Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 18 (67) No. 2 – 2025
https://doi.org/10.31926/but.ms.2025.67.18.2.3

YELLOW FEVER VACCINATION – LIFELONG PROTECTION THROUGH A SINGLE DOSE: A NARRATIVE REVIEW

EM. CONSTANTINESCU[1] C. TAPOSU[1] AC. CONSTANTINESCU[1]

***Abstract**: Yellow fever, caused by a flavivirus transmitted by Aedes and Haemagogus mosquitoes, remains a major public health concern in the tropical regions of Africa and South America, affecting approximately 900 million people living in at-risk areas. The live attenuated 17D vaccine, developed by Max Theiler in the 1930s and awarded the Nobel Prize in 1951, is one of the most effective vaccines ever created, providing lifelong immunity with a single dose to over 95% of vaccinees. This comprehensive narrative review examines the immunological mechanisms behind the substantial and durable of the vaccine, its historical development from the Asibi strain to the current 17D substrain, current vaccination strategies, contraindications, and the risk–benefit analysis. While the vaccine has an excellent safety profile with rare serious adverse events (0.09–0.4 per 10,000 doses), the benefits far outweigh the risks for most populations, contributing to the elimination of yellow fever as a major public health threat.*

***Key words:** yellow fever, 17D vaccine, lifelong immunity, Max Theiler, flavivirus, vaccination*

1. Introduction

Yellow fever persists as a dominant challenge among human arboviral infections, maintaining an omnipresent threat within the endemic landscapes of Africa and South America. In these regions, a synergistic mix of ecological variables, fluctuating climates, and socioeconomic fragility sustains the circulation of the virus. Although a potent live-attenuated vaccine has been accessible for eight decades, the disease continues to inflict heavy morbidity and mortality, with annual estimates reaching tens of thousands of severe cases and deaths. This persistent burden is largely a consequence of inconsistent vaccination coverage, heightened human migration, and the adaptive dynamics of mosquito vectors.

Taxonomically, the yellow fever virus is the prototypical member of the *Flavivirus* genus within the *Flaviviridae* family. It is capable of precipitating catastrophic outbreaks marked by systemic hemorrhage, acute hepatic failure, and high lethality. These epidemiological realities emphasize the

[1] *Transilvania* University of Braşov.

vaccine's critical role in an era of rapid urbanization and global travel.

Among the arsenal of viral immunizations, the 17D vaccine is a landmark of medical innovation. Its development—forged through rigorous passage experiments—established the core tenets of modern vaccinology. Today, it remains one of the most immunogenic biologicals ever engineered, inducing a protective state that often spans a lifetime. Recent advancements in systems biology and long-term cohort monitoring have shed light on the mechanisms driving this durability, including the creation of resilient memory B cells, the persistence of neutralizing antibodies, and the orchestration of polyfunctional T-cell responses.

2. Yellow Fever – Definition and Manifestations of the Epidemiological Process

Mosquitoes of the *Aedes* and *Haemagogus* genera transmit yellow fever, an acute infection caused by a virus within the Flaviviridae family [1]. This viral hemorrhagic disease creates a major burden on global public health systems [2].

Patients may experience a spectrum of symptoms ranging from minor flu-like indications to catastrophic multi-organ failure, hemorrhaging, and severe hepatitis. For those developing severe forms, the risk of mortality approaches 50% [3]. This virus endures in the tropical climates of sub-Saharan Africa and South America, exposing an estimated 900 million inhabitants to potential infection [4]. While underreporting obscures the total impact, WHO models suggest that between 84,000 and 170,000 severe cases occur annually, resulting in a death toll of 29,000 to 60,000 [2].

These variations reflect differences in surveillance methodologies, reporting systems, and the use of different estimation models across countries. The transmission cycle includes three types: urban (Aedes aegypti), sylvatic (Haemagogus and Sabethes), and intermediate, each with distinct epidemiological characteristics [3]. The current geographic distribution includes 47 countries in Africa and 13 in South America considered at risk for active transmission [5]. Epidemiological studies have documented the geographic distribution and transmission patterns of yellow fever across endemic regions [6], [7].

The virus propagates through distinct transmission cycles, each facilitated by specific mosquito species adapted to unique ecological niches. In the sylvatic (jungle) cycle, the pathogen is maintained within forest-dwelling primate populations; however, the intermediate and urban cycles involve human populations, resulting in varying degrees of transmission intensity [8].

Because these separate loops rely on specific environmental contexts—ranging from remote forests to densely populated cities—comprehending these epidemiological patterns is critical. Such insight is essential for accurately predicting outbreak risks and strategically targeting vaccination campaigns in high-risk zones [9].

