Grading of recommendations, assessment, development, and evaluation (GRADE) for yellow fever vaccine booster doses

Background

Yellow fever (YF) is a mosquito-borne viral disease that is endemic to sub-Saharan Africa and tropical South America. YF virus causes an estimated 200,000 cases of clinical disease and 30,000 deaths annually [WHO 1992]. Clinical disease ranges from a mild, undifferentiated febrile illness to severe disease with jaundice and hemorrhage. The case-fatality ratio for severe YF is 20%-50% [Monath 2013]. Because no specific treatment exists for YF, prevention is critical to reduce disease risk. One of the most effective prevention measures against YF is vaccination with the live, attenuated YF 17D substrain virus vaccine.

YF vaccine is recommended for persons aged ≥9 months who are traveling to or living in areas with risk for YF virus transmission [CDC 2010]. In addition, International Health Regulations allow countries to require proof of YF vaccination from travelers entering their country [WHO 2005]. These requirements are intended to minimize the potential importation and spread of YF virus. Proof of YF vaccination is recorded on the International Certificate of Vaccination or Prophylaxis (i.e., yellow card). International Health Regulations specify that the International Certificate of Vaccination or Prophylaxis is valid for 10 years. Therefore, if 10 or more years have elapsed since the last vaccination, people planning travel to a country with a YF vaccination entry requirement need to receive a booster dose of the vaccine.

The Strategic Advisory Group of Experts on Immunization (SAGE), the principal advisory group to the World Health Organization (WHO) for vaccines and immunization, concluded in April 2013 that a single dose of YF vaccine is sufficient to confer sustained immunity and lifelong protection against YF disease, and a booster dose of the vaccine is not needed [WHO 2013]. This conclusion was based on a systematic review of published studies on the duration of immunity following a single dose of YF vaccine, and on data that suggest vaccine failures are extremely rare and do not increase in frequency with time since vaccination [Gotuzzo 2013]. SAGE noted that future studies and surveillance data should be used to identify specific risk groups, such as infants or persons infected with human immunodeficiency virus (HIV), who could benefit from a booster dose. In May 2014, the World Health Assembly adopted the recommendation to remove the 10 year booster dose requirement from the International Health Regulations by June 2016 [WHO 2014].

In the United States, the current ACIP YF vaccine recommendations note that "[International Health Regulations] require revaccination at intervals of 10 years to boost antibody titer. Evidence from multiple studies demonstrates that YF vaccine immunity persists for many decades and might provide life-long protection" [CDC 2010]. The ACIP Japanese Encephalitis Vaccine Work Group was reformed to include YF vaccine in October 2013 to discuss the need for booster doses of YF vaccine.

Policy questions

The primary policy question was "Should booster doses of YF vaccine every 10 years continue to be recommended for healthy travelers and laboratory workers?"

Population: Healthy travelers and laboratory workers
Intervention: Remove current recommendation for booster doses of YF vaccine
Current option: Continue current recommendation for booster doses of YF vaccine

An additional policy question was created for special populations for whom their initial immunologic response to the vaccine might be suboptimal: "Should booster doses of YF vaccine every 10 years continue to be recommended for travelers or laboratory workers who had a precaution to vaccination that might have negatively impacted their immune response to their primary dose of YF vaccine (e.g., age 6–8 months, asymptomatic HIV infection with moderate immune suppression, pregnancy, or age ≥60 years)?"

Population: Travelers or laboratory workers who have a precaution to vaccination that might negatively impact their immune response to their primary dose of YF vaccine (e.g., age 6-8 months, HIV infection, pregnancy, and age ≥60 years)

Intervention: Remove current recommendation for booster doses of YF vaccine for these populations

Current option: Continue current recommendation for booster doses of YF vaccine for these populations

The Work Group also discussed and examined data on booster doses for travelers and laboratory workers in high-risk settings for exposure to YF virus. Data for these populations and those with conditions that might negatively impact their response to a primary dose of YF vaccine were reviewed and summarized but a further evaluation of the potential benefits and harms of booster doses could not be performed given the limited amount of data that existed.

Identify and rank relative importance of outcome measures

For the GRADE evaluation of YF vaccine booster doses, the benefits considered as critical outcomes included vaccine efficacy, effectiveness (i.e., lack of vaccine failures), and seroprotection. However, there are no vaccine efficacy data or long-term seroprotection data for YF vaccine. Given this, seropositivity was used as a surrogate for seroprotection (**Table 1**). The harms considered critical outcomes were any vaccine-related serious adverse event, vaccine associated-viscerotropic disease, and vaccine associated-neurologic disease. Evidence type for each critical outcome was derived through a review of study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations (i.e., publication bias, strength of association, dose response, or direction of all plausible confounding would reduce the effect) [Ahmed 2011].

Evidence retrieval

To identify published literature that contained relevant evidence, we conducted PubMed and Embase searches of papers in any language published as of May 19, 2014. We used the keyword "yellow fever vaccine" and then used additional keywords to identify articles that pertained to the critical outcomes. For benefits related to vaccine immunity, the following keywords were used: "immunogenicity", "immunity", or "long-term". For harms related to adverse events, the following keywords were used: "adverse events", "safety", or "side effects". The titles of the articles were first reviewed to identify potentially relevant articles and then the abstracts were reviewed of any article with a relevant title. If no abstract was provided, the paper itself was reviewed. In addition, reference lists of relevant articles were reviewed to identify any additional articles that might be of relevance but were not obtained through searching PubMed or Embase.

