Background Paper on Yellow Fever Vaccine

SAGE Working Group

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Introduction

Yellow fever is a vector-borne disease resulting from the transmission of yellow fever virus to a human from the bite of an infected mosquito. It is endemic to sub-Saharan Africa and tropical South America. Infection in humans is capable of producing hemorrhagic fever and is fatal in 20-50% of person with severe disease. Because no treatment exists for yellow fever disease, prevention is critical to lower disease risk and mortality.

Yellow fever vaccine has been used since 1937 in the prevention of yellow fever disease with more than 600 million doses of the vaccine having been delivered worldwide. Currently all yellow fever vaccines in use are live attenuated viral vaccine from the 17D lineage. The vaccine has been proven to be highly immunogenic and a single dose provides long-term protection against yellow fever. In general, the vaccine is well tolerated inducing mild local and systemic side effects in up to a third of recipients. However, rare but serious side effects have been observed following yellow fever vaccination including: 1) immediate hypersensitivity or anaphylactic reactions; 2) yellow fever vaccine-associated neurologic disease (YEL-AND); and 3) yellow fever vaccine-associated viscerotropic disease (YEL-AVD). YEL-AND is a group of neurologic conditions that are either due to direct viral invasion of the central nervous system by the vaccine virus resulting in meningitis or encephalitis or due to an autoimmune reaction resulting in conditions such as Guillain-Barré syndrome or acute disseminated encephalomyelitis. YEL-AVD results from the replication and dissemination of the vaccine virus similar to the wild-type virus. YEL-AVD cases typically develop multi-organ system dysfunction or failure and over 60% of cases have been fatal. To date, YEL-AND and YEL-AVD only have been reported in primary vaccine recipients.

Yellow fever vaccine is recommended for person aged ≥9 months who are living in or traveling to areas at risk for yellow fever virus transmission in South America and Africa. Because of the risk of spread of the virus through infected mosquitoes or more likely infected humans, policies regarding the use of yellow fever vaccination are included in International Health Regulations (IHR). Under IHR (2005), countries can require proof of yellow fever vaccine receipt from persons upon entry. Individuals who arrive in a country with a yellow fever vaccination entry requirement without proof of vaccination may be quarantined for up to 6 days. Per IHR, a single dose of yellow fever vaccine is consider to provide protection against yellow fever virus infection starting 10 days following the administration of the vaccine and continuing for 10 years when a booster dose of the vaccine should be given.

The SAGE Working Group on Yellow Fever Vaccines was tasked with reviewing evidence and preparing recommendations related to the use of yellow fever vaccines in order to update the 2003 WHO position paper for SAGE review. This report reviews the evidence related to main topics considered by the working group, including:

1. Need for booster doses every 10 years to maintain protection against yellow fever
2. Safety of the vaccine in selected special populations
    a. Persons aged 60 years and older
    b. HIV-infected persons
    c. Persons with other immunocompromising conditions
    d. Pregnant women
    e. Lactating women, specifically the safety of vaccine exposure in their breastfed infants

3. Interference between yellow fever and other co-administered vaccines
4. Impact of vaccination strategies on control of yellow fever
    a. Routine vaccination versus outbreak control
    b. Combined routine immunizations and preventive campaigns

Methodology

To update the 2003 WHO position paper on yellow fever vaccine, the SAGE working group for yellow fever vaccination considered several key issues (outlined above). To address these issues and review current data relating to yellow fever vaccination, the working group first met in December 2011 conducting monthly teleconferences through July 2012 and having two face-to-face meetings conducted in April 2012 and January 2013. Published, peer-reviewed studies were the primary source of data used. When relevant to issues under discussion, unpublished data available to WHO also were considered.

To address the question related to the need of a booster of yellow fever vaccine and safety of yellow fever vaccine in persons age 60 years and over, the WHO Secretariat collaborated with both external (Eduardo Gotuzzo and Gabriela Córdova) and internal investigators (Ellen Rafferty) to review available data. This work was also supplemented by the following questions that were assessed by personnel from the WHO Secretariat using the GRADE approach:

- Is there evidence that a booster dose is required in immunocompetent individuals to ensure long-term protection?
- Is there evidence that elderly individuals over 60 years of age in endemic settings are at greater risk of YEL-AVD?
- Is there evidence that elderly travelers over 60 years of age are at greater risk of YEL-AVD?

Findings and Recommendations

The findings and recommendations of the working group for each of the main topics reviewed are presented below in distinct sections. Each section includes key findings, more in-depth information, and the recommendations of the working group.

Booster Doses

Key Findings

- No efficacy study has been performed for yellow fever vaccine; however, neutralizing antibodies have been used as a surrogate to indicate a protective immune response.
- The current recommendation of a booster dose of yellow fever vaccine every ten years has been in place under IHR since 1965 and was determined based on limited evidence.
- Data suggest that the majority of vaccine recipients will develop a protective antibody titer against yellow fever virus within 28 days of vaccination and will maintain protective antibody titers for potentially several decades, or possibly life-long, following vaccination.
- Children less than 2 years of age have lower seroconversion rates following a single dose of yellow fever vaccine.
- Very few primary vaccine failures following yellow fever vaccination have been reported and there are no reports of secondary vaccine failures due to time elapsed after immunization.
- Recent data suggest that, in addition to neutralizing antibodies, both innate and cell-mediated immunity also contribute to the initial immune response and the maintenance of long-term protection against yellow fever virus in those who are vaccinated.

Although no human efficacy studies have been performed with yellow fever vaccine, several observations support yellow fever vaccine being protective in humans, including: 1) the reduction of laboratory-associated infections in vaccinated workers; 2) the observation following initial use of the vaccine in Brazil and other South American countries that yellow fever only occurred in unvaccinated people; 3) the rapid disappearance of cases during yellow fever vaccination campaigns initiated during epidemics, and 4) the protection of rhesus monkeys against virulent yellow fever virus by neutralizing antibodies generated in response to yellow fever vaccination [1, 2].

From the dose-response study conducted in rhesus monkeys, a minimal level of neutralizing antibodies needed to protect the monkeys against virulent yellow fever virus was established. Testing using a $\log_{10}$ neutralization index (LNI) demonstrated that LNI >0.7 was correlated strongly with protection [1]. Although the amount of serum needed for LNI testing is suitable for animal studies or clinical trials, it precludes routine screening among humans [3]. Therefore, a similar test, plaque reduction neutralization test (PRNT), is used most frequently in diagnostic tests and follow-up studies to determine the absence or presence of neutralizing antibodies and the specific serum antibody titer.

Clinical trials have found 80% to 100% of vaccinated individuals develop yellow fever virus neutralizing antibodies by 10 days after vaccination [4-6]. Most studies find >99% of the vaccinated individuals developed neutralizing antibodies by 28 days after vaccination [3].

Yellow fever vaccine is recommended for persons aged ≥9 months who are traveling to or living in areas where there is a risk of yellow fever virus transmission. Per IHR (2005), a single dose of yellow fever vaccine is consider to provide protection against yellow fever virus infection starting 10 days following the administration of the vaccine and continues for 10 years [7]. The booster dose requirement for yellow fever vaccine was put into place in 1959 under the precursor to IHR, International Sanitary Regulations, with booster doses initially being required every 9 years based on available data [8, 9]. The booster dose interval was changed in 1965 to every 10 years based published studies that showed

neutralizing antibodies were present in the majority of vaccine recipients for at least 10 years after vaccination (Table 1) [10, 11].

