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Systematic review

Immunogenicity and duration of protection after yellow fever vaccine in people living with human immunodeficiency virus: a systematic review

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ABSTRACT

Background: We lack the rationale on which to base the development of a yellow fever (YF) vaccination schedule for people living with human immunodeficiency virus (PLWHIV).
Objectives: To report on the current evidence regarding the seroconversion rate and the duration of humoral protection after YF vaccine, as well as the impact of revaccination in PLWHIV.
Data sources: MEDLINE, Google Scholar, LILACS and Cochrane CENTRAL were searched.
Methods: We selected studies on PLWHIV of all ages (including perinatally HIV-infected patients) and all settings (YF endemic and non-endemic zones). Intervention investigated was vaccination against YF, at least once after the HIV diagnosis. The research questions were the seroconversion rate, duration of humoral immunity after YF vaccine and impact of revaccination in PLWHIV. Selected studies were assessed for quality using the Newcastle–Ottawa scale.
Results: Ten, six and six studies were selected for the systematic review of each question, respectively. Only one study addressed the first question in perinatally HIV-infected children. The quality of the studies was assessed as Poor (n = 16), Fair (n = 2) or Good (n = 4). A meta-analysis demonstrated that 97.6% (95% CI 91.6%–100%) of the included population seroconverted. Between 1 and 10 years after YF vaccine, reported persistence of neutralizing antibodies was 72% (95% CI 53.6%–91%), and it was 62% (95% CI 45.4%–78.6%) more than 10 years after YF vaccine. No conclusions could be drawn on impact of revaccination because of the small number of patients.
Conclusions: The current evidence regarding seroconversion rate, duration of humoral protection after YF vaccine and impact of revaccination in PLWHIV is limited by the low number and quality of studies. Based on the presently available data, it is difficult to rationally develop yellow fever vaccination guidelines for PLWHIV. **Charlotte Martin, Clin Microbiol Infect 2021;27:958**

Introduction

Yellow fever (YF), an RNA virus of the *Flavivirus* genus, is considered as a re-emerging disease. Incidence of YF has increased globally over the past 30 years as the result of a combination of factors including poor vaccination coverage, deforestation, urbanization, population movements and climate change. In recent years,

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several YF epidemics have occurred both in sub-Saharan Africa and Latin America with secondary imported cases to China and Europe [1]. YF also remains a continuous threat to unimmunized travellers to tropical regions, with the subsequent risk of introducing the infection into disease-free regions [1,2]. As a zoonosis with a cycle involving monkeys and mosquitoes, the disease cannot be eradicated. There is no specific treatment for this potentially lethal disease and immunization is the most efficient method of prevention. Vaccination of travellers as well as vaccination in endemic countries are therefore of major importance in YF control [3]. It is estimated that an 80% vaccination coverage is required to prevent virus circulation in endemic areas [4]. Live attenuated yellow fever vaccines (YFV) (17D/17DD strains and its derivatives) were developed by Max Theiler in the 1930s and are currently the only YFV available.

The efficacy of the YFV has not been assessed in randomized controlled clinical trials but through epidemiological observations [5] and in an animal study using a model in rhesus macaques [6]. The latter allowed the identification of the only accepted (although discussed) surrogate of protection against YF, namely a neutralizing titre of antibodies (NT Ab) > 1/10 [5,7].

Despite the fact that YF is endemic in regions with high prevalence of human immunodeficiency virus (HIV), there are no data on the proportion of people living with HIV (PLWHIV) accounting for the YF case load during the outbreaks or on morbidity or mortality due to YF virus infection in this population. During reactive immunization campaigns against YF epidemics, an unknown proportion of PLWHIV are exposed to the vaccine, with little information on safety and efficacy. In addition, PLWHIV increasingly travel because of improved health conditions and life expectancy, to areas where YF is endemic, for leisure and to visit friends and relatives. They need to be protected from the risk of YF by vaccination. In our reference centre for both HIV care and travel medicine, about 23% (754/3300) of the active cohort of HIV patients has received a YFV at least once (personal data).

HIV infection jeopardizes the quality of response to vaccination, with both poorer humoral and cellular responses [8–10]. The mechanisms include persistent infection of T follicular helper cells resulting in altered germinal centre reactions and systemic immune activation, caused by low-level viraemia and microbial translocation [9,11]. Antiretroviral therapy (ART) initiated during chronic infection does not fully restore immune functions with HIV persisting in latently infected cells and levels of residual immune activation remaining elevated compared with HIV-negative healthy individuals [12], even after several months of effective treatment and independent of CD4 nadir [8,13]. These persisting immune alterations are associated with a lower seroconversion rate and a higher antibody decay rate following immunization compared with HIV-negative individuals [14,15]. In 2016, WHO recommended a single lifetime administration of the YFV for the general population instead of the previous 10-year schedule. However, because of the lack of data available in this field, WHO did not extend this recommendation to PLWHIV.

