

1 **Duration of protection after vaccination against yellow fever - systematic review and**  
2 **meta-analysis**

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22 **Running title: Protection after yellow fever vaccine**

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1 **Abstract**

2 The duration of protection after a single dose of yellow fever vaccine is a matter of debate.  
3 To summarize the current knowledge, we performed a systematic literature review and  
4 meta-analysis. Studies on the duration of protection after 1 and  $\geq 2$  vaccine doses were  
5 reviewed. Data were stratified by time since vaccination. In our meta-analysis, we used  
6 random-effects models. We identified 36 studies from 20 countries, comprising over 17,000  
7 participants aged 6 months to 85 years. Among healthy adults and children, pooled  
8 seroprotection rates after single vaccination dose were close to 100% by 3 months and  
9 remained high in adults for 5 to 10 years. In children vaccinated before age 2, the  
10 seroprotection rate was 52% within 5 years after primary vaccination. For immunodeficient  
11 persons, data indicate relevant waning. The extent of waning of seroprotection after yellow  
12 fever vaccination depends on age at vaccination and immune status.

13  
14 **Keywords.** yellow fever vaccine; duration of protection; risk group; immunodeficiency;  
15 systematic review

16

## 1 **Introduction**

2 Yellow fever (YF) is a vector-borne disease transmitted by mosquitoes of the *Aedes* and  
3 *Haemagogus* species. In 2020, 40 countries in Africa and South America were classified as  
4 endemic by the World Health Organization (WHO) [1]. The case fatality rate with the severe  
5 form of YF can reach 60% or more in persons with underlying diseases (such as diabetes  
6 mellitus) [2, 3]. Each year, approximately 200,000 YF cases and 30,000 YF deaths occur  
7 worldwide [4]. As no licensed drugs are available to treat YF, reduction of disease burden is  
8 exclusively accomplished through vaccination and vector control. Despite effective YF  
9 vaccines being available since the 1930s, outbreaks continue to occur and the disease has  
10 spread into new areas during recent decades [5-7]. To date, it is unknown to what extent a  
11 lack of seroconversion (primary vaccine failure) and waning immunity (secondary vaccine  
12 failure) influence the individual risk of YF.

13 For many years, YF vaccine booster doses were recommended every 10 years for those at  
14 risk of exposure, including people living in endemic countries and travellers. In 2013, WHO  
15 decided that a single dose of the YF vaccine is usually sufficient to confer lifelong protection  
16 against YF, except for certain sub-populations such as persons with immunodeficiencies (e.g.  
17 HIV). Accordingly, International Health Regulations (IHR) were adapted in 2016 concerning  
18 validity of vaccination certificates. Since then, the sufficiency of a single dose for life-long  
19 protection has been questioned for various reasons [8-12]. To provide an up-to-date  
20 overview of the currently available data and knowledge, we performed a systematic review  
21 (SR) and meta-analysis on the duration of protection after vaccination against YF.

22

## 23 **Methods**

### 24 ***Inclusion and exclusion criteria***

25 We performed a SR in accordance with the methods recommended by Cochrane (formerly  
26 The Cochrane Collaboration) and the Centre for Reviews and Dissemination [13, 14]. Studies  
27 were selected for inclusion based on the following criteria:

- 28 • Population: People living in areas where YF is endemic (list of countries as defined by  
29 WHO) as well as travellers from non-endemic areas. Subgroups: children,  
30 adults ( $\geq 18$  years), older adults ( $\geq 60$  years), those with any form of

1 immunodeficiency, pregnant women, and persons who have received a vaccine  
2 against another flavivirus

- 3 • Intervention: Any full single dose of a licenced YF vaccine
- 4 • Comparators: Placebo, no vaccine, other vaccine, fractional dose or booster dose(s)  
5 of YF vaccine alone or with another vaccine against another related viral disease, e.g.  
6 dengue fever, Japanese encephalitis
- 7 • Outcomes: Proportion (%) of individuals with YF; proportion (%) of individuals with  
8 death due to YF; seropositivity rates – e.g. proportion (%) of individuals who are  
9 seropositive for neutralising antibodies against YF

10 We included randomised controlled trials (RCT), non-randomized (observational) studies  
11 with control groups and prospective single-armed observational studies with  
12 ≥50 participants (non-RCT). Retrospective single arm studies, prospective single arm studies  
13 with <50 participants and case reports/series were excluded.

