

**EFFICACY AND DURATION OF IMMUNITY FOLLOWING YELLOW FEVER VACCINE: A
SYSTEMATIC REVIEW ON THE NEED OF YELLOW FEVER BOOSTER EVERY 10 YEARS**

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INTRODUCTION

Yellow fever (YF) disease poses a considerable health care burden and a serious risk to residents of endemic regions, non-immunized travellers entering endemic areas, and people moving within their own country from low-risk to high-risk regions(1).

Because there is no effective treatment for YF disease, prevention is critical to lower morbidity and mortality. The 17D yellow fever vaccine has been available for more than 70 years now. This live-attenuated virus vaccine has had a major impact on the incidence of YF disease (2). Its efficacy and safety profile has been well established during more than 50 years of large-scale use involving more than 500 million doses (3).

Administration of YF vaccine is recommended for persons aged ≥ 9 months who are traveling to or living in areas of South America and Africa in which a risk exists for YF virus transmission(4). International Health Regulations stipulate that the vaccination certificate for YF is valid beginning 10 days after administration of YF vaccine for primary vaccine recipients and requires a revaccination after 10 years(5). This recommendation has been questioned because many studies have suggested that the duration of immunity following YF vaccine may last for several years in as many as 80% of vaccinees. Most of these studies used the titre of 1:10 as a surrogate of protective immunity. A question arises: Does the presence of neutralizing antibodies in a titre $>1:10$ really indicate protection? If so, is 80% a broad enough coverage to discourage yellow fever booster? Is it the same for yellow fever endemic areas and travellers? How is the antibody response to the booster in healthy people and in special groups such as HIV-population, pregnant woman, children, severe malnourished?

To address these interrogations, we performed a systematic review on the protective efficacy of YF vaccine and the duration of immunity following vaccination in residents of endemic areas and in travellers. The aim of this review was to assess the need for YF booster doses every 10 years based on the efficacy profile and the available evidence on duration of immunity. We also searched for any reports of YF disease that developed in YF vaccine recipients post-vaccination and the time since they were immunized. A thorough discussion is offered about the possible external factors influencing the development of immunity such as conditions of vaccine storage, handling of the cold chain, use of multidose vials or vaccine administration.

We explored as well the scenario of especial groups in which the booster may need to be considered such as children, pregnant woman, HIV-population or severe malnourished. Finally, we provide recommendations based on the best available evidence for travellers and people living in endemic areas as well as lines for future investigation.

SEARCH METHOD

We used the EndNote X5 Software. We searched in two databases: PUBMED NCBI and SCIELO (scientific electronic library online). The search was conducted in four languages: english, french, portuguese and spanish applying 2006 as a date limit. When searching in PUBMED database we used Mesh terms and MeshTerm-pertinent combinations: “yellow fever vaccine” [Mesh], “immunity” [Mesh], “antibody formation” [Mesh], “antibodies” [Mesh], “neutralizing antibodies” [Mesh], “travel” [Mesh], “immunization” [Mesh], “booster immunization” [Mesh], “Secondary Immunizations” [Mesh], “revaccination” [Mesh], “Human Immunodeficiency Virus” [Mesh], “Acquired Immune Deficiency Syndrome” [Mesh], “HIV seropositivity” [Mesh], “Malnutrition” [Mesh], “Immunocompromised Hosts” [Mesh], “Immunocompromised Patient” [Mesh], “pregnancy” [Mesh], “infant” [Mesh], “Child, Preschool” [Mesh] and “aged” [Mesh]. We also combined Mesh Terms with relevant terms as textword: efficacy[Text Word], neutralization test[Text Word], endemic[Text Word], immunocompromised[Text Word], elderly[Text Word].

We identified 419 related studies in the electronic databases. After removal of duplicates we obtained 216 abstracts. According to title, 55 were selected for full text retrieval because they were relevant to YF vaccine and efficacy or duration of immunity in the general population or in special groups (eg. HIV, pregnant). We also scanned reference lists of included papers in order to identify additional relevant studies. No date limit was applied in this case. All but two of the included papers identified in the SCIELO database were also found in PUBMED database.

PROTECTIVE EFFICACY

Correlates of protection

In order to assess the protective efficacy of YF vaccine; we first need to establish the correlates of protection. There are no studies on humans that determine the correlates of protection for this live-attenuated virus vaccine. Therefore, the minimal protective level of neutralizing antibodies induced by 17D YF vaccine is estimated from dose-response studies in rhesus monkeys that were challenged after immunization with virulent YF virus (6, 7). Based on the evidence of these studies, the Food and Drug Administration approved a log₁₀ neutralization index (LNI) > 0.7 as a surrogate of protection against YF disease following YF vaccination. However, the LNI assay requires an amount of serum suitable for animal studies or clinical trials but not for routine screening among humans(4). As a result, a plaque reduction neutralization test that uses a constant amount of virus and varying dilutions of serum has replaced the LNI as the diagnostic test to determine the serum antibody titre. The 1:10, 1:20 titres frequently used as cut-off titres have been estimated by extending the results of studies on passive immunization in hamsters to define the level of antibodies required to protect against virus challenge(8) and the available evidence on the titres considered to be protective for other related viruses such as Japanese encephalitis virus(9). Overall, there is agreement in the assumption that a titre of >1:10 is associated with protective immunity considering the

paucity of YF cases in immunized persons(10, 11). Nonetheless, antibody titres measured by serum-dilution plaque-reduction tests have shown to be variable across studies and still no level of serology considered to be protective is fully established.