The purpose of this review is to report on the current evidence regarding the seroconversion rate and the duration of humoral protection after YF vaccination, as well as the impact of revaccination in PLWHIV, and, where possible, to compare available data with what is observed in HIV-uninfected individuals.

Materials and methods

The three research questions were the following. (a) What is the seroconversion rate after YF vaccine in PLWHIV? (b) What is the duration of humoral immunity after YF vaccine in PLWHIV? (c) What is the impact of YF revaccination in PLWHIV? The results were split between non-perinatally HIV-infected and perinatally HIV-infected individuals.

We selected studies on PLWHIV of all ages (including perinatally HIV-infected individuals) and all settings (YF endemic and non-endemic zones) (Population), vaccinated at least once against YF after the HIV diagnosis (Intervention). When available, we selected studies comparing the target population with HIV-negative individuals and/or PLWHIV with different baseline predictive variables (Comparison). Main outcomes were the presence of protective levels of YF NT antibodies within 1 year after YF vaccination (seroconversion rate), the presence of protective levels of YF NT antibodies more than 1 year after YF vaccination (duration of humoral immunity) and the changes of YF NT antibodies after one or several YF revaccination(s) (Outcomes).

This review does not cover safety data about YF vaccination in PLWHIV.

Search strategy and selection criteria

The protocol of the review was published in the PROSPERO international prospective registry of systematic reviews (registration no CRD42021225090). The following databases were searched: MEDLINE (Pubmed), CENTRAL (Cochrane Library), Google Scholar and LILACS (Bireme). We also consulted reference documents prepared by WHO and by the Centers for Disease Control and Prevention, and HIV conferences abstracts, including the International AIDS Society online Resource Library. References of included primary studies were searched to identify other relevant studies. We restricted the search to studies published before 31 December 2020. We searched for articles published in French, English or Portuguese, using a combination of the key terms: 'yellow fever vaccine', 'HIV', 'humoral immunity', 'seroconversion', 'neutralizing antibodies', 'duration of immunity', 'perinatally HIV-infected', 'vertical transmission', 'HIV-infected children', 'revaccination'. The detailed Search Strategy is available in the Supplementary material (Table S1). The search results were combined, and duplicate articles were removed. The titles and abstracts were reviewed by two authors (CM and ND). All articles that potentially met the inclusion criteria were retrieved and fully assessed. We conducted the systematic literature review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16] for reporting.

Study selection and quality assessment

Possible articles of interest, which addressed each key question, were retrieved and reviewed independently by two authors (CM and ND). The quality of each study included in the literature review was assessed using the Newcastle–Ottawa quality assessment scale [17]: disagreement was resolved by discussion between the two authors. Quality was assessed at study level and was expressed as Poor, Fair or Good. The detailed quality assessment of the individual studies included in the systematic review is available in the Supplementary material (Table S2).

Data extraction

For each study, the data were independently collected by two authors (CM and ND). These data were the number of participants enrolled, the study setting (YF endemic versus non-endemic), the study design, the YF seropositivity rate before YF vaccination, the number of YFV doses received, the $CD4^+$ T-cell count, presence of antiretroviral treatment and HIV viral load at time of YF vaccination, the timing of YF vaccination in relation to the HIV diagnosis, the method used for measuring neutralizing antibodies, the cut-off values used, the comparison group when existing, and the proportion of PLWHIV with NT Ab regarding the research question.

Data synthesis and meta-analysis

We used a conservative statistical analysis approach, assuming that the between-study variance must be taken into account to estimate the true effect size of the overall proportion. We therefore chose a random-effects model. The random effects were estimated using the restricted maximum-likelihood estimator. As the sample sizes were small and extreme proportions were present, we transformed them by a double-arcsine transformation to ensure a normal distribution as far as possible. The I^2 values were calculated as measures of heterogeneity and the meta-analysis was only performed if the measure of heterogeneity between the studies did not exceed 50%. Forest plots were used to illustrate the point estimate with 95% CI. The analyses were carried out on the R software with the metaphor [18] and meta [19] packages.

Results

Study selection

Ten, six and six studies were selected for the first, second and third research questions, respectively. The search and selection of included studies for the three research questions and the meta-analysis are shown in Fig. 1.

