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REVIEW

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Yellow fever virus vaccination: an emblematic model to elucidate robust human immune responses

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ABSTRACT

By preventing infectious diseases, vaccines contribute substantially to public health. Besides, they offer great opportunities to investigate human immune responses. This is particularly true for live-attenuated virus vaccines which cause resolving acute infections and induce robust immunity. The fact that one can precisely schedule the time-point of vaccination enables complete characterization of the immune response over time, short-term and over many years. The live-attenuated Yellow Fever virus vaccine strain YF-17D was developed in the 1930's and gave rise to the 17D-204 and 17DD vaccine sub-strains, administered to over 600 million individuals worldwide. YF vaccination causes a systemic viral infection, which induces neutralizing antibodies that last for a lifetime. It also induces a strong T cell response resembling the ones of acute infections, in contrast to most other vaccines. In spite of its use since 1937, learning how YF vaccination stimulates such strong and persistent immune responses has gained substantial knowledge only in the last decades. Here we summarize the current state of knowledge on the immune response to YF vaccination, and discuss its contribution as a human model to address complex questions on optimal immune responses.

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1. The live-attenuated vaccine sub-strains 17D-204 and 17DD

Yellow Fever (YF) disease is caused by the Yellow Fever Virus (YFV) transmitted by mosquitoes belonging to the Aedes,[1,2] Haemagogus, and Sabethes genera[3,4] and is endemic to sub-Saharan African regions as well as tropical and subtropical regions of South America.[1,5] YFV infection can cause subclinical to severe illness with acute hemorrhagic disease, including fever, hemorrhagic shock and multi-organ failure of liver, kidneys and heart.[3] While a majority of infected people develop no or only minor symptoms, an estimated 1 in 7 infected people enter a toxic phase, over which half of them do not survive.[6,7] The liver is a major target organ, and liver dysfunction results in jaundice, hence the name "Yellow Fever". YFV is the prototype virus of the family of flaviviridae. YFV is a single-stranded, positive-sense RNA virus that varies in size between 40 and 60 nm. The virus consists of three structural proteins (core C, membrane M and envelope E), and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) that are necessary for viral replication. The virus particle is made of the genome (approximately 10'800 nucleotides) surrounded by C protein, and the viral proteins (M- and E-proteins) embedding the virus envelope.[1,5]

There is no antiviral therapy to treat the disease but prophylaxis is efficient thanks to the vaccine strains 17D-204 and 17DD, live-attenuated viruses that are considered as highly efficient vaccines. The original 17D strain was developed in 1937 by Max Theiler and colleagues.[8] The virus was isolated from a cured African patient and passaged 176 times in mouse and chicken tissue. This process led to viral attenuation while maintaining the immunogenicity, giving rise to this highly efficient vaccine. This discovery was awarded with the Nobel Prize in Physiology or Medicine in 1951. Two sub-strains are currently used for vaccine production: 17D-204 and 17DD, originating from the 17D strain. These vaccine sub-strains show only subtle nucleotide variations (ca. 99.9% nucleotide sequence identity).[9,10] The mutations observed in the gene encoding the E protein are thought to have a role in attenuation.[9,11,12] Both 17D-204 and 17DD sub-strains are regularly used and provide efficient protection against the disease.[13] To simplify, we use the short term "17D" whenever we mean the 17D-204, 17DD, or both vaccines.

In clinical practice, many vaccines that are made from viruses are inactivated vaccines (e.g. polio and influenza vaccines) which do not replicate *in vivo*. Even many live-attenuated viral strains (such as measles and oral polio vaccines) show usually only limited replication.[14,15] In contrast, the live-attenuated YF-17D vaccine replicates substantially and therefore causes a systemic viral infection and is strongly immunogenic because the immune system has evolved to react to microbial invasion and multiplication.[16–20]

The YF-17D vaccine represents an enormous success in terms of protection against Yellow Fever.[21] In addition to its exceptional efficacy, the YF-17D vaccine has an acceptable safety record. Viscerotropic and neurotropic serious adverse events were observed after YF vaccination and were defined as

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YF-17D vaccine-associated neurotropic and viscerotropic disease (YEL-AND and YEL-AVD, respectively).[22,23] These events occur rarely, and there exist large differences in the quality of surveillance systems, making it difficult to report exact rates (approximatively 0.3 and 0.8 cases per 100′000 doses for YEL-AVD and YEL-AND, respectively).[24–26] Unfortunately, these adverse events are often severe and may even be lethal.[27–30] For the development of novel vaccines, this type of risk moderates the risk–benefit balance toward avoidance of the use of live-attenuated viruses, in favor of synthetic vaccines. In the case of YF, the vaccine benefit is very high and synthetic vaccine alternatives are not available to date.