The body's defense mechanism against yellow fever—whether triggered by natural infection or immunization—is marked by the rapid generation of neutralizing antibodies. This process is exceptionally efficient, with seroconversion occurring in over 99% of those who receive the vaccine [7].

Despite this high success rate, the focus of current research into vaccine immunogenicity has shifted toward more nuanced challenges. Specifically,

investigators are working to define the qualitative nature of this immune response and the exact molecular pathways that facilitate its durability. Understanding these underlying mechanisms is essential for confirming how the vaccine sustains long-term, and often life-long, protection [10].

3. The Yellow Fever Vaccine – Characteristics and Efficacy

The severe clinical trajectory of yellow fever, characterized by its significant hemorrhagic potential, necessitates a proactive and robust public health strategy. As international borders become increasingly porous due to the demands of modern business and the global expansion of the tourism industry, the risk of "exporting" cases into non-endemic regions renders widespread immunization a vital component of global health security. Within the hierarchy of vaccinology, the 17D strain is frequently cited as the "gold standard"; it achieves a rare balance of near-total protection and a manageable safety profile, setting a high benchmark for all subsequent live-virus vaccine development [11].

The attenuation process involved a meticulous biological "domestication" of the wild-type virus. By repeatedly culturing the pathogen in non-human tissues via serial passage, researchers effectively forced the virus to adapt to chick embryos, thereby stripping its ability to cause systemic disease in humans while ensuring it remained recognizable to the human immune system [12]. It is a testament to the original design's robustness that, even in an era of advanced recombinant technology, the primary manufacturing platform still relies on the traditional cultivation of the virus within embryonated chicken eggs—a method that has proven both reliable and scalable for nearly a century.

The potency of the vaccine is evidenced by its ability to achieve protective thresholds through a solitary intervention. The vast majority of recipients develop a defensive barrier against the virus within a mere four-week window post-administration [2]. The kinetic profile of the 17D vaccine is remarkably swift; early-phase neutralizing antibodies emerge almost immediately in nearly all recipients, culminating in a near-universal state of seroconversion as the immune response matures during the first thirty days [2]. Beyond its immediate impact, the vaccine confers a durable "immunological memory". Long-term data indicates that the overwhelming majority of vaccinated individuals remain shielded from infection even a decade after their initial exposure to the 17D strain [9]. Furthermore, systematic reviews of clinical cohorts suggest that the vaccine may provide life-long protection, a finding that has led many health authorities to move away from the requirement for decennial booster doses in most populations [13].

The enduring success of the vaccine stems from its ability to orchestrate a complex "cellular symphony". Specifically, follicular helper T cells stimulate B cells to differentiate into long-lived memory cells and high-output plasmablasts, ensuring a permanent reserve of targeted antibodies [14]. Industrial consistency remains a hallmark of the 17D platform; whether produced by different entities or under different brand names, the biological integrity of the vaccine remains uniform. Comparative studies of formulations such as ARILVAX and YF-VAX demonstrate identical safety profiles and seroconversion rates, yielding consistent clinical outcomes regardless of the manufacturer [1].

Finally, in the face of critical vaccine shortages or sudden epidemic surges, public health officials have successfully implemented a dose-sparing strategy—administering only 20% of the standard volume (fractional dosing)—to maximize the number of individuals protected during a crisis. Clinical trials confirm that this fractional approach is biologically viable, as the smaller quantity of the attenuated virus is still sufficient to prime both the antibody-producing and cell-mediated arms of the immune system, thereby maintaining robust herd immunity [10], [15].

4. Mechanisms of Lifelong Immunity

The induction of a resilient, T-cell-mediated defense following immunization is rooted in the stimulation of thymic epithelial cells and the subsequent birth of highly versatile CD8+ and CD4+ T-cell cohorts [16]. These specific populations are characterized by their "polyfunctional" nature—possessing the unique capability to generate an array of cytokines concurrently. Once established, these cells reside within lymphoid structures for decades, serving as a permanent cellular sentry against viral reinvasion; notably, the diversity and caliber of this T-cell repertoire are the primary determinants of both the vaccine's immediate success and its decadal endurance [16].

The 17D vaccine's capacity for inducing lifelong protection is anchored in sophisticated biological pathways [17]. Research monitoring patients over several decades indicates that both specific memory T cells and neutralizing antibodies remain at functionally relevant concentrations for 35 to 40 years following a solitary dose [9].