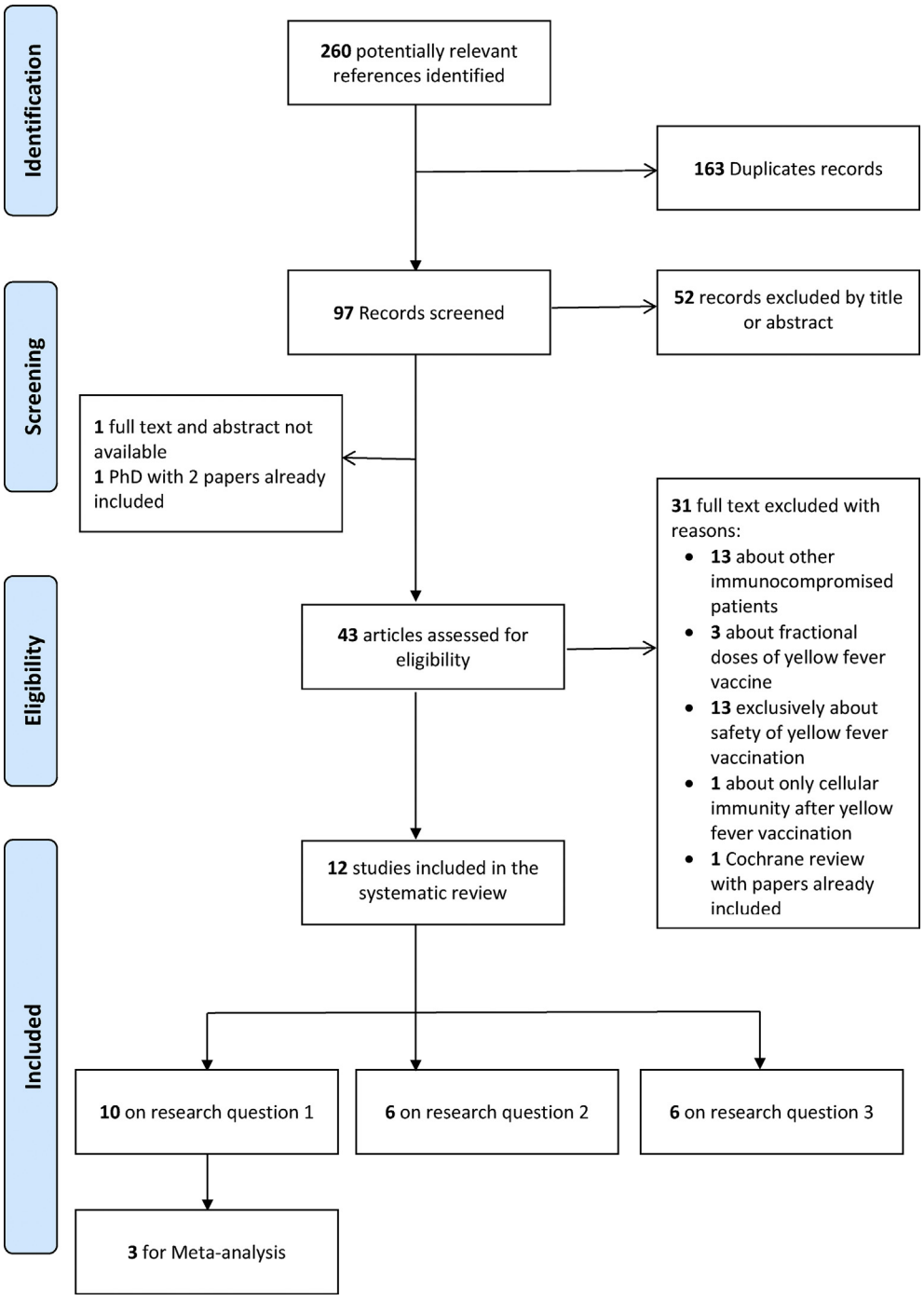

Fig. 1. Flow diagram for search and selection of included studies.

Table 1
Seroconversion after yellow fever vaccination in people living with HIV

	Quality	Study setting	Enrolled participants, *n*	Study design	Proportion with positive NT Ab before YFV, *n* (%)	CD4 at time of vaccination median,/mm^3 (range unless specified)	Undetectable HIV viral load at time of vaccination, *n* (%)	Primary YF vaccination, *n* (%)	Lab test and cut-off	Sero-conversion, n (%)	Comments
ADULTS											
Tattevin 2004 [20]	NOS: Poor	Non-endemic	7	Cohort Retrospective Observational	NA	Mean 561 ± 363	3/7 (43%, <200 copies/mL)	NA	Sero-neutralization	7 (100%)	NT Ab of 7/12 patients were measured within 12 months of vaccination
Veit 2009 [21]	NOS: Poor	Non-endemic	78	Cohort Retrospective Observational	NA	496 (72−1730)	37 (48%)	63 (81%)	PRNT 90 ≥1/10	65 (83%)	All vaccinated after HIV diagnosis Seroconversion in 81% of primary vaccinated Comparison to historical (probably) HIV-negative cohort with 64/66 (97%) seroconversion Higher CD4 T-cell count (p 0.04) and HIV RNA suppression (p 0.06) correlated to higher levels of NT Ab
Pistone 2010 [22]	NOS: Poor	Non-endemic	23	Cohort Retrospective Observational	9 (39%)	410 (159−1035)	11 (48%)	11 (48%)	PRNT 90 ≥10 UI/L	16 (70%)	One 12-year-old child is included- Seroconversion in 13/14 (93%) of those without baseline immunity 12/23 HCV and/or HBV co-infections Delayed seroconversion (>5 weeks) in 3/5 vaccine recipients tested within 5 weeks
Pacanowski 2012 [23]	NOS: Poor	Non-endemic	45	Cohort Retrospective[a] Observational	NA	451 (IQR 266 −560)	36 (80%) (<400 copies/mL)	10 (22%)	PRNT 80 ≥1/10	44 (98%)	Risk of no seroconversion directly proportional to HIV VL (p 0.01) (trend for NT Ab decay over time)
Sidibe 2012 [24]	NOS: Poor	Endemic	83	Cohort Retrospective Observational	NA	437 (IQR 274 −544)	24 (52%) NB: only 46/83 tested	NA	PRNT 90 ≥1/20	76 (92%)	HIV RNA suppression correlated to seroconversion rate (p 0.045) and higher CD4 with NT (p 0.01)
Mullaert 2015 [25]	NOS: Poor	Non-endemic	72	Cohort Prospective observational	57 (79%)	472 (IQR 379 −600)	68 (94%)	NA	PRNT 90 >1/10	16/20 (80%)	152 patients already had high titres at baseline, in whom a threefold increase of the titres could technically not be measured Seroconversion in 13/15 (86%) of those with negative Ab at baseline Factors favouring seroconversion have not been investigated