2. Immune responses to primary vaccination with YF-17D

In this section, we highlight the major findings on the cellular and humoral immune responses to YF-17D vaccination. We examine both the innate and the adaptive arms of the immune response, as summarized in Figure 1. Given the scarcity of animal models for YFV immunobiology,[31,32] the evidence on YF-17D vaccination largely originates from human studies (Supplemental Table 1).

2.1. Innate immunity

2.1.1. Dendritic cells (DCs)

DCs are major professional antigen-presenting cells (APCs) inducing adaptive immunity.[33] Two major subsets of DCs have been identified: conventional DCs (cDCs) and plasmacytoid DCs (pDCs).

In vitro analysis showed that YF-17D is able to infect DCs and to activate various subsets of DCs via multiple Toll-Like Receptors (TLRs), including TLR2, 7, 8 and 9.[34–36] Infection of DCs seems to allow antigen processing and presentation.[35] In addition, YFV was shown to induce the secretion of type I and III IFNs from pDCs upon TLR7 ligation or cell contact.[37] It was hypothesized that the YF-17D vaccine contains sufficient amounts of individual TLR ligands, producing synergistically broad and polyvalent immune responses.[34] The frequency of circulating pDCs (CD123+) is transiently and significantly increased at day 7 post-vaccination (approximatively from 1% to 5%), while no changes were observed for the frequency of cDCs (CD11c+).[38] However, the latter are activated, rising to a peak at day 7 of CD11c+ HLA-DR+ DCs in peripheral blood.[39]

2.1.2. Monocytes and macrophages

Monocytes are rapidly recruited to infected and inflamed tissues, where they differentiate into DCs and macrophages.[40] The percentage of macrophage-like (CD14+ CD16+) and activated monocytes (CD14+ CD16++) are slightly but significantly increased at day 7 post-vaccination with YF-17D compared to baseline (approximatively from 10% to 17% and 2.5% to 5%, respectively).[41] Activation of total monocytes is observed, as shown by the up-regulation of the activation marker CD86.[20] In addition, TNFα+ monocytes are increased at day 7 compared to baseline and are maintained over 30 days. Also, the frequency of IL-10+ monocytes was found to be increased at day 15 compared to baseline.[42]

Macrophages are large phagocytes and are able to act as APCs.[40] One study showed that YF-17D is able to infect macrophages *in vitro*.[43,44] Infection of macrophages might serve as a vehicle for dispersion of the virus to lymphoreticular tissues, where viral replication takes place.[44] Otherwise very little is known about macrophages in the context of YF-17D vaccination.

2.1.3. ILC

Innate lymphoid cell (ILC) is the collective term for a group of lymphoid cells lacking rearranged antigen-specific receptors of which the natural killer (NK) cells are the most well characterized.[45]