Additionally, the studies included in this analysis vary in relation to the assay used to determine the neutralizing antibody titre. The earlier studies used the mouse protection test either by intracerebral or intraperitoneal technic. The later ones replaced tests in mice with tissue culture neutralization tests. See Table 1. Even across studies that used plaque-reduction neutralization test, the percentage of plaque-reduction used to define the titre end-point was also variable (between 50% and 90%). The lack of a standardized test makes it difficult to compare efficacy data from multiple studies. However, seroconversion rates seem to be similar across studies suggesting that it is not significantly influenced by differences in test method.

Immunogenicity

Nine studies (12-20) were included in this review that addressed the efficacy of YF vaccine in terms of immunogenicity. See table 1. Seroconversion rates were consistently above 90% among eight out of nine studies. Only one study (13) reported a 75% seroconversion rate 6 months after a mass vaccination campaign. In this study, operational failures were considered by the authors although they could not confirm the external factors were indeed the cause of the lower seroconversion rate. See section on influence of external factors.

The bibliographic search identified two large randomized controlled trials in children and adults using two different YF vaccines (Arilvax and YF-VAX) and LNI as the method to determine neutralizing antibodies: Belmusto (17) reported seroconversion rates of 90.6% to 94.9% among 1107 healthy children whereas Monath (21) found seroconversion rates as high as 98.6% to 99.3% among 1440 healthy adults. Following antibody kinetic studies, Monath also described that protective levels of neutralizing antibodies are found in 90% of recipients within 10 days and in 99% within 30 days (20). Seroconversion rates are similar regardless of vaccine substrain, manufacturer, assay used to measure neutralizing antibodies or method of administration(15, 17, 21).

It is to be noted that 4 of the studies evaluated vaccine performance in the context of mass vaccination campaigns (12, 13, 16, 19). The seroconversion rates were in the range of 89.7% to 98.2%. Moreover, Tavares reported a seroconversion rate of 94% (363/387) following a vaccination campaign in a remote region of Brazil characterized by its difficult access. He used minimally trained personnel and very limited resources. These findings suggest that YF vaccine can be as effective following mass vaccination campaigns as in controlled clinical trials.

Even though the effectiveness of YF vaccine in humans has not been formally tested in controlled clinical trials, several observations attest to its effectiveness: the reduction of laboratory-associated infections in vaccinated workers, the fact that jungle YF in Brazil and other South American countries occurs only in unimmunized persons, that immunization during outbreaks results in rapid disappearance of cases and the fact that populations with high vaccine coverage have experienced a marked reduction in YF incidence despite continued human exposure to the enzootic cycle(22). In conclusion, the YF vaccine is very effective in healthy individuals displaying high seroconversion rates among different study populations.

Finally, there is little conclusive evidence on the cell-mediated protective effect of YF vaccine. It has been demonstrated that CD4+ and CD8+ T cells increase during the first 14 days following YF vaccination, before the onset of neutralizing antibody production. This suggests an activation of the cellular immune system (23, 24). These findings have had authors suggest that vaccinees without detectable NT titres could also be properly protected due to cellular immunity and as a consequence, studies focusing exclusively on antibody titres may underestimate YF vaccine protection efficacy (23).

Infants and Children

Infants and children represent one of the main populations in which YF vaccine is indicated in endemic areas (17). This mainly constitutes the preventive component of YF strategy given the fact that children are not usually involved in activities with high risk of exposure to YF virus. However, during outbreaks children are equally affected. An old study carried in a YF endemic area in Peru suggested young age was a host factor affecting susceptibility. They found that infection with viscerotropic strains during an outbreak was more lethal in infants than older children (25).

The main strategies to control yellow fever combine immunization against the disease and surveillance. The prevention component contemplates the administration of YF vaccine as part of routine infant immunization and preventing outbreaks in high risk areas through mass campings. In order to be effective, WHO states that these strategies should ensure a minimum coverage of 80%. Regarding infant immunization, the WHO perspective is that the vaccine should be routinely administered at the same time as measles vaccine, i.e. around nine months of age but with a different syringe and at a different spot (26, 27).

The UNICEF/WHO Technical Group on Immunization in Africa has recommended routine childhood immunization against YF since 1988. Vaccine uptake has been slow, however, and there is a disparity between at-risk countries and countries with immunization programs, with very few countries achieving coverage rates greater than 80%. In South America YF vaccine has also been included in childhood immunization programs although most of them tend to focus on Amazonian jungle regions, leaving urban areas at risk of YF outbreaks. Moreover, in South America the immunization strategies and vaccine coverage rates vary considerably. Some enzootic regions of Brazil and Bolivia have achieved vaccine coverages over 70% while some endemic areas have only reached 30% coverage (3).

Infants and children constitute a special population in the YF efficacy analysis. Some old studies suggested that children did not develop an effective immunological response as well as adults after YF vaccination or lost immunity more rapidly (28, 29). These studies had methodological limitations such as the use of intraperitoneal protection test in young mice that was later found to be less sensitive than later techniques. However, several more recent studies have also shown that the seroconversion rate of children is significantly lower than that of adults (13, 17, 21, 30, 31). See table 1.