(*continued on next page*)

Table 1 (*continued*)

	Quality	Study setting	Enrolled participants, *n*	Study design	Proportion with positive NT Ab before YFV, *n* (%)	CD4 at time of vaccination median,/mm^3 (range unless specified)	Undetectable HIV viral load at time of vaccination, *n* (%)	Primary YF vaccination, *n* (%)	Lab test and cut-off	Sero-conversion, n (%)	Comments
Avelino-Silva 2016 [26]	NOS: Good	Non-endemic	12	Cohort Prospective Controlled	4 (33%)	722 (IQR 526 −795)	8 (67%)	8 (67%)	PRNT 50 Cut-off not specified	11 (92%)	Comparison to 45 HIV-negative participants with 43/45 (96%) seroconversion Same viraemia, NT Ab and seroconversion rate at mo 1 and 3 HIV infection (p 0.021) and CD4/CD8 ratio (p 0.024) correlated to seroconversion rate
Veit 2018 [27]	NOS: Good	Non-endemic	201	Cohort Retrospective Observational	106 (53%)	536 (IQR 412 −697)	150 (75%)	201 (100%)	PRNT 90 ≥1/10	191 (95%)	All vaccinated after HIV diagnosis Seroconversion = 95% if HIV undetectable at vaccination HIV RNA suppression correlated to seroconversion rate (p 0.03) NT Ab decay over time
Colin de Verdière 2018 [28]	NOS: Good	Non-endemic	40	Cohort Prospective Controlled	2 (5%)	702 (314–1381)	37 (93%)	40 (100%)	PRNT 80 ≥1/10	40 (100%)	All treated since at least 6 months Comparison with 31 HIV negative participants Higher levels of NT Ab in HIV negative participants without statistical significance
CHILDREN											
Sibailly 1997 [29]	NOS: Fair	Endemic	18	Cohort Prospective Controlled	0 (0%)	NA	NA	100%	PRNT ≥1/10	3 (17%)	Pre-HAART era (1990–1994) Comparison to 57 HIV-uninfected children with 74% seroconversion (42/57) (38 born from HIV-uninfected mothers and 19 HEU)

Abbreviations: Ab, antibodies; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HEU, HIV-exposed uninfected (children); HIV, human immunodeficiency virus; IQR, interquartile range; NA, non-available; NOS, Newcastle–Ottawa Scale for Quality Assessment;[b] NT, neutralizing titres; PRNT, plaque reduction neutralization test; VL, viral load; YFV, yellow fever vaccine.

[a] 'prospective' but in reality, prospective enrolment of HIV-infected patients retrospectively vaccinated.

[b] Newcastle–Ottawa Scale was used to assess quality of each study, according to the following thresholds: Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain OR 0 star in comparability domain OR 0 or 1 star in outcome/exposure domain.

Seroconversion after YF vaccination in PLWHIV

We identified ten cohort studies, nine in adults and one in children. The nine cohort studies (detailed in Table 1) covered a total of 561 HIV-positive adults and described seroconversion data after YF vaccination, defined as presence of neutralizing antibodies within 1 year after vaccination [20–28]. The quality of these studies was rated as Poor ($n = 6$) and Good ($n = 3$). Only one study reported data in a YF endemic area, and six of the nine studies were retrospective. The rate of pre-vaccination seropositivity (due to previous vaccination or natural exposure to YF) was reported in five studies. Interpreting seroconversion rate in the remaining four studies was, therefore, difficult. The proportion of patients with undetectable HIV viral load at time of vaccination was below 70% in five of the nine studies. The laboratory methods and cut-off values used to determine protection, when specified, varied widely from study to study. Overall, the reported seroconversion rate ranged from 70% to 100%. HIV RNA suppression correlated with the seroconversion rate in three studies [23,24,27], and to higher levels of NT Ab in one study (p 0.06) [21]. The single study conducted in a YF endemic area reported a seroconversion rate of 92% (76/83) 9 months after vaccination [24].