#### 15 ***Literature search***

16 We performed a systematic literature search in 15 databases (date of last search:  
17 12.11.2021).

18 Search strategies combined relevant search terms comprising indexed keywords (e.g.,  
19 Medical Subject Headings [MeSH]) and free text terms appearing in the titles and/or  
20 abstracts of database records. Search terms were identified through discussion, by scanning  
21 background literature and ‘key articles’ already known to the project team, and by browsing  
22 database thesauri. Searches were not limited by language, geographic location, publication  
23 status or date of publication. The Embase search strategy was peer reviewed by a second  
24 information specialist. After removal of duplicates, 4,800 records remained for further  
25 screening based on titles and abstracts. Full details of all search strategies are provided in  
26 Supplementary Data.

27 Titles and abstracts identified through electronic database and web searching were  
28 independently screened by 2 reviewers. Subsequently, full texts were independently  
29 examined by 2 reviewers to determine whether they met the criteria for inclusion in the  
30 review (see Supplementary Data for studies excluded at this stage). Any discrepancies  
31 between reviewers were resolved through discussion or a 3rd reviewer. The study selection

1 process is detailed in accordance with the Preferred Reporting Items for Systematic Reviews  
2 and Meta-Analyses (PRISMA) statement [15].

3

#### 4 ***Data extraction***

5 Data extraction forms were individually designed and piloted using Microsoft Excel. Data  
6 extraction was performed by 1 reviewer and checked for accuracy by a 2<sup>nd</sup> reviewer. Any  
7 discrepancies were resolved through discussion or through the intervention of a 3<sup>rd</sup>  
8 reviewer. Where necessary and feasible, we requested additional information from the  
9 authors (details available upon request).

10

#### 11 ***Risk of bias assessment***

12 Risk of bias in randomised trials (RCT) was assessed using the Cochrane risk of bias tool [16].  
13 For assessment of non-randomised studies we used the JBI (formerly Joanna Briggs Institute)  
14 checklist for non-randomised experimental studies [17]. Assessments were made by 2  
15 reviewers independently and discrepancies were resolved through discussion or a 3<sup>rd</sup>  
16 reviewer.

17

#### 18 ***Statistical analyses***

19 A narrative summary of all included studies was prepared in tabular form. Where available,  
20 separate data were described for subgroups.

21 To investigate the duration of vaccine-induced protection against YF, data were stratified  
22 according to the follow-up time period after vaccination:  $\leq 3$  months;  $> 3$  months to  $\leq 5$   
23 years;  $> 5$  to  $\leq 10$  years;  $> 10$  to  $\leq 20$  years;  $> 20$  years.

24 The outcome of interest was the proportion of people who were seropositive at a given time  
25 point post-vaccination. The presence of neutralizing antibody titers  $\geq 1:10$  in the serum  
26 neutralization assay (which is the reference test for the detection of humoral immunity to  
27 YF) is an established correlate of protection in vaccinated individuals [18-20] for which  
28 equivalent efficacy of the 17D- and its 17DD-substrain has been extensively demonstrated  
29 [11, 21, 22].

1 Meta-analyses were performed using the metprop command with exact 95% confidence  
2 intervals (95% CI) in R version 4.1.0. Study arms not containing a YF vaccine (i.e. placebo)  
3 were excluded. If a study reported results at multiple time points for the same groups of  
4 participants, only the results for time-points closest to 3 months, 5 years, 10 years, and  
5 20 years, respectively, were included. All analyses have been grouped by the follow-up time  
6 period after vaccination. Results for the larger datasets (e.g., for single dose applications and  
7 endemic regions) were additionally grouped by study design and person subgroups (adults,  
8 children, persons with immunodeficiency).

9 This review was registered in PROSPERO (CRD42020223939).

10

## 11 **Results**

### 12 ***Characteristics of the included studies***

13 The systematic literature search revealed a total of 4,800 records. Thirty-six studies [9, 21-  
14 55] (reported in 61 references) met the inclusion criteria (see Supplementary Data). These  
15 studies comprised 18 RCT (reported in 32 references), 12 non-randomised comparative  
16 studies (non-RCT, reported in 18 references), and 6 single arm studies (reported in  
17 11 references). For the study selection process see PRISMA flow chart in Supplementary  
18 Data.

19 The included studies were conducted during 1993-2019 and entailed about 10,000  
20 participants in 11 endemic and about 7,000 participants in 9 non-endemic countries, aged 6  
21 months to 85 years (see Table 1 for study characteristics). All but one study in children  
22 examined children who received their YF vaccination before the age of 2. Eight studies  
23 included participants with immunodeficiencies (including HIV, autoimmune diseases, organ  
24 transplantation recipients and patients under immunosuppressive therapy for various  
25 reasons). The duration of protection beyond 3 months after YF vaccination was analysed in  
26 20 studies. All included studies reported the titers of detectable neutralizing antibodies as  
27 surrogate markers for protection. None of the studies reported the proportion of individuals  
28 with clinical endpoints such as YF or death due to YF.