Interestingly, a recent pediatric trial showed lower neutralizing antibody responses to YF-VAX® and Arilvax® (90.6 and 94.9% seroconversion and geometric mean LNIs of 1.26 and 1.32, respectively) (17) compared to a study of the same vaccines in adults (99.3% and 98.6%

seroconversion and geometric mean LNIs of 2.21 and 2.06, respectively) (21). Moreover, Belmusto and collaborators found that the difference in seroconversion rate was most pronounced in the two youngest age groups (9–18 and 18–36 months old) which is exactly the age at which the childhood immunization programmes recommend YF vaccine administration.

It is important to consider that some other studies have not supported these observations, reporting that there is no significant difference in the percentage developing antibodies or in the duration of the immune response when children are compared with adults. (32, 33). These studies used periods of approximately 5 years after immunization to reach these conclusions.

This subject remains unsolved and it is of vital importance in the formulation of public health regulations which is why it is necessary to further assess YF vaccine immune response in children in prospective studies. The ideal study population should focus on children immunized as part of their routine childhood immunization schedule. Additionally it would be interesting to investigate not only the antibody titres in this population but also the incidence of overt YF disease in this age group. Most YF endemic areas have children with malnutrition, parasites and anemic. Therefore, these host factors should be considered in future investigation regarding immune response and duration of immunity in children.

The importance of external factors in YF vaccine immune response

Since YF vaccine is a live-attenuated virus vaccine its performance can be affected by vaccine storage, handling or administration. It is possible that this explains the higher seroconversion rates in adults than in children considering the fact that operational failures in the conservation or application of the vaccine may have occurred because most of these studies used cohorts following mass immunization campaigns. In these settings, vaccines may have not been properly handled or administered.

The handling of cold chain may be difficult in low-income endemic areas. Moreover, mass campaigns usually use multidose vials of reconstituted vaccine. Vaccine manufacturers recommend these multidose vials should be stored at 2–8°C for up to an hour. Any vaccine that is not used within 1 hour of reconstitution must be discarded. The quality of information systems used by health services has to be properly considered as well in order to discard external factors as the cause of YF vaccine failure.

The evidence on children's lower seroconversion and some studies that showed up to 26% of seronegativity in vaccinees following mass immunization campaigns (31, 34) emphasizes the need of routine systematic monitoring by health services of antibody titres months after this kind of campaigns to ensure vaccine coverage. For this to be possible it is necessary to develop a tool for rapid and low-cost diagnosis that does not require samples to be sent to special institutions.

In relation to this subject, Niedrig reported in 2008 high sensitivity and specificity of indirect immunofluorescence assay for the detection of immunoglobulin M (IgM) and IgG antibodies against yellow fever virus following vaccination. He concluded that the detection of IgG antibodies by IFA is a good marker for the presence of an antibody response after YFV vaccination compared to the time consuming PRNT (35). However, the performance of this

test depended on the previous exposure to flaviviral antigens (natural infection of previous immunization for another agent of the flaviviral family) because YFV vaccinees with preexisting heterologous flaviviral immunity developed broadly cross-reactive IgG antibodies. Ig M antibodies were fairly specific in cases of primary vaccination even in individuals with preexisting flavivirus antibodies but it was also less sensitive.

Influence of dengue immunity on YF immune response

Since many YF endemic areas overlap with those of dengue transmission, we found it relevant to explore whether dengue immunity affected the immune response to YF vaccine. If this were to be true, it would be crucial in our interpretation of the protective efficacy of YF vaccine in dengue endemic areas. Our search identified studies with conflicting results.

Yellow fever virus and dengue virus share some epitopes and therefore, induce crossreactive antibodies (36). Gomez et al reported that YF 17 D virus was neutralized (52-100 %) by dengue sera more efficiently than non-dengue immune sera ($p < 0.001$) (31). One retrospective study reported cross-reactivity rates as high as 40% using dengue antibody capture ELISA and YF neutralisation test (37). Eventhough the ELISA is a highly sensitive test, it is hampered by non-specific reactions which is exactly the problem in flavivirus diagnosis (38). Therefore, these results should be taken with precaution. Moreover, in this study the 19 samples following YF vaccination showed neutralizing antibodies by PRNT and 12/13 samples of YF cases were confirmed by PRNT. It can be concluded that the high seropositivity rate as measured by PRNT in YF vaccine efficacy studies may be trustworthy even in dengue endemic areas where other tests show high cross-reactivity.

In contrast to the above mentioned studies which show high crossreactivity rate, others show that there is no evidence to suggest that natural flaviviral infection contributes to YF seropositivity(39-41) nor that prevaccination with Group B arboviruses interferes with YF neutralizing antibody pattern formation (42). In the retrospective study conducted by Poland et al. it was found that seropositivity rates in second world war veterans differed according to the branch of service (60% for army personnel versus 97% in navy/air corp personnel) (43).Logically, natural exposure to heterologous flaviviruses as a possible cause of persisting YF antibodies would be expected to occur more frequently among army veterans who have a greater risk of exposure to vector-borne diseases. These findings suggest that the high seropositivity rates found many years following vaccination were not explained by natural flaviviral infection with other related viruses. Moreover, a recent study in Brazil showed no difference in the neutralizing titres against YFV between dengue virus-naïve and dengue virus-exposed subjects. (44).