Heterogeneity was moderate ($I^2 = 48.9$) when including only the three studies ranked as Good quality [26–28]. Hence, we carried out the meta-analysis on the three studies of Good quality, demonstrating that 97.6% (95% CI 91.6%–100%) of the included population seroconverted (242 out of 253 patients) (Fig. 2).

Only one study reported data on 18 perinatally HIV-infected children. This prospective controlled study was conducted in a YF endemic zone during the era before highly active antiretroviral therapy and showed a 17% (3/18) seroconversion rate (compared with 74% (42/57) in HIV-uninfected children) on average 5 months after YF vaccination of the children (mean 10 months of age) [29]. We rated the quality of this study as Fair (Table 1).

Persistence of humoral immunity after YF vaccination in PLWHIV

Six retrospective cohort studies addressed persistence of neutralizing antibodies in PLWHIV more than 1 year after YF vaccination, totalling 315 patients and all in non-endemic countries [20–22,27,30,31] (summarized in Table 2). The quality of these studies was rated as Poor ($n = 5$) and Good ($n = 1$). Reported persistence of NT Ab ranged from 54% to 86% between 1 and 10 years after YF vaccine ($n = 4$ studies) and from 45% to 78% more than 10 years after YF vaccine ($n = 4$ studies). When an HIV-negative comparison group was available, NT Ab decreased more rapidly in PLWHIV than in HIV-negative individuals [21,31]. In one study rated as Good, HIV RNA suppression correlated with longer duration of humoral immunity (p 0.01) [27]. Heterogeneity among studies was high (I^2 ranging from 70% to 80%).

Effect of revaccination on persistence of humoral immunity after YF vaccination in PLWHIV

We identified six cohort studies addressing the impact of one or several YF revaccination(s) on the persistence of humoral immunity [21–23,25–27]. Overall, the quality of these studies was rated as Poor ($n = 5$) and Fair ($n = 1$). None of these studies was initially designed to explore the question of the impact of revaccination on persistence of humoral immunity after YF vaccination. Moreover, the cumulative number of enrolled participants was very small (total $n = 137$) (Table 3). Two studies showed a booster effect on NT Ab after a YF revaccination ($n = 6$ vaccine recipients) [22,25] and two studies observed that PLWHIV who received multiple vaccinations were more likely to have positive NT Ab or had higher NT Ab levels ($n = 21$ vaccine recipients) [21,26].

Discussion

In this systematic review, we assessed three research questions in PLWHIV: seroconversion rate after YF vaccine, persistence of protective humoral immunity following vaccination in this population and impact of revaccination on YF NT Ab. We found that the seroconversion rate ranged from 70% to 100%, that the antibody positivity rate was between 45% and 78% more than 10 years after YF vaccine. There were no explicit data on the impact of revaccination among PLWHIV with only two studies reporting non-specific data related to this question. Following quality assessment of the studies and evaluation of their heterogeneity, meta-analysis was deemed reliable only for the seroconversion rate. It included three studies rated as Good quality and showed a seroconversion rate of 97.6% (95% CI 91.6%–100%).

Seroconversion rate after YF vaccination is defined as the presence of protective NT Ab within 1 year after vaccination. Knowing the seroconversion rate after primary vaccination is essential to determine the need for early revaccination or double-dose primary vaccination. In HIV-negative vaccine recipients, for whom several good-quality studies are available [32–34], seroconversion rates following YF immunization are excellent, ranging from 84% to 99.4% [35,36]. The seroconversion rate appears to be equivalent in PLWHIV who live in non-endemic areas (>97%), especially when the HIV viral load is controlled in a large number of vaccine recipients (Table 1).

Determination of the long-term post-vaccination protection against YF is critical for the development of an appropriate vaccination schedule for PLWHIV. The persistence of protective humoral immunity after YF vaccination seems to be significantly impaired in PLWHIV. Indeed, a rapid NT Ab decay, sometimes in the first 5 years after YF vaccination in PLWHIV, has been described [21], consistent with what has also been described for other live vaccines in PLWHIV. However, this has also been described in HIV-negative YFV