A systematic review conducted by external collaborators and WHO secretariat identified at least 6 additional studies on the presence of neutralizing antibodies in yellow fever vaccine recipients 10 or more years since vaccination [12-18]. Although different techniques and assay PRNT cutoff values were used in the studies, most studies document a high proportion of vaccine recipients (>90%) with detectable levels of serum neutralizing antibodies up to 20 years post vaccination (Table 1). Studies that have looked at persons 20 or more years after vaccination have found that approximately 80% of vaccine recipients still have detectable levels of neutralizing antibodies [12, 14, 15, 17]. One of these long-term immunity studies was conducted among U.S. military veterans from World War II and found that more than 80% of military personnel had neutralizing antibody 30-35 years following a single dose of yellow fever vaccine [12]. In a separate study, neutralizing antibodies were detected in one vaccine recipient 60 years following their vaccination [17].

Since the 1930s when yellow fever vaccine was first used, only 12 cases of yellow fever disease have been identified among vaccine recipients of over 600 million doses of the vaccine administered (Table 2) [19-23]. Of the 12 cases, some (n=3) lacked any laboratory data to confirm them as yellow fever cases while others had questionable or inadequate laboratory findings (n=7). Two of the yellow fever disease cases occurred in person who received the vaccine within two weeks of their illness onset and thus may not have had adequate time to develop neutralizing antibodies against the vaccine before being exposed to wild-type yellow fever virus. For these cases, nucleotide sequencing was performed and identified wild-type yellow fever virus rather than vaccine virus (i.e., not YEL-AVD cases) [23]. All 12 of the cases of yellow fever disease among vaccine recipients developed within 5 years of vaccination suggesting that secondary vaccine failures due to waning immunity do not occur.

In addition to the systematic review, the following question related to the need for a booster dose of yellow fever vaccine was evaluated using GRADE: 1) Is there evidence that a booster dose is required in immunocompetent individuals to ensure long-term protection? (Table 3). The conclusions from GRADE were that healthy persons rarely fail to develop neutralizing antibodies after vaccination. Despite some observed time-dependent waning, neutralizing antibody titers can be found in the vast majority more than 10 years after vaccination. Further evidence suggests that even with no detectable neutralizing antibodies, protective immunity might be induced due to cell-mediated immunity. Post-licensing monitoring of break-through infections is missing yet observational studies attest the effectiveness of the vaccine. In endemic settings high primary vaccination coverage (60-80%) is sufficient to prevent yellow fever outbreaks and waning of antibody titers seems not to be relevant in affected regions. In immunocompetent persons, there is no demonstrated need for a booster dose every ten years. However, the confidence in the estimate of the effect on the outcome is limited.

Working Group Discussion and Conclusions

The need and timing of booster doses of yellow fever vaccine was discussed by the previous SAGE Yellow Fever Working Group that provided the recommendations for the 2003 yellow fever vaccine position paper. It was noted at that time that the booster dose recommendation predominantly applied to travelers, most of which were traveling from non-endemic areas.

The current working group reviewed information: 1) collected through the systematic review [18]; 2) from outbreaks of the yellow fever disease in endemic countries; and 3) on the mechanism of

immunologic memory following yellow fever vaccination. The working group agreed that the information collected from the systematic review (presented above) suggest that immunity following yellow fever vaccination is likely to be life-long. The working group also noted the rarity of primary vaccine failures and the lack of identified secondary vaccine failures in persons from endemic areas or in travelers who have been vaccinated against yellow fever. However, the working group did note issues and concerns with interpreting published study data as different PRNT levels (e.g., 50% to 90% cutoff) were used in the various studies and the lack of a clear correlate of protection in the immune response to yellow fever vaccination. It was also noted that persons living in an endemic area are likely to have some degree of "boosting" that occurs due to exposure either to yellow fever virus or to related viruses, such as dengue, West Nile, or Zika viruses. Furthermore, endemic populations are likely to have some effect of herd immunity in regards to protection as humans are a potential amplifying reservoir of yellow fever virus. So if there is adequate vaccine coverage, an unvaccinated individual may be "protected" due to decrease in amplifying reservoirs around them. Another potential concern raised by working group members are data suggesting that children (<2 years) do not seem to develop the same high level of neutralizing antibodies as is seen in adults and this could lead to some yellow fever cases among persons who received the vaccine as a child if a booster dose is not given [24]. However, this observation is confounded by the fact that seroprotective levels of neutralizing antibodies, using a PRNT, have not been determined.

In regards to outbreaks of yellow fever disease, the working group discussed unpublished data from the large outbreaks of yellow fever that occurred in Nigeria during the 1980s. Nigeria had good levels of yellow fever vaccination in their population until the 1960s, when routine vaccination was discontinued. In the 1980s, large outbreaks of the disease were seen in several areas of the country and hundreds of thousands of persons were believed to develop disease [25, 26]. During these outbreaks, yellow fever disease only occurred in unvaccinated individuals and persons who received yellow fever vaccine several decades previously were protected from developing yellow fever disease (Tomori, personal communication).

In response to concerns over the lack of a correlate of protection and potential waning antibody titers against yellow fever virus over time following yellow fever vaccination, the working group briefly discussed the mechanism of immunologic memory following vaccination. Recent research suggests cellular immunity and innate immunity contribute to the initial immune response and sustaining the immune memory to yellow fever vaccination [27, 28]. Therefore, the working group felt that a lack of detectable neutralizing antibodies may not mean a lack of protection against yellow fever viral infection among yellow fever vaccine recipients; however, detection of neutralizing antibodies was clearly associated with a protective immune response.

Finally, the working group noted that yellow fever surveillance needs to be improved and maintained in order to detect potential yellow fever cases due to vaccine failure. Testing of acute samples for viral RNA will be critical for these cases to differentiate vaccine failures from other causes of jaundice and hemorrhage.

Recommendations: Based on currently available data, a single dose of yellow fever vaccine appears to confer life-long protective immunity against yellow fever disease. Therefore, a booster dose of yellow fever vaccine is not needed to maintain immunity. However, further study is needed

in certain groups, who may have suboptimal seroconversion rates following a single dose of the vaccine to determine if they may benefit from a single booster dose.