Articles that presented data on YF vaccine were included if they met the following criteria: 1) involved human subjects; 2) reported primary data; and 3) included data relevant to the outcome measures being assessed. Publications that met the above criteria but represented case reports of adverse events were excluded.

Of 1,166 articles in PubMed identified using the terminology "yellow fever vaccine", 560 articles included keywords related to the critical outcomes. Of these, 263 articles included keywords related to benefits and 412 article related to harms. Following the removal of articles that did not meet the inclusion criteria, 30 articles were included in the GRADE evaluation. The Embase search identified 1,719 articles related to YF vaccine but no additional studies meeting the selection criteria were found. From the reference lists of relevant articles, two additional articles were identified and included in the GRADE evaluation. This search was repeated on February 2, 2015 to identify any literature that was recently published; no additional articles were identified.

Unpublished data were also considered, including data from studies conducted by the Brazilian Ministry of Health on duration of immunity and vaccine safety, CDC data on antibody titers in vaccine recipients, and VAERS data on vaccine safety.

Summarize relevant evidence for critical outcomes

Vaccine effectiveness

The evidence used to evaluate vaccine effectiveness was derived from eight published studies and one unpublished study that documented YF disease in persons who reported receiving YF vaccine. Of the eight published studies, four were from Brazil and likely contained individuals who were included in more than one of the studies. In response to an inquiry regarding the potential overlap between studies, the Brazilian Ministry of Health provided national level data that covered both the populations and the time period of the four studies; these data were used in place of the four published studies from Brazil (**Table 2**).

A total of 23 vaccine failures were identified following the administration of >540 million doses of YF vaccine [WHO 2013]. Of the 23 cases, five occurred <10 days after vaccination and were excluded as most persons are not expected to develop protective titers before 10 days after vaccination [Monath 2013]. Of the remaining 18 cases, 16 (89%) occurred in individuals who reported receiving a dose of the vaccine within the previous 10 years. Two vaccine failures occurred ≥10 years after the last dose of YF vaccine, including one at 20 years and one at 27 years post vaccination. Eleven cases (61%) lacked any YF laboratory testing. For seven cases, there was laboratory confirmation of YF virus infection; however, for some cases the only laboratory evidence of infection was detection of anti-YF virus IgM antibodies [Brazil 2014]. Since YF IgM antibodies can persist for several years following YF vaccination [Gibney 2012], these cases lacked definitive evidence of a recent infection with wild-type YF virus.

Seropositivity

The evidence used to evaluate seropositivity at ≥10 years following YF vaccination was derived from 12 published studies and one unpublished study (**Table 3**). The studies were published over a 60 year period (1952–2014) and included data for several different vaccines, some of which are no longer manufactured, and results from tests that are no longer used.

Of the 13 observational studies, immunogenicity data were available on 1,137 persons vaccinated ≥10 years previously. Of these, 1,002 (88%) were seropositive for YF virus neutralizing antibodies. Of 164 persons who reported receiving YF vaccine ≥20 years previously, 132 (80%) had detectable levels of neutralizing antibodies (i.e., seropositive). When study size differences and variability between studies was accounted for using a random effects model, the estimate of seropositivity for persons vaccinated ≥10 years previously was 92% (95% confidence interval [CI] 85%–96%) and those vaccinated ≥20 years previously was 80% (95% CI 74%–

86%).

Serious adverse events (SAE)
The evidence used to evaluate SAE following YF vaccine was derived from eight published and one unpublished observational studies. These studies included surveillance data from national authorities as well as data from vaccine manufacturers for approximately 333 million doses of distributed vaccine. There were 1,255 subjects reported to have a SAE following YF vaccination (**Table 4**). For the majority (84%) of subjects, it was unknown if the SAE occurred following a primary or booster dose of the vaccine. Furthermore, it was not known how many of the 333 million doses of vaccine were administered as a primary or booster dose. Of the 201 subjects with a SAE where dose type was known, 14 (7%) occurred following a booster dose of vaccine.

Viscerotropic disease
The evidence used to evaluate YF vaccine-associated viscerotropic disease (YEL-AVD) was derived from eight observational studies. These studies included surveillance data from national authorities as well as data from vaccine manufacturers for approximately 437 million doses of distributed vaccine. There were 72 subjects reported as having YEL-AVD (**Table 5**). Most of these YEL-AVD cases likely also were reported as SAE. For 41 (57%) subjects, it was unknown if YEL-AVD occurred following a primary or booster dose of the vaccine. Furthermore, it was not known how many of the 437 million doses of vaccine were administered as a primary or booster dose. Of the 31 subjects where dose type was known, 1 (3%) subject had YEL-AVD after receiving a booster dose of the vaccine; no laboratory testing was performed for that case.

Neurologic disease
The evidence used to evaluate YF vaccine-associated neurologic disease (YEL-AND) was derived from eight observational studies. These studies included surveillance data from national authorities as well as data from vaccine manufacturers for approximately 462 million doses of distributed vaccine. There were 218 subjects reported as having YEL-AND (**Table 6**). For 108 (50%) subjects, it was unknown if YEL-AND occurred following a primary or booster dose of the vaccine. Furthermore, it was not known for most of the 462 million doses of vaccine how many were administered as a primary or booster dose. Of the 110 subjects where dose type was known, 3 (3%) subjects reported YEL-AND after receiving a booster dose of the vaccine. All three of these YEL-AND cases were reported as an autoimmune-mediated event rather than direct vaccine viral invasion of the central nervous system. With autoimmune neurologic events seen following YF vaccination, there is no specific laboratory testing that is available to assess vaccine causality.