It has not been demonstrated that previous dengue immunity protects against YF. However, it has been observed in old studies that in areas of simultaneous circulation of both flaviviruses people infected with yellow fever remain asymptomatic or develop a minor illness. (45-47). Besides, dengue endemicity has been proposed as the reason for YF absence in some Asian regions (48). If this were to be true,crossreacting antibodies would mean crossprotection and we could be certain that neutralizing antibodies reflect YF immunity even in areas of dengue or other flavivirusendemicity.

Immunological response to booster

Our search identified two studies that suggest the titres found in revaccinees do not differ from the ones found in first-time vaccinees. Rosenzweig reported that 9 out of 24 subjects were revaccinated within 8 years of testing. The titres of revaccinated individuals did not differ from the ones who had received only one dose (49). Another study monitored early and late events of immune system activation after primary and secondary YF vaccination in 17 healthy individuals, five of whom had been vaccinated once at least 10 years before. The authors showed that revaccination was followed by a minor and transient increase of neutralizing antibodies that disappeared approximately 7 months after the primary challenge (23). In this study, all 5 revaccinees were found to have neutralizing antibodies at a protective level before secondary immunization. These findings indicate that if proper immunity has developed following primary vaccination, then revaccination would not provide any additional benefit.

In contrast, when pre-booster serology is low or negative, the efficacy of revaccination is well documented. This remains true regardless of the reason for seronegativity. Whether there was no seroconversion or the neutralizing antibodies decreased below detectable levels over time; when serology is low or negative YF booster elicits an effective immunological response (11, 50, 51). Hepburn conducted a retrospective study on YF vaccination among laboratory workers receiving annual serologic assessment. He defined an appropriate immune response to booster as a four-fold increase in serologic titres. He found a 78% (646/829) immune response rate among subjects with low serological titres (1:10) versus 10% (8/79) among individuals with pre-vaccination titres above 1:40, meaning that pre-vaccination serology correlates inversely with the immune response to YF booster. In the study conducted by Bonnevie-Nielsen, only one out of ten subjects who had received a dose of YF vaccine 2 years before had an antibody titre < 1:10. At 7 days following revaccination this subject successfully developed protective neutralizing antibodies. The remaining nine were seropositive throughout.

DURATION OF IMMUNITY

Evidence on duration of immunity in healthy individuals

Historical studies are very valuable in assessing the duration of YF immunity following YF vaccine. Most of them are retrospective studies including cohorts of special populations with specific characteristics: they received a single vaccine dose in the past during periods where vaccination was required for defined groups, they lived in areas where yellow fever is not endemic and they did not travel to areas where immunization is required since they received their primary vaccination.

Seven studies adequately addressed the duration of immunity more than ten years after yellow fever vaccination (Groot 1962)(Rosenzweig 1963)(Poland 1981)(Niedrig 1999)(Gómez 2008)(Coulange 2011)(de Melo 2011). The time elapsed since last immunization was in the range 10-40 years. The percentage of individuals with antibody titres at a protective level varied from 74.5% - 100%.

One of the most representative historical studies is the one of Poland et al. He found that neutralizing antibodies persisted for more than 30 years in 80.6% of veterans of the Second World War (43). Interestingly, he found that seropositivity was especially high in the subgroup of navy/air corp personnel (97% versus 60% for army personnel). It was speculated that a significant proportion of army veterans either did not receive the vaccine or received improperly handled vaccine. Several other studies have demonstrated the long-lasting immunity following YF vaccination as many as 38 years after in as many as 80% of vaccinees. (39, 49, 52). See table 1. Groot reported in 1962 that 76% of 108 residents of a non-endemic YF region in Brazil had readily demonstrable neutralizing antibodies to the french neurotropic virus (FNV) strain of YF virus(21% were partially positive). A year later, Rosenzweig et al. conducted a retrospective study with 24 retiring Marine and Navy personnel and found that 100% had neutralizing antibodies with a LNI of 2.6 after 16-19 years following immunization. In 1999 Niedrig further lengthed the duration of immunity to 40 years. He reported a titre >1:10 in 74.5% of 209 subjects more than 10 years after vaccination. A recent study reported antibody titres at a protective level in 95% of persons older than 60 years with a median time after immunization of 14 years(53). Moreover, the fact that there are no known cases of YF infection in patients who have been vaccinated and developed a documented appropriate initial response supports the hypothesis that protection may be life-long (21). Only one study (de Melo 2011) reported that only 65% (13/20) had neutralizing antibodies at a level >1:10 at ten years after immunization. This was a small retrospective study that used randomly selected subjects from immunization records. All 20 patients evaluated had neutralizing antibodies after 10 years. However 35% (7/20) had an antibody titre < 1:10.

Eventhough there is evidence suggesting YF immunity may persist for life, it is to be noted that neutralization titre values show a time-dependent decrease(13, 31, 44, 52). One study showed NT titre > 1:10 decreases from 94% in the first year following vaccination to 75% 10 years after(52). This has been the main argument behind the recommendation to booster YF vaccination every 10 years (10). However, vaccination coverage of approximately 60 to 80% of the population at risk seems to prevent YF outbreaks throughout the affected regions(54). Therefore, from a public health point of view the fact that antibody titres decrease over time is not revelant to endemic regions unless this decrease falls below 60%.