References

1. Mason RA, et al. Yellow fever vaccine: direct challenge of monkeys given graded doses of 17D vaccine. Appl Microbiol. 1973; 25: 539-544.
2. Staples JE, et al. Centers for Disease Control and Prevention (CDC). Yellow fever vaccine: recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep. 2010; 59: 1-27.
3. Monath T, Gershman MD, Staples JE, Barrett AD. Yellow fever vaccine. In: Plotkin SA, Orenstein, W.A., Offit, P.A., editor. Vaccines. 6th ed: Saunders Elsevier; 2013.
4. Courtois G. Time of appearance and duration of immunity conferred by 17D vaccine. In: Yellow Fever Vaccine. WHO Series. Geneva, Switzerland; 1956.
5. Monath TP. Neutralizing antibody responses in the major immunoglobulin classes to yellow fever 17D vaccination of humans. Am J Epidemiol. 1971; 93: 122-129.
6. Monath TP, et al. Clinical proof of principle for ChimeriVax: recombinant live, attenuated vaccines against flavivirus infections. Vaccine. 2002; 20: 1004-1018.
7. World Health Organization. International Health Regulations (2005). Switzerland; 2008. Available at: http://whqlibdoc.who.int/publications/2008/9789241580410_eng.pdf, Accessed February 19, 2013.
8. Courtois G. [Duration of immunity following yellow fever vaccination.] Ann Soc Belg Med Trop. 1954; 34: 9-12.
9. Dick GWA, Gee FL. Immunity to yellow fever nine years after vaccination. Trans Roy Soc Trop Med Hyg. 1952; 46(4): 449-458.
10. Groot H, Riberiro RB. Neutralizing and haemagglutination-inhibiting antibodies to yellow fever 17 years after vaccination with 17D vaccine. Bull World Health Organ. 1962; 27: 699-707.
11. Rosenzweig EC, et al. Immunological studies with group B arthropod-borne viruses. IV. Persistence of yellow fever antibodies following vaccination with 17D strain yellow fever vaccine. Am J Trop Med Hyg. 1963; 12: 230-235.
12. Poland JD, et al. Persistence of neutralizing antibody 30-35 years after immunization with 17D yellow fever vaccine. Bull World Health Organ. 1981; 59: 895-900.
13. Reinhardt B, et al. Development of viremia and humoral and cellular parameters of immune activation after vaccination with yellow fever virus strain 17D: a model of human flavivirus infection. J Med Virol. 1998; 56: 159-167.
14. Niedrig M, et al. Assessment of IgG antibodies against yellow fever virus after vaccination with 17D by different assays: neutralization test, haemagglutination inhibition test, immunofluorescence assay and ELISA. Trop Med Int Health. 1999; 4: 867-871.
15. Gomez SY, Ocazionez RE. [Yellow fever virus 17D neutralizing antibodies in vaccinated Colombian people and unvaccinated ones having immunity against dengue.] Rev Salud Publica. 2008; 10: 796-807.
16. de Melo AB, et al. Description of a prospective 17DD yellow fever vaccine cohort in Recife, Brazil. Am J Trop Med Hyg. 2011; 85: 739-47.
17. Coulange Bodilis H, et al. [Long-term persistence of yellow fever neutralizing antibodies in persons aged 60 years and older]. Bull Soc Pathol Exot. 2011; 104: 260-265.
18. Gotuzzo E, et al. Efficacy and duration of immunity following yellow fever vaccine: a systematic review on the need of yellow fever booster every 10 years. *Manuscript in preparation*.
19. Elliott M. Yellow fever in the recently inoculated. Trans Roy Soc Trop Med Hyg. 1944; 38: 231-234.
20. Ross RW, et al. A fatal case of yellow fever in a European in Uganda. East Afr Med J. 1953; 30: 1-11.
21. Nolla-Salas J, et al. Imported yellow fever in vaccinated tourist. Lancet. 1989; 334: 1275.
22. Tuboi SH, et al. Clinical and epidemiological characteristics of yellow fever in Brazil: analysis of reported cases 1998-2002. Trans Roy Soc Trop Med Hyg. 2007; 101: 169-175.
23. de Filippis AM, et al. Isolation and characterization of wild type yellow fever in cases temporally associated with 17DD vaccination during an outbreak of yellow fever in Brazil. Vacc. 2004; 22: 1073-1078.
24. Nascimento Silva JR, et al. Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps, and rubella. Vaccine. 2011; 29: 6327-6334.
25. DeCook KM, et al. Epidemic yellow fever in eastern Nigeria, 1986. Lancet. 1988; 1(8586): 630-633.

26. Nasidi A, et al. Urban yellow fever epidemic in western Nigeria, 1987. Trans Roy Soc Trop Med Hyg. 1989; 83: 401-406.
27. Wrammert J, et al. Human immune memory to yellow fever and smallpox vaccination. J Clin Immunol. 2009; 29(2): 151-157.
28. Kohler S, et al. The early cellular signatures of protective immunity induced by live viral vaccination. Eur. J. Immunol. 2012; 42: 2363–2373.

Table 1. Studies documenting long-term immunity following yellow fever (YF) vaccination. *(Adapted from reference 18)*

Study author – year published[reference]	Number of subject evaluated	Population	Time since yellow fever vaccination	Laboratory test*	Findings
Courtois - 1954 [8]	79	Endemic population; adult males	12 years	Mouse protection	Protective immunity documented in 76/79 (96%)
Dick - 1952 [9]	202	Endemic population; children and adults	~9 years	Mouse protection	156/202 (77%) were immune to YF; 36/57 (63%) of children and 120/145 (83%) of adults
Groot - 1962 [10]	108	Nonendemic area of Brazil; All ages	17 years	Mouse protection	82 (76%) strong positive neutralizing antibody results; 23 (21%) weak positive neutralizing antibody results; 3 (3%) negative neutralizing results
Rosenzweig - 1963 [11]	29	Traveler population; Adult U.S. military	6-15 years	Mouse protection	All with protective antibody titers; 6-15 years mean LNI† 3.9, range 3.5-4.4; 16-19 years mean LNI 4.2, range 2.6-5.0
Poland - 1981 [12]	116	Traveler population; Adult U.S. military	30-35 years	$PRNT_{90}$	90/116 (78%) with detectable PRNT titer (≥2); titers varied by service between 60 and 97% with detectable titers. Not all could be confirmed to be vaccinated. OF NOTE: Also ran mouse protection studies and found test to be less sensitive than PRNT.
Reinhardt - 1988 [13]	5	Traveler population; adults	10 years	$PRNT_{90}$	All vaccinees had neutralizing antibodies at 10 years post vaccination; Mean titer 72 (SE ± 11.2); all above 40.
Niedrig - 1999 [14]	59	Traveler population; children and adults	11-38 years	$PRNT_{90}$	At 11-38 years, 38/51 (75%) were seroprotected (titer ≥10).
Gomez - 2008 [15]	19	Endemic population; children and adults	5-24 years	$PRNT_{75}$	13/19 (68%) had seroprotective (titer ≥10) levels of antibodies
de Melo - 2011 [16]	20	Endemic population;	10 years	$PRNT_{50}$	All had protective levels (≥20) of

		aged 16-83 years			neutralizing antibodies with a GMT of 113 (95%CI = 102–188) and a range of titers from 20 to 320
Coulange Bodilis - 2011 [17]	84	Traveler population; 60-89 years	1-60 years	$PRNT_{80}$	80/84 (95%) of cases had seroprotective (≥10) titers; 13/15 (87%) of those vaccinated ≥20 years previously had seroprotective titers; 25/27 (93%) between 10-19 years were seroprotected

*PRNT = plaque reduction neutralization test. $PRNT_{\#}$ is the reciprocal of the highest serum dilution at which #% of virus is inhibited.

†LNI = log neutralization index; LNI > 0.7 is seroprotective.

Table 2. Reports of yellow fever vaccine failures. (*Adapted from reference 18)*

Subject [reference]	Evidence of yellow fever vaccine	Time from vaccination to disease onset	Date of disease onset	Outcome	Testing
32 yo male solider (traveler) [19]	Unknown*	1 year, 4 months	Jan 1942	Died	None; diagnosed based on clinically compatible illness
35 yo male solider (traveler) [19]	Unknown	1 year, 3 months	Feb 1942	Died	None; diagnosed based on clinically compatible illness
25 yo male solider (traveler) [19]	Unknown	1 year, 4 months	Feb 1942	Recovered	None; diagnosed based on clinically compatible illness
39 yo male traveler [20]	Unknown	4 years, 81 days	Jan 1952	Died	Testing inconclusive; postmortem findings consistent
37 yo female traveler [21]	Written evidence of vaccination	5 years	Oct 1988	Recovered	Antibody testing with complement fixation
21 yo male endemic area [22]	Written evidence of vaccination	8 months	1998-2002†	Recovered	Confirmed‡
20 yo female endemic area [22]	Written evidence of vaccination	5 years, 2 months	1998-2002†	Recovered	Confirmed‡
17 yo female endemic area [22]	Written evidence of vaccination	1 year, 6 months	1998-2002†	Recovered	Confirmed‡
62 yo male endemic area [22]	Written evidence of vaccination	1 year	1998-2002†	Died	Confirmed‡
30 yo female endemic area [22]	Written evidence of vaccination	5 months	1998-2002†	Died	Confirmed‡
39 yo male endemic area [23]	Vaccinated in reactive campaign	2 days	March 2001	Died	Yellow fever virus isolation and sequencing
69 yo male endemic area [23]	Vaccinated in reactive campaign	14 days	March 2001	Died	Yellow fever virus isolation and sequencing

*Not clearly stated in article how proof of vaccination was verified

†Does not specify a specific date of disease onset in article

‡Clinically compatible illness with laboratory data of yellow fever infection (e.g., IgM antibodies, isolation of yellow fever virus, histopathologic changes in liver consistent with yellow fever, four-fold rise in yellow fever virus-specific antibodies, yellow fever virus antigen detected in tissue); death within 10 days of symptom onset in someone with a clinically compatible illness but no laboratory testing was also considered a confirm case.