This enduring protection is facilitated by a heterogeneous population of CD8+ memory T cells that exhibit a terminal-effector signature while retaining a high capacity for self-renewal [7]. Detailed kinetic analysis reveals that the proliferation of these virus-specific CD8+ cells tapers significantly after the initial phase, eventually stabilizing at a turnover rate of roughly 0.1% daily within the first twelve months post-inoculation [18].

The maintenance of a constant humoral defense is driven by a synergy between long-lived memory B cells and plasma cells that reside in the bone marrow, providing a steady secretion of neutralizing antibodies [19]. This long-term output is the result of intricate processes within secondary lymphoid organs, where the formation of germinal centers allows B cells to undergo somatic hypermutation, thereby refining their antibody affinity over time [20].

A deeper exploration of the T-cell response shows that the 17D strain elicits a multifaceted CD8+ reaction. These cells are capable of the simultaneous expression of critical cytokines, including IFN-γ, TNF-α, and IL-2, while preserving their direct cytotoxic effectiveness [7]. Phenotypic mapping six months after the primary injection identifies these specific cells within diverse subsets—ranging from late-differentiated (CD45RA+CD27–) to “naive-like” (CD45RA+CD27+) populations—both of which maintain high-functioning, polyfunctional profiles [9].

Advancements in systems biology have isolated specific genetic "signatures" that can forecast the strength of an individual's immune response. Specifically, the immediate activation of dendritic cells and interferon-mediated signaling pathways has been shown to correlate directly with the eventual volume of protective antibodies produced [21]. This holistic, integrative perspective helps clarify why

certain individuals manifest a significantly more vigorous or enduring immunological defense than others [22].

In summary, the permanence of the immunity is an inherent property of the vaccine's design. As a live attenuated agent, it effectively mirrors a natural viral encounter, thereby engaging the full spectrum of the host's humoral and cellular machinery. This dual-track stimulation culminates in a broad and exceptionally polyfunctional immunological memory that is unparalleled in its longevity [18].

5. History of the Vaccine – from Discovery to the Nobel Prize

In 1900, the U.S. Army Yellow Fever Commission, led by Walter Reed, demonstrated that yellow fever is transmitted by the mosquito Aedes aegypti.

The development of the yellow fever vaccine represents one of the most important achievements in the history of vaccinology, being the first and only viral vaccine to be awarded the Nobel Prize [23]. The story begins in 1927, when the Rockefeller Foundation team isolated the virus from the blood of an African patient named Asibi [23]. Max Theiler, a South African virologist who initially worked at Harvard, played the decisive role in the development of the vaccine. In 1928, he and his colleagues definitively demonstrated that yellow fever is caused by a virus and that African and South American strains are immunologically identical [24]. In 1930, Theiler moved to the Rockefeller Foundation in New York, where he demonstrated that the virus can be propagated in mice [24].

The actual development of the vaccine began with serial passage of the Asibi strain through embryonic tissues, followed by culture in chick embryo tissues [12]. After more than 100 passages, at passage 176, Theiler and Hugh Smith observed that the virus no longer killed mice when injected intracerebrally—the virus had begun to adapt to the mouse brain environment [12]. Thus, the virus was attenuated, and this mutation gave rise to the 17D strain.

The first clinical trials began in Brazil in 1938, demonstrating strong safety and efficacy [23]. During World War II, the Rockefeller Foundation produced and distributed more than 34 million doses free of charge for U.S. military personnel [25]. For this exceptional achievement, Max Theiler was awarded the Nobel Prize in Physiology or Medicine in 1951 [26]. The process of viral attenuation through serial passage in culture was critical to vaccine safety and efficacy. Studies on the molecular basis of attenuation have revealed that specific genomic mutations in the non-structural proteins contribute to the attenuated phenotype while maintaining immunogenicity [27]. The historical development of the 17D vaccine strain represents one of the most significant achievements in virology and public health, establishing principles of live attenuated vaccine design that continue to inform modern vaccine development.

6. Indications for Vaccination and Current Strategies

The World Health Organization (WHO) coordinates a dual-focused immunization policy aimed at safeguarding both native populations in endemic territories and transcontinental visitors to these specific geographic locales [28]. At the core of this institutional strategy lies the preservation of a stringent herd immunity benchmark; a minimum coverage of 80% is targeted within eligible demographics to stifle viral circulation and preclude epidemic flares. In

countries where the virus is established, the primary vehicle for achieving this is the systematic inclusion of the vaccine within early childhood medical protocols. Current WHO guidelines favor a specific window of administration for infants aged 9 to 12 months, an approach designed to be synchronized with measles inoculation to streamline public health logistics and improve pediatric outcomes [2].