29

30

## 1 ***Risk of Bias (RoB) assessment***

2 Six of the 36 included studies (4 RCT and 2 non-randomized studies) had a low RoB, while  
3 RoB was high in 23 studies (10 RCT and 13 non-randomized studies). The remaining 7 studies  
4 were of unclear RoB (Supplementary Data).

## 6 **Protection after single dose of YF vaccine**

7 Up to 3 months: A total of 29 studies investigated the protection up to 3 months after a  
8 single dose of YF vaccine. In all groups with healthy individuals (adults [16 studies], children  
9 [10 studies]), pooled seroprotection rates were close to 100%. In persons with  
10 immunodeficiency (3 studies), pooled seroprotection rate was 92% (Table 2 and  
11 Supplementary Forest Plots 001-009).

12 >3 months up to 5 years: Protection up to 5 years was addressed in 15 studies. In adults (8  
13 studies), the pooled seroprotection rate remained as high as 97%. In contrast, the  
14 seroprotection rate was 52% in children (3 studies), with all 3 studies being conducted in  
15 endemic countries. In persons with immunodeficiency, the pooled seroprotection rate was  
16 slightly lower than for the preceding time interval (86%; 4 studies; Table 2 and  
17 Supplementary Forest Plots 010-014 and 016-018).

18 >5 years up to 10 years: Eleven studies addressed protection up to 10 years. In adults from  
19 both endemic and non-endemic countries, seroprotection rates were 88% (6 studies). In  
20 children, the respective value was 54% (3 studies in endemic settings). Two studies in  
21 persons with immunodeficiency in non-endemic settings showed a pooled seroprotection  
22 rate of 75% (Table 2 and Supplementary Forest Plots 019-023, 025 and 027).

23 >10 years up to 20 years: Protection up to 20 years was evaluated in 5 studies. In 4 studies (3  
24 from endemic countries, 1 from a non-endemic country), the pooled seroprotection rate was  
25 71% for healthy adults. No studies were conducted in children. The only study in  
26 immunodeficient persons in a non-endemic country showed a seroprotection rate of 62%  
27 (Table 2 and Supplementary Forest Plots 028-030, 034 and 036).

28 >20 years: The only study for this time period was performed in immunodeficient adults in a  
29 non-endemic setting and showed a seroprotection rate of 94% in 16 of 17 persons who had

1 been vaccinated prior to immunosuppressive therapy (Table 2 and Supplementary Forest  
2 Plots 037, 039, 043 and 045).

3

#### 4 ***Protection after one booster dose of YF vaccine***

5 Up to 3 months, seroprotection rates were 98% in adults and 100% in patients with  
6 immunodeficiency. Between 3 months and 5 years after the booster dose, one study in an  
7 endemic and one in a non-endemic setting reported a pooled seroprotection rate of 92%. Up  
8 to 10 years after the booster dose, 3 studies in adults resulted in a pooled seroprotection  
9 rate of 88%.

10 Two studies in adults, one of which was performed in an endemic country, reported a  
11 pooled seroprotection rate of 86% for 10 to 20 years after booster dose.

12 For protection >20 years after booster dose, a study in immunodeficient persons receiving  
13 corticosteroid therapy showed a seroprotection rate of 88% (Table 3 and Supplementary  
14 Forest Plots 046-048, 052, 054, 055-057, 064-066, 073-075, 088 and 090).

15 In children, none of the studies met the inclusion criteria.

16

#### 17 ***Protection after two or more booster doses of YF vaccine***

18 In two studies which investigated the protection from 3 months to 5 years after multiple  
19 booster doses in adults a pooled seroprotection rate of 90% was reported. For >10 years,  
20 one study which was performed in a non-endemic setting with patients receiving  
21 corticosteroid therapy, demonstrated a seroprotection rate of 100%. The participants had  
22 their first YF vaccination before the onset of immunosuppression (Table 4 and  
23 Supplementary Forest Plots 100, 101, 124, 126, 133 and 135).

#### 24 ***Subgroup analysis: Protection in immunocompromised persons***

25 In persons with HIV, reduced antibody levels and a faster waning of YF immunity within 10  
26 years were found compared to healthy controls, especially in patients with unsuppressed  
27 HIV RNA [44, 47, 55]. In persons with autoimmune diseases, seroprotection rates ranged  
28 between 73-85% one month after primary vaccination, depending on the underlying disease  
29 [49].



