader public health benefit. However, the development of vector-based vaccines faces challenges, such as pre-existing immunity to the vector itself, which can reduce the vaccine's effectiveness. Addressing these challenges through the use of novel vector systems and exploring non-viral delivery methods are active areas of research, positioning vector-based vaccines as a promising direction for future yellow fever vaccination strategies.

3 Challenges and Limitations in Yellow Fever Vaccination

Yellow fever (YF) vaccination has proven to be an effective tool in controlling outbreaks and preventing the spread of this potentially deadly disease. However, several challenges persist, including vaccine shortages, safety

concerns related to adverse reactions, and issues with achieving sufficient population coverage. These challenges impact the overall efficacy of vaccination programs, especially in endemic regions of Africa and South America.

3.1 Vaccine shortages and distribution issues

Vaccine shortages have been a recurring issue in yellow fever control, often exacerbated during large-scale outbreaks. A notable example is the 2016 yellow fever outbreak in Angola and the Democratic Republic of Congo, where a global shortage of the 17D-204 yellow fever vaccine necessitated the use of fractional dosing strategies. This involved administering smaller doses to stretch limited supplies, which, although effective, raised concerns about the duration of immunity provided by these doses (Nnaji et al., 2019). Fractional dosing was used in a preemptive campaign in Kinshasa, resulting in high rates of seroconversion, suggesting that this approach could be a viable stop-gap solution during supply crises (Ahuka-Mundeke et al., 2018).

The shortage issue is often compounded by manufacturing difficulties, as the production of the yellow fever vaccine relies on specialized egg-based technology, which limits the rapid scale-up of production. During the 2017 shortage in the United States, the importation of STAMARIL® under an expanded access investigational new drug protocol provided an alternative, but this solution required coordinated efforts between regulatory bodies and limited distribution sites (Gershman et al., 2017). The reliance on a single manufacturer for vaccine production further exacerbates supply vulnerabilities, emphasizing the need for diversified manufacturing sources and investments in new vaccine production technologies, such as cell culture-based methods.

3.2 Adverse reactions and safety concerns

While the 17D yellow fever vaccine is highly effective, its administration is not without risks. Serious Adverse Events (SAEs), although rare, have been a significant concern, especially in certain populations. Yellow Fever Vaccine-Associated Viscerotropic Disease (YEL-AVD) and yellow fever vaccine-associated neurotropic disease (YEL-AND) are two of the most severe reactions that can occur post-vaccination, characterized by multi-organ failure and neurological complications, respectively (Rojas et al., 2023). These reactions tend to be more common in individuals over the age of 60 and those with compromised immune systems, such as those receiving immunosuppressive therapy or with underlying autoimmune conditions (Croce et al., 2017).

Safety surveillance during emergency vaccine importation programs, such as the introduction of STAMARIL® in the United States, has been crucial for monitoring these risks. A study of STAMARIL® administration during the U.S. vaccine shortage found a very low incidence of SAEs, consistent with previous safety profiles of the vaccine, with reported adverse events mainly including mild reactions such as fever and localized pain at the injection site (Rojas et al., 2023). Despite these low rates, the potential for severe reactions necessitates a careful risk-benefit analysis for vaccination, especially in non-endemic regions where the risk of exposure is lower.

Efforts are ongoing to develop safer alternatives, such as inactivated or recombinant yellow fever vaccines, which could reduce the risk of these severe adverse reactions. However, these alternatives are still in experimental stages and have not yet replaced the widespread use of the 17D vaccine in routine immunization programs.

3.3 Population coverage and immunization gaps

Achieving adequate immunization coverage is critical for controlling yellow fever outbreaks, yet many endemic regions face significant immunization gaps. These gaps are often due to logistical challenges, such as difficult-to-reach populations, inadequate healthcare infrastructure, and fluctuating political stability, which can hinder vaccination campaigns. A systematic review highlighted that mass vaccination campaigns have been effective in increasing coverage in some regions, but coverage often falls short of the levels needed to achieve herd immunity, particularly in rural and isolated areas (Jean et al., 2020).

Immunization gaps are further exacerbated by vaccine hesitancy and misinformation, which can reduce community acceptance of vaccination programs. For example, misinformation about vaccine safety has been shown to decrease uptake, even in areas where the risk of yellow fever transmission is high. Addressing these challenges requires targeted communication strategies and community engagement to build trust in the vaccination process and address concerns about vaccine safety.