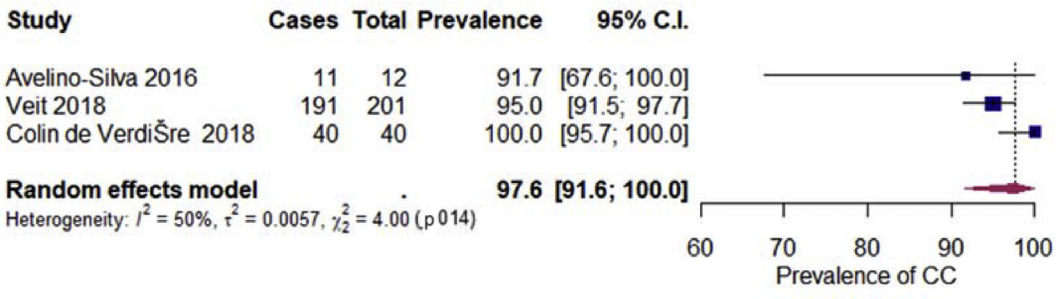

Fig. 2. Forest plots for the seroconversion rate after yellow fever vaccination in people living with human immunodeficiency virus.

Table 2
Persistence of humoral immunity after yellow fever vaccination in people living with HIV

	Quality	Study setting	Study design	Enrolled participants, *n*	Primary YF vaccination, *n* (%)	CD4 at time of vaccination (median,/mm^3)	Undetectable HIV viral load at time of vaccination, *n* (%)	Lab test and cut-off	Time since vaccination (median, years)	Protective humoral immunity, *n* (%)	Comments
Receveur 2000 [30]	NOS: Poor	Non-endemic	Case series Retrospective Observational	2	NA	1000 and 674	<20 000 copies/mL	Seroneutralization	22 and 35 months	2 (100%)	
Tattevin 2004 [20]	NOS: Poor	Non-endemic	Cohort Retrospective Observational	5	NA	Mean 561 ± 363	2 (40% to <200 copies/mL)	Seroneutralization	4	5 (100%)	
Veit 2009 [21]	NOS: Poor	Non-endemic	Cohort Retrospective Observational	81	83	496	48	PRNT 90 ≥1/10	1–10 ($n = 70$) >10 ($n = 11$)	60 (74%)	Comparison to historical (probably) HIV-negative cohort 1–10 years after YFV: 77% in HIV-positive vs 88% in HIV-negative >10 years: 5/11 still protected Lower NT Ab in HIV-positive Similar delay pattern over time 11/78 lost Ab in med 1.8 years after YFV when HIV VL detectable at vaccination
Pistone 2010 [22]	NOS: Poor	Non endemic	Cohort Retrospective Observational	12	7 (58%)	433	7 (58%)	PRNT 90 ≥10 UI/L	1–10 ($n = 3$) >10 ($n = 9$)	9 (75%)	7/9 (78%) if vaccinated more than 10 years before
Avelino-Silva 2016 [31]	NOS: Poor	Non-endemic	Cohort Retrospective Observational Controlled	30	30 (100%)	NA	NA	PRNT 50 Cut-off not specified	42 months	7/13 (54%) at >5 years 4/8 (50%) at >10 years	Comparison to 58 HIV-negative Shorter time since vaccination in the HIV-positive group (42 months vs 69 months) NT Ab decay correlated with time since vaccination (p 0.027) and with lower CD4/CD8 (p 0.014)
Veit 2018 [27]	NOS: Good	Non-endemic	Cohort Retrospective Observational	185 (122 at 5 years, 63 at 10 years)	185 (100%)	536	93/151 (62%)	PRNT 90 ≥1/10	1, 5, 10 y	105/122 (86%) at 5 years 47/63 (75%) at 10 years	46% had already NT Ab before YFV HIV RNA suppression correlated to longer duration of humoral immunity (p 0.01) Suppressed HIV RNA at baseline was also the strongest predictor of the magnitude of immune response to YFV at 1, 5 and 10 years If undetectable at vaccination: 95% protective humoral immunity at all time points, if detectable: 83%, 83%, 43% at 1, 5, 10 years, respectively

Abbreviations: Ab, antibodies; HIV, human immunodeficiency virus; NA, non-available; NOS, Newcastle–Ottawa Scale for Quality Assessment; NT, neutralizing titres; PRNT, plaque reduction neutralization test; VL, viral load; YFV, yellow fever vaccine.
'prospective' but in reality, prospective enrolment of HIV-infected patients retrospectively vaccinated.

Table 3
Effect of revaccination on persistence of humoral immunity after yellow fever vaccination in people living with HIV

	Quality	Study setting	No. of participants enrolled	No. of previous YF vaccine(s)	Conclusion
Veit 2009 [21]	NOS: Poor	Non-endemic	17	NA	NT Abs: 1/15 (6.6%) negative in multiple vaccinations vs 12/63 (19%) negative in primovaccination
Pistone 2010 [22]	NOS: Poor	Non-endemic	12	2 ($n = 4$), 3 ($n = 1$)	2/12 who had lost NT abs seroconverted and 3/12 benefited from a booster effect
Pacanowski 2012 [23]	NOS: Poor	Non-endemic	70	NA	No association between number of YF vaccines and NT levels (NT Abs: 3/70 negative in multiple vaccinations vs 6/170 negative in primovaccination)
Mullaert 2015 [25]	NOS: Poor	Non-endemic	5	NA	3/5 benefited from a booster effect at 9 weeks
Avelino-Silva 2016 [26]	NOS: Fair	Non-endemic	4	NA	Compared with individuals with primary YF vaccination, those who reported a previous YFV had higher NT Ab titres ($p < 0.001$)
Veit 2018 [27]	NOS: Poor	Non-endemic	29	2 ($n = 27$), 3 ($n = 2$)	Same protective humoral immunity rate at 5 and 10 years after YFV No association between reactive PRNT before YFV and YF NT Ab after revaccination