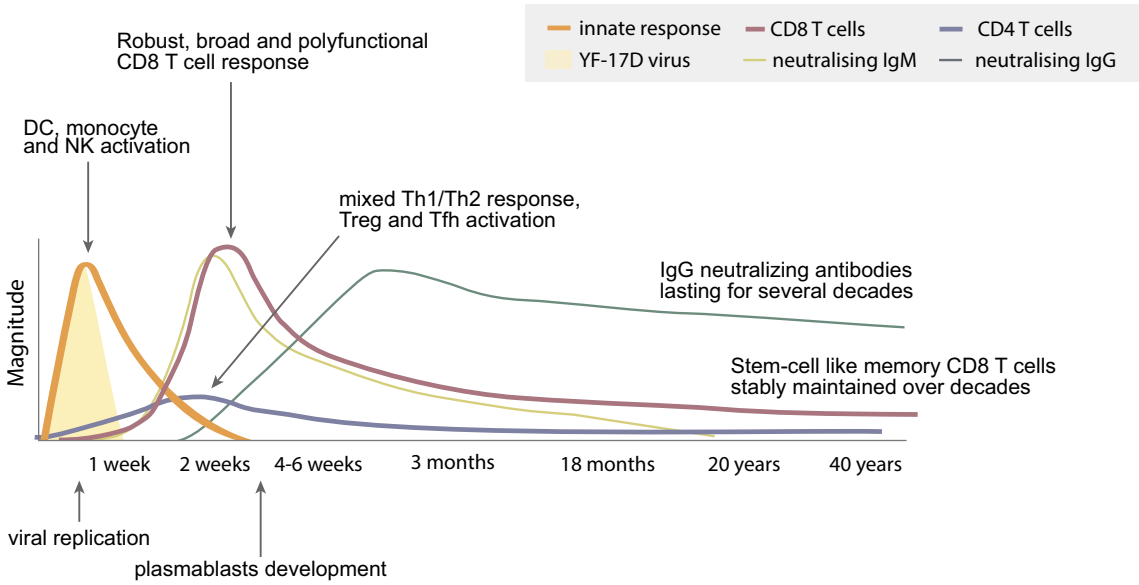

Figure 1. Overview of the immune responses to YF-17D vaccination. Kinetics of viral replication and the innate & specific immune response, illustrating the acute response and the long-term persistence of immune memory consisting of neutralizing antibodies and memory T cells. Bovay et al., "Yellow Fever virus vaccination: an emblematic model to elucidate robust human immune responses"

It was shown that vaccination with YF-17D induces a robust NK cell response with increased expression of several markers such as Ki-67, CD69 and HLA Class II molecules.[18,20,46,47] NK cells producing IFNγ and showing cytotoxic activity are also increased.[38,42] There is no substantial change in NK cell numbers and NK subsets after YF-17D vaccination.[20] So far, only one study characterized the other known ILC subsets in the context of YF-17D vaccination, revealing that their total numbers transiently decreased 7 days after primary vaccination.[20]

2.1.4. Granulocytes

Granulocytes have granules containing anti-microbicidal agents and are capable of ingesting foreign cells.[48] There are three types of granulocytes: neutrophils, eosinophils, and basophils.

Evidence shows that, whereas no changes in the percentages of circulating granulocytes are observed, both neutrophils and eosinophils are activated upon YF-17D vaccination.[41] Along the same line, TNFα+ neutrophils were increased at day 7 post-vaccination compared to baseline.[42] To our knowledge, there are no reports on basophils in the context of YF-17D vaccination. Overall, there are only few reports investigating granulocytes in the context of YF-17D vaccination as most studies analyzed peripheral blood mononuclear cells (PBMCs) that were isolated by Ficoll gradient centrifugation which eliminates granulocytes. Therefore, these cell types can only be assessed in fresh and whole blood samples, requiring immediate laboratory processing and analysis, which is often challenged by the logistics of longitudinal human studies.

2.2. Adaptive immunity

Unlike the responses of innate immune cells that are based on typical microbial patterns, the adaptive immune cells are highly specific for their target antigens. Adaptive responses are based primarily on the antigen-specific receptors expressed on the surfaces of T- and B-lymphocytes and become prominent only after several days, the time required for antigen-specific T and B cells to locate their cognate antigen, to undergo clonal expansion, and to differentiate into effector cells.

2.2.1. CD8 T cells

CD8 T cells (also called cytotoxic T cells) control viral infections by inducing apoptosis of infected cells through perforin- or Fas ligand-dependent pathways or producing antiviral cytokines such as IFNγ and TNFα.[49]

In humans, total CD8 T cells rapidly expand and peak at 2 weeks after primary vaccination with YF-17D, showing expression of the proliferation marker Ki-67 and downregulation of the anti-apoptotic marker Bcl-2.[16,17,20,50,51] In addition, the CD8 T cells have an activated phenotype as revealed by the transient up-regulation of CD69, HLA-DR and CD38.[16,20,39,50–55] This activation leads to clonal expansion, which is associated with differentiation to effector T cells that migrate throughout the body to defend from the infection.[56]This effector response contracts by 4 weeks after vaccination, followed by the memory phase with its long-term surviving memory T cells.[57]

The magnitude of the effector CD8 T cell response correlates directly with the viral serum titer, reflecting that the CD8 T cell proliferation is driven by viral expansion and the amount of antigen.[17] CD8 T cells may respond to epitopes from all 10 YF-17D proteins. Multiple proteins are targeted in each individual, with several epitopes per protein.[51,53,58] In particular, CD8 T cells specific for the immunodominant HLA-A2-restricted epitope $NS4B_{214-222}$ ("A2/LLW") form a large part of the total response in HLA-A2 positive individuals.[51] Surprisingly, A2/LLW-specific CD8 T cells can be detected already in unvaccinated HLA-A2 individuals, revealing an extraordinary high precursor frequency that relates to the dominance of these cells in the response to YF-17D vaccination.[59,60] A2/LLW-specific CD8 T cells undergo an initial phase of expansion peaking at 2 weeks after YF-17D vaccination. These cells are strongly activated, expressing high levels of HLA-DR, CD38 and PD1.[20,51] Upon peptide recognition *in vitro*, A2/LLW-specific CD8 T cells produce a variety of pro-inflammatory cytokines, such as IFNγ, TNFα, MIP-1β and IL-2.[51,53,59] They also express granzyme B and the degranulation marker CD107a, reflecting the cytotoxicity of these cells.[51,53,59]