Despite institutional mandates, the actual rate of vaccine administration is frequently dictated by intricate socio-behavioral variables. Scholarly inquiries indicate that while those in high-risk environments often exhibit a baseline acceptance of the vaccine, the decision to undergo immunization is heavily mediated by subjective interpretations of safety and the perceived severity of local outbreaks [29]. On a molecular level, the 17D strain exhibits significant immunological stability; its capacity to induce a protective state remains intact even in patients with previous exposure to the dengue virus. This ensures that pre-existing flavivirus antibodies do not interfere with the vaccine's ability to generate a robust and dedicated defensive response [13].

For more than forty years, the international medical consensus dictated that protection required periodic reinforcement via decennial boosters. This long-standing orthodoxy was overturned in April 2013 following an exhaustive longitudinal assessment by the WHO Strategic Advisory Group of Experts on Immunization (SAGE). Their analysis catalyzed a fundamental policy transformation: a solitary administration of the 17D vaccine was validated as being sufficient for establishing an enduring, lifetime defensive state, thereby removing the requirement for decennial revaccination in the general populace [3].

This revaluation was substantiated by exhaustive systematic reviews which confirmed that vaccine breakthroughs are statistically exceptional and show no temporal correlation with the date of the original injection [3]. Consequently, the current global directive stipulates a one-time dose for all qualified persons over 9 months of age who inhabit or visit known transmission corridors in sub-Saharan Africa or the South American continent [4].

The regulation of international mobility serves as a critical pillar of yellow fever control, with requirements varying based on the destination's endemicity and the specific parameters of the traveler's itinerary [5]. Guided by the International Health Regulations, numerous nations exercise their sovereign right to require validated certification of vaccination—often recorded in the "Yellow Card" document—as a mandatory condition of entry. While these rules primarily target high-endemicity zones, clinical discretion is often applied to travelers visiting lower-risk areas if they face unavoidable mosquito exposure or lack adequate protective equipment [4]. Finally, to address the profound bio-risks inherent in research settings, laboratory technicians and scientists working with active viral cultures are subject to non-negotiable vaccination requirements to prevent accidental occupational infection [4].This conclusion was based on a systematic review of published studies on the duration of immunity after a single dose of the yellow fever vaccine and on data suggesting that vaccine failures are extremely rare and do not increase in frequency with time elapsed since vaccination [3]. The advisory group noted that future studies and surveillance data should be used to identify specific high-risk groups, such as individuals infected with

HIV or infants, who might benefit from a booster dose.

Although the medical community has transitioned toward a single-dose regimen for lifelong protection, the Advisory Committee on Immunization Practices (ACIP) and other health authorities have identified specific vulnerable cohorts for whom the standard protocol may be insufficient [4]. For instance, individuals living with HIV are recommended to undergo revaccination every ten years, provided they remain at a heightened risk of exposure [4]. Similarly, women who received the vaccine during pregnancy should be administered a second dose prior to any subsequent travel or residence in endemic regions [4].

Patients who have undergone hematopoietic stem cell transplantation following their initial immunization also require a new dose to effectively restore their immunity [4]. Furthermore, a booster dose remains a consideration for travelers whose last vaccination occurred more than a decade ago, particularly if they intend to visit highly endemic areas during peak transmission seasons or engage in activities that increase their risk of mosquito exposure [4].

7. Contraindications and Precautions

Absolute contraindications include age under 6 months, severe primary or acquired immunodeficiencies, thymus disorders associated with immune dysfunction, and a history of anaphylactic reactions to a previous vaccine dose or to egg proteins [4].

Immunocompromised individuals have an increased risk of developing vaccine-associated viscerotropic disease (YEL-AVD, yellow fever vaccine-associated viscerotropic disease) or encephalitis (YEL-AND) [30]. Studies involving over 500 asymptomatic individuals infected with HIV with moderate immunosuppression have not identified severe adverse events, but the immune response may be diminished [4].

Pregnancy represents a relative contraindication because the vaccine is live attenuated, with a theoretical teratogenic potential [31]. Advanced age (over 60 years) is associated with a higher risk of severe adverse events, especially YEL-AVD, with an estimated incidence of 1.4–2.3 per 100,000 doses [16]. Severe egg allergies constitute an absolute contraindication due to the vaccine being produced in embryonated eggs [4].