Summary of quality of evidence across outcomes
For the benefits considered critical outcomes, there were very few vaccine failures documented and most [92% (95% CI 85%–96%)] primary vaccine recipients were seropositive at ≥10 years post vaccination. However, evidence type is 4 for both vaccine effectiveness and seropositivity as there were only observational studies available that were downgraded because of the risk of bias (i.e., incomplete case capture, no comparison group, and bias in those tested for long-term seropositivity) and indirectness (i.e., different populations of interest, unknown how many persons had received a booster dose, and indirect measure of efficacy and seroprotection) (**Table 7**). For harms considered critical outcomes, very few safety concerns were reported after booster

doses. The evidence type is 4 for observational studies that were downgraded due to indirectness (i.e., unknown how many of the doses were administered as booster doses versus primary doses and thus the rates of adverse events for booster doses specifically could not be calculated). The overall quality of evidence is type 4 (**Table 8**).

Summary of other relevant evidence

In addition to the critical outcomes, data were reviewed on certain populations who had a condition that might have compromised their immune response to YF vaccine, including pregnant women, hematopoietic stem cell transplant recipients, HIV-infected individuals, and young children.

Pregnant women: The proportion of women who develop YF virus antibodies is variable and might be related to the trimester in which they received the vaccine. Of 83 pregnant woman receiving YF vaccine predominantly in their third trimester, 32 (39%) had evidence of seroconversion to YF virus at 2–4 weeks post vaccination compared to 94% (89/95) in the general population [Nasidi 1993]. Of 433 women vaccinated predominantly in the first trimester (mean gestational age 5.7 weeks; 95% CI 5.2–6.2), 425 (98%) developed YF virus-specific neutralizing antibodies at 6 weeks post vaccination [Suzano 2006].

Hematopoietic stem cell transplant recipients: There are limited safety and immunogenicity data (i.e., a few case reports) for YF vaccination of hematopoietic stem cell transplant recipients [Yax 2009, Gowda 2004, Ljungman 2005]. However, data for other live virus vaccines suggest most recipients become seronegative following transplantation [Ljungman 1994]. Infectious Diseases Society of America guidelines recommend re-administering live viral vaccines, such as measles, mumps, and rubella (MMR) vaccine and varicella vaccine, to hematopoietic stem cell transplant recipients if they are seronegative and no longer immunosuppressed [Rubin 2014].

HIV-infected individuals: Published studies on the immunogenicity of YF vaccines in HIV-infected persons are limited. One retrospective cohort study found 65 (83%) of 78 HIV-infected persons had specific antibodies against YF virus in the first year after vaccination; however this was significantly lower than vaccinated persons without HIV infection (97%, 64/66) (P=0.01) [Veit 2009]. The rate of detectable YF virus-specific antibodies was also lower among HIV-infected persons at 1 to 10 years post vaccination (77%, 54/70) compared to uninfected controls (88%, 81/92) but this difference was not significant (P=0.07) [Veit 2009]. One additional study noted that only 3 (17%) of 18 HIV-infected infants in Cote d'Ivoire developed YF virus-specific neutralizing antibodies following vaccination compared to 42 (74%) of 57 HIV-uninfected controls matched for age and nutritional status (P<0.01) [Sibailly 1997]. The mechanisms for the diminished immune response in HIV-infected persons are uncertain but appear to be correlated with HIV RNA levels and inversely correlated with CD4+ cell counts [Veit 2010].

Young children: Twelve studies were identified that provided data on the initial immune response to YF vaccine in children aged 4 months to 10 years (**Table 9**). All the studies included children who resided in endemic areas and 10 (83%) studies included children who received at least one other vaccine co-administered with YF vaccine. Of the 4,675 children, 4,101 (88%) seroconverted 1–2 months following their primary YF vaccination. When study size differences and variability between studies were accounted for using a random effects model, the estimate of seroconversion rate was 93% (95% CI 88%–96%). Furthermore, when the random effects model was used to compare seroconversion rates between children aged <9 months and those aged ≥9 months, there was no difference. For children aged <9 months, data from four studies provided an estimated seroconversion rate of 95% (95% CI 91%–98%). In children aged ≥9 months, data

from 11 studies provided an estimated seroconversion rate of 92% (95% CI 86%–96%). There are limited data on the persistence of YF antibodies in children; with no data available on seropositivity by the time since last YF vaccination.

The data for seroconversion rates in children following YF vaccination were presented to the American Academy of Pediatrics Committee on Infectious Diseases (COID) in November 2014. Upon review of these data and comparing them to seroconversion rates in adults, COID members agreed that the response to YF vaccine in children did not appear to be different than adults. Given this, they concluded that children can be included with adults regarding their need for YF vaccine booster doses. However, they noted the need for long-term immunogenicity data from persons vaccinated as children to ensure the antibody decay kinetics are similar compared to persons vaccinated initially as an adult.

Higher-risk exposures: Finally, the Work Group considered persons who might be in a higher-risk setting for YF virus exposure based on season, location, activities, and duration of their travel. Limited epidemiologic data suggest that West Africa has the highest risk of disease with 90% of all YF disease cases over the preceding 20 years being reported from countries in West Africa [Monath 2013]. Furthermore, the Work Group considered persons traveling to an area with an ongoing outbreak, persons traveling for a prolonged period of time in an endemic area, and persons who routinely handle wild-type YF virus in the laboratory to be at higher-risk for YF virus exposure than other persons for whom YF vaccine is recommended.