Additionally, global vaccination strategies like the World Health Organization's Eliminate Yellow Fever Epidemics (EYE) strategy aim to close these gaps by focusing on high-risk populations and improving vaccine accessibility. This strategy involves coordinated efforts to stockpile vaccines, increase the number of trained healthcare workers, and implement robust surveillance systems to quickly detect and respond to outbreaks (Mokaya et al., 2021). Despite these efforts, achieving the target of protecting 1 billion people by 2026 requires sustained commitment and resources, highlighting the need for international collaboration to bridge remaining immunization gaps and ensure global preparedness.

4 Case Study

The Yellow Fever (YF) outbreak in Nigeria between 2017 and 2022 represents a critical example of the challenges and successes in managing YF through vaccination strategies. Despite the availability of an effective vaccine, Nigeria faced recurrent outbreaks, revealing gaps in immunization coverage, challenges in rapid response, and the need for booster doses to maintain immunity. This section explores the dynamics of the outbreak, evaluates the impact of vaccination campaigns, discusses changes in immunization policy, and considers the role of long-term immunity in YF management.

4.1 Case analysis: yellow fever outbreak in nigeria (2017-2022)

The resurgence of yellow fever in Nigeria, starting in 2017, marked a significant public health crisis, with outbreaks affecting all 36 states. The initial case in September 2017 ended a 21-year period with no confirmed YF cases in Nigeria. Factors contributing to this resurgence included low routine vaccination coverage, poor vector control, and environmental conditions conducive to Aedes mosquito proliferation, which is responsible for transmitting the yellow fever virus (YFV) (Figure 1) (Nomhwange et al., 2020). Between 2017 and 2019, Nigeria reported 7 894 suspected cases, with 287 laboratory-confirmed infections and a case fatality rate of 2.7%. The outbreaks were most severe in Kwara, Kogi, Edo, Ebonyi, and Bauchi states, which became major epicenters of transmission.

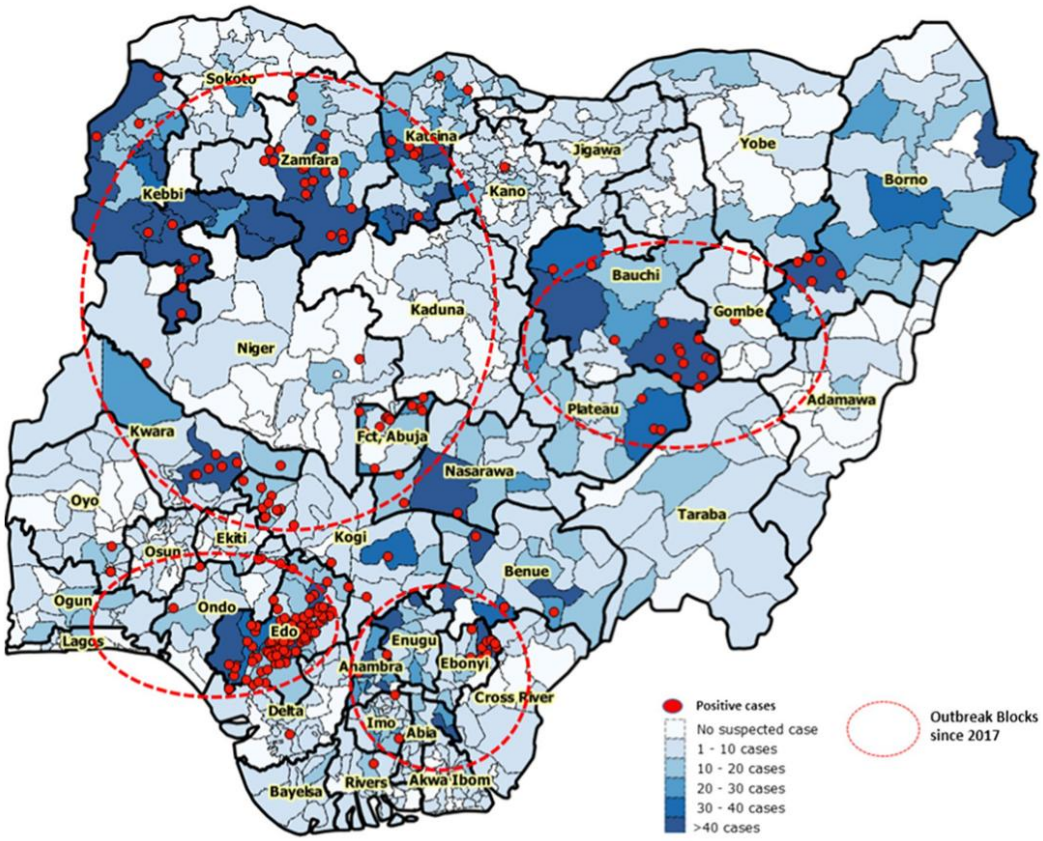

Figure 1 Bar chart showing average duration for various phases of the yellow fever detection and response by year and ICG application 2017-2019 (Adopted from Nomhwange et al., 2020)