8. Advantages of Vaccination

Comprehensive surveillance systems coordinated by the CDC (2020) and European Centre for Disease Prevention and Control (2019) monitor vaccine effectiveness, safety, and adverse event profiles across different demographic groups and geographic regions. These data demonstrate that the 17D vaccine provides population-level protection through vaccination of high-risk groups and travelers, reducing transmission risk to unvaccinated populations in endemic areas. The WHO/PAHO (2021) recommendations emphasize vaccination as the cornerstone of yellow fever prevention in endemic and epidemiologically relevant areas [28].

The vaccine provides significant benefits both individually and for global public health. At the individual level, the main advantage is the nearly complete protection (>99%) against a disease with high mortality (up to 50%), with a single dose conferring lifelong immunity [2]. Out of more than 500 million doses administered over the past 80 years, only a

few cases of infection with virulent strains have been reported in vaccinated individuals [1].

Economic benefits are substantial, as the cost of a dose (5–40 USD) is incomparable to the cost of treating a severe infection [2]. The vaccine is inexpensive to produce, stable under standard refrigeration, and can be administered in a single medical visit [3]. From a public health perspective, vaccination has contributed to the elimination of yellow fever as a major problem in many regions. Mass vaccination campaigns have led to the rapid disappearance of cases during outbreaks [32].

9. Risks and Limitations of Vaccination

Mild adverse events are relatively common, affecting 10–30% of vaccinated individuals, and include fever, headache, myalgia, and local discomfort, symptoms that appear 5–10 days post-vaccination and resolve spontaneously [32]. Allergic reactions to egg proteins affect approximately 1% of vaccinated individuals [4].

The most severe adverse event is vaccine-associated viscerotropic disease (YEL-AVD). Global vaccine safety monitoring systems, including the CDC's Vaccine Adverse Event Reporting System (VAERS) and international surveillance networks, track the incidence and characteristics of YEL-AVD and other serious adverse events [5]. The European Centre for Disease Prevention and Control similarly monitors yellow fever vaccine safety through coordinated surveillance of adverse events in vaccination programs across member states [33]. These surveillance systems provide critical epidemiological data on vaccine safety profiles across diverse populations [34], with an incidence of 0.09–0.4 cases per 10,000 doses in populations without prior exposure and a mortality rate of approximately 50% [30]. Risk factors include advanced age, thymectomy, and possible genetic factors not yet fully understood [35].

In clinical practice, risk stratification involves careful assessment of these factors, with vaccination contraindicated or deferred in patients with thymectomy history and individualized risk–benefit evaluation required for elderly patients (>60 years) and those with immunocompromise. Vaccine-associated encephalitis (YEL-AND) has a higher incidence in infants under 9 months and adults over 60 years, but with a more favorable prognosis [36].

Limitations of the vaccine include multiple contraindications that exclude certain vulnerable populations, creating “gaps” in community protection [4]. Limited global supplies can be problematic during major outbreaks, a situation that led to the use of fractional dosing [10]. The immune response may be diminished in immunocompromised individuals, elderly people, or those infected with HIV, requiring additional serological monitoring [9]. Special attention must be paid to immunocompromised persons, as adverse event profiles may differ from the general population [37].

10. Conclusion

The yellow fever 17D vaccine remains one of the most significant accomplishments in the history of infectious disease prevention, combining unparalleled efficacy, long-term safety, and the capacity to induce lifelong immunity from a single dose. Its development, built on decades of scientific rigor and culminating in the first Nobel Prize awarded for a viral vaccine, transformed the landscape of global health and set standards for modern vaccinology. Today, the vaccine continues to serve as

the cornerstone of yellow fever control, protecting individuals living in or traveling to endemic regions and preventing potentially devastating outbreaks.

Advances in immunology and systems biology have deepened our understanding of the durable protection conferred by the 17D vaccine. The yellow fever vaccine serves as an outstanding model for learning immunology and understanding fundamental principles of vaccine-induced immunity [35], revealing a complex and coordinated immune response involving long-lived memory B cells, persistent neutralizing antibodies, and polyfunctional T-cell populations. These insights not only explain the vaccine's extraordinary longevity but also provide valuable models for designing future vaccines targeting other high-impact pathogens.

Recent epidemiological studies document yellow fever transmission patterns in endemic regions [38], [39]. Global surveillance coordinated by the World Health Organization and partner agencies [28] CDC, [33] tracks vaccine safety and efficacy. The molecular basis of vaccine protection involves complex interactions between innate immune responses [35] and adaptive immunity, with antibody responses [40] contributing to long-term protection.