REPORTS OF VACCINE FAILURES

Wild type yellow fever that developed in YF vaccinated persons has been reported only on rare occasions. Our literature search identified 12 reported cases from 1942 to January 2012. See table 2.

Historically, three cases (two fatal) were reported in soldiers serving in West Africa during World War Second. All three men had received preventive inoculation at least one year before developing the disease(55). In 1952, a fatal case of yellow fever was reported in an immunized European working in Uganda. He had been vaccinated four years and eighty-one days before his attack(56). Later, in 1988, another case of yellow fever occurred in a vaccinated European tourist who travelled to Africa. She was a 37 year-old Spanish woman who had been

vaccinated against yellow fever 5 years earlier in Madrid and showed a valid international certificate of vaccination(57). In an analysis of confirmed yellow fever cases from the National Surveillance System from 1998-2002 in Brazil, it was noted that 5 cases (two fatal) had a history of previous immunization 8 to 62 months before onset of disease (58). The clinical presentation varied from mild to severe. In this study reasons for possible vaccine failure could not be eluted.

In 2001 there was a mass vaccination to control an outbreak of sylvatic yellow fever in a Brazilian region. During the outbreak the surveillance system identified two fatal cases temporally associated with YF vaccination. In both cases, the sequence data on the 3'NCR and the prM/E regions confirmed wild-type YFV as the etiologic agent responsible(59). The first case was a 39 year-old man with chronic leucopenia who died 8 days after returning from an enzootic area and 4 days after vaccination. The second case was a 69 year old man living in a rural area where cases of sylvatic yellow fever had been confirmed. He turned sick 14 days after immunization and died 8 days after. This second patient used corticosteroids frequently due to allergy. For this later case it was suggested by the author that the immune response mounted at the time of the infection with wild type yellow fever virus may have been insufficient to be protective given the fact that neutralizing antibodies may take as long as two weeks to develop (23).

Our literature search could not identify any report in which antibody response to yellow fever vaccination had been demonstrated prior to the development of clinical yellow fever. On the other hand, it is well known that because the current17-D strain of YF vaccine is a live-attenuated vaccine,vaccine efficacy may be affected by several external factors(60). Therefore, it remains uncertain whether these reported cases failed to develop immunity to a properly administered vaccine or received a vaccine that had deteriorated due to improper cold chain handling, storage or usage.

SPECIAL GROUPS

Safety profile in immunocompromised patients

Serious adverse events following yellow fever vaccination are rare. Moreover, the number of these serious adverse events attributable to yellow fever vaccine that have been proven by clinical examination and detailed laboratory investigations is very small (3). However, since it is a live-attenuated virus vaccine, yellow fever vaccine raises especial concerns regarding safety in immunocompromised patients. The severe adverse events related to yellow fever vaccination include neurologic, multisystem, or anaphylaxis reactions.

The US Advisory Committee on Immunization Practices (ACIP) indicates that YF vaccine is contraindicated in those people with sensitivity to eggs or chicken, infants younger than 6 months, individuals with thymus disorders or who have had a thymectomy, individuals with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), and individuals on immunosuppressive therapies. ACIP advises precaution in vaccinating infants 6–8 months, individuals > 60 years, individuals with asymptomatic HIV infection and moderate

immune suppression (CD4 count = 200–499/mm³ for persons > 6 years or 15–24% of total lymphocytes for children < 6 years), pregnant women, and breastfeeding women (4). The important issue regarding safety is that there is limited database for these recommendations.

The safety profile of yellow fever vaccine is beyond the scope of this review. Nonetheless, it is crucial to consider it before making recommendations for some documented vulnerable groups. Here we present a summary of the main findings regarding yellow fever vaccine safety in immunocompromised patients. Special groups considered were HIV, pregnancy, and other immunocompromised patients including malnutrition, thymus disease, transplantation and immunosuppressive therapy.

HIV

Published studies on the safety and immunogenicity of YF vaccines in HIV-positive people are limited to small studies and case reports, mainly of travellers with CD4 >200 cells/mm³. Scarce data exists on the safety of yellow fever vaccine and HIV infection with advanced disease.

The World Health Organization (WHO) states that monitoring vaccination campaigns in countries where the prevalence of HIV is about 1–5% has identified only a few HIV-positive individuals among those with any serious adverse events following immunization (AEFI) which mean a lot of people with undiagnosed HIV may have received the vaccine without developing any serious adverse event. No clear risk has been identified that precludes the use of YF vaccine in HIV infected people(61).

Several studies have supported the recommendation that patients infected with HIV with stable clinical status and T CD4-cell count above 200 cells per millimetre cube may be vaccinated (62). Data about the immune response to the vaccine are scarce but show consistent immunogenicity in HIV positive people with CD4 counts >200 cells/mm³.