Following expansion, A2/LLW-specific CD8 T cells differentiate into central memory cells (CM: CCR7+ CD45RA-) and effector memory cells (EM: CCR7- CD45RA-; EMRA: CCR7- CD45RA+). These cells decrease over time, but remain detectable for decades.[59,61] Strikingly, a stem cell-like memory population persists stably for at least 25 years, showing self-renewing capacity and rapid proliferation upon re-stimulation *in vitro*.[59] Although such long-term persistence of memory cells at stable frequencies over decades is expected in immune individuals, this has not been documented in any other human or animal model situation.

2.2.2. CD4 T cells

CD4 T cells play a central role in the adaptive immune system.[62] They are called T helper (Th) cells because they provide help to B cells for antibody production and to CD8 T cells for becoming efficient in killing infected cells. Upon antigen stimulation, CD4 T cells polarize toward different subsets depending on the nature of the cytokines present at the site of activation. While Th1 cells support cell-mediated immune responses, Th2 cells support humoral and allergic responses. In addition, T follicular helper (Tfh) cells play a central role in activating B cells leading to isotype switch and production of long-lasting neutralizing antibodies (nAbs). Regulatory T cells (Tregs) is another subset of CD4 T cells. They express CD25 and FOXP3. Tregs can suppress effector T cells and thus reduce inflammation and reactivity to self or non-self-antigens.

The overall CD4 T cell response to YF-17D is of lower magnitude compared to CD8 T cells but develops slightly earlier, peaking at day 7 post-vaccination with YF-17D.[20,52–54] The YF-17D vaccine induces a mixed Th1/Th2 cytokine signature.[42,55,63] A recent study investigated the dynamics of Tfh cells and observed that the frequency of circulating Tfh cells is stable following primary YF-17D vaccination.[64] However, Tfh cells become activated early after primary vaccination. The Tfh response was found to be dominated by

CXCR3+ CCR6- Tfh cells (Tfh1 subset), which increased 2 weeks post-vaccination, whereas CXCR3- CCR6+ Thf cells (Thf17 subset) were decreased. The frequency of Tregs increased early upon YF-17D vaccination and these cells became transiently activated.[53,64,65]

Few studies aiming at identifying CD4 epitopes revealed that such epitopes are present within all YFV proteins.[58,66–68] A study analyzed DRB1*03:01- and DRB1*15:01-restricted CD4 T cells *ex vivo* using fluorescent peptide-HLA tetramers, revealing transiently increased frequencies of these cells within the first two weeks after vaccination.[58] Interestingly, they could detect $NS3_{145\text{-}161}$-specific CD4 T cells by tetramers even in an unvaccinated DRB1*15:01 individual.

2.2.3. B cells and antibody response

B cells mediate the humoral response, consisting of antibodies, i.e. antigen-specific immunoglobulins (Ig) directed against invasive pathogens.[69] Following cognate antigen encounter, B cells undergo differentiation. IgM is the first class of antibody made by a developing B cells, providing a rapid initial response. IgM secreting plasma cells do not have somatically mutated Ig genes and are short lived. In germinal centers, B cells receive help from CD4 T cells to proliferate, perform antibody class switch to produce IgG, IgA or IgE antibodies, and undergo affinity maturation.

Increased frequencies of activated B cells are observed 15 days after YF-17D vaccination.[20,42,52] Single-cell analysis showed that the early memory B cell response is mediated by classical IgM+ and switched memory B cells, whereas the late memory B cell response was dominated by atypical IgM+, IgD + and switched memory B cells.[70] Plasmablasts, which secreted antibodies in larger quantities than B cells, showed increased frequencies 2 weeks after vaccination.[20,39,64,70] However, although the frequency of plasmablasts almost doubled, this frequency remained low (below 1%) and only a minority of these cells produced antibodies with potent neutralizing activity.[70]

Infection or vaccination often results in the production of nAbs, characterized by their capability to bind a virus in a manner that directly blocks its infectious action. The level of nAb titers is generally considered as the main correlate of protection from viral disease. However, because of ethical reasons that preclude challenging humans with wild-type virus, there is no direct correlate of protection in humans and no consensus on the cutoff for protection. Some laboratories set it at 50%, 80% or even 90% reduction of Plaque Forming Units of Virus in the 1:10 dilution in the varying serum-constant virus Plaque Reduction Neutralizing Test.[71–74] These methodological differences make the direct comparison of studies difficult.