1 Another study in patients with autoimmune diseases examined the duration of immunity  
2 after 1 or more vaccine doses. All seronegative participants had only received a single YF  
3 vaccine dose. Those with 2 doses (or more) were seropositive for up to 33 years after the  
4 last dose [41] (Table 2, 3 and 4).

#### 5 ***Subgroup analysis: Protection in persons aged >60 years***

6 Two studies reported on persons >60 years [48, 56]. A group of 28 persons was followed up  
7 10 years after having received their first dose between 60-80 years of age. All of the 22  
8 participants that could be contacted at the end of the observation period maintained a  
9 protective titer 10 years after primary vaccination [56].

#### 10 ***Subgroup analysis: Cross-reactive antibodies against other flavivirus***

11 In one study with cross-reactive antibodies from a prior vaccination against Japanese  
12 encephalitis, an enhanced YF immunogenicity was detected after YF vaccination [26].  
13 Crossreactive antibodies facilitated immune cell interactions and provoked greater pro-  
14 inflammatory responses.

#### 15 **Discussion**

16 This systematic review shows that the YF vaccine confers high rates of seroprotection within  
17 3 months after primary vaccination. After a single vaccine dose, reduced seroprotection  
18 rates were observed 5 and 10 years after vaccination of healthy adults and 3 months to 5  
19 years after vaccination of children. There is only scarce data on the persistence of humoral  
20 immunity beyond 10 years after a single YF vaccine dose. Beyond 20 years, no studies have  
21 been published in healthy adults. In immunodeficient persons, only limited data for different  
22 groups are available, which make general statements difficult. However, our subgroup  
23 analysis allows the conclusion that waning occurs in all groups examined. In the majority of  
24 studies, waning was more pronounced in immunodeficient persons than in healthy adults.

25 Only very limited data exist on the effects of booster vaccinations. For the time span beyond  
26 20 years, either after a single YF vaccine dose or after booster doses, the only available data  
27 are derived from one study with immunodeficient persons. Due to the small sample size and  
28 a wide 95% CI, the results are difficult to interpret [41].

1 Our data revealed no epidemiologically relevant differences between endemic and non-  
2 endemic settings, suggesting that natural boosters in endemic settings are either rare or do  
3 not play a major role in maintaining protection.

4 The Strategic Advisory Group of Experts on Immunization, the principal advisory group to the  
5 WHO for vaccines and immunization, concluded in 2013 that YF booster doses are not  
6 needed for lifelong protection against YF in immunocompetent persons. The conclusion was  
7 based on a SR published in 2013 by Gotuzzo et al. [57]. However, this SR has been criticized  
8 for its methodological weaknesses. Other experts questioned the development of long-term  
9 protective immunity in a considerable proportion of those vaccinated with only one dose [8,  
10 10, 12, 58]. The SR by Gotuzzo et al. mainly relies on retrospective cohort and small  
11 observational studies including case reports.

12 Since the data cut of the SR by Gotuzzo et al. [57], 23 additional studies have been  
13 published that were incorporated in our meta-analysis. To ascertain high quality evidence,  
14 we excluded retrospective studies, case reports and case series. Prospective single-arm  
15 studies were only accepted if they comprised  $\geq 50$  participants. Moreover, we included  
16 studies with different entities of immunodeficiency, such as patients seropositive for HIV  
17 (adults and children), patients with autoimmune diseases and organ transplantation  
18 recipients.

19 In persons with immunodeficiency, seroprotection after primary vaccination was only  
20 slightly lower than in healthy persons, but appeared to wane faster. Some countries  
21 recommend booster doses for patients with some but not all conditions leading to  
22 immunodeficiency [59]. The analysis of the various diseases associated with  
23 immunodeficiency supports to extend this recommendation to other patient groups with  
24 immunodeficiencies, provided that there are no contra-indications for a YF vaccination of  
25 the individual.

26 Persons aged 60 years and older often exhibit immunosenescence, which increases with age  
27 but also depends on other factors such as comorbidities. Although in one study all analysed  
28 participants aged  $>60$  years still showed a protective YF titer 10 years after primary  
29 vaccination, the studied cohort was too small to draw firm conclusions [56].

30 The only study that measured antibodies against Japanese encephalitis [26] indicated a  
31 potential impact of antibodies cross-reactive with the YF virus, but the duration and

1 relevance of this cross-reactivity remains uncertain. In endemic settings with high dengue  
2 seropositivity, pre-existing antibodies against dengue might lead to an overestimation of the  
3 seroprotection against YF.