Our search identified a 2012 systematic review of the published literature on adverse events associated with yellow fever that included HIV patients in their analysis (63). They found only one study that used active surveillance to identify adverse events. It was conducted on 174 HIV+ patients of the Swiss Cohort and no serious adverse events were observed among the entire study population. This study reported the characteristics of 102 of those HIV+ patients. The median CD4+ cell count was 537 cells/mm³ and the HIV RNA level was undetectable in 41 of 102 patients. It is to be highlighted that 7 patients had CD4 cell counts <200 cells/mm³ at the time of immunization (64). The systematic review also described six retrospective studies that used passive surveillance to identify adverse events in HIV patients who attended travel clinics in France (five studies) and the University of Sao Paulo in Brazil (one study) and received 17D vaccine(65-70).Pistone et al reported that among the 23 HIV patients included in his study, one had a CD4+ cell count <200 cells/mm³. Two out of seven of the reported HIV patients who received yellow fever vaccine in the brazilian study conducted by Ho had also CD4+ cell count below 200 cells/mm³. These six studies included a total of 191 HIV+ patients. None of them reported serious adverse events, not even among the 10 patients with CD4+ < 200 cells/mm³.

Our search identified one fatal case of meningoencephalitis, occurring shortly after the receipt of 17D vaccine. It was reported in a Thai adult with a previously undiagnosed HIV infection and a CD4 cell count of 108 cells/mm³, but testing to prove causality was not available (71).

Finally, it is to be noted that even when we combine all the above study subjects, the total population of HIV infected individuals analyzed is still small and therefore, conclusions must be taken with precaution.

Pregnancy

The systematic review conducted by Thomas and collaborators on adverse events associated with yellow fever identified four studies on active surveillance and four studies on passive surveillance to identify YF vaccine adverse events in pregnant women (63). All the studies were of vaccination campaigns. On the active surveillance studies, a total of 1,381 pregnant females was studied, and rates of AEs above those AEs routinely expected in pregnancy were not found. The four studies that used passive surveillance consisted of small samples with substantial risk of underenumeration and underinvestigation. Three of them reported no serious adverse events. Only one small study provides some evidence that women vaccinated with YF vaccine during early pregnancy have an increased risk of having spontaneous abortion (72). It was a hospital-based case-control study conducted in a Brazilian town after a YF vaccine campaign that followed an epidemic of dengue. The study included 39 women who attended a university hospital with spontaneous abortion (cases) and 74 pregnant women attending the antenatal clinic of that hospital (controls).

A prospective study was conducted by Nasidi et al during an outbreak of yellow fever in Nigeria in 1986-1987, women at various stages of pregnancy were vaccinated against YF, either because those pregnancies were not known at the time or because they requested vaccination out of fear of acquiring the disease. Follow-up of these women and their newborn children for 3-4 years showed no abnormal effect that could be attributed to the YF vaccine, which suggests that vaccination of pregnant women, particularly during a YF epidemic, may not be contraindicated (73).

In a 2006 Brazilian study of the effects of yellow fever immunization inadvertently used in early pregnancy during a mass campaign in Brazil. A total of 19.6% of women reported mild adverse events (headache, fever or myalgia) and the frequency of malformations (2.3% or 7/304 babies), miscarriages (2.5% or 11/441 pregnancies), stillbirths (0.7%) and premature delivery (7.8%) was similar to that found in the general population (19).

There is very limited safety data on the use of YF vaccine in breastfeeding women and their children. However, there have been five reports that have raised concern in this group, two of whom are well documented. The first report occurred in Brazil 2009. It was a case of meningoencephalitis requiring hospitalization in an exclusively breast-fed infant whose mother recently had received YF vaccine during a postpartum visit. The presence of 17DD yellow fever virus was detected by reverse transcription--polymerase chain reaction (RT-PCR) in the infant's cerebrospinal fluid (CSF). The patient recovered completely, was

discharged after 24 days of hospitalization, and had normal neurodevelopment and growth through age 6 months. (74) The second was a probable case of transmission. Kuhn reported that the mother of a Canadian infant received 17D and inactivated typhoid vaccines when her infant was 10 days old, and at 40 days of age the child had seizures. Serum IgM enzyme-linked immunosorbent assay (ELISA) was positive for YF, a plaque reduction neutralization test (PRNT) was positive at 1:5,120, and the hemagglutination inhibition titer was positive at 1:160, but YF IgG was negative. CSF IgM ELISA was positive, but PCR was negative for YF virus. The clinical presentation, temporal relationship to maternal vaccination, absence of alternative pathogens and immunologic evidence in both serum and cerebrospinal fluid of the infant were strongly supportive of acute central nervous system infection with vaccine strain of yellow fever (75). The other three cases came from a brief note of the Global Advisory Committee on Vaccine Safety that stated that they had reviewed recent data suggesting that three neonates (aged 10 days, 23 days, and 5 weeks) developed encephalitis as a result of infection with YFV virus transmitted to them from recently vaccinated mothers. All three infants were being breastfed, but the mode of transmission was not established and no further detail was provided. All three mothers had received the vaccine for the first time during the infant's first month of life (76).

In conclusion, the revised data on pregnant women provide no indication that in utero exposure to YFV carries an increased risk of major malformations. Only one small study using passive surveillance found a statistically significant difference in the spontaneous abortion rate for pregnant women exposed to YFV. There is important evidence on the risk of neurological complications in breast-fed infants whose mothers received YF vaccine although the evidence is not strong enough to provide formal recommendations. Evidence is still scarce and regarding pregnancy and breastfeeding our data does not support any change in the current recommendations of the ACIP or CDC.