GRADE Table 3. Need for a booster dose of yellow fever vaccine in immunocompetent individuals

Population : Immunocompetent individuals
Intervention : Primary yellow fever vaccination
Comparison : No primary vaccination
Outcome : Duration of immunity

Is there evidence that a booster dose is required in immunocompetent individuals to ensure long-term protection?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		10/ observational[1]	2
	Factors decreasing confidence	Limitation in study design	None Serious[2]	0
		Inconsistency	None serious	0
		Indirectness	None serious[3]	0
		Imprecision	None Serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Our confidence in the estimate of the effect on the outcome is limited.**
Conclusions	In total over 540 million doses of yellow fever have been used globally(1) . So far only 12 cases of secondary vaccine failure have been reported in literature (2-6)[4]. Healthy persons rarely fail to develop neutralizing antibodies after vaccination (7). Despite some observed time-dependent waning, neutralzing antibody titers can be found in the vast majority more than 10 years after vaccination (8-19). Further evidence suggests that even with no detectable neutralizing antibodies, immunity might be given due to cell-mediated protective effects (13;15). Post-licensing monitoring of break-through infections is missing yet observational studies attest the effectiveness of the vaccine. In endemic settings high primary vaccination coverage (60-80%) is sufficient to prevent yellow fever outbreaks and waning of antibody titers seems not to be relevant in affected regions (20). In immunocompetent persons there is no demonstrated need for a booster dose every ten years.			

[1] 6 observational studies reported 74.5-100% neutralizing antibody (NTAb) ≥10years after vaccination. One small study reported 65% (n=13/20) with protective NTAb after 10 years (De Melo et al. 2011). One study (Gomez SY et al. 2008) reported NTAb in >68% in vaccinees after ≥4years post vaccination. One study (Veit et al.2009) reported 88% NTAb 1-10 years after vaccination and one study reported 73% with NTAb 3- 4 years after vaccination (Gibney et al. 2012).
[2] Limitations in only 2 of 8 studies/therefore no downgrading: No clear description of method and incomplete medical records of vaccinated (Poland et al. 1981). Non-standardized methods such as mouse-protection test used (Groot et al. 1962).
[3] Serological marker as proxy to assess level of clinical protection, yet overall agreement in the assumption that titer>1:10 in plaque reduction neutralization test is associated with protective immunity (Hepburn at al. 2006; Monath et al. 2005), therefore no downgrading.
[4] Reporting of 10 cases of secondary vaccine failure, with disease onset >5 month after vaccination (3-6).Two cases with onset of disease 2-14 days after vaccination (Fillipis et al.2004).

Reference List for GRADE table 3

(1) Barrett AD, Teuwen DE. Yellow fever vaccine - how does it work and why do rare cases of serious adverse events take place? Curr Opin Immunol 2009 Jun;21(3):308-13.

(2) Filippis AM, Nogueira RM, Jabor AV, Schatzmayr HG, Oliveira JC, Dinis SC, et al. Isolation and characterization of wild type yellow fever virus in cases temporally associated with 17DD vaccination during an outbreak of yellow fever in Brazil. Vaccine 2004 Mar 12;22(9-10):1073-8.

(3) Nolla-Salas J, Saballs-Radresa J, Bada JL. Imported yellow fever in vaccinated tourist. Lancet 1989 Nov 25;2(8674):1275.

(4) ROSS RW, HADDOW AJ, RAPER AB, TROWELL HC. A fatal case of yellow fever in a European in Uganda. East Afr Med J 1953 Jan;30(1):1-11.

(5) Tuboi SH, Costa ZG, da Costa Vasconcelos PF, Hatch D. Clinical and epidemiological characteristics of yellow fever in Brazil: analysis of reported cases 1998-2002. Trans R Soc Trop Med Hyg 2007 Feb;101(2):169-75.

(6) M.Elliott. Yellow Fever in the recently inoculated. Transactions of The Royal Society of Tropical Medicine and Hygiene - TRANS ROY SOC TROP MED HYG , 1944;38(3):231-4.

(7) Monath TP, Nichols R, Archambault WT, Moore L, Marchesani R, Tian J, et al. Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III multicenter, double-blind clinical trial. Am J Trop Med Hyg 2002 May;66(5):533-41.

(8) Coulange BH, Benabdelmoumen G, Gergely A, Goujon C, Pelicot M, Poujol P, et al. [Long term persistence of yellow fever neutralising antibodies in elderly persons]. Bull Soc Pathol Exot 2011 Oct;104(4):260-5.

(9) de Melo AB. Description of a prospective 17DD yellow fever vaccine cohort in Recife, Brazil. 2011 Oct.

(10) Gomez SY, Ocazionez RE. [Yellow fever virus 17D neutralising antibodies in vaccinated Colombian people and unvaccinated ones having immunity against dengue]. Rev Salud Publica (Bogota) 2008 Nov;10(5):796-807.

(11) Groot H, RIBERIRO RB. Neutralizing and haemagglutination-inhibiting antibodies to yellow fever 17 years after vaccination with 17D vaccine. Bull World Health Organ 1962;27:699-707.

(12) Hepburn MJ, Kortepeter MG, Pittman PR, Boudreau EF, Mangiafico JA, Buck PA, et al. Neutralizing antibody response to booster vaccination with the 17d yellow fever vaccine. Vaccine 2006 Apr 5;24(15):2843-9.

(13) Niedrig M, Lademann M, Emmerich P, Lafrenz M. Assessment of IgG antibodies against yellow fever virus after vaccination with 17D by different assays: neutralization test, haemagglutination inhibition test, immunofluorescence assay and ELISA. Trop Med Int Health 1999 Dec;4(12):867-71.

(14) Poland JD, Calisher CH, Monath TP, Downs WG, Murphy K. Persistence of neutralizing antibody 30-35 years after immunization with 17D yellow fever vaccine. Bull World Health Organ 1981;59(6):895-900.

(15) Reinhardt B, Jaspert R, Niedrig M, Kostner C, L'age-Stehr J. Development of viremia and humoral and cellular parameters of immune activation after vaccination with yellow fever virus strain 17D: a model of human flavivirus infection. J Med Virol 1998 Oct;56(2):159-67.

(16) Rosenzweig EC, BABIONE RW, Wisseman CL, Jr. Immunological studies with group B arthropod-borne viruses. IV. Persistence of yellow fever antibodies following vaccination with 17D strain yellow fever vaccine. Am J Trop Med Hyg 1963 Mar;12:230-5.

(17) Veit O, Niedrig M, Chapuis-Taillard C, Cavassini M, Mossdorf E, Schmid P, et al. Immunogenicity and safety of yellow fever vaccination for 102 HIV-infected patients. Clin Infect Dis 2009 Mar 1;48(5):659-66.

(18) Gibney KB, Edupuganti S, Panella AJ, Kosoy OI, Delorey MJ, Lanciotti RS, et al. Detection of anti-yellow Fever virus immunoglobulin m antibodies at 3-4 years following yellow Fever vaccination. Am J Trop Med Hyg 2012 Dec;87(6):1112-5.