4 One reason for no longer recommending routine booster doses was the extremely low  
5 number of reported YF vaccine failures. This rationale can be misleading, since vaccine  
6 failures can only be detected upon exposure of the vaccinated person to the YF virus as it  
7 occurs during outbreaks or in highly endemic sylvatic areas in Latin America. In addition, an  
8 underestimation of vaccine failures can result from insufficient local surveillance, case  
9 detection and reporting, especially in endemic countries in Africa, where 90% of all YF cases  
10 occur [4].

11 In Africa, reliable laboratory diagnostics are developing and recent examples, such as the YF  
12 outbreak in Uganda, might also show secondary vaccine failures [60].

13 For control and elimination of YF, it is crucial to improve the epidemiological surveillance not  
14 only for vaccine failures, but also for outbreaks [61].

### 15 ***Strengths and limitations***

16 Our review has several strengths. It adheres to rigorous methods recommended by relevant  
17 bodies such as Cochrane and the Centre for Reviews and Dissemination. With the last  
18 literature search performed in November 2021, our review reflects the current state of the  
19 evidence. With our meta-analysis we provide numerical estimates for protection at different  
20 time points after vaccination. High risk of bias and statistical heterogeneity of some of the  
21 included studies limits the ability to generate firm implications. The limitations associated  
22 with a functional assay and the variability among protocols represent a challenge for the  
23 comparison of results. As serum neutralization assays are usually only carried out in  
24 reference or specialized laboratories for the assessment of the immune response in  
25 vaccinated individuals, they certainly can provide a robust estimation on the presence of  
26 protective immunity against YF. Although we excluded prospective studies with less than 50  
27 participants, for some study arms the number of subjects was too small to draw firm  
28 conclusions, which particularly applies to the studies with immunodeficient persons. Based  
29 on our data, it is not possible to make definitive statements on the necessity and impact of  
30 one or several YF booster doses in immunodeficient patients.

31

1 **Conclusions**

2 A single dose of YF vaccine confers high levels of immunity (as measured by seroprotection  
3 rates) in healthy adults for up to 10 years, after which waning occurs, thereby increasing the  
4 risk for secondary vaccine failures. The extent to which immunity wanes depends on the age  
5 at primary vaccination and immune status.

6  
7 **NOTES**

8  
9 **Author contributions.** *KK, TH, JK, and RW developed the protocol and SD developed the*  
10 *search strategy. KK, TH, CD and OW conceptualized the study, developed the PICO question*  
11 *and finalized the manuscript. KK, SD, JH, JK, KM, and RW reviewed full-text articles and*  
12 *abstracted the data. RW and KK performed the analysis. KK, CD and TH checked data*  
13 *extraction. KK wrote the first draft of the manuscript. CB provided immunological expertise*  
14 *and contributed to the writing of the paper. AWS contributed to the interpretation of data*  
15 *and writing of the final manuscript. TH supervised study conduct and all authors reviewed*  
16 *the manuscript for final revisions before submission.*

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29 *position as Chairman of the WHO EYE (Eliminating Yellow Fever Epidemics) Laboratory*  
30 *Technical Working Group.*

31

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1 **Table 1: Characteristics of included studies**

Study	Country (endemic region Y/N)	Subjects	n	Vaccine specification	Specific Assay	Serology after YF vaccination up to
<b>RCT</b>						
Asante et al., 2020 [23]	Ghana (Y)	Children	709	17D (Stamaril)	PRNT50	1 month
Belmusto-Worm et al., 2005 [24]	Peru (Y)	Children	1107	17D (Arilvax, YF-VAX)	LNI	1 month
Camacho et al., 2004 [21]	Brazil (N)	Adults	1087	17D (Amaril), 17DD	PRNT50	1 month
Campi-Azevedo et al., 2014 [25]	Brazil (N)	Adults	590	17DD	PRNT50	1 year
Chan et al., 2016 [26]	Singapur (N)	Adults	70	17D (Stamaril)	PRNT50	1 month
Collaborative Group, 2015 [22]	Brazil (Y)	Children	1966	17D (Amaril), 17DD	PRNT50	1 month
Coursaget et al., 1995 [27]	Senegal (Y)	Children	220	17D (Amaril)	PRNT90	1 month
Edupuganti et al., 2012 [28]	US (N)	Adults	40	17D (YF-VAX)	PRNT90	3 months
Guirakhoo et al., 2006 [29]	US (N)	Adults	42	17D (YF-VAX)	LNI	3 years
Juan-Giner et al., 2021 [30]	Uganda, Kenya (Y)	Adults	960	17D (different vaccines), 17DD	PRNT50, PRNT90; non-inferiority with PRNT50	1 year
Lang et al., 1999 [31]	UK (N)	Adults	185	17D (Stamaril, Arilvax)	PRNT80	1 month
Lopez et al., 2016 [32]	Colombia and Peru (Y)	Children	792	17D (Stamaril)	PRNT50	1 month
Monath et al., 2002 [33]	US (N)	Adults	1440	17D (Arilvax, YF-VAX)	LNI	1 month
Nasveld et al., 2010 [34]	US (N)	Adults	90	17D (Stamaril)	PRNT50	6 months
NOVARTIS, 2012 [35]	Czech Republic, Germany (N)	Adults	101	17D (Stamaril)	NR	1 month
Osei-Kwasi et al., 2001 [36]	Ghana (Y)	Children	384	17D (Amaril)	microNT	3 months
Roukens et al., 2008 [37]	Netherlands (N)	Adults	175	17D (Stamaril)	PRNT80	1 year
Stefano et al., 1999 [38]	Brazil (Y)	Children	294	17DD	PRNT50	1 month
<b>Non-RCT</b>						
Avelino-Silva et al., 2016* [39]	Brazil (N)	Adults with HIV	63	NR	PRNT50	1 year
Avelino-Silva et al., 2016* [40]	Brazil (N)	Adults with HIV	92	17DD	PRNT50	11 years