Historically, the humoral response was the first laboratory parameter that was studied in the research of YF-17D vaccination. Several studies revealed that primary YF-17D vaccination leads to the production of nAbs in >98% of individuals from non-endemic regions.[20,39,54,75] The YF-17D vaccine is outstanding for the nAbs raised, as they are not only frequent but also persist for very long, i.e. at least 30–40 years.[61,75–77] However, the percentage of seropositive individuals after primary vaccination was considerably lower, down to ~75%, in vaccinees from endemic regions, reflecting the general notion that individuals in endemic regions require stronger or more frequent vaccination.[18,75]

3. Immune responses to YF-17D booster vaccination

Since 1959, booster vaccinations every 10 years was declared as required for the YF-17D vaccine. However, over the years, numerous studies were performed which identified only low numbers of vaccine failures and high seropositivity. Therefore, the WHO Strategic Advisory Group of Experts on immunization concluded in 2013 that a single dose the YF-17D vaccine was sufficient to provide lifelong protection against the YF disease.[75,78] In 2016, the recommendation to remove the requirement for a 10-year booster dose was enacted. Despite the WHO recommendations, some countries, in particular endemic regions such as Brazil, questioned this decision and still require a booster dose every 10 years.[79,80] The precise level of nAbs required for protection from YF disease remains unknown. Several studies observed an increase after booster vaccination.[20,54,61,80] However, the titers after booster vaccination were significantly lower compared to the titers post-primary vaccination.[20,54] It was suggested that the nAbs that are present prior to booster vaccination negatively influence the booster response through blockade of YF-17D replication.[20] The cellular memory response may further hamper viral replication. Several studies in individuals from non-endemic regions showed that the YF-17D virus remained undetectable in serum after booster vaccination, whereas viremia was detected in most individuals receiving the vaccine for the first time.[16,17,51] Importantly, several studies concluded that nAb titers also decline over time after vaccination.[54,61,77,79–82] These observations, added to the aforementioned observation that primary vaccination induces less seroconversion in individuals from endemic regions, support that endemic regions may profit more from booster vaccinations as compared to non-endemic areas,[18,83] as discussed further below.

Although the exact role of T cell-mediated immunity for protection remains to be elucidated, the latter is gaining increasing attention because T cells may contribute to protection and are likely reducing disease severity. Booster YF-17D vaccination induces minimal CD8 T cell responses compared to primary vaccination.[20,54] This is visible in the limited activation of total CD8 T cells. Also, the magnitude of the A2/LLW-specific CD8 T cell responses is much lower to booster than primary vaccination.[20,54] Nonetheless, booster YF-17D vaccination restored the level of EM CD8 T cells.[80] Although not substantially expanding, A2/LLW-specific CD8 T cells show significant up-regulation of activation and proliferation markers.[20] Interestingly, neither the frequency nor the activation of CD4 T cells was significantly increased upon booster vaccination,[20,54,55,84] reflecting the notion that CD4 T cells generally expand less in response to immunization as compared to CD8 T cells. Together, these data suggest that the CD8 T cell adaptive response is mobilized upon booster vaccination even if not massively as in primary vaccination, reflecting effective immunity and likely also the effectiveness of nAbs that rapidly clear the YF-17D vaccine virus.

Finally, regarding the innate response to revaccination with YF-17D, there is no substantial change in cell frequencies and activation after booster YF-17D vaccination for NK cells, ILCs or monocytes.[20] Granulocytes and DCs have not yet been studied upon YF-17D booster vaccination.

4. Immune responses to YF-17D vaccination in specific populations

Most studies investigating vaccine efficacy were performed on healthy adults, while data on YF vaccination in individuals with specific immune status remain scarce. Of note, studies may involve individuals in endemic or non-endemic regions.