Other immunocompromised patients

Duchet et al. investigated yellow fever vaccine safety and efficacy in four groups of immunocompromised patients (solid organ and hematopoietic stem cells transplant recipients, HIV infected persons and patients treated by immunosuppressive drugs for a systemic disease) (77). They concluded that YF vaccine remained well tolerated and proved to be immunogenic most of the time, although the percentage of immune responders was found to be lower compared to non-immunocompromised patients.

Regarding immunosuppressive therapy, two studies on rheumatological patients were identified. Both reported that adverse reactions following YF vaccine were rare and they were similar between patients using immunosuppressors and immunocompetent individuals. Mota et al. investigated 70 patients, most of them female, with different rheumatic diseases and different therapeutic schemes (78). Scheinberg worked with 17 rheumatoid arthritis patients receiving infliximab therapy (79).

In relation to transplantation, our search identified 3 case reports of yellow fever vaccination on recipients of bone marrow transplantation (80, 81). They were patients with myeloma,

chronic myelogenous leukemia and multiple myeloma, respectively. None of the three patients presented any adverse event following vaccination.

The relationship between thymoma and yellow fever vaccine adverse events has long been established. In one study with 4 cases with a history of thymus disease (benign or malignant thymoma, all of them with a thymectomy) it was reported that all four of them developed YF vaccine associated adverse events. Two of them survived, and two were fatal (82).

In the elderly, we identified 5 studies that used pharmacovigilance databases and reviewed large number of individuals vaccinated with YF vaccine (83-87). They all concluded that rates of adverse events following YF vaccination were higher among elderly vaccinees compared with younger YF vaccinees and therefore for this age group, the benefit must outweigh the risks of developing serious adverse events following vaccination. However, it has to be considered that some of these studies had slightly overlapping periods and that it is inappropriate to compute rates per 100,000 patients or compare rates for age groups with the small number of serious adverse events reported, although trends may be perceived.

No Articles Found in the following Risk Factors: Neoplasms, Malnutrition, Corticosteroids, Alkylating Agents, Antimetabolites, Antineoplastic, Tumor Necrosis Factors, IL-1 Blocking Agents, Antineoplastic Agents.

Efficacy in special groups

Healthy persons rarely fail to develop neutralizing antibodies following YF vaccination. In controlled clinical trials, the primary failure rate is generally about 1% (21). However, there are certain host factors that have been associated with a reduced immunologic response. We explored the available evidence on three of these host factors: HIV infection, pregnancy and severe malnutrition.

HIV

Studies regarding seroconversion rate in HIV infected persons is conflicting. Nonetheless, all of the studies seem to agree in the fact that the level of immunosuppression plays a key role in the immune response.

Three retrospective observational studies (Receveur 2000)(Tattevin 2004)(Pistone 2010) reported a good immunological response in HIV patients with CD4 > 200 and variable viral load. The seroconversion rates varied between 93% to 100% but the number of subjects included in the analysis was very small (2, 12 and 14 respectively).

The two largest studies identified were a case-control study (Sibbally 1997) and the Swiss Cohort Study (Veit 2009). Both concluded that seroconversion rate following YF vaccine is significantly lower in HIV infected patients. Veit also reported that 17% (11/65) HIV infected

patients who had initially develop immunity lost it by the end of the 5th year and the the number of unprotected HIV individuals after 10 years of vaccination was twice that of HIV uninfected individuals.

Receveur et al. reported two cases of HIV patients with CD4 cell count of >500 cells/mm³. and HIV viral load < 20 000 whose YF vaccine was followed by a good immune response(67). The authors noticed that in both cases a decrease in CD4 cell count of approximately 200 occurred in the first month following vaccination, without any disease manifestation and with a steady recovery. However, they concluded that this transitory decrease in CD4 cell count reinforced the recommendation that only patients with good immune function should be vaccinated. Another retrospective study showed favourable efficacy results of YF vaccine 17D in HIV-infected patients with CD4 cell counts >200 cells/mm³(68). The 12 included subjects had a mean CD4 of 561 (range 240–1300) and a mean viral load of 5477 (range 20–31 100). In contrast to the results in Receveur's study, there were no significant changes in CD4cell count following vaccination. Serological values indicated a good immune response for all patients. A more recent study evaluated neutralizing antibodies in 23 french HIV-infected patients and found that 93% (13/14) of patients without baseline immunity had a successful seroconversionafter vaccination. However, time to seroconversionwas prolonged with only 2 of the 5 patients tested within 5 weeks having neutralizing antibodies (69).

The evidence of these previous studies was not supported by some other authors. Sibailly followed a cohort of 18 HIV-infected children in Abidjan and compared their immune response to yellow fever vaccine with 57 controls matched for age, sex and nutritional status. He found that only 3 (17%) of the 18 HIV-infected children had an adequate YF antibodyresponse compared with 42 (74%) of the 57 HIV-uninfected children(88). An important limitation of these findings is that the percentage of immunogenicity in the HIV-uninfected children is lower than expected suggesting that the vaccine antigenicity, storage or administration were suboptimal. Furthermore, in the HIV-infected children, data on the level of immunosuppression is lacking.