(19) DICK GW, GEE FL. Immunity to yellow fever nine years after vaccination with 17D vaccine. Trans R Soc Trop Med Hyg 1952 Jul;46(4):449-58.

(20) Weekly Epidmiological Record. (http://www.who.int/wer). Yellow fever fact sheet. No. 5, 2010, 85, 29-36.

Special Populations

Use of yellow fever vaccine in people over 60 years old

Key Findings

- There are published reports identifying a higher risk of serious adverse events following immunization (AEFI), namely YEL-AVD, in persons 60 years old and older compared to younger persons who are receiving the vaccine for travel to an endemic area.
- There are insufficient data to determine if the risk of serious AEFI may be elevated among elderly persons who reside in an endemic area and receive yellow fever vaccine.

Previous studies have suggested that there is a higher risk of serious adverse events following immunization (AEFI) with yellow fever vaccine, in particularly YEL-AVD, among the elderly [1, 2, 3]. These studies primarily used age-specific reporting rates (RRs) and reporting rate ratios (RRRs) as proxies for determining risk in the elderly population and have used a variety of case definitions for YEL-AVD and YEL-AND. A systematic review was conducted by the WHO secretariat that utilized the recently published Brighton case definition for viscerotropic disease in order to better quantitate the current risk of YEL-AVD among the elderly for both travelers and endemic populations [4].

The review found that the crude number of reported cases of YEL-AVD among the elderly (≥60) was quite high (n=19) compared to all the other age groups combined (n=24) (Table 4). After applying the Brighton Classification for both diagnostic certainty and causality to published studies on travelers, the re-calculated RRs were statistically significant and remained the highest among persons aged 70 years or older but also were higher in those aged ≥60 years as well with significant RRR with ratios of 34 to 47 (Table 5) [1, 2]. Currently, there is only one published article that calculates age-specific RRs of YEL-AVD in an endemic country (Table 6) [5]. Although this study does demonstrate a slightly higher RR of YEL-AVD among the elderly than the average RR, the calculated RRR [RRR=2.57, 95% CI (0.57, 8.54)] showed no significant difference for those aged ≥60 years compared to those aged 15-59 years (reference population). From these data, the systematic review concluded that: 1) there are data to support an increased risk of YEL-AVD among elderly travelers; and 2) the evidence of increased risk of YEL-AVD in older endemic population is undetermined.

In addition to the systematic review, two questions related to the use of yellow fever vaccine in elderly were as evaluated using GRADE: 1) Is there evidence that elderly individuals 60 years of age and older in endemic settings are at greater risk of YEL-AVD than those less than 60 years? and 2) Is there evidence that elderly travelers 60 years of age and older are at greater risk of YEL-AVD than those less than 60 years? Relative to the question on yellow fever vaccine use in elderly individuals living in endemic areas, the conclusion from GRADE found age-related tendencies between YEL-AVD and older age in endemic settings can be seen, yet the evidence is limited (Table 7). For yellow fever vaccine use in elderly travelers, the conclusion from GRADE was age-related tendencies showed an association between higher rates of serious adverse events after yellow fever vaccination in travelers ≥60 years than those <60 years (Table 8). Yet the evidence to support association is limited. Further research was felt to be necessary to support either hypothesis.

Working Group Discussion and Conclusions

The working group felt the main difference between endemic and traveler populations that might account for the higher rates of AEFIs in travelers is that travelers are more likely to be immune naïve to yellow fever virus (both vaccine and wild-type virus) and thus are potentially more "susceptible" to developing serious AEFIs than those living in endemic areas. The association between serious AEFIs, like YEL-AVD, and primary vaccination is likely due to the fact that primary vaccine recipients often become viremic following vaccination while viremia has not been documented in persons receiving a booster dose of yellow fever vaccine. A recent study also found more frequent viremia with a higher yellow fever vaccine RNA copy numbers in elderly when compared to younger naïve vaccine recipients [6]. In addition, there was also a delayed antibody response seen among the elderly. The authors hypothesized that slower antibody response and increase in viremia may lead to an increased risk of developing serious AEFI, such as YEL-AVD, and therefore could explain the higher rates of serious AEFI in the elderly population. Based on the current data, the working group concluded that caution be used when vaccinating persons aged ≥60 years who have not received the vaccine previously regardless if they live in an endemic area or not. They also concluded that further research is needed on this topic as well as exploring the age-specific rates of YEL-AND.

Recommendations: Based on the currently available data, it is advisable to recommend caution in vaccinating persons ≥60 years of age against yellow fever if they have not been previously vaccinated. A risk-benefit assessment for yellow fever vaccination should be performed for any person ≥60 years of age who has not been vaccinated but for whom the vaccine is recommended. The risk assessment should take into account risk of acquiring yellow fever disease (e.g., location, season, duration of exposure, occupational and recreational activities, and local rate of virus transmission in the potential area of exposure) versus the risk of a potential adverse event following immunization (e.g., age, underlying medical conditions, medications). Further research is needed to better quantitate the risk for vaccine recipients who is ≥60 years and might reside in or near a yellow fever endemic area.

References

1. Martin M, et al. Advanced age a risk factor for illness temporally associated with yellow fever vaccination. Emerg Infect Dis. 2001; 7(6): 945-951.
2. Khromava AY, et al. Yellow fever vaccine: An updated assessment of advanced age as a risk factor for serious adverse events. Vaccine. 2005; 23(25): 3256-3263.
3. Lindsey NP, et al. Adverse event reports following yellow fever vaccination. Vaccine 2008; 26(48):6077-6082.
4. Rafferty E, et al. Risk of yellow fever vaccine-associated viscerotropic disease among the elderly: A systematic review. *Manuscript in preparation*.
5. de Menezes Martins R, et al. Yellow fever vaccine post-marketing surveillance in Brazil. Procedia Vaccinol. 2010; 2(2): 178-183.
6. Roukens AH, et al. Elderly subjects have a delayed antibody response and prolonged viraemia following yellow fever vaccination: A prospective controlled cohort study. PLoS One. 2011; 6(12): e27753.
7. Gershman MD, et al. Viscerotropic disease: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2012; 30(33): 5038-5058.
8. Lawrence GL, et al. Age-related risk of adverse events following yellow fever vaccination in Australia. Commun Dis Intell. 2004; 28(2): 244-248.
9. Monath TP, et al. Yellow fever 17D vaccine safety and immunogenicity in the elderly. Hum Vaccin. 2005; 1(5): 207-214.
10. Fitzner J, et al. Safety of the yellow fever vaccine during the September 2001 mass vaccination campaign in Abidjan, Ivory Coast. Vaccine. 2004; 23(2): 156-62.

11. Struchiner CJ, et al. Risk of fatal adverse events associated with 17DD yellow fever vaccine. Epidemiol Infect. 2004; 132(5): 939-946.
12. Belmusto-Worn VE, et al. Randomized, double-blind, phase III, pivotal field trial of the comparative immunogenicity, safety, and tolerability of two yellow fever 17D vaccines (Arilvax and YF-VAX) in healthy infants and children in Peru. Am J Trop Med Hyg. 2005; 72(2): 189-197.
13. Whittembury A, et al. Viscerotropic disease following yellow fever vaccination in Peru. Vaccine. 2009; 27: 5974-5981.
14. Breugelmans G, et al. Adverse events following yellow fever preventive vaccination campaigns in eight African countries from 2007 to 2010.Vaccine. Epub 2013 Feb 7.