4.1. Individuals in endemic regions

An elegant study compared the immune responses of individuals in endemic (Uganda) and non-endemic (Switzerland) regions.[18] The number of individuals with detectable viremia at days 3 and 7 after YF-17D vaccination was higher in the non-endemic compared to the endemic group. The endemic group showed higher activation of the innate immune system, such as increased frequency of exhausted NK cells at baseline and after vaccination, as well as an increased frequency of proinflammatory monocytes at baseline in the endemic group compared to the non-endemic group. In addition, they observed a higher baseline activation of the adaptive immune system in endemic compared to non-endemic groups, such as higher frequencies of terminally differentiated CD8 T cells, activated CD4 and CD8 T cells, and plasmablasts. The cellular (frequency of YF-specific CD8 T cells) and the humoral (nAb titers) immune responses following YF-17D vaccination was impaired and showed decreased persistence in the endemic group. The increased immune activation at baseline in the endemic group was associated with lower magnitudes of cellular and humoral responses to YF-17D and with reduced memory persistence. One hypothesis is that exposure to more frequent infectious diseases can lead to sustained inflammation and immune activity. The causes and mechanisms of this baseline immune activation in the endemic group remain to be elucidated.

4.2. Children

The WHO recommends that all individuals aged 9 months or older and living in countries or areas at risk should receive yellow fever vaccination. Due to the increased incidence of YEL-AND, the YF-17D vaccine is contraindicated in infants under 6 months of age and is not recommended for those aged 6–8 months, except during epidemics when the risk of YFV transmission may be very high.[21]

As the YF-17D vaccine is routinely given to infants at 9–12 months of age as part of the Expanded Programme on Immunization in endemic countries, infants constitute an important vaccination target in YF-endemic countries. A study reported that children of 23 months seroconvert at lower rates and develop weaker antibody titers compared to healthy adults.[85]

Another study showed that 30 children seroconverted (PRNT $\geq$ 2.5 $\log_{10}$ mIU/mL), whereas 10 children remained seronegative 30 days after primary YF-17D vaccination. A proinflammatory microenvironment, as demonstrated by enhanced synthesis of IL-12 and TNF-α by neutrophils and monocytes, and decreased IL-4 production by CD4 T cells, was observed upon YF-antigen recall in seropositive compared to seronegative children after primary YF-17D vaccination.[86] These findings were corroborated by another study.[87] In addition, the nAb titers after YF-17D vaccination in children was associated with the overall signature of high cytokine production upon YF-antigen re-stimulation.[86] Seronegative children revaccinated 1 year after primary YF-17D vaccination became seropositive (PRNT $\geq$ 2.5 $\log_{10}$ mIU/mL). Upon such revaccination and induction of nAbs, the synthesis of IL-12 and TNF-α by neutrophils was increased.[86]

A long-term longitudinal study followed the antibody response in children concomitantly vaccinated at 8–12 months of age under the Expanded Programme on Immunization schedule against yellow fever and measles. Humoral immunity after 2–6 years largely declined relative to the findings at 4 weeks after vaccination. However, it cannot be excluded that the drop in immunity was due to interference by the concomitantly administered live-virus vaccine against measles.[88]

4.3. The elderly

One study compared nAb titers and viremia in young (18–28y) and elderly (60–81y) travelers vaccinated with YF-17D.[89] This study found that elderly subjects had a delayed antibody response and higher viremia levels. Indeed, ten days after YF-17D vaccination, the geometric mean titer was higher in young individuals compared to the elderly, whereas the difference was no longer statistically significant at day 28. Viremia was significantly more common in the elderly than in the younger participants with higher YF-17D RNA copy numbers in the elderly participants.

4.4. Pregnant women

The use of YF-17D vaccine during pregnancy has not been studied in a large prospective trial, and the WHO stated that the YF-17D vaccine should be avoided during pregnancy or breastfeeding. However, pregnant or nursing women may be vaccinated during epidemics or if travel to a country or area at risk of transmission is unavoidable.[21]

Only one study assessed the immunogenicity of YF-17D in women at various stages of pregnancy during a YF outbreak in Nigeria in the 80's.[90] The results showed that the antibody responses of these pregnant women were much lower than those of YF-vaccinated, non-pregnant women in a comparable control group. Safety assessment from limited data showed that there is no increased risk for major malformations,[91] nor an increased risk for fetal death,[92] however a higher rate of spontaneous abortion was observed.[93]

4.5. Immunocompromised and autoimmune disease patients

In immune-compromised individuals and patients with autoimmune diseases (AID), the YF-17D vaccine is contraindicated due to a risk of uncontrolled viral replication and risk of adverse events. However, such individuals are sometimes vaccinated inadvertently or vaccinated after careful weighting of the risk of YEL-AVD versus the risk of acquiring yellow fever, providing some evidence about vaccine efficacy. For instance, nAbs were produced in 2 patients undergoing different immunosuppressive treatments.[94] In addition, 15 immune-compromised patients were found to mount protective nAbs (>80% virus neutralization with a 1:10 serum dilution) following YF-17D vaccination.[95]