A larger cohort of 102 HIV-infected patients in whom neutralizing antibodies were measured following immunization with 17D vaccine showed that at one year vaccination significantly fewer HIV-infected patients than HIV-uninfected patients revealed reactive NTs, and their NTs were significantly lower than in HIV-uninfected individuals(64). In this study the median CD4 cell countwas 537 (range, 11-1730), and the HIV RNA level was undetectable in 41 of 102 HIV-infected patients.

Regarding duration of immunity in this special population, there is evidence suggesting that the protective effects of the vaccine wears off more quickly in HIV-infected persons. In the Swiss HIV cohort study, 11 patients who initially had protective responses showed non-protective NTs within five years after vaccination. Over the first decade following vaccination, the rate of non-protective response in HIV-positive recipients was 23%, twice that of HIV-negative recipients. (64)

Two recent and well designed studies (Veit 2009)(Pacanowski 2012) have suggested that the HIV- viral load determines the immune response meaning that the lower the viral load is at the time of vaccine administration, the stronger the immune response. Veit et al reported that

higher NTs during the first year after vaccination were associated with undetectable HIV RNA levels at the time of vaccination(64).To emphasize this finding, a prospective cohort study of 364 patients found that among patients immunized after HIV diagnosis (n=240), NT <1:10 was associated only with detectable plasma HIV-RNA at immunization (89). Overall it remains clear that the level of immunosuppression influences the immune response to yellow fever vaccine and it is likely that viral load is a better predictor of a good immune response than CD4.

Our search did not identify any study specifically addressing the response to YF vaccine booster in HIV-infected patients. However, one study showed that a booster effect was noted in only 3 of the 9 patients with baseline immunogenicity(69). Since evidence at this point comes from retrospective studies with very few subjects, the results should be taken with precaution. However, evidence suggests that HIV patients more often demonstrate nonprotective NTs, and may experience a more rapid decline in NTs during follow-up. Some authors have recommended that patients who are not receiving cART and who have low CD4 cell counts should preferably postpone receipt of 17D vaccine until the plasma HIV RNA level is undetectable, to attain a more vigorous vaccine response. Furthermore, and taking into account safety data which is beyond the scope of this review, we recommend that booster recommendations be readdressed since a 10 year interval between vaccine doses may be too long for this special population. Moreover, the 10 day interval following vaccination recommended for the general population before exposure may be too short for this group.

PREGNANCY

Pregnancy is one of the host factors associated with an immunodeficient state. Therefore they are more prone to develop severe forms of disease. As an example, in confirmed US cases of H1N1 in 2009 pregnant women had a higher rate of admission to the hospital and a higher lethality rate than the general population (90). Additionally pregnancy has been associated with failure to respond immunologically to certain vaccines such as Hepatitis B vaccine. One study showed that only 49% (39/80) pregnant women had seroprotective HbsAb conversion after a series of three recombinant Hepatitis B vaccine doses (91). This is why it is important to evaluate efficacy of YF vaccine in this special group.

As discussed earlier in the safety analysis, most identified studies involving pregnant woman and yellow fever vaccine were designed to evaluate the possible effects of the vaccine on pregnancy and conceptus or to assess congenital infection or structural defects resulting from immunization(19, 72, 92) However, some of them also provided valuable evidence on seroconversion rates in this special population.

Only two studies (19, 73) addressed the immunogenicity of yellow fever vaccine following its administration in pregnant women. Both reported opposite results showing high seroconversion rates in women vaccinated in their early pregnancy versus low seropositivity following vaccination of women in their third trimester.

Suzano et al. described the results of the inadvertent immunization of pregnant women during a mass vaccination campaign in Brazil. This study included 480 pregnant women who had

received the vaccine at a mean of 5.7 weeks of gestation. In the 6 weeks following vaccination, 98.2% pregnant women were IgGpositive by neutralization test (19).

In contrast, another study conducted in Nigeria found that pregnant women had significantly lower neutralizing antibody responses to yellow fever vaccine than nonpregnant females of child-bearing age, male students, and the general population(73). Only 38.6% of the pregnant women developed neutralizing antibodies, compared to 81.5–93.7% of the other groups. In this study 88% of immunizations had taken place during the third trimester.

No evidence was found in relation to duration of immunity on women who were pregnant at the time of vaccination.

Revaccination might not be necessary in women who received vaccine during early pregnancy but still antibody titers should be checked to ensure an appropriate immune response in women at risk. Further studies should asses if there is indeed a relationship between seroconversion and the trimester in which the vaccine was administered and the duration of immunity following seroconversionin pregnant women.

SEVERE MALNUTRITION

There is little information on the efficacy and duration of immunity following yellow fever vaccination in malnurished children. Protein malnutrition has been associated with impaired antibody responses to the yellow fever virus vaccine (93). In this small study of 8 children with kwashiorkor only 1 seroconverted following vaccination compared to 5 out of 6 controls. A review on the effects of malnutrition on small pox and yellow fever vaccination found that children with mild to moderate protein-calorie malnutrition were successfully vaccinated against smallpox and showed normal reaction. In contrast, a small group of children with kashiorkor had an impaired antibody response to inoculation with yellow fever vaccine(94).

Our search could not identify any paper adressing the duration of immunity to yellow fever vaccine in this special population.

Further investigation is needed to determine the relevance of these results regarding immunization programmes in countries where severe malnutrition is prevalent.

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