Study	Country (endemic region Y/N)	Subjects	n	Vaccine specification	Specific Assay	Serology after YF vaccination up to
Burkhard et al., 2020 [41]	Switzerland (N)	Adults with immunosuppressive therapy	75	NR	PRNT90/PRNT 80	31 years
Campi-Azevedo et al., 2016 [9]	Brazil (Y)	Adults	171	17DD	PRNT50	13 years
Collaborative Group, 2019 [42]	Brazil (Y)	Adults	323	17DD	PRNT50	> 10 years
Collaborative Group, 2019 [43]	Brazil (Y)	Adults	326	17DD	PRNT50	30 years
De Verdier et al., 2018 [44]	France (N)	Adults with HIV	71	17D (Stamaril)	PRNT80	1 year
Kerneis et al., 2013 [45]	France (N)	Adults under corticosteroids	131	17D (Stamaril)	PRNT	3 months
Michel et al., 2015 [46]	Senegal, French Guyana (N)	Children	284	17D (different vaccines)	PRNT90	2 months
Project RETRO-CI, 1997 [47]	Ivory Coast (Y)	Children with HIV	75	17D (Amaril)	PRNT	> 5 months
Roukens et al., 2011** [48]	Netherlands (N)	Adults	58	17D (Stamaril)	PRNT80	10 years
Valim et al., 2020 [49]	Brazil (Y)	Adults with autoimmune diseases	278	17DD	PRNT50	1 month
<b>Single arm studies</b>						
Campi-Azevedo et al., 2019 [50]	Brazil (Y)	Children	673	17DD	PRNT50	10 years
Domingo et al., 2019 [51]	Ghana, Mali (Y)	Children	1023	17D (Stamaril), 17DD	microNT	6 years
Idoko et al., 2020 [52]	Gambia, Mali (Y)	Children	481	17D (Stamaril), 17DD	microNT	6 years
Jia et al., 2019 [53]	China (N)	Adults	2411	Based on 17D (produced in China)	PRNT50	11 years
Kareko et al., 2018 [54]	US (N)	Adults	92	17D (YF-VAX)	PRNT90	14 years
Veit et al., 2017 [55]	Switzerland (N)	Adults with HIV	247	17D (different vaccines)	PRNT90	10 years

- 1 \*Personal communication with Dr Avelino-Silva confirmed that “the study populations in these two publications have some overlap but were not exactly the same”.
- 2 Participants in Avelino-Silva 2016 [40] were previously vaccinated and referred for booster YF vaccine while some participants in Avelino-Silva 2016 [39] were previously included in Avelino-Silva 2016 [40] but some were vaccinated for the first time. In this systematic review, the publications were handled as two separate studies.
- 3
- 4 \*\*Updated information is available in Rosenstein et al. [56]
- 5 PRNT = Plaque reduction Neutralization Test; LNI = log10 Neutralization Index; microNT = microNeutralization Test; HIV = Human Immunodeficiency Virus; NR = not reported