A controlled study showed that the geometric mean of nAb titers was not different between patients under different immunosuppressive drugs and healthy individuals. The detection of YF-specific CD4 and CD8 T cells was similar between the two groups. Furthermore, early-differentiated memory-like T cells persisted, associated with effective expansion upon re-encounter with antigen, suggesting that memory T cells had good potential.[96] A study conducted in patients with AID assessed the immunogenicity of the YF-17D vaccine. These patients seroconverted later than healthy individuals and seropositivity rate was lower after 28 days. The viremia peak was 5–6 days after vaccination in all groups but was lower in patients with AID.[97]

Overall, these results highlight the importance of evaluating the immunogenicity of the YF-17D vaccine in specific populations and how the prior immune status influences the immune response to YF-17D vaccination. In addition, these studies pinpoint to important immune parameters at baseline or linked to immune status that interfere or hinder with the induction of optimal immune responses.

5. Immunogenicity of YF-17D fractional doses

Currently, manufacturers are limited in their production capacity and can only produce 80 million doses worldwide each year, although it has been estimated that 400 million doses are required for unvaccinated populations in high-risk countries.[98,99] Despite the reserve stockpile of 6 million doses maintained by UNICEF, unpredictable YF outbreaks have recurrently resulted in vaccine stockpile depletion. To reduce the consequence of global shortage of YF-17D vaccine, the WHO was urged to the emergency solution of vaccinating with a fractional dose.[100,101]

Three randomized controlled non-inferiority clinical studies were conducted. First, the study from the Netherlands compared the intradermal administration of 0.1 ml fractional dose (1/5th of the standard dose) to subcutaneous administration of the standard dose of 0.5 ml. The volunteers involved in this study were young (20–50y) healthy men and women.[99,102] The choice of the administration route arose from the hypothesis that intradermal injection would be highly immunogenic due to the direct targeting of antigen-presenting cells in the papillary dermis. Second, the study from Brazil compared several fractional doses (10′447 IU, 3′013 IU, 158 IU, and 31 IU) via regular route of administration (intramuscular or subcutaneous) compared to the standard dose (27′476 IU). Only young male army recruits (18–20y) were enrolled in this study.[103–105] Third, the study performed in research centers in Uganda and in Kenya, with healthy female and male volunteers (18–59y), compared standard and fractional doses (1/5th of the standard dose) administrated subcutaneously.[106]

The Dutch study showed that seroconversion (defined as serum dilution at which 80% viral neutralization occurred) induced by an intradermal 1/5th reduced dose and by the standard dose did not differ between 2 weeks and 1 year after vaccination.[102] A follow-up study reported that participants had nAbs at protective levels more than 10 years after fractional dose vaccination,[99]

The Brazilian study showed that seroconversion (determined by a 50% viral plaque reduction by anti-YFV nAbs) was equivalent in participants vaccinated with 1/46 dilution (587 IU) or standard dose.[103] Additional investigation showed that peak of viremia was reduced and delayed at 1/46 dilution, while the serum cytokines were equivalent to standard dose.[105] The follow-up study of this group showed that seroconverted participants in reduced doses remained seropositive 8 years later.[104]

The study conducted in Africa showed that most participants had high nAb titers and that the rate of seroconversion (determined as post-vaccination nAb titers at least 4 times of pre-vaccination, measured by 50% plaque reduction neutralization test) 28 days after YF-17D vaccination were non-inferior to standard dose (non-inferiority criteria defined as less than 10% decrease in seroconversion in fractional compared to standard dose 28 days after vaccination). Seroconversion rates and nAb titers remained high up to 1 year after YF-17D vaccination for both fractional and standard doses.[106]

Based on these data, the WHO recommended that dose sparing should contain at least 1′000 IU.[100] The number of vaccinated individuals in the described studies is too low to assess the rate of serious adverse events upon vaccination with fractional dose of YF-17D.

6. Profiling and modeling immune events during YF-17D vaccination

Because of its renown efficacy, the YF-17D vaccine has also been used to profile and model immune responses and to investigate associations between various immune parameters, with the overall goal to identify key immune determinants able predict immunogenicity and immunity, i.e. protection from YF disease.

6.1. Correlations between immune events during YF-17D vaccination

As mentioned above, although most vaccinated individuals develop long-lasting nAbs, the titers vary amongst individuals. In order to identify prognostic markers, it is important to identify parameters that correlate with nAb titers.