The epidemic was characterized by a delayed response in some areas, with emergency vaccination campaigns initiated only after the disease had spread significantly. The average response time ranged from 15 to 132 days, indicating room for improvement in surveillance and rapid response measures (Umar et al., 2020). This delay was particularly problematic in rural and remote regions, where access to healthcare services is limited, and local vaccination coverage was low. As a result, the outbreak underscored the need for stronger health infrastructure and more efficient coordination in public health response efforts.

4.2 Vaccination campaigns: recent successes and challenges

In response to the outbreak, Nigeria implemented a series of mass vaccination campaigns, which were critical in controlling the spread of the virus. The campaigns, supported by the International Coordinating Group (ICG) on Vaccine Provision, targeted populations under 45 years of age, with over 45 million individuals vaccinated between 2017 and 2019. These efforts contributed to a decline in cases by boosting population immunity, particularly in high-risk areas. However, challenges persisted, including logistical barriers, vaccine shortages, and vaccine hesitancy among certain communities.

One major challenge was the implementation of fractional-dose vaccination during periods of vaccine shortage. This approach allowed a larger population to receive some level of protection but raised concerns about the duration of immunity provided by smaller doses (Ahuka-Mundeke et al., 2018). Furthermore, the COVID-19 pandemic disrupted routine immunization services, exacerbating the risk of YF spread due to delayed catch-up campaigns and reduced vaccination rates during the pandemic lockdowns (Gaythorpe et al., 2021). Despite these setbacks, the success of reactive vaccination efforts in slowing the outbreak demonstrated the importance of rapid deployment and mass immunization campaigns in outbreak settings.

4.3 Impact on immunization policy

The recurring YF outbreaks in Nigeria prompted significant changes in immunization policies at the national and regional levels. The outbreak response emphasized the need for integrating yellow fever vaccination into routine immunization schedules, particularly for children under the Expanded Programme on Immunization (EPI). This change aimed to increase the baseline immunity in younger populations and prevent future outbreaks (Jean et al., 2020).

Moreover, the outbreak accelerated the implementation of the World Health Organization's Eliminate Yellow Fever Epidemics (EYE) strategy in Nigeria, which focuses on increasing vaccination coverage, improving surveillance systems, and ensuring rapid response capabilities. The EYE strategy aims to prevent future outbreaks through preemptive vaccination campaigns targeting at-risk populations before the occurrence of cases (Adogo and Ogoh, 2019). Additionally, the integration of yellow fever vaccination into broader health programs allowed for a more comprehensive approach to managing the disease, combining vaccination with vector control and health education initiatives to reduce transmission.

4.4 Long-term immunity and the role of booster doses

The yellow fever vaccination campaign in Nigeria highlighted debates about the duration of immunity provided by a single dose of the 17D vaccine, especially in populations vaccinated during infancy. While the World Health Organization (WHO) currently endorses a single dose for lifelong immunity, emerging evidence suggests that immunity can wane, particularly in children vaccinated at nine months of age (Domingo et al., 2019). Studies in West African populations, including Ghana and Mali, have shown that seropositivity rates decline significantly within 6 years post-vaccination, raising concerns about the adequacy of a single-dose strategy in endemic regions.

This decline in immunity has led to discussions on the potential need for booster doses, particularly for individuals at higher risk, such as those living in endemic areas or healthcare workers with frequent exposure to the virus (Vasconcelos and Barrett, 2019). Additionally, research in Nigeria indicates that a considerable proportion of adults might require a booster dose to maintain protective immunity, especially considering that natural exposure to the virus can be unpredictable and variable across different regions (Campi-Azevedo et al., 2019). As a result,

Nigeria's experience has underscored the importance of continuous monitoring of immunity levels among vaccinated populations to inform policy decisions about the potential need for booster doses.

5 Innovative Approaches in Yellow Fever Vaccine Development

With the persistence of Yellow Fever (YF) outbreaks and challenges related to traditional vaccine production and administration, new vaccine platforms are being explored to provide safer, more efficient, and scalable immunization solutions. These innovative approaches include DNA and RNA-based vaccines, nanoparticle and Virus-Like Particle (VLP) platforms, and multivalent vaccines that could potentially integrate protection against multiple flaviviruses.