Despite its excellent safety profile, awareness of contraindications, rare but serious adverse events, and variable immune responses in specific populations remains essential for optimizing vaccination strategies. Continued surveillance, equitable vaccine distribution, and tailored recommendations for vulnerable groups are critical components of global control efforts. Furthermore, maintaining adequate vaccine supplies—especially during outbreaks—and expanding coverage in endemic regions remain central challenges.

Overall, the benefits of yellow fever vaccination far outweigh its risks, and its widespread implementation has already transformed the epidemiology of the disease in many regions. With sustained commitment to vaccination programs, improved public health infrastructure, and ongoing scientific research, the global community can move closer to eliminating yellow fever as a major public health threat.

References

1. Monath TP, Nichols R, Archambault WT, Moore L, Marchesani R, Tian J, Shope RE, Thomas N, Schrader R, Furby D, Bedford P. Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III multicenter, double-blind clinical trial. *Am J Trop Med Hyg*. 2002; 66(5):533-41. doi: 10.4269/ajtmh.2002.66.533. PMID: 12201587.
2. World Health Organization. Yellow fever vaccines [Internet]. Geneva: WHO; 2024 [cited 18 november 2025]. Available at: https://www.who.int/news-room/fact-sheets/detail/yellow-fever.
3. Staples JE, Gershman M, Fischer M; Centers for Disease Control and Prevention (CDC). Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010 Jul 30; 59(RR-7):1-27. PMID: 20671663.
4. Centers for Disease Control and Prevention. Yellow Fever Vaccine Information for Healthcare Providers [Internet]. Atlanta: CDC; 2024 [cited 18 november 2025]. Available at: https://www.cdc.gov/yellow-fever/hcp/clinical-care/vaccination.html
5. Centers for Disease Control and Prevention. Yellow Fever Vaccine and

Malaria Prevention Information, by Country [Internet]. Atlanta: CDC; 2025 [cited 18 november 2025]. Available at: https://wwwnc.cdc.gov/travel/yellow-fever-vaccination-maps-africa-americas

6. Vasconcelos PF. Yellow fever in Brazil: epidemiological aspects and control. Rev Saude Publica. 2010; 44(3):555-64. doi: 10.1590/S0034-89102010000300018.
7. Miller JD, van der Most RG, Akondy RS, Glidewell JT, Albott S, Masopust D, Murali-Krishna K, Mahar PL, Edupuganti S, Lalor S, Germon S, Del Rio C, Mulligan MJ, Staprans SI, Altman JD, Feinberg MB, Ahmed R. Human effector and memory CD8+ T cell responses to smallpox and yellow fever vaccines. *Immunity.* 2008 May; 28(5):710-22. doi: 10.1016/j.immuni. 2008.02.020. Epub 2008 May 8. PMID: 18468462.
8. Monath TP, Nichols R, Archambault WT, Moore L, Marchesani R, Tian J, Shope RE, Thomas N, Schrader R, Furby D, Bedford P. Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III multicenter, double-blind clinical trial. *Am J Trop Med Hyg.* 2002 May; 66(5):533-41. doi: 10.4269/ ajtmh.2002.66.533. PMID: 12201587.
9. Wieten RW, Jonker EF, van Leeuwen EM, Remmerswaal EB, Ten Berge IJ, de Visser AW, van Genderen PJ, Goorhuis A, Visser LG, Grobusch MP, de Bree GJ. A Single 17D Yellow Fever Vaccination Provides Lifelong Immunity; Characterization of Yellow-Fever-Specific Neutralizing Antibody and T-Cell Responses after Vaccination. *PLoS One*. 2016 Mar 15; 11(3):e0149871. doi: 10.1371/journal.pone.0149871. PMID: 26977808; PMCID: PMC4792480.
10. Hansen CA, Staples JE, Barrett ADT. Fractional Dosing of Yellow Fever Live Attenuated 17D Vaccine: A Perspective. *Infect Drug Resist*. 2023 Nov 8; 16:7141-7154. doi: 10.2147/IDR.S370013. PMID: 38023411; PMCID: PMC10640814.
11. Barrett ADT. Live attenuated yellow fever 17D vaccine: a legacy vaccine still controlling outbreaks in modern day. *PLOS Negl Trop Dis*. 2017; 11(3):e0005118. doi: 10.1007/s11908-017-0566-9
12. Theiler M, Smith HH. THE EFFECT OF PROLONGED CULTIVATION IN VITRO UPON THE PATHOGENICITY OF YELLOW FEVER VIRUS. *J Exp Med.* 1937 May 31;65(6):767-86. doi: 10.1084/jem.65.6.767. PMID: 19870633; PMCID: PMC2133530.
13. Gotuzzo E, Yactayo S, Córdova E. Review of data regarding yellow fever vaccine-induced immunity. *Vaccine*. 2020; 38(33):5190-7. doi: 10.1016/j.vaccine.2020.06.014.
14. Campi-Azevedo AC, de Almeida Estevam P, Coelho-Dos-Reis JG, Peruhype-Magalhães V, Villela-Rezende G, Quaresma PF, et al. Subdoses of 17DD yellow fever vaccine elicit equivalent virological/ immunological kinetics timeline. *BMC Infect Dis*. 2014; 14:391. doi: 10.1186/1471-2334-14-391
15. Frierson JG. The yellow fever vaccine: a history. *Yale J Biol Med*. 2010 Jun; 83(2):77-85. PMID: 20589188; PMCID: PMC2892770
16. Lindsey NP, Schroeder BA, Miller ER, Braun MM, Hinckley AF, Marano N, Slade BA, Barnett ED, Brunette GW, Horan K, Staples JE, Kozarsky PE, Hayes EB. Adverse event reports following yellow fever vaccination. *Vaccine.* 2008 Nov 11; 26(48):6077-82. doi:

10.1016/j.vaccine.2008.09.009. Epub 2008 Sep 20. PMID: 18809449.

17. Akondy RS, Johnson PLF, Brasher NA, Zarnitsyn VG, Mohanka R, Newman S, et al. Initial viral load determines the magnitude of the human CD8 T cell response to yellow fever vaccination. *Proc Natl Acad Sci U S A*. 2015; 112(10):3050-5. doi: 10.1073/pnas.1500475112
18. Akondy RS, Monson ND, Miller JD, et al. The yellow fever virus vaccine induces a broad and polyfunctional human memory CD8+ T cell response. *J Immunol.* 2009; 183(12):7919-30. doi: 10.4049/jimmunol.0901105.
19. Hammarlund E, Lewis MW, Hansen SG, Strelow LI, Nelson JA, Sexton GJ, Hanifin JM, Slifka MK. Duration of antiviral immunity after smallpox vaccination. *Nat Med*. 2003 Sep; 9(9):1131-7. doi: 10.1038/nm917. Epub 2003 Aug 17. PMID: 12925846.
20. Victora GD, Nussenzweig MC. Germinal centers. *Annu Rev Immunol*. 2012; 30:429-57. doi: 10.1146/annurev-immunol-020711-075032. Epub 2012 Jan 3. PMID: 22224772.
21. Querec TD, Akondy RS, Lee EK, Cao W, Nakaya HI, Teuwen D, Pirani A, Gernert K, Deng J, Marzolf B, Kennedy K, Wu H, Bennouna S, Oluoch H, Miller J, Vencio RZ, Mulligan M, Aderem A, Ahmed R, Pulendran B. Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans. *Nat Immunol*. 2009 Jan; 10(1):116-125. doi: 10.1038/ni.1688. Epub 2008 Nov 23. PMID: 19029902; PMCID: PMC4049462.
22. Pulendran B. Systems vaccinology: probing humanity's diverse immune systems with vaccines. *Proc Natl Acad Sci U S A*. 2014 Aug 26; 111(34):12300-6. doi: 10.1073/pnas.1400476111. Epub 2014 Aug 18. PMID: 25136102; PMCID: PMC4151766.
23. Frierson JG. The yellow fever vaccine: a history. *Yale J Biol Med*. 2010 Jun; 83(2):77-85. PMID: 20589188; PMCID: PMC2892770.
24. Theiler M. SUSCEPTIBILITY OF WHITE MICE TO THE VIRUS OF YELLOW FEVER. *Science*. 1930 Apr 4; 71(1840):367. doi: 10.1126/science.71.1840.367. PMID: 17731835.
25. Rockefeller Foundation. The Rockefeller Foundation Annual Report 1942 [Internet]. New York: The Rockefeller Foundation; 1943 [cited Jun 16 2025]. p. 22-25. Available at: https://www.rockefellerfoundation.org/wp-content/uploads/Annual-Report-1942.pdf
26. Norrby E. Yellow fever and Max Theiler: the only Nobel Prize for a virus vaccine. *J Exp Med*. 2007 Nov 26; 204(12):2779-84. doi:10.1084/jem.20072290. PMID: 18039952; PMCID: PMC2118520.
27. Guirakhoo F, Pugachev K, Arroyo J, Miller C, Zhang ZX, Weltzin R, Georgakopoulos K, Catalan J, Ocran S, Draper K, Monath TP. Viremia and immunogenicity in nonhuman primates of a tetravalent yellow fever-dengue chimeric vaccine: genetic reconstructions, dose adjustment, and antibody responses against wild-type dengue virus isolates. *Virology*. 2002 Jun 20; 298(1):146-59. doi: 10.1006/viro.2002.1462. PMID: 12093182.
28. World Health Organization / Pan American Health Organization. Recommendations for yellow fever vaccination [Internet]. Geneva: WHO; 2021 [cited 18 november 2025] Available at: https://www.paho.org/en/topics/yellow-fever.
29. Mentzer AJ, Brenner N, Allen N, Littlejohns TJ, Chong AY, Cortes A,