Assess the values related to management options and outcomes

From 1970–2014, nine cases of YF were reported in unvaccinated travelers from the United States (n=3) and Europe (n=6) who traveled to West Africa or South America [McFarland 1997; Digoutte 1981; Rodhain 1979; CDC 1999; Colebunders 2002; CDC 2002; Teichmann 1999; WHO 1998; WHO 2000]. Eight of these nine travelers died. Only one case of YF has been documented in a vaccinated traveler from Spain who received the vaccine 5 years before traveling to several West African countries and being diagnosed with YF; the traveler survived [Nolla-Salas 1989]. YF vaccine has been available since the 1930s, including in the United States, and it is not known how many cases have been prevented due to vaccination or how many cases are not diagnosed or reported. Reports from U.S. travel clinics or international airports have documented that 91%–93% of travelers for whom YF vaccine was recommended received the vaccine [Jentes 2013; Lown 2014; Toovey 2004]. In one study of 3,207 travelers who received YF vaccine at a travel clinic visit in the United States, only 149 (5%) had reportedly received a previous dose of YF vaccine ≥10 years previously [Jentes 2013].

A traveler's risk of acquiring YF is determined by multiple factors, including immunization status, use of personal protection measures against mosquito bites, location of travel, duration of exposure, occupational and recreational activities while traveling, and local rate of virus transmission at the time of travel. In both West Africa and South America, YF virus transmission typically is seasonal and is associated with the mid-to-late rainy season [Monath 2002]. However, YF virus can be transmitted by *Aedes aegypti* even during the dry season in both rural and densely settled urban areas [Beeuwkes 1933]. Although the number of reported cases of human disease often is used to estimate the crude level of endemic transmission, cases might not be reported because of a low level of transmission, a high level of immunity in the local population, or cases not being detected by local surveillance systems. Therefore, a lack of human disease cases in an area does not equate to absence of risk for transmission.

The risk of acquiring YF is difficult to predict because of variations in ecologic determinants of virus transmission. For a 2-week stay, the estimated risks for illness and death attributed to YF for an unvaccinated traveler traveling to an area of West Africa where the disease is endemic are 50 and 10 per 100,000 population, respectively; for South America, the risks for illness and death are five cases and one case per 100,000 population, respectively [Monath 2002]. These crude estimates for unvaccinated travelers are based on risk to indigenous populations, often during peak transmission season. Thus, these risk estimates might not reflect accurately the actual risk to travelers, who might have a different immunity profile, take precautions against getting bitten by mosquitoes, and have less outdoor exposure. Furthermore, it is unknown how the potential risk of the disease differs in persons who have received at least one dose of YF vaccine ≥10 years previously.

Recommendations regarding the use of YF vaccine booster doses for travelers must weigh the overall risk for travel-associated YF disease in persons who have previously received a dose of the vaccine, the lack of treatment, high mortality (80%) in travel-related cases, the low probability of serious adverse events following revaccination, and the cost of the vaccine (**Table 10**). High value is placed on preventing this life-threatening disease. A survey performed in the United States in 2001 found that both parents and community members were willing to pay a median of $500 to reduce the risk of bacterial meningitis from 21 per 100,000 to 6 per 100,000 [Prosser 2004]. Although the disease presentation and population used in the survey are different than what would be expected for YF among travelers, they establish a willingness to pay to prevent a serious outcome.

Review health economic data

There are no studies of the potential cost-effectiveness of vaccinating travelers or laboratory workers against YF either with primary or booster doses of the vaccine. However, given the large numbers of travelers to endemic areas (~3 million annually of which an estimated 150,000 could need a booster dose of vaccine), the risk for YF disease for unvaccinated travelers (5–50 case per 100,000 unvaccinated travelers), and the cost of YF vaccine ($150–$350) [Monath 2002; Costhelper 2014], providing a booster dose of YF vaccine to all travelers going to endemic areas would not be cost-effective. In addition, for some travelers with lower risk itineraries, even a very low probability of vaccine-related serious adverse events might be higher than the risk for disease. Therefore, YF vaccine booster doses should be targeted to travelers who, on the basis of their planned travel itinerary and activities, are at increased risk for disease.

Travel vaccines, such as YF vaccine, are usually paid for by the travelers themselves; they are not covered under the Vaccines for Children (VFC) program or by most private insurance plans. As a result, we decided not to perform a cost-effectiveness study of removing booster doses of YF vaccine for U.S. travelers or laboratory workers. Furthermore, none of the Work Group members consider cost-effectiveness study critical to make recommendations regarding YF vaccine booster doses for healthy travelers and laboratory workers.

Assess the balance of risks and benefits

A primary dose of YF vaccine is effective with very few vaccine failures documented and most (92%) of vaccine recipients maintaining seropositive levels of neutralizing antibodies at ≥10 years post vaccination. However, the number of persons from whom the seropositivity data are derived is limited and over half (59%) of the data come from persons living in YF endemic areas. The data also suggest that 20% (95%CI 14%–26%) of persons who received YF vaccine ≥20

years previously do not have detectable levels of neutralizing antibodies. For previously vaccinated persons without evidence of circulating neutralizing antibodies, it is not known if other immunologic measures (e.g., cell-mediated immunity or memory B cell response) would provide adequate protection against YF.

Very few serious adverse events, including vaccine-related viscerotropic and neurologic disease, have been reported following booster doses of the vaccine. However, for most of the adverse event data, it is unknown whether the patients had received a primary or booster dose prior to their reported event, and how many of the total doses of vaccine where given as primary or booster doses.

In general, there is high value placed on prevention of a serious disease with no treatment and substantial mortality. The overall disease risk in persons who have already received a dose of the vaccine is likely quite low and vaccine cost is high.