5.1 DNA and RNA-based vaccines: advantages and potential

DNA and RNA-based vaccines represent a significant advancement in the field of vaccinology, offering the potential for rapid development and production. Unlike traditional vaccines that rely on cultivating live or inactivated viruses, DNA and RNA vaccines utilize genetic material that encodes for antigens, allowing cells in the body to produce these antigens and trigger an immune response. This approach offers a flexible platform that can be adapted quickly to emerging variants or pathogens. DNA-launched vaccines, for example, have been investigated for yellow fever, demonstrating the ability to induce specific immune responses by using plasmid DNA encoding the full-length yellow fever virus RNA. This technology enables the replication of the viral RNA in vivo, initiating a controlled immune response.

RNA-based vaccines, particularly mRNA vaccines, have gained attention due to their role in the COVID-19 pandemic, highlighting their capacity for rapid production and high efficacy. For yellow fever, the potential of RNA vaccines lies in their ability to produce strong humoral and cellular immunity with a lower risk of reversion to virulence compared to live-attenuated vaccines. This platform could be especially valuable in addressing vaccine shortages during outbreaks, as it can be scaled up faster than traditional egg-based production systems (Oreshkova et al., 2021).

While promising, DNA and RNA vaccines face challenges such as the need for advanced storage conditions (especially for mRNA vaccines) and the requirement for delivery systems that enhance cellular uptake. Electroporation is commonly used to improve DNA vaccine uptake, but its scalability and application in low-resource settings remain to be addressed.

5.2 Nanoparticle and virus-like particle (VLP) vaccine platforms

Nanoparticles and VLPs have emerged as versatile platforms for the development of safe and effective vaccines. VLPs are non-infectious, self-assembling structures that mimic the outer structure of viruses without containing their genetic material. This characteristic allows VLPs to stimulate strong immune responses while avoiding the risks associated with live virus vaccines. For yellow fever, VLP-based approaches have shown potential, particularly through the production of yellow fever VLPs using recombinant expression systems. Recent studies have demonstrated that purified yellow fever VLPs can be produced with high yields and retain structural integrity, making them suitable for use as vaccines (Lima et al., 2019).

VLPs have also been explored in combination with novel adjuvant systems, such as nanoparticle-encapsulated Toll-like receptor (TLR) ligands, which can enhance the immune response by activating innate immune pathways (Kasturi et al., 2016). This approach has been shown to produce robust and durable immune responses, offering a promising route for long-lasting immunity with fewer doses. Nanoparticle-based platforms also provide the advantage of protecting vaccine components from degradation and improving delivery to target cells, making them an attractive option for future yellow fever vaccines (Dekevic et al., 2023).

5.3 Multivalent vaccines: integrating yellow fever with other flavivirus vaccines

Given the co-circulation of several flaviviruses, such as dengue, Zika, and Japanese encephalitis, in many regions, there is growing interest in developing multivalent vaccines that can offer protection against multiple flaviviruses simultaneously. Multivalent vaccines can potentially simplify immunization schedules and improve coverage,

especially in regions with overlapping flavivirus transmission. This approach is particularly relevant for yellow fever-endemic areas where the population is also at risk for other flavivirus infections.

One promising approach involves using virus replicon particles that can express antigens from multiple flaviviruses. For example, a study utilized a replicon system derived from Venezuelan equine encephalitis virus (VEEV) to express antigens from yellow fever and other flaviviruses, achieving cross-protective immune responses in animal models (Petrov et al., 2015). Another strategy involves chimeric constructs, where genetic elements of the yellow fever virus are combined with those of other flaviviruses to create a single vaccine that can induce immunity against multiple targets. The comparison of different immunization strategies demonstrated the IgG and neutralizing antibody (NtAb) responses to homologous and heterologous DENV serotypes following the use of the DENV-2 RD vaccine. The homologous DENV-2 antibody titers using the RD DNA-VLP combination were significantly higher than those of other combinations and also showed a significant advantage in cross-reactive IgG responses to DENV-3 (Figure 2) (Galula et al., 2018). This approach has been explored with chimeric yellow fever-dengue constructs, offering insights into the potential for broad-spectrum protection.