Table 4. Number of yellow fever vaccine associated-viscerotropic disease cases by age group and by the Brighton viscerotropic case definition for diagnostic certainty and yellow fever vaccine causality [7] (*Table adapted from reference 4)*

Age group (years)	Traveler Population			Endemic Population			Total		
	Both*	One†	Neither‡	Both*	One†	Neither‡	Both*	One†	Reported
0-9	-¶	-	-	2	-	-	2	-	2
10-19	-	-	-	1	2	1	1	2	4
20-29	3	1	-	3	-	1	6	1	8
30-39	-	-	-	-	-	1	-	-	1
40-49	-	1	-	1	1	2	1	2	5
50-59	1	1	2	-	-	-	1	1	4
60-69	3	6	2	1	-	1	4	6	13
≥70	1	2	2	1	-	-	2	2	6
Subtotal <60 years	*4*	*3*	*2*	*7*	*3*	*5*	*11*	*6*	*24*
Subtotal ≥60 years	*4*	*8*	*4*	*2*	*-*	*1*	*6*	*8*	*19*
Total	**8**	**11**	**6**	**9**	**3**	**6**	**17**	**14**	**43**

*Both = met both diagnostic criteria (any level) AND causality (any level)

†One = met either diagnostic criteria (any level) OR causality (any level)

‡Neither = met neither diagnostic criteria (any level) OR causality (any level)

¶No cases

Table 5. Reporting rates (RRs) and reporting rate ratios (RRRs) based on the Brighton viscerotropic case definition for diagnostic certainty and yellow fever vaccine causality for yellow fever vaccine-associated viscerotropic disease (YEL-AVD) in elderly travel population (*Table adapted from reference 4)*

Reference	Population Years Surveillance type	Number of YEL-AVD cases	Original RR*	New RR* Diagnostic criteria	RRR* Diagnostic criteria	New RR* Causality	RRR* Causality
Martin et al. [1]	USA 1990-1998 Passive	4	serious AEFI 15-24 = 1.05 25-44 = 0.29 45-64 = 1.13 65-74 = 3.48 ≥75 = 9.06	15-24 = 0 25-44 = 0 45-64 = 0.23 65-74 = 1.16 ≥75 = 9.05	15-64 = Ref (n=1 357 434) ≥65 = 47.23 (95%CI 4.91, 454) (n=86 222)	15-24 = 0 25-44 = 0 45-64 = 0.26 65-74 = 0 ≥75 = 4.53	15-64 = Ref (n=1 357 434) ≥65 = 15.74 (95%CI 0.98, 252) (n=86 222)
Khromava et al. [2]	USA 1990-2002 Passive	7	YEL-AVD 1-18 = 0 19-29 = 0.2 30-39 = 0.3 40-49 = 0 50-59 = 0.3 60-69 = 1.1 ≥70 = 3.2	1-18 = 0 19-29 = 0.23 30-39 = 0 40-49 = 0 50-59 = 0 60-69 = 1.6 ≥70 = 3.2	<60 = Ref ≥60 = 34.49 (95%CI 4.03, 295)	1-18 = 0 19-29 = 0.2 30-39 = 0.3 40-49 = 0 50-59 = 0.3 60-69 = 1.1 ≥70 = 3.2	<60 = Ref ≥60 = 13.8 (95%CI 1.25, 152)
Lawrence et al. [8]	Australia 1993-2002 Passive	1	serious AEFI 15-24 = 0 25-44 = 2.49 45-64 = 8.21 ≥65 = 22.26	15-24 = 0 25-44 = 0 45-64 = 2.05 ≥65 = 0	<65 = Ref ≥65 = 0 (95%CI 0, 427)	15-24 = 0 25-44 = 0 45-64 = 2.05 ≥65 = 0	<65 = Ref ≥65 = 0 (95%CI 0, 427)
Monath et al. [9]	UK 1995-1999 Active/Passive	Unknown	serious AEFI <15 = 0 15-24 = 2.09 25-44 = 3.05 45-64 = 5.55 65-74 = 8.58 ≥75 = 0	NA†	NA	NA	NA
Lindsey et al. [3]	USA 2000-2006 Passive	6	YEL-AVD ≤18 = 0 19-29 = 0.5 30-39 = 0 40-49 = 0	NA	NA	NA	NA

	50-59 = 0 60-69 = 1.0 ≥70 = 2.3

* by age group in years and reports per 100,000 doses

† Not available (e.g., not enough information available to perform the calculations)

Table 6. Reporting rates (RRs) and reporting rate ratios (RRRs) based on the Brighton viscerotropic case definition for diagnostic certainty and yellow fever vaccine causality for yellow fever vaccine-associated viscerotropic disease (YEL-AVD) in elderly endemic population (*Table adapted from reference 4)*

Reference	Population Years	Number of YEL-AVD cases	Original RR*	New RR*	RRR*
De Menezes Martins et al. [5]	Brazil 1999-2009	20	YEL-AVD <1 = 0 1 = 0 2 = 0 3 = 0.053 4 = 0.098 5-9 = 0.018 10-14 = 0.017 15-59 = 0.019 ≥60 = 0.047	NA†	15-59 = Ref ≥60 = 2.53 (95%CI 0.56, 8.54)
Fitzner et al. [10]	Ivory Coast 2001	0	YEL-AVD 0	0	0
Struchiner et al. [11]	Brazil 1991-2001 1998-2001	4	YEL-AVD 0.0056 to 0.213	NA	NA
Belmusto-Worn et al. [12]	Peru No year	0	YEL-AVD 0	0	0
Whittembury et al. [13]	Peru 2007	5	YEL-AVD 7.9	6.3	NA
Breugelmans et al. [14]	Benin, Cameroon, Liberia, Mali, Senegal, Sierra Leone 2007-2010	5	YEL-AVD 0.013	NA	NA

* by age group in years and reports per 100,000 doses

† Not available (e.g., not enough information to be able to classify cases based on the Brighton case definition or to perform the calculations)

GRADE Table 7. Yellow fever vaccination in elderly living in endemic areas

Population: Elderly individuals ≥ 60 years of age in endemic settings
Intervention: Yellow Fever Vaccination ≥ 60 years of age
Comparison: Yellow Fever Vaccination < 60 years of age
Outcome: Yellow Fever vaccine-associated viscerotropic disease

Is there evidence that elderly individuals 60 years of age older in endemic settings are at greater risk of yellow fever vaccine-associated viscerotropic disease (YEL-AVD) than those younger than 60 years?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ observational[1]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None Serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Our confidence in the estimate of the effect on the outcome is limited.**
	Conclusion			**Age-related tendencies between YEL-AVD and older age in endemic settings can be seen, yet the evidence to support association between older age and YEL-AVD in endemic populations is limited. Further research is needed to support the hypothesis.**

[1] Only 1 observational study reported a non-significant relation of increased YEL-AVD incidence for elderly in an endemic population (Martins RdM et al. 2010). Some additional trials included reports of YEL-AVD in elderly, but these are either in non-endemic populations or do not include age-related analysis (Martin et al.2001, Monath et al.2005; Lawrence et al 2004; Lindsey et al. 2008, Khromava et al.2005, Fitzner et al. 2004; Struchiner et al. 2004; Whittembury et al.2009).

Reference List for GRADE table 7

(1) Fitzner J, Coulibaly D, Kouadio DE, Yavo JC, Loukou YG, Koudou PO, et al. Safety of the yellow fever vaccine during the September 2001 mass vaccination campaign in Abidjan, Ivory Coast, 1. Vaccine 2004 Nov 25;23(2):156-62.$

(2) Khromava AY, Eidex RB, Weld LH, Kohl KS, Bradshaw RD, Chen RT, et al. Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. Vaccine 2005 May 9;23(25):3256-63.

(3) Lawrence GL, Burgess MA, Kass RB. Age-related risk of adverse events following yellow fever vaccination in Australia. Commun Dis Intell 2004;28(2):244-8.

(4) Lindsey NP, Schroeder BA, Miller ER, Braun MM, Hinckley AF, Marano N, et al. Adverse event reports following yellow fever vaccination, 1. Vaccine 2008 Nov 11;26(48):6077-82.