Formulate recommendations and determine the category

Current ACIP recommendations for YF vaccine were approved in 2009 and contain the following wording in regards to the use of booster doses. "[International Health Regulations] require revaccination at intervals of 10 years to boost antibody titer. Evidence from multiple studies demonstrates that YF vaccine immunity persists for many decades and might provide life-long protection. To minimize the occurrence of adverse events and optimize the immune response, efforts should be taken to observe a 10-year interval between YF vaccine doses." [CDC 2010].

The GRADE evaluation found that there are very few vaccine failures documented following primary doses of YF vaccine, most (92%) primary vaccine recipients maintain detectable levels of neutralizing antibodies ≥10 years post vaccination, and very few serious adverse events have been reported following booster doses of YF vaccine (Evidence type 4). However, additional data suggest that certain populations (e.g., pregnant women or HIV-infected person) might not have as robust or sustained immune response to YF vaccine compared to "healthy" persons. Furthermore, certain groups were felt to be at increased risk of the disease either due to their location and duration of travel or due to more consistent exposure to virulent virus (e.g., laboratory workers).

Upon reviewing the available data, the majority of the Work Group felt that booster doses of YF vaccine should not be recommended for most travelers or laboratory workers. However, based on limited data, YF vaccine should be recommended in certain populations at increased risk of YF disease either due to an increased risk of exposure to YF virus or due to suboptimal immune response to a dose of YF vaccine. The Work Group recommends the following language regarding booster doses of YF vaccine:

- A single dose of YF vaccine provides long-lasting protection and is adequate for most travelers. (Recommendation Category A)
- Additional doses of YF vaccine are recommended for certain travelers, including*:
    - Women who were pregnant when they received their initial dose of YF vaccine should receive one additional dose of YF vaccine prior to their next travel that puts them at risk for YF virus infection.
    - Persons who received a hematopoietic stem cell transplant after receiving a dose of YF vaccine and who are sufficiently immunocompetent to be safely vaccinated should be revaccinated prior to their next travel that puts them at risk for YF virus infection.

    - Persons who were HIV-infected when they received their last dose of YF vaccine should receive a dose every 10 years if they continue to be at risk for YF virus infection.

  *Persons being considered for additional doses of YF vaccine should be assessed for contraindications or precautions. (Recommendation Category A)
- A booster dose may be given to travelers who received their last dose of YF vaccine at least 10 years previously and who will be in a higher-risk setting based on season, location, activities, and duration of their travel. This would include travelers who plan to spend a prolonged period in endemic areas or those traveling to highly endemic areas such as rural West Africa during peak transmission season or an area with an ongoing outbreak. (Recommendation Category B)
- Laboratory workers who routinely handle wild-type YF virus should have YF virus-specific neutralizing antibody titers measured at least every 10 years to determine if they should receive additional doses of the vaccine. For laboratory workers who are unable to have neutralizing antibody titers measured, YF vaccine should be given every 10 years as long as they remain at risk. (Recommendation Category A)

Further study

The Work Group members prioritize the following areas of study to address gaps in our current knowledge regarding the need for YF vaccine booster doses in U.S. travelers and laboratory workers:

1. Assessing neutralizing antibody levels ≥10 years post initial vaccination in non-endemic populations (e.g., travelers)
2. Evaluating anamnestic immune response to revaccination in persons from non-endemic YF locations who fail to have detectable levels of neutralizing antibodies years ≥10 years following their initial YF vaccination
3. Determining seroprotective level of antibodies using a plaque reduction neutralization test (PRNT) by correlating to established level of seroprotective neutralizing antibodies by $\log_{10}$ neutralization index (LNI) (LNI ≥ 0.7)
4. Assessing long-term neutralizing antibody levels among certain populations, such as infants or HIV-infected persons, to obtain more information on the need for additional doses of YF vaccine
5. Establishing the role of cell-mediated immunity in long-term protection against YF disease in non-endemic populations

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Table 1. Summary of outcome measure ranking and inclusion for yellow fever (YF) vaccine booster doses

Outcome	Importance	Include in evidence profile	Data available
Benefits			
Vaccine efficacy	Critical	Yes	No
Vaccine effectiveness[1]	Critical	Yes	Yes
Seroprotection[2]	Critical	Yes	No
Seropositivity	Critical	Yes	Yes
Harms			
Serious adverse events[3]	Critical	Yes	Yes
Viscerotropic disease	Critical	Yes	Yes
Neurologic disease	Critical	Yes	Yes
Anaphylaxis	Important	No	--
Systemic adverse events	Important	No	--

[1]Vaccine effectiveness was assessed as vaccine failures

[2]There are no long-term immunogenicity data using $\log_{10}$ neutralization index (LNI), the only test for which a seroprotective titer has been established (i.e., LNI $\geq$0.7). Given this, it was decided that seropositivity (i.e., having detectable YF virus-specific antibodies) would be used as a surrogate for seroprotection and included in the evidence profile even though seropositivity was originally rated as important not critical.

[3]Serious adverse event is an event that is plausibly related to YF vaccination and was considered to be life-threatening or required hospitalization.