1 Table 2: Protection after single dose of YF vaccine - results of the meta-analysis

Forest Plot	Population	N studies	N data-points	N subjects	Effect estimate	95% CI	I <sup>2</sup>
<b>≤3 months</b>							
<b>001</b>	<b>Adults</b>	<b>16</b>	<b>27</b>	<b>3115</b>	<b>0.98</b>	<b>0.97 to 0.98</b>	<b>64%</b>
002	Endemic	4	7	587	0.97	0.95 to 0.99	0%
003	Non-endemic	12	20	2528	0.98	0.97 to 0.99	68%
<b>004</b>	<b>Children</b>	<b>10</b>	<b>21</b>	<b>5654</b>	<b>0.94</b>	<b>0.90 to 0.96</b>	<b>92%</b>
005	Endemic	10	21	5654	0.94	0.90 to 0.96	92%
006	Non-endemic	0	0	0	N/A	N/A	N/A
<b>007</b>	<b>Immunodeficient</b>	<b>3</b>	<b>3</b>	<b>208</b>	<b>0.92</b>	<b>0.65 to 0.98</b>	<b>66%</b>
008	Endemic	1	1	160	0.78	0.71 to 0.84	N/A
009	Non-endemic	2	2	48	0.98	0.84 to 1.00	0%
<b>&gt;3 months to ≤5 years</b>							
<b>010</b>	<b>Adults</b>	<b>8</b>	<b>13</b>	<b>790</b>	<b>0.97</b>	<b>0.95 to 0.98</b>	<b>0%</b>
011	Endemic	3	6	514	0.98	0.95 to 0.99	0%
012	Non-endemic	5	7	276	0.96	0.93 to 0.98	0%
<b>013</b>	<b>Children</b>	<b>3</b>	<b>4</b>	<b>1208</b>	<b>0.52</b>	<b>0.33 to 0.71</b>	<b>96%</b>
014	Endemic	3	4	1208	0.52	0.33 to 0.71	96%
015	Non-endemic	0	0	0	N/A	N/A	N/A
<b>016</b>	<b>Immunodeficient</b>	<b>4</b>	<b>4</b>	<b>198</b>	<b>0.86</b>	<b>0.31 to 0.99</b>	<b>91%</b>
017	Endemic	1	1	18	0.17	0.04 to 0.41	N/A
018	Non-endemic	3	3	180	0.94	0.77 to 0.99	56%
<b>&gt;5 years to ≤10 years</b>							
<b>019</b>	<b>Adults</b>	<b>6</b>	<b>7</b>	<b>267</b>	<b>0.88</b>	<b>0.78 to 0.93</b>	<b>53%</b>
020	Endemic	2	2	45	0.88	0.75 to 0.95	0%
021	Non-endemic	4	5	222	0.89	0.74 to 0.96	63%
<b>022</b>	<b>Children</b>	<b>3</b>	<b>3</b>	<b>1044</b>	<b>0.54</b>	<b>0.37 to 0.70</b>	<b>97%</b>
023	Endemic	3	3	1044	0.54	0.37 to 0.70	97%
024	Non-endemic	0	0	0	N/A	N/A	N/A
<b>025</b>	<b>Immunodeficient</b>	<b>2</b>	<b>2</b>	<b>67</b>	<b>0.75</b>	<b>0.64 to 0.84</b>	<b>0%</b>
026	Endemic	0	0	0	N/A	N/A	N/A
027	Non-endemic	2	2	67	0.75	0.64 to 0.84	0%

Forest Plot	Population	N studies	N data-points	N subjects	Effect estimate	95% CI	I <sup>2</sup>
<b>&gt;10 years to ≤20 years</b>							
<b>028</b>	<b>Adults</b>	<b>4</b>	<b>4</b>	<b>231</b>	<b>0.71</b>	<b>0.62 to 0.79</b>	<b>36%</b>
029	Endemic	3	3	193	0.74	0.63 to 0.82	43%
030	Non-endemic	1	1	38	0.63	0.46 to 0.78	N/A
<b>031</b>	<b>Children*</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>N/A</b>	<b>N/A</b>	<b>N/A</b>
<b>034</b>	<b>Immunodeficient</b>	<b>1</b>	<b>1</b>	<b>8</b>	<b>0.62</b>	<b>0.24 to 0.91</b>	<b>N/A</b>
035	Endemic	0	0	0	N/A	N/A	N/A
036	Non-endemic	1	1	8	0.62	0.24 to 0.91	N/A
<b>&gt;20 years</b>							
<b>037</b>	<b>Adults</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>0.00</b>	<b>0.00 to 0.98</b>	<b>N/A</b>
038	Endemic	0	0	0	N/A	N/A	N/A
039	Non-endemic	1	1	1	0.00	0.00 to 0.98	N/A
<b>040</b>	<b>Children*</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>N/A</b>	<b>N/A</b>	<b>N/A</b>
<b>043</b>	<b>Immunodeficient</b>	<b>1</b>	<b>1</b>	<b>17</b>	<b>0.94</b>	<b>0.71 to 1.00</b>	<b>N/A</b>
044	Endemic	0	0	0	N/A	N/A	N/A
045	Non-endemic	1	1	17	0.94	0.71 to 1.00	N/A