Abbreviations: Ab, antibodies; HIV, human immunodeficiency virus; NA, non-available; NOS, Newcastle–Ottawa Scale for Quality Assessment; NT, neutralizing titres; PRNT, plaque reduction neutralization test; VL, viral load; YFV, yellow fever vaccine.

Table 4
Gaps in knowledge in the field of yellow fever vaccine in people living with HIV identified from the literature review

Knowledge gap(s)	Relevance for patient management and health policy	Methodology to address knowledge gap(s)
Seroconversion rate after YF vaccine in PLWHIV		
Exact role of individual factors such as - gender, genetic background and/or ethnicity - incomplete immune reconstitution in PLWHIV - timing of HIV infection in relation to YF vaccine - role of perinatally acquired HIV infection **Influence of environmental factors** - YF endemicity - mass vaccination - poor vaccine storage	Adapt immunization schedules according to the setting Adapt vaccination schedules depending on immune reconstitution Adapt vaccination schedules depending on the timing of HIV infection/diagnosis in relation to YF vaccine Adapt vaccination schedules in perinatally HIV-infected patients Adapt YF vaccination schedules according to the setting	Prospective comparison of seroconversion rate in different subgroups of PLWHIV Prospective comparison of seroconversion rate in PLWHIV with and without HIV RNA control, with and without complete immune reconstitution Prospective comparison and/or case–control study of seroconversion rate in PLWHIV vaccinated before and after their HIV diagnosis Explore, if possible, prospectively, seroconversion rate in populations of perinatally HIV-infected children/adolescents/adults under ART Prospective comparison of seroconversion rate in PLWHIV living in endemic areas
Persistence of humoral immunity after YF vaccine in PLWHIV		
Exact role of individual factors such as - lack of adequate HIV control - incomplete immune reconstitution - timing of HIV infection in relation to YF vaccine - role of perinatally acquired HIV-infection **Exact role of environmental factors such as** YF endemicity, e.g. due to natural boosters such as other flavivirus	Adapt YF vaccination schedules according to the early-ART status, to the immune reconstitution of to the timing of HIV infection in relation to YF vaccination Adapt vaccination schedules in perinatally HIV-infected patients Special (re-)vaccination programmes for perinatally HIV-infected children National vaccination schedules in endemic areas and International Health Regulation for travellers	Compare persistence of humoral immunity between historical cohorts in whom ART was started several years after HIV diagnosis and current cohorts in whom ART is started immediately when HIV is diagnosed Explore persistence of humoral immunity in populations of perinatally HIV-infected children/adolescents/adults under ART Mathematical modelling of the persistence of NT Ab Compare persistence of humoral immunity after one YF vaccine in YF endemic and in non-endemic areas
Impact of revaccination in PLWHIV		
No study in PLWHIV was initially designed to explore this question	National vaccination schedules in endemic areas and International Health Regulation for travellers	Prospective cohort study or controlled study (compared with HIV-negative vaccine recipients) in a homogeneous group of PLWHIV or in different homogeneous subgroups of PLWHIV

Abbreviations: ART, antiretroviral therapy; NT Ab, neutralizing titres of antibody; PLWHIV, people living with human immunodeficiency virus; YF, yellow fever.

recipients [37]. The studies included in our analysis consistently reported lower NT Ab after YF vaccination in in PLWHIV than in HIV-negative vaccine recipients. A deleterious effect of immune activation on the persistence of NT Ab is observed in several studies with the role of CD4 nadir before treatment (proxy for early ART), the role of the number of circulating $CD4^+$ $CD28^+$ cells at the time of vaccination and/or the role of CD4/CD8 ratio [9,31] having been highlighted. Similarly, because HIV replication is correlated with immune activation, HIV suppression correlates with longer duration of humoral immunity. Overall, we found that time since vaccination and HIV viral load control seem to be the main determinants for robustness and duration of humoral immune response.