Table 2. Vaccine effectiveness measured by vaccine failures reported following yellow fever (YF) vaccination

Study	Population	Type	Age Group	No.	Lab confirmed	Timing post vaccination	Outcome
Elliot 1944	Non-endemic	Obs	Adult	3	0	15 mo, 16 mo, 16 mo	Died (2), Survived (1)
Ross 1953	Non-endemic	Obs	Adult	1	0	4 yr	Died
Nolla Salas 1989	Non-endemic	Obs	Adult	1	0	5 yr	Survived
Akoua-Koffi 2001	Endemic	Obs	Unknown	6	0	Unknown	Survived (6)
Brazil 2014[1]	Endemic	Obs	Unknown	7[2]	7[3]	10 dy-10 yr (5), 20 yr (1), 27 yr (1)	Unknown
All	**Non-endemic/ Endemic**	**Obs (5)**	**Adult or Unknown**	**18**	**7**	**10 dy – 27 yr**	**Died (3), Unknown (7), Survived (8)**

Obs = observational study; dy = days; mo = months; yr = years

[1]Data were provided by the Brazilian Ministry of Health to resolve overlap and errors in four published studies regarding vaccine failures in Brazil (Tuboi 2007, de Filippis 2004, Saraiva 2013, and Camara 2013).
[2]A total of 12 vaccine failures were identified but five occurred <10 days after vaccination and were excluded.
[3]Laboratory confirmation defined in the study as 1) detection of YF virus-specific IgM antibodies, 2) isolation of YF virus, 3) YF-compatible pathological changes in liver tissue, 4) detection of YF virus antigen by immunohistochemistry, or 5) four-fold or greater rise in YF virus-specific IgG antibody titers. The specific laboratory criteria used to confirm the seven cases was not noted. Due to the persistence of IgM antibodies that can occur following vaccination [Gibney 2012], these cases lacked definitive evidence of a recent infection with wild-type YF virus.

Table 3. Seropositivity at ≥10 years following yellow fever (YF) vaccination

Study	Population	Type	Seropositivity criteria[1]	Years post vaccination	Seropositive No.	(%)
Dick 1952	Endemic	Obs	Mouse protection	10	156/202	(77)
de Melo 2011	Endemic	Obs	$PRNT_{50}$ ≥20	10	20/20	(100)
Reinhardt 1998	Non-endemic	Obs	$PRNT_{90}$ ≥10	≥10	5/5	(100)
Machado 2013	Endemic	Obs	$PRNT_{80}$ ≥10	≥10	19/19	(100)
CG YF vaccines 2014[2]	Endemic	Obs	$PRNT_{50}$ ≥10	10-18	307/329	(93)
Rosenzweig 1963	Non-endemic	Obs	Mouse protection	10-15	24/24[3]	(100)
Courtois 1954	Endemic	Obs	Mouse protection	12	76/79	(96)
Groot 1962	Non-endemic	Obs	Mouse protection	17	105/108	(97)
Gomez 2008	Endemic	Obs	$PRNT_{75}$ ≥10	10-24	13/19[3]	(68)
Niedrig 1999	Non-endemic	Obs	$PRNT_{90}$ >10	11-38	38/51	(75)
Coulange Bodilis 2011	Non-endemic	Obs	$PRNT_{80}$ ≥10	10-60	80/84	(95)[4]
CDC 2014	Non-endemic	Obs	$PRNT_{90}$ ≥10	10-69	68/81	(84)[5]
Poland 1981	Non-endemic	Obs	$PRNT_{90}$ ≥2	30-35	91/116	(78)
All	**Non-endemic/Endemic**	**Obs (13)**	**Multiple**	**10-60**	**1,002/1,137**	**(88)**

Obs = observational study; PRNT = plaque reduction neutralization test

[1]For mouse protection assays, vaccine recipient serum for which ≥3 of 6 mice survived are included as seropositive. PRNTx% is the reciprocal of the highest serum dilution at which x% of YF virus is inhibited.

[2]CG YF vaccines = Collaborative group for studies on yellow fever vaccines (Brazil).

[3]Numbers are estimated as some cases included in the data received their vaccination <10 years previously.

[4]88% (15/17) of subjects who received YF vaccine ≥20 years previously were seropositive [Coulange Bodilis 2011]

[5]84% (26/31) of subjects who received YF vaccine ≥20 years previously were seropositive [CDC 2014]

Table 4. Serious adverse events reported following yellow fever (YF) vaccination by dose type

Study	Location	Reporting Period	Type	Doses	Number of cases by dose type		
					Primary	Booster	Unknown
CDC 2015	Non-endemic	2007-2013	Obs	3,631,535	96	11[1]	0
Cottin 2013	Non-endemic/Endemic	1993-2010	Obs	276,000,000[2]	--[3]	--	805
Schumacher 2010	Non-endemic	1991-2001	Obs	272,727	--	--	7
Lindsey 2008	Non-endemic	2003-2006[4]	Obs	902,500	54	1[5]	0
Khromava 2005	Non-endemic	1990-2002	Obs	9,600,000	13	2[6]	32
Biscayart 2014	Endemic	2008-2009	Obs	1,940,000	24	--	9
Breugelmans 2013	Endemic	2007-2010	Obs	38,009,411	--	--	164
Fernandes 2007	Endemic	1999-2005	Obs	499,714	--	--	24
Fitzner 2004	Endemic	2001	Obs	2,600,000	--	--	13[7]
All	**Non-endemic/Endemic**	**1990-2013**	**Obs (9)**	**333,455,887**	**187**	**14**	**1054**

Obs = observational study

[1]All 11 serious adverse event cases were reported in adults who were hospitalized following their second (n=10) or third (n=1) dose of YF vaccine. The cases included: 1) Guillain-Barré syndrome (GBS) 16 days post vaccination; 2) GBS 7 days post vaccination; 3) encephalitis 4 days post vaccination; 4) bilateral optic neuritis 2 days post vaccination; 5) anaphylaxis with angioedema on the day of vaccination; 6) lower extremity cellulitis 7 days post vaccination; 7) acute appendicitis requiring surgery 2 days post vaccination; 8) fever and right lower quadrant pain 5 days post vaccination; 9) fever and syncope 1 day post vaccination; 10) myalgia and upper extremity weakness 3 days post vaccination; and 11) lymphadenitis 26 days post vaccination, subsequently diagnosed as Hodgkin's lymphoma.