Using high-throughput technologies, Querec at al. identified the gene encoding for the B cell growth factor BLyS-BAFF (*TNFRSF17*) as a central positive predictor of the antibody

response.[50] Furthermore, nAb titers were positively correlated with the frequency of A2/LLW-specific CD8 T cells at day 14.[18] In contrast, the nAb titers were negatively associated with baseline immune activation (baseline frequencies of activated naïve cells B cells, CD38+ tissue-like memory B cells, PD1 + memory CD8 T cells, and CD14+ CD16+ monocytes).[18] A negative association was also found between the nAb levels detected before revaccination and after boosting, again suggesting that preexisting nAbs inhibit the humoral response following booster vaccination.[18,54,80] The frequencies of Tfh1 cells at day 14 and day 28 positively correlated with nAb titers, whereas Tfh17 cells negatively correlated with nAb titers.[64] For CD8 T cells, both the magnitude of the response and the activation levels in CD8 T cells showed positive correlations with the viral load.[17,20] As the virus load increased above a certain threshold, the magnitude of the CD8 T cell response saturated.[17,20]

Interestingly, lymphocyte levels transiently dropped in peripheral blood early after YF-17D vaccination. The T cell drop was restricted to cells expressing the chemokine receptor CCR7. Furthermore, the CD8 T cell drop positively correlated with the percentage of CD8 T cells co-expressing CCR7 and CD69,[107] suggesting that lymphocytes are trapped in lymphoid tissues. This T cell drop was negatively correlated to immunogenicity parameters, including T cell activation, the magnitude of the antigen-specific CD8 T cells, and nAbs.[107]

A systems biology approach made many interesting observations of the molecular and cellular dynamics induced by YF-17D vaccination. For example, it revealed that gene signatures involved in glucose metabolism and the integrated stress response predicted the T cell response.[18] Future immune profiling studies could improve and predict the immunogenicity of emerging vaccines. However, while investigations on YF-17D vaccination have increased the mechanistic understanding of this efficient immune response, the individual observations made across studies do not yet provide a comprehensive unified picture (Figure 1, Supplemental Table 1). This reveals the complexity of immune actors and parameters that determine an optimal immune response. Furthermore, whether the findings from YF-17D studies may be applicable to other immune responses remains to be elucidated.

6.2. Modeling T cell responses

With major technical advances to track immune responses, many basic questions on the kinetics of virus-specific immunity in humans can be addressed. In particular, the mechanisms regulating proliferation and differentiation of T cells remains unclear. Multidisciplinary studies combining experimental data and mathematical modeling are increasingly used to gain insights into this kinetics in the context of YF-17D vaccination.

The recent identification of YFV-specific stem cell-like memory CD8 T cells raised the question whether this subset is responsible for memory maintenance. New evidence supports the notion that stem cell-like memory T cells originate directly from naïve CD8 T cells,[108] whereas other studies concluded that memory CD8 T cells derive from effector cells.[19,109] Several models of T cell differentiation have been proposed.[110] A recent elegant murine study formerly demonstrated that central memory T cells derive from rare stem-like memory CD8 T cells present during the acute response to viral infection.[111] Human data on YF-17D vaccination revealed the presence of CD8 T cell memory subsets already in the acute phase of the response, supporting models where memory cells arise very early without an obligatory transition through an effector stage.[112] Interestingly, the latter human data submitted to mathematical modeling suggest that the kinetics of stem cell-like memory T cells is compatible with their role in memory maintenance.[112,113]

The initiation of T cell responses occurs in the draining lymph nodes, where the cells are activated and then migrate to the tissues where they are required for immune defense. Unfortunately, obtaining human samples to delineate the spatial dynamics of T cells throughout the body is very limited. Nevertheless, computational analysis and available experimental data obtained from YF-17D vaccinated individuals can be used to address these questions. We believe that the identification of critical immune parameters, the understanding of the complex interplay, and the prediction of immunogenicity will benefit from such mathematical modeling. While well designed mouse studies may provide mechanistic proof, human studies evaluate whether such findings are translatable and explore the effects of the wide genetic and phenotypic heterogeneity.

7. Conclusion and perspectives

YF-17D vaccination is highly successful, inducing robust and long-term immune responses. It can be used as a model to answer longstanding questions of the immune system, and to identify the key determinants of optimal immunogenicity. Such insights may improve the knowledge and the rationale for the design of more powerful vaccines against microbial infections as well as for other medical interventions such as cancer immunotherapy.

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Conflicts of Interest

The authors declare that they have no competing interests.

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