Few studies have been performed on the effect of YF revaccination, which has been applied every 10 years for decades, on NT Ab. Studies performed in HIV-negative YFV recipients have shown that secondary or multiple YF vaccination(s) lengthen protective immunity in the majority of vaccine recipients, even $\geq$10 years after secondary vaccination [38–40]. Several articles have demonstrated an inverse correlation between the NT Ab before vaccination and the increase in NT Ab after boosting [24,36,41–44]. In HIV-negative YFV recipients, these NT Ab may become undetectable again in 15%–17% of cases 5–10 years after revaccination [38,45]. The effect of YF revaccination is one of the most relevant issues in the evaluation of a (re)vaccination schedule for PLWHIV. However, the relevant data identified in this systematic review were scarce and of overall poor quality, so no practical conclusions can be drawn. It is known that in HIV infection, the number of specific memory B and $CD4^+$ T cells is significantly reduced in blood, meaning that replenishing of bone marrow long-lived plasma cells might be hampered in the absence of an antigen booster [37,46]. Therefore, it is crucial that further studies on this subject are carried out.

Interestingly, among environmental factors influencing the immune response to YFV, YF endemicity could be a determinant factor. However, in both PLWHIV and HIV-negative individuals, the majority of studies were conducted in non-endemic areas for both seroconversion and persistence of humoral immunity data [20–23,25–28,30–34]. Seroconversion rate is generally lower in endemic areas. Potential explanations include, among others, poor storage of the vaccine and in Sub-Saharan Africa and patient-specific immune microenvironment generating deleterious immune activation [38,41]. In contrast, the few studies conducted among HIV-negative vaccine recipients generally show better persistence of humoral immunity in endemic versus non-endemic areas [32]. Historically, there are descriptions of YF epidemics showing a higher attack rate in children compared with adults, suggesting some naturally acquired YF or heterologous flavivirus immunity [5]. It has been hypothesized that the same phenomenon could play a role in maintaining circulating humoral immunity in endemic areas [33].

Lower seroconversion rate and a shorter duration of protective immunity have been reported in perinatally HIV-infected children for most vaccines administered in childhood [47]. In endemic areas, when YF vaccination of HIV-uninfected children is carried out usually around 9 months, a rapid and important decrease in NT Ab has usually been observed in the following 2–5 years [48]. In the post-highly active ART era, seroconversion rate after live attenuated vaccines in perinatally HIV-infected children is similar to that in uninfected children but with lower antibody levels and more rapid decline over time [10,45,49–51]. Indeed, ART does not fully restore vaccine immunity [28,52]; moreover, it does not ensure long-lasting immunity after these vaccines [45]. Generalizing from the available data on other (live) vaccines, it is reasonable to assume that early ART initiation in perinatally HIV-infected children is probably a major predictor of the persistence of protective immune response for YF vaccine [46,51]. There are currently no real-world data to confirm this hypothesis and this unique population probably deserves a specific YF vaccination schedule.

The studies we reviewed were highly heterogeneous in terms of the laboratory methods and the cut-off values used to determine protection: there is an urgent need to establish a widely accepted YF serological standard to homogenize the interpretation of results and allow comparability between studies. There is a lack of data in terms of the exact role of ethnicity and timing of HIV infection in relation to YF vaccination and incomplete immune reconstitution on seroconversion rate or persistence of humoral immunity after YF vaccination in PLWHIV. Special attention should be paid to the growing population of perinatally HIV-infected patients. Finally, to build a rational and evidence-based YF vaccination schedule, more data on revaccination need to be collected. The gaps in knowledge identified through this literature review are listed in Table 4.

Our review has several limitations, mainly the overall small number of studies, the low quality of most of them, and consequently, the possibility of performing the meta-analysis only for the first research question and with only three studies of good quality. The role of cellular immunity was not in the scope of our review, although it plays an important role in YF vaccination and data in PLWHIV are scarce. The other causes of immunosuppression have not been addressed because immunosuppression is a very heterogeneous entity, and the conclusions drawn from our review cannot be extended to other conditions. However, this is the only systematic review on this topic since 2014, when a Cochrane review captured only three observational cohort studies, and concluded that the quality of evidence of the literature was low to very low [49]. In 2013, the WHO Strategic Advisory Group of Experts on Immunization recommended performing studies on the efficacy and safety of YF vaccination in PLWHIV [53]. Despite the publication of some important articles, our review highlighted the great rarity and rather poor quality of studies to address the three research questions.

We advocate for further targeted quality studies in key settings, including in endemic areas, on the effect of YF revaccination in PLWHIV, on the effect of early antiretroviral therapy on immunogenicity of YF vaccination in PLWHIV and, in particular, in perinatally HIV-infected patients [47]. Many knowledge gaps still need to be addressed to allow the elaboration of adequate YF vaccination guidelines for PLWHIV.

Author contributions

CM wrote the original manuscript and performed the research. CM and ND reviewed all abstracts and all selected studies, and contributed to conceptualization and manuscript editing. EB provided the idea for a systematic literature review and reviewed the manuscript. CDC reviewed the manuscript and searched for additional information on laboratory methods and cut-offs. DB provided expertise on systematic reviews. YVL and SDW reviewed the manuscript.

Transparency declaration

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

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