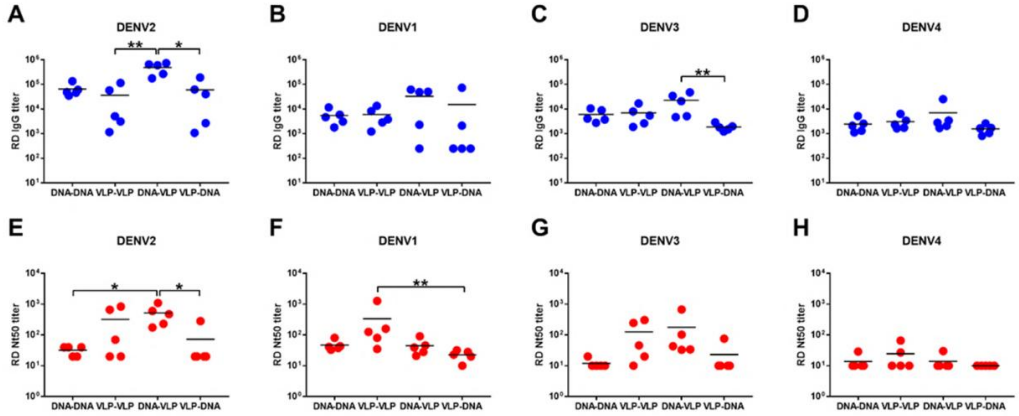

Figure 2 DENV-specific antibody responses induced by CRR DENV-2 RD vaccine using various prime-boost immunization strategies (Adopted from Galula et al., 2018)

The development of multivalent vaccines poses challenges, such as ensuring balanced immune responses to each component of the vaccine and avoiding the risk of antibody-dependent enhancement (ADE), a phenomenon where non-neutralizing antibodies enhance viral entry into host cells. Nevertheless, the potential to protect against multiple diseases with a single immunization makes multivalent vaccines a promising frontier in the fight against flavivirus-related diseases.

6 Future Directions and Research Priorities

Yellow fever (YF) continues to pose a significant challenge to global health, despite the availability of a highly effective live-attenuated vaccine. Future efforts must focus on improving vaccine production and accessibility, enhancing vaccine safety through next-generation formulations, integrating vaccination with other control measures, and addressing vaccine hesitancy through effective public education and policy strategies. These priorities are essential to achieving the goals of the World Health Organization's Eliminate Yellow Fever Epidemics (EYE) initiative.

6.1 Strategies for improving vaccine production and accessibility

The supply of yellow fever vaccines has historically struggled to meet global demand, especially during large outbreaks. One major issue is that the production process for the 17D vaccine relies on pathogen-free embryonated eggs, a method that is time-consuming and difficult to scale up rapidly during emergencies. Innovative approaches such as cell-culture-based production and the use of advanced bioreactor systems for Virus-Like Particle (VLP) production have shown promise in increasing scalability and reducing production time (Alvim et al., 2021).

Fractional dosing strategies, where smaller doses of the vaccine are used to extend supply, have also been employed successfully in emergency settings, such as the 2016 outbreak in Angola and the Democratic Republic of Congo. Studies have shown that fractional doses can maintain high levels of seroconversion, making this a viable stop-gap solution during vaccine shortages (Nnaji et al., 2019). However, more research is needed to understand the long-term efficacy of fractional dosing and its applicability for routine immunization.

6.2 Enhancing vaccine safety through next-generation formulations

While the 17D live-attenuated vaccine is effective, rare severe adverse reactions such as viscerotropic disease have prompted the need for safer alternatives. Next-generation formulations, including inactivated vaccines and recombinant subunit vaccines, are being developed to mitigate these risks. For example, inactivated vaccines grown in Vero cells have demonstrated safety and efficacy in animal models, providing a potential alternative for immunocompromised individuals (Pereira et al., 2015).

Additionally, DNA and RNA vaccine platforms are being explored for yellow fever, capitalizing on their ability to generate immune responses without the risks associated with live virus replication. These platforms can also be adapted quickly to emerging strains or new variants, making them a flexible option for future vaccine development. As these technologies advance, they offer a pathway to safer vaccines that can be rapidly deployed during outbreaks.

6.3 Integrating vaccination with other control measures (e.g., vector control)

Successful control of yellow fever requires a comprehensive approach that goes beyond vaccination alone. Integrating vaccination campaigns with vector control strategies is crucial, especially in areas where Aedes mosquitoes are abundant. Traditional methods such as insecticide spraying and the use of bed nets have been complemented by novel approaches, including the release of genetically modified mosquitoes designed to reduce mosquito populations and inhibit virus transmission (Silva et al., 2018).

The EYE strategy has also emphasized the importance of enhanced surveillance systems that can detect and respond to outbreaks quickly. By combining vaccination efforts with early detection and rapid vector control measures, the spread of yellow fever can be curtailed more effectively. Such integrated approaches are essential for protecting populations in high-risk areas and preventing cross-border transmission during outbreaks.