Almond R, Hill M, Sheard S, McVean G; UKB Infection Advisory Board; Collins R, Hill AVS, Waterboer T. Identification of host-pathogen-disease relationships using a scalable multiplex serology platform in UK Biobank. *Nat Commun*. 2022 Apr 5;13(1):1818. doi: 10.1038/s41467-022-29307-3. PMID: 35383168; PMCID: PMC8983701.

30. Lindsey NP, Rabe IB, Miller ER, Fischer M, Staples JE. Adverse event reports following yellow fever vaccination, 2007-13. *J Travel Med*. 2016 Jul 4; 23(5). doi: 10.1093/jtm/taw045. PMID: 27378369.
31. Cavalcanti DP, Salomão MA, López-Camelo J, Pessoto MA. Early exposure to yellow fever vaccine during pregnancy. *Trop Med Int Health*. 2012; 17(8):938-46. doi: 10.1111/j.1365-3156.2007.01851.x
32. World Health Organization. Yellow fever vaccines [Internet]. Geneva: WHO; 2024 [cited 18 november 2025]. Available at: https://www.who.int/ news-room/fact-sheets/detail/yellow-fever
33. European Centre for Disease Prevention and Control. Expert consultation on yellow fever surveillance and prevention in the EU/EEA [Internet]. Stockholm: ECDC; 2021 [cited 2025 may 28]. Available from: https://www.ecdc.europa.eu/en/publications-data/expert-consultation-yellow-fever-surveillance-and-prevention-eueea
34. Hagan T, Nakaya HI, Subramaniam S, Pulendran B. Systems vaccinology: Enabling rational vaccine design with systems biological approaches. *Vaccine*. 2015 Sep 29;33(40):5294-301. doi: 10.1016/j.vaccine.2015.03.072. Epub 2015 Apr 6. PMID: 25858860; PMCID: PMC4581890.
35. Pulendran Smith HH, Theiler M. THE ADAPTATION OF UNMODIFIED STRAINS OF YELLOW FEVER VIRUS TO CULTIVATION IN VITRO. *J Exp Med.* 1937 May 31; 65(6):801-8. doi: 10.1084/jem.65.6.801. PMID: 19870635; PMCID: PMC2133529.
36. Staples JE, Gershman M, Fischer M. Yellow fever vaccine: recom-mendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep [Internet]. 2010 [cited 2026 Jan 18]; 59(RR-7):1-27. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5907a1.htm
37. Wieten RW, Jonker EF, Pieren DK, Hodiamont CJ, van Thiel PP, van Gorp EC, de Visser AW, Grobusch MP, Visser LG, Goorhuis A. Comparison of the PRNT and an immune fluorescence assay in yellow fever vaccinees receiving immunosuppressive medication. *Vaccine*. 2016 Mar 4; 34(10):1247-51. doi: 10.1016/j.vaccine.2016.01.037. Epub 2016 Feb 1. PMID: 26845742.
38. Vasconcelos PF. Yellow fever in Brazil: thoughts and hypotheses on the emergence in previously free areas. *Rev Saude Publica*. 2010 Dec; 44(6):1144-9. doi: 10.1590/s0034-89102010005000046. Epub 2010 Oct 15. PMID: 21109907.
39. Zeller H, Marrama L, Sudre B, Van Bortel W, Warns-Petit E. Mosquito-borne disease surveillance by the European Centre for Disease Prevention and Control. *Clin Microbiol Infect.* 2013 Aug; 19(8):693-8. doi: 10.1111/1469-0691.12230. Epub 2013 Apr 22. PMID: 23607415.
40. Thomas SJ, Endy TP. Critical issues in dengue vaccine development. *Curr Opin Infect Dis*. 2011 Oct; 24(5):442-50. doi: 10.1097/QCO. 0b013e32834a1b0b. PMID: 21799408