[2]Of the 276 million doses, 16.2 million (5.8%) doses were given to non-endemic populations (e.g., travelers).

[3]Indicates that cases are not reported for the specific dose type.

[4]The published study includes data from 2000–2006 but 2000–2002 removed to prevent overlap with data from Khromova 2005.

[5]One case of appendicitis requiring surgery at 1 day post vaccination.

[6]One case reporting numbness and weakness at 12 days post vaccination and one case with abdominal pain and yellow stools requiring hospitalization at 7 days post vaccination.

[7]Cases not explicitly defined as having serious adverse events but 13 out of 87 adverse events required hospitalization and were considered to be serious.

Table 5. Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) by dose type

Study	Location	Reporting Period	Type	Doses	Number of cases by dose type		
					Primary	Booster	Unknown
Cottin 2013	Non-endemic/Endemic	1993-2010	Obs	276,000,000[1]	4	1[2]	7
Lindsey 2008	Non-endemic	2003-2006[3]	Obs	902,500	6	--[4]	--
Khromava 2005	Non-endemic	1990-2002	Obs	9,600,000	8	--	--
Kitchner 2004	Non-endemic	1991-2003	Obs	3,046,007	--	--	4
Biscayart 2014	Endemic	2008-2009	Obs	1,940,000	12	--	--
Breugelmans 2013	Endemic	2007-2010	Obs	38,009,411	--	--	5
Martins 2010	Endemic	1999-2009	Obs	107,649,393	--	--	20
Whittembury 2009	Endemic	2007	Obs	42,742	--	--	5
All	**Non-endemic/Endemic**	**1990-2010**	**Obs (8)**	**437,190,053**	**30**	**1**	**41**

Obs = observational study

[1]Of the 276 million doses, 16.2 million (5.8%) doses were given to non-endemic populations (e.g., travelers).

[2]One suspect case in a 55-year-old male who had illness onset 2 days following a booster dose of yellow fever (YF) vaccine. He presented with polyarthralgia, and liver cytolysis; no YF specific-testing was performed. He was reported as recovering from his illness.

[3]The published study includes data from 2000–2006 but 2000–2002 removed to prevent overlap with data from Khromova 2005.

[4]Indicates that cases are not reported for the specific dose type.

Table 6. Yellow fever vaccine-associated neurologic disease (YEL-AND) by dose type

Study	Location	Reporting Period	Type	Doses	Number of cases by dose type		
					Primary	Booster	Unknown
Cottin 2013	Non-endemic/Endemic	1993-2010	Obs	276,000,000[1]	10	1[2]	13
Lindsey 2008	Non-endemic	2003-2006[3]	Obs	902,500	6	--[4]	--
Khromava 2005	Non-endemic	1990-2002	Obs	9,600,000	10	--	--
Kitchner 2004	Non-endemic	1991-2003	Obs	3,046,007	--	--	4
Martins 2014	Endemic	2009-2012[5]	Obs	30,745,743[6]	59	2[7]	--
Biscayart 2014	Endemic	2008-2009	Obs	1,940,000	12	--	--
Breugelmans 2013	Endemic	2007-2010	Obs	38,009,411	--	--	6
Martins 2010	Endemic	2000-2008	Obs	101,564,083	--	--	85
All	**Non-endemic/Endemic**	**1990-2010**	**Obs (8)**	**461,807,744**	**107**	**3**	**108**

Obs = observational study

[1]Of the 276 million doses, 16.2 million (5.8%) doses were given to non-endemic populations (e.g., travelers).

[2]One suspected case in a 45-year-old female who had illness onset 13 days following a booster dose of the vaccine. Her clinical features were listed as a suspected "multiple sclerosis syndrome"; no yellow fever (YF) specific-testing performed. She had "favorable outcome with corticosteroids".

[3]The published study includes data from 2000–2006 but 2000–2002 removed to prevent overlap with data from Khromova 2005.

[4]Indicates that cases are not reported for the specific dose type.

[5]The study includes data from 2007–2012 but 2007–2008 removed to prevent overlap with Martins 2010.

[6]Approximately 13 million doses were administered as booster doses. Total number of booster doses was derived by dividing the total number of booster doses administered by the number of years and assumed roughly the same number of doses delivered each year.

[7]One probable case in a 62-year-old female who was diagnosed with Guillain Barre syndrome at an unknown time post vaccination; one probable case in a 20-year-old male who became symptomatic 14 days post vaccination and was diagnosed with acute disseminating encephalomyelitis.

Table 7. Evidence type for benefits and harms for yellow fever (YF) vaccine booster doses in healthy travelers and laboratory workers

Outcome	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other[1]	Evidence type[2]
Benefits							
Vaccine effectiveness	Obs (5)	Yes[3]	No serious	Yes[4]	No serious	None	4
Seropositivity	Obs (13)	Yes[5]	No serious	Yes[6]	No serious	None	4
Harms							
Serious adverse events	Obs (9)	No serious	No serious	Yes[7]	No serious	None	4
Viscerotropic disease	Obs (8)	No serious	No serious	Yes[7]	No serious	None	4
Neurologic disease	Obs (8)	No serious	No serious	Yes[7]	No serious	None	4

Obs = observational study

[1]Publication bias, strength of association, dose response, or direction of all plausible confounding would reduce the effect.