6.4 Addressing vaccine hesitancy: public education and policy strategies

Vaccine hesitancy remains a significant barrier to achieving high immunization coverage for yellow fever, particularly in communities that have low trust in health systems or where misinformation about vaccines is prevalent. Public education campaigns that address concerns and provide clear information about the safety and efficacy of the yellow fever vaccine are crucial for increasing uptake (Chen and Wilson, 2020).

Policy strategies that support mandatory vaccination in high-risk areas, such as requiring proof of vaccination for travelers to endemic regions, have also been effective in increasing coverage. Moreover, community engagement initiatives that involve local leaders and healthcare workers can help build trust and acceptance of vaccination programs. Addressing these social and cultural factors is key to ensuring that yellow fever vaccination campaigns reach all vulnerable populations and achieve their intended impact.

7 Concluding Remarks

Yellow Fever (YF) remains a critical global health challenge, particularly in endemic regions of Africa and South America. Despite the availability of a highly effective vaccine, the persistence of outbreaks and evolving epidemiological patterns necessitate ongoing innovation in vaccination strategies and public health approaches. This section summarizes key findings, explores their implications for policy and public health, and outlines recommendations for future research. The analysis of current yellow fever vaccination strategies highlights the effectiveness of the live-attenuated 17D vaccine, which continues to provide long-lasting immunity in most individuals. However, rare adverse events such as yellow fever vaccine-associated viscerotropic and neurotropic disease have driven the exploration of safer alternatives. Innovations such as fractional dosing, which has proven

effective during vaccine shortages, and next-generation formulations like DNA and RNA-based vaccines are being developed to address these concerns. Notably, fractional dosing strategies have been instrumental in managing vaccine shortages, as seen during the 2016 outbreaks in Angola and the Democratic Republic of Congo. Studies have demonstrated that these smaller doses can maintain adequate immune responses, making fractional dosing a viable solution when vaccine supplies are limited.

The insights from these studies carry important implications for public health policy. One of the primary considerations is the need for policy adjustments that facilitate the recognition and use of fractional dosing during emergencies, which could greatly improve the speed and effectiveness of responses to yellow fever outbreaks. Furthermore, integrating vaccination campaigns with robust vector control measures has proven to be an effective strategy in containing outbreaks. This approach, emphasized in the World Health Organization's EYE (Eliminate Yellow Fever Epidemics) strategy, demonstrates the importance of combining vaccination with other interventions like enhanced surveillance and mosquito control. Additionally, addressing vaccine hesitancy through targeted community engagement is crucial for increasing vaccination coverage. Public education campaigns that clearly communicate the benefits and safety of vaccination can help build trust, particularly in communities with low trust in health systems .

Moving forward, several areas of research are critical to improving yellow fever control strategies. One priority is understanding the long-term efficacy of fractional doses. While short-term studies suggest that fractional doses maintain protective immunity, more research is needed to confirm their effectiveness over several years, especially in diverse populations. Additionally, advancing next-generation vaccines, such as mRNA-based platforms, could offer safer and more scalable options for both routine immunization and emergency responses. Moreover, further studies are needed to develop effective strategies for community engagement to address vaccine hesitancy, ensuring that vaccination efforts reach all at-risk populations and achieve the intended public health impact.

In conclusion, while significant progress has been made in controlling yellow fever through vaccination, ongoing innovation and strategic planning are essential to address existing challenges. By focusing on improving vaccine accessibility, safety, and public acceptance, and by integrating vaccination with other control measures, the global community can better manage and eventually eliminate yellow fever epidemics.

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Adogo L., and Ogoh M., 2019, Yellow fever in Nigeria: a review of the current situation, African Journal of Clinical and Experimental Microbiology, 21(1): 1-13.
https://doi.org/10.4314/ajcem.v21i1.1

Ahuka-Mundeke S., Casey R.M., Harris J.B., Dixon M.G., Nsele P.M., Kizito G.M., Staples J.E, 2018, Immunogenicity of fractional-dose vaccine during a yellow fever outbreak-preliminary report, The New England Journal of Medicine, 36: 4112-4117.
https://doi.org/10.1056/NEJMoa1710430

Alvim R., Lima T., Silva J.L., and de Oliveira G.A.P., 2021, Process intensification for the production of yellow fever virus-like particles as potential recombinant vaccine antigen, Biotechnology and Bioengineering, 118: 3581-3592.
https://doi.org/10.1002/bit.27864