(5) Martin M, Weld LH, Tsai TF, Mootrey GT, Chen RT, Niu M, et al. Advanced age a risk factor for illness temporally associated with yellow fever vaccination. Emerg Infect Dis 2001 Nov;7(6):945-51.

(6) Martins RdM, Maia MdLd, Santos EMd, Cruz RLd, dos Santos PR, Carvalho SMD, et al. Yellow Fever Vaccine Post-marketing Surveillance in Brazil. Procedia in Vaccinology 2010;2(2):178-83.

(7) Monath TP, Cetron MS, McCarthy K, Nichols R, Archambault WT, Weld L, et al. Yellow fever 17D vaccine safety and immunogenicity in the elderly. Hum Vaccin 2005 Sep;1(5):207-14.

(8) Struchiner CJ, Luz PM, Dourado I, Sato HK, Aguiar SG, Ribeiro JG, et al. Risk of fatal adverse events associated with 17DD yellow fever vaccine. Epidemiol Infect 2004 Oct;132(5):939-46.

(9) Whittembury A, Ramirez G, Hernandez H, Ropero AM, Waterman S, Ticona M, et al. Viscerotropic disease following yellow fever vaccination in Peru. Vaccine 2009 Oct 9;27(43):5974-81.

GRADE Table 8. Yellow fever vaccination in elderly travelers

Population: Elderly travelers ≥ 60 years of age
Intervention: Yellow Fever Vaccination ≥ 60 years of age
Comparison: Yellow Fever Vaccination < 60 years of age
Outcome: Yellow Fever vaccine-associated viscerotropic disease

Is there evidence that elderly travelers 60 years of age and older are at greater risk of yellow fever vaccine-associated viscerotropic disease (YEL-AVD) than those younger than 60 years?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ observational[1]	2
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None Serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[3]	1
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Our confidence in the estimate of the effect on the outcome is limited.**
	Conclusion			**Age-related tendencies showing association between higher rates of serious adverse events after yellow fever vaccination in travelers can be seen. Yet the evidence to support association between older age and YEL-AVD in travelers is limited. Further research is needed to support the hypothesis.**

[1] Two observational studies reported reporting rate ratio of YEL-AVD in elderly travelers (Khormava et al.2005, Lindsey et al.2008). Some additional trials included reports of YEL-AVD in elderly, but either in endemic settings or no age-related analysis (Martin et al.2001, Martins RdM et al. 2010, Monath et al.2005; Lawrence et al 2004;,Fitzner et al. 2004; Martins et al. Struchiner et al. 2004; Whittembury et al.2009*)*.
[2] Source of data was from passive public health surveillance. Reporting rate ratio possibly overestimated if the true rate for elderly travelers increased since 1998.
[3] RRR significantly higher compared to reference group 5.9 (95%CI 1.6-22.2) for 60-69 years of age and 10.4 (95%CI 2.7-40.2) for ≥70 years (Khormava et al.2005).

Reference List for GRADE table 8

(1) Fitzner J, Coulibaly D, Kouadio DE, Yavo JC, Loukou YG, Koudou PO, et al. Safety of the yellow fever vaccine during the September 2001 mass vaccination campaign in Abidjan, Ivory Coast 1. Vaccine 2004 Nov 25;23(2):156-62.

(2) Khromava AY, Eidex RB, Weld LH, Kohl KS, Bradshaw RD, Chen RT, et al. Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. Vaccine 2005 May 9;23(25):3256-63.

(3) Lawrence GL, Burgess MA, Kass RB. Age-related risk of adverse events following yellow fever vaccination in Australia. Commun Dis Intell 2004;28(2):244-8.

(4) Lindsey NP, Schroeder BA, Miller ER, Braun MM, Hinckley AF, Marano N, et al. Adverse event reports following yellow fever vaccination, 1. Vaccine 2008 Nov 11;26(48):6077-82.

(5) Martin M, Weld LH, Tsai TF, Mootrey GT, Chen RT, Niu M, et al. Advanced age a risk factor for illness temporally associated with yellow fever vaccination. Emerg Infect Dis 2001 Nov;7(6):945-51.

(6) Martins RdM, Maia MdLd, Santos EMd, Cruz RLd, dos Santos PR, Carvalho SMD, et al. Yellow Fever Vaccine Post-marketing Surveillance in Brazil. Procedia in Vaccinology 2010;2(2):178-83.

(7) Monath TP, Cetron MS, McCarthy K, Nichols R, Archambault WT, Weld L, et al. Yellow fever 17D vaccine safety and immunogenicity in the elderly. Hum Vaccin 2005 Sep;1(5):207-14.

(8) Struchiner CJ, Luz PM, Dourado I, Sato HK, Aguiar SG, Ribeiro JG, et al. Risk of fatal adverse events associated with 17DD yellow fever vaccine. Epidemiol Infect 2004 Oct;132(5):939-46.

(9) Whittembury A, Ramirez G, Hernandez H, Ropero AM, Waterman S, Ticona M, et al. Viscerotropic disease following yellow fever vaccination in Peru. Vaccine 2009 Oct 9;27(43):5974-81.

Use of yellow fever vaccine in HIV-infected persons

Key Findings

- Data on the safety and immunogenicity of yellow fever vaccines in HIV-positive persons are from a limited number of small studies and case reports, mainly among travelers with CD4 counts >200 cells/mm^3.
- Monitoring vaccination campaigns in countries where the prevalence of HIV is about 1–5% has identified only a few HIV-positive individuals among those with any serious AEFI.
- Data suggest that the immunologic response to yellow fever vaccine in HIV-infected individuals wanes more rapidly than non-infected vaccinated persons.

Language below is from the Weekly Epidemiological Record (No. 5, 2011, 86, 37–44) that summarized the GACVS Meeting from December 2010 where yellow fever vaccine use in HIV-infected persons was discussed [1].
The benefits of mass vaccination campaigns for yellow fever are recognized in endemic countries, and millions of individuals are vaccinated against the disease every year in countries where the prevalence of HIV is 1–5% among those aged 15–49 years. In many places access to laboratory testing and other resources for diagnosing and treating HIV infection is poor, and many people with undiagnosed advanced HIV infection are likely to have received the vaccine.

Published studies on the safety and immunogenicity of yellow fever vaccines in HIV-positive people are limited to small studies and case reports, mainly of travelers with CD4 counts >200 cells/mm^3. With the exception of 1 case of fatal meningoencephalitis, these studies did not detect any other serious [AEFI] among HIV-positive individuals. However, little evidence has accumulated about the safety of this vaccine in people with advanced HIV infection. Data about the immune response to the vaccine are scarce but show consistent immunogenicity in HIV positive people with CD4 [counts] >200 cells/mm^3.

In West and Central Africa, between 2007 and 2010, 10 countries undertook vaccination campaigns against yellow fever, during which about 50 million people were vaccinated. In these countries, surveillance efforts have been implemented in collaboration with national health authorities and local expert committees. Analyses of the safety data are continuing in 7 countries, but so far around 194 serious AEFI have been reported, and more than three quarters of patients have been tested for HIV. Only a few individual cases of serious AEFI have occurred in HIV-positive individuals. Similar findings have been reported from vaccination campaigns in Latin America.

In summary, monitoring vaccination campaigns in countries where the prevalence of HIV is about 1–5% has identified only a few HIV-positive individuals among those with any serious AEFI; no clear risk has been identified that precludes the use of yellow fever vaccine in people infected with HIV. However, the sensitivity of these studies to detect serious AEFI has not been established. In addition, GACVS is awaiting data about the completeness of case investigation, the classification of serious AEFI and the HIV status of those cases.