1 \*No data

1 Table 3: Protection after one booster dose of YF vaccine - results of the meta-analysis

Forest Plot	Population	N studies	N data-points	N subjects	Effect estimate	95% CI	I <sup>2</sup>
<b>≤3 months</b>							
046	Adults	2	2	64	0.98	0.89 to 1.00	0%
047	Endemic	1	1	45	1.00	0.92 to 1.00	N/A
048	Non-endemic	1	1	19	1.00	0.82 to 1.00	N/A
049	Children*	0	0	0	N/A	N/A	N/A
052	Immunodeficient	1	1	11	1.00	0.72 to 1.00	N/A
053	Endemic	0	0	0	N/A	N/A	N/A
054	Non-endemic	1	1	11	1.00	0.72 to 1.00	N/A
<b>&gt;3 months to ≤5 years</b>							
055	Adults	2	2	62	0.92	0.82 to 0.97	0%
056	Endemic	1	1	47	0.91	0.80 to 0.98	N/A
057	Non-endemic	1	1	15	1.00	0.78 to 1.00	N/A
058	Children*	0	0	0	N/A	N/A	N/A
061	Immunodeficient*	0	0	0	N/A	N/A	N/A
<b>&gt;5 years to ≤10 years</b>							
064	Adults	3	3	258	0.88	0.84 to 0.92	0%
065	Endemic	2	2	249	0.88	0.83 to 0.91	0%
066	Non-endemic	1	1	9	1.00	0.66 to 1.00	N/A
067	Children*	0	0	0	N/A	N/A	N/A
070	Immunodeficient*	0	0	0	N/A	N/A	N/A
<b>&gt;10 years to ≤20 years</b>							
073	Adults	2	2	17	0.86	0.61 to 0.96	0%
074	Endemic	1	1	12	0.83	0.52 to 0.98	N/A
075	Non-endemic	1	1	5	1.00	0.48 to 1.00	N/A
076	Children*	0	0	0	N/A	N/A	N/A
079	Immunodeficient*	0	0	0	N/A	N/A	N/A
<b>&gt;20 years</b>							
082	Adults*	0	0	0	N/A	N/A	N/A
085	Children*	0	0	0	N/A	N/A	N/A

Forest Plot	Population	N studies	N data-points	N subjects	Effect estimate	95% CI	I2
088	Immunodeficient	1	1	40	0.88	0.73 to 0.96	N/A
089	Endemic	0	0	0	N/A	N/A	N/A
090	Non-endemic	1	1	40	0.88	0.73 to 0.96	N/A

1 \*No data

2

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1 **Table 4: Protection after two or more booster doses of YF vaccine - results of the meta-analysis**

Forest Plot	Population	N studies	N data-points	N subjects	Effect estimate	95% CI	I <sup>2</sup>
<b>≤3 months</b>							
092	Adults*	0	0	0	N/A	N/A	N/A
095	Children*	0	0	0	N/A	N/A	N/A
097	Immunodeficient*	0	0	0	N/A	N/A	N/A
<b>&gt;3 months to ≤5 years</b>							
100	Adults	2	2	14	0.90	0.62 to 0.98	0%
101	Endemic	2	2	14	0.90	0.62 to 0.98	0%
102	Non-endemic	0	0	0	N/A	N/A	N/A
103	Children*	0	0	0	N/A	N/A	N/A
106	Immunodeficient*	0	0	0	N/A	N/A	N/A
<b>&gt;5 years to ≤10 years</b>							
109	Adults*	0	0	0	N/A	N/A	N/A
112	Children*	0	0	0	N/A	N/A	N/A
115	Immunodeficient*	0	0	0	N/A	N/A	N/A
<b>&gt;10 years to ≤20 years</b>							
118	Adults*	0	0	0	N/A	N/A	N/A
121	Children*	0	0	0	N/A	N/A	N/A
124	Immunodeficient*	1	1	2	1.00	0.16 to 1.00	N/A
125	Endemic	0	0	0	N/A	N/A	N/A
126	Non-endemic	1	1	2	1.00	0.16 to 1.00	N/A
<b>&gt;20 years</b>							
127	Adults*	0	0	0	N/A	N/A	N/A
130	Children*	0	0	0	N/A	N/A	N/A
133	Immunodeficient	1	1	3	1.00	0.29 to 1.00	N/A
134	Endemic	0	0	0	N/A	N/A	N/A
135	Non-endemic	1	1	3	1.00	0.29 to 1.00	N/A

2 \*No data

3