Bassi M.R., Larsen M.A.B., Kongsgaard M., Rasmussen M., Buus S., Stryhn A., Thomsen A., and Christensen J.P., 2016, Vaccination with replication-deficient adenovectors encoding YF-17D antigens induces long-lasting protection from severe yellow fever virus infection in mice, PLoS Neglected Tropical Diseases, 10(2): e0004464.
https://doi.org/10.1371/journal.pntd.0004464

Beck A.S., and Barrett A., 2015, Current status and future prospects of yellow fever vaccines, Expert Review of Vaccines, 14: 1479-1492.
https://doi.org/10.1586/14760584.2015.1083430

Campi-Azevedo A.C., Reis L.R., and Peruhype-Magalhães V., 2019, Short-lived immunity after 17DD yellow fever single dose indicates that booster vaccination may be required to guarantee protective immunity in children, Frontiers in Immunology, 10: 2192.
https://doi.org/10.3389/fimmu.2019.02192

Chen L., and Wilson M., 2020, Yellow fever control: current epidemiology and vaccination strategies, Tropical Diseases, Travel Medicine and Vaccines, 6(1): 1.
https://doi.org/10.1186/s40794-020-0101-0

Croce E., Hatz C., Jonker E.F., Visser L.G., Jaeger V.K., and Bühler S., 2017, Safety of live vaccinations on immunosuppressive therapy in patients with immune-mediated inflammatory diseases, solid organ transplantation or after bone-marrow transplantation, Vaccine, 35(9): 1216-1226.
https://doi.org/10.1016/j.vaccine.2017.01.048

Dekevic G., Tertel T., Tasto L., Schmidt D., Giebel B., Czermak P., and Salzig D., 2023, A bioreactor-based yellow fever virus-like particle production process with integrated process analytical technology based on transient transfection, Viruses, 15(10): 2013.
https://doi.org/10.3390/v15102013

Domingo C., Fraissinet J., Ansah P., Kelly, C., Bhat N., Sow S.O., and Mejía J.E., 2019, Long-term immunity against yellow fever in children vaccinated during infancy: a longitudinal cohort study. The Lancet. Infectious Diseases, 19(12): 1363-1370.
https://doi.org/10.1016/S1473-3099(19)30323-8

Faria N., Kraemer M., Hill S., and Goes de Jesus J., 2018, Genomic and epidemiological monitoring of yellow fever virus transmission potential, Science, 361: 894-899.
https://doi.org/10.1126/science.aat7115

Galula J.U., Yang C.Y., Davis B.S., Chang G.J.J., and Chao D.Y., 2018, Cross-reactivity reduced dengue virus serotype 2 vaccine does not confer cross-protection against other serotypes of dengue viruses, bioRxiv, 2018: 480210.
https://doi.org/10.1101/480210

Gaythorpe K., Abbas K., Huber J.H., Karachaliou A., Thakkar N., Woodruff K., and Jit M., 2021, Impact of COVID-19-related disruptions to measles, meningococcal A, and yellow fever vaccination in 10 countries, eLife, 10: e67023.
https://doi.org/10.7554/eLife.67023

Gershman M.D., Angelo K.M., Ritchey J., Greenberg D.P., Muhammad R.D., Brunette G., Cetron M.S., and Sotir M.J., 2017, Addressing a yellow fever vaccine shortage-united states, 2016-2017, Morbidity and Mortality Weekly Report, 66: 457-459.
https://doi.org/10.15585/mmwr.mm6617e2

Hansen C.A., and Barrett A., 2021, The present and future of yellow fever vaccines, Pharmaceuticals, 14(9): 891.
https://doi.org/10.3390/ph14090891

Jean K., Hamlet A., Benzler J., Cibrelus L., Gaythorpe K.A.M., and Ferguson N., 2020, Eliminating yellow fever epidemics in Africa: vaccine demand forecast and impact modelling, PLoS Neglected Tropical Diseases, 14(5): e0008304.
https://doi.org/10.1371/journal.pntd.0008304

Julander J.G., Testori M., Cheminay C., and Volkmann A., 2018, Immunogenicity and protection after vaccination with a modified vaccinia virus Ankara-vectored yellow fever vaccine in the hamster model, Frontiers in Immunology, 9: 1756.
https://doi.org/10.3389/fimmu.2018.01756