[2]Evidence type:
1 = Randomized control trials (RCTs) or overwhelming evidence from observational studies
2 = RCTs with important limitations, or exceptionally strong evidence from observational studies
3 = Observational studies, or RCTs with notable limitations
4 = Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

[3]Risk of bias because of incomplete case capture and no comparison group.

[4]Indirectness due to different population (majority of data are from endemic areas) and it is unknown how many persons at risk of YF would not receive a booster dose of the vaccine.

[5]Risk of bias among those tested for long-term seropostivity.

[6]Indirectness due to different population (majority of data are from endemic areas). No efficacy data are available, no correlate of protection established for the assays used to assess long-term immunity, and different assays and antibody levels were used to assess either seropositivity or "seroprotection".

[7]Indirectness as it is not known for all but one study the number of doses that were administered as booster doses versus primary doses and thus rates for the adverse events could not be calculated.

Table 8. Overall quality of evidence for yellow fever (YF) vaccine booster doses in healthy travelers and laboratory workers

Outcome	Study design (# studies)	Finding	Evidence type[1]	Overall quality of evidence
Vaccine effectiveness	Obs (5)	Very few vaccine failures documented	4	4
Seropositivity	Obs (13)	Most (92%) seropositive at ≥10 years post vaccination	4	
Serious adverse events	Obs (9)	Very few events reported after booster doses	4	
Viscerotropic disease	Obs (8)	Very few events reported after booster doses	4	
Neurologic disease	Obs (8)	Very few events reported after booster doses	4	

Obs = observational study

[1]Evidence type:
1 = Randomized control trials (RCTs) or overwhelming evidence from observational studies
2 = RCTs with important limitations, or exceptionally strong evidence from observational studies
3 = Observational studies, or RCTs with notable limitations
4 = Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

Table 9. Seroconversion rates following a primary dose of yellow fever (YF) vaccine in young children

Study	Population	YF Vaccine	Other vaccine(s)[1]	Age	Assay used	Seroconverted[2] No.	(%)
Belmusto-Worn 2005	Endemic	17D-204	None	9 mo-10 yo	LNI	917/981	(93)
Nascimento 2011[3]	Endemic	17DD/17D-213	None MMR	12-23 mo	$PRNT_{50}$	718/819 552/792	(88) (70)
Yvonnet 1986	Endemic	17D-204	BCG, DTP, HepB, M, Polio	9-36 mo	$PRNT_{90}$	170/183	(93)
Coursaget 1995	Endemic	17D-204	HepB, M	9 mo	$PRNT_{90}$	165/172	(96)
Lhuillier 1989	Endemic	17D-204	M	6-9 mo	HIA	122/135	(90)
Mouchon 1990	Endemic	17D-204	M	6-10 mo	$PRNT_{80}$	131/139	(94)
Stefano 1999	Endemic	17DD	M	9 mo	$PRNT_{50}$	228/294	(78)
Adu 1996	Endemic	17D-204	M	6-12 mo	ELISA	379/400	(95)
Soula 1991	Endemic	17D-204	M	4-24 mo	PRNT	158/167	(95)
Ruben 1973	Endemic	17D-204	M, DPT, S	6-24 mo	$PRNT_{90}$	158/165	(96)
Gateff 1973	Endemic	17D-204	BCG, M, S, T	1-5 yo	HIA	119/139	(86)
Osei-Kwasi 2001	Endemic	17D-204	None	6-9 mo	PRNT	284/289	(98)

BCG = Bacillus Calmette-Guerin vaccine; DTP = diphtheria, tetanus, and pertussis combined vaccine; ELISA = enzyme-linked immunosorbent assay; HepB = hepatitis B vaccine; HIA = hemagglutination inhibition assay; LNI = $\log_{10}$ neutralization index; M = measles vaccine; MMR= measles, mumps, and rubella combined vaccines; mo = months old; PRNT = plaque reduction neutralization test; S = Smallpox; T = tetanus; yo = years old

[1]Except for Nascimento, serocoversion rates following concurrent administration of YF vaccine with other vaccines compared to administration alone was not significantly different so the proportion are for all children who received YF vaccine. For Nascimento, a significant difference was seen between seroconversion rates when YF vaccine was co-administered with MMR vaccine versus given 30 days post MMR vaccine; these data are presented individually.

[2]Measured 30–90 days post YF vaccination.

[3]Percent seroconversion is for per protocol population; numerator and denominator data estimated from total numbers in each cohort.

Table 10. Considerations for formulating recommendations for use of yellow fever (YF) vaccine booster doses in healthy travelers and laboratory workers at increased risk of exposure to YF virus

Key factors	Comments
Evidence type for benefits and harms	• Overall evidence type 4 for vaccine effectiveness, seroprotection, and serious adverse events • Downgraded due to risk of bias (incomplete case capture, those tested for long-term seropositivity), and indirectness (data from endemic populations, no efficacy data, and unknown rates of adverse events with booster doses)
Balance between benefits and harms	• Very few vaccine failures identified following YF vaccine • Most (92%) of primary vaccine recipients are seropositive at ≥10 years post vaccination • Serious adverse events are uncommon following booster doses of the vaccine
Value	• Prevent a serious disease with no treatment and poor outcomes • Inform decisions about YF vaccination based on a traveler's planned itinerary
Cost-effectiveness	• Not evaluated • Likely low risk of disease in persons receiving a dose of YF vaccine • High vaccine cost for vaccines that is usually paid for by the travelers themselves; YF vaccine is not covered under the Vaccines for Children program or most insurance plans.