Kasturi S.P., Kozlowski P.A., Nakaya H.I., Burger M.C., Russo P., Pham M., and Pulendran B., 2016, Adjuvanting a simian immunodeficiency virus vaccine with toll-like receptor ligands encapsulated in nanoparticles induces persistent antibody responses and enhanced protection, Journal of Virology, 91(4): e01844-16.
https://doi.org/10.1128/JVI.01844-16

Lima T., Souza M., and Castilho L., 2019, Purification of flavivirus VLPs by a two-step chromatographic process, Vaccine, 37(47): 7061-7069.
https://doi.org/10.1016/J.VACCINE.2019.05.066

Mokaya J., Kimathi D., Lambe T., and Warimwe G., 2021, What constitutes protective immunity following yellow fever vaccination? Vaccines, 9(6): 671.
https://doi.org/10.3390/vaccines9060671

Nnaji C., Shey M., Adetokunboh O., and Wiysonge C., 2019, Immunogenicity and safety of fractional dose yellow fever vaccination: a systematic review and meta-analysis, Vaccine, 38(6): 1291-1301.
https://doi.org/10.1016/j.vaccine.2019.12.018

Nomhwange T.I., Jean Baptiste A.E., Ezebilo O., Oteri J., Olajide L., Emelife K., and Tomori O., 2020, The resurgence of yellow fever outbreaks in Nigeria: a 2-year review 2017-2019, BMC Infectious Diseases, 21: 1-12.
https://doi.org/10.1186/s12879-021-06727-y

Oreshkova N., Myeni S.K., Mishra N., Albulescu I., and Kikkert M., 2021, A yellow fever 17D virus replicon-based vaccine platform for emerging coronaviruses, Vaccines, 9(12): 1492.
https://doi.org/10.3390/vaccines9121492

Pereira R.C., Silva A.M.V., O Souza M.C., and Freire M., 2015, An inactivated yellow fever 17DD vaccine cultivated in Vero cell cultures, Vaccine, 33(35): 4261-4268.
https://doi.org/10.1016/j.vaccine.2015.03.077

Petrov A., Plekhanova T.M., Sidorova O.N., Borisevich S., and Makhlay A., 2015, The vaccines based on the replicon of the *Venezuelan equine* encephalomyelitis virus against viral hemorrhagic fevers, Voprosy Virusologii, 60(3): 14-18.

Rojas A., Hachey W., Kaur G., Korejwo J., and Muhammad R., 2023, Enhanced safety surveillance of STAMARIL® yellow fever vaccine provided under the expanded access investigational new drug program in the USA, Journal of Travel Medicine, 30(7): taad037.
https://doi.org/10.1093/jtm/taad037

Shou C.J., and Cai X.P., 2024, Analysis of animal vaccine classification and current status, Journal of Vaccine Research, 14(1): 10-16.
https://doi.org/10.5376/jvr.2024.14.0002

Silva J.V.J., Lopes T.R.R., Oliveira-Filho E.F., Durães-Carvalho R., and Gil L., 2018, Current status, challenges and perspectives in the development of vaccines against yellow fever, dengue, Zika and chikungunya viruses, Acta Tropica, 182: 257-263.
https://doi.org/10.1016/j.actatropica.2018.03.009

Tottey S., Shoji Y., Jones R.M., Chichester J., Green B., Musiychuk K., and Yusibov V., 2017, Plant-produced subunit vaccine candidates against yellow fever induce virus neutralizing antibodies and confer protection against viral challenge in animal models, The American Journal of Tropical Medicine and Hygiene, 98(2): 420-431.
https://doi.org/10.4269/ajtmh.16-0293

Umar K., Anka A., Abdullahi I., Emeribe A., Babayo A., Adekola H., Danmusa U., and Uzairue L., 2020, The interplay between epigenetics, vector competence and vaccine immunodynamics as a possible explanation for recent yellow fever resurgence in Nigeria, African Journal of Health Sciences, 32: 38-52.

Vasconcelos P.F., and Barrett A., 2019, Are booster doses of yellow fever vaccine needed? The Lancet, Infectious Diseases, 19(12): 1275-1276.
https://doi.org/10.1016/S1473-3099(19)30411-6

Wang H., Guo Y., He M., Liu Z., Ye Q., Huang X., Deng Y., Li X., and Qin C., 2022, Development of a bicistronic yellow fever live attenuated vaccine with reduced neurovirulence and viscerotropism, Microbiology Spectrum, 10(5): e02246-22.
https://doi.org/10.1128/spectrum.02246-22

Yang L.B., 2024, Genome driven personalized drug therapy, International Journal of Clinical Case Reports, 14(1): 40-47.
https://doi.org/10.5376/ijccr.2024.14.0005