No changes have been suggested by GACVS to WHO's recommendation that individuals known to be severely immunocompromised should not receive yellow fever vaccine; the available data do not identify a significant problem with mass vaccination in populations where a moderate proportion of individuals are HIV-positive. However, GACVS strongly recommends that additional data on safety and immunogenicity should be obtained on the effect of vaccination in HIV-positive individuals, and

especially in those with advanced HIV infection. Also, additional clinical studies of yellow fever vaccines administered to HIV-positive individuals should be conducted.

Working Group Discussions and Conclusions

The working group reviewed published and unpublished data from the large preventive campaigns that have been conducted in West and Central Africa [2]. These data did not suggest additional safety concerns beyond those noted by GAVCS previously. The working group also reviewed new data on the immunologic response to yellow fever vaccine in HIV-infected travelers. In a recent retrospective cohort study, 65 (83%) of 78 HIV-infected persons developed specific antibodies against yellow fever virus in the first year after vaccination; however this was significantly lower than vaccinated persons without HIV infection (97%, 64/66) [3]. An older study noted that, only 3 (17%) of 18 HIV-infected infants in developing nations developed yellow fever virus-specific neutralizing antibodies within 10 months of vaccination compared to 42 (74%) of 57 HIV-uninfected controls matched for age and nutritional status [4]. The mechanisms for the diminished immune response in HIV-infected persons are uncertain but appear to be correlated with HIV RNA levels and CD4+ cell counts [5]. Further studies are required to assess the relevance of these findings.

Recommendations: *[Maintain current language]* Yellow fever vaccine is contraindicated for severely immunocompromised persons, including persons with AIDS or CD4+ counts < 200 cells/mm^3. Yellow fever vaccination may be offered to asymptomatic HIV-infected persons with CD4+ counts ≥200 cells/mm^3 who require vaccination. Additional data on safety and immunogenicity should be obtained on the effect of vaccination in HIV-positive individuals.

References

1. World Health Organization. Meeting of the Global Advisory Committee on Vaccine Safety, December 2010: Yellow fever vaccine and HIV infection. Wkly Epidemiol Rec. 2011; 86 (5): 37–44.
2. Sidibe M, et al. Immunogenicity and safety of yellow fever vaccine among 115 HIV-infected patients after a preventive immunisation campaign in Mali. Trans Roy Soc Trop Med Hyg. 2012 Jul; 106(7): 437-444.
3. Veit O, et al. Immunogenicity and safety of yellow fever vaccination for 102 HIV-infected patients. Clin Infect Dis. 2009; 48: 659-666.
4. Sibailly TS, et al. Poor antibody response to yellow fever vaccination in children infected with human immunodeficiency virus type 1. Pediatr Infect Dis J. 1997; 16: 1177-1179.
5. Veit O, et al. Yellow fever vaccination in HIV‐infected patients. HIV Ther. 2010; 4(1): 17–26.

Use of yellow fever vaccine in persons with immunocompromising conditions (other than HIV)

Key Findings

- The contraindication of yellow fever vaccine in persons with immunocompromising conditions is based on historical experience with vaccines as a whole rather than yellow fever vaccine specifically.
- There are limited data on the safety and immunogenicity of yellow fever vaccine in persons with specific immunocompromising conditions.

Although there have been case reports and case series published regarding the safe use of yellow fever vaccine in immunocompromised persons, clinical trials with control groups and appropriate surveillance data with clear numerator and denominator data are lacking. The rationale behind contraindicating yellow fever vaccine in immunocompromised persons is based on historical experience with live attenuated vaccines, rather than yellow fever vaccine specifically, and is from the observation that immunocompromised persons may not mount an appropriate immune response to live vaccines and thus the vaccine could cause disease similar to the wild-type disease it is meant to prevent. The only condition where yellow fever vaccine has been associated with an increased risk of serious AEFIs is thymus disease. Four (17%) of the initial 23 YEL-AVD reported cases were noted to occur in persons who had had thymectomies performed for thymomas [1].

Currently, all yellow fever vaccine manufacturers note that yellow fever vaccine is contraindicated in immunocompromised individuals in their package inserts. They note that yellow fever vaccine poses a risk of encephalitis or other serious adverse events to patients with illnesses that commonly results in immunosuppression or patients whose immunologic responses are suppressed by treatments/drugs. Furthermore, they note that persons with a history of thymus dysfunction should not be vaccinated.

Working Group Discussion and Conclusions

The working group reviewed available data on the use of yellow fever vaccine in persons with immunocompromising conditions and did not find any evidence to change the current recommendation that contradicts the use of yellow fever vaccine in persons who are severely immunocompromised. The working group did, however, think that additional clarity is warranted about the specific conditions that might contraindicate or require special caution for the use of yellow fever vaccine. The working group considered the following conditions and treatments to be severely immunocompromising:

1. Severe primary immunodeficiencies (i.e., conditions affecting IgG and/or T cell responses)
2. Thymus disorder
3. Symptomatic HIV-infection or CD4+ T-lymphocyte values < 200 per mm^3 (*see previous section*)
4. Malignant neoplasm being treated with chemotherapy
5. Recent (< 2 years) hematopoietic stem cell transplantation
6. Drugs with known immunosuppressive or immunomodulatory properties (e.g., high-dose systemic corticosteroids*, alkylating drugs, antimetabolites, TNF-α inhibitors, IL-1 blocking agent, or other monoclonal antibodies targeting immune cells)
7. Current or recent radiation therapies that target immune cells

* Dose of either ≥2 mg/kg of body weight or a total ≥ 20 mg/day of prednisone or its equivalent for persons who weigh >10 kg when administered for ≥2 weeks is considered sufficiently immunosuppressive to contraindicate the use of live-attenuated vaccines. Corticosteroids are not a contraindication when administration is under any of the following circumstances: short-

term (i.e., < 2 weeks); a low-to-moderate dose (<20 mg of prednisone or its equivalent per day); long-term, alternate-day treatment with short-acting preparations; maintenance physiologic doses (replacement therapy); or administered topically (skin or eyes), inhaled, or by intra-articular, bursal, or tendon injection.

Recommendations: [*Maintain current wording from 2003 position paper but further clarify possible immunocompromising conditions*] Contraindications against yellow fever vaccination include… severe immunodeficiency. Conditions and treatments that would be considered severely immunocompromising include: certain primary immunodeficiencies, thymus disorder, symptomatic HIV-infection or CD4+ T-lymphocyte values < 200 per mm^3, malignant neoplasm treated with chemotherapy, recent hematopoietic stem cell transplantation, drugs with known immunosuppressive or immunomodulatory properties (e.g., high-dose systemic corticosteroids, alkylating drugs, antimetabolites, TNF-α inhibitors, IL-1 blocking agent, or other monoclonal antibodies targeting immune cells), and current or recent radiation therapies targeting immune cells.

References

1. Barwick R. History of thymoma and yellow fever vaccination. Lancet. 2004; 364: 936.

Use of yellow fever vaccine in pregnant women

Key Findings

- Based on the available albeit limited data, yellow fever vaccine is believed to represents minimal risk to a pregnant woman and her fetus.
- Immune response to yellow fever vaccine may be suboptimal for pregnant women and may depend on the timing of vaccination during pregnancy.

There are no specific data on the yellow fever disease risk for pregnant women and their fetuses. However, from available surveillance and outbreak data, pregnant women do not appear to be at risk for more severe yellow fever disease.

The use of yellow fever vaccine during pregnancy has not been studied in a large prospective trial. Limited data are available from several small studies where pregnant women were either inadvertently vaccinated or given the vaccine in outbreak settings. Since the last position paper, two studies have been published regarding yellow fever vaccine and pregnant women [1, 2]. In the first study, 304 infants born to women who were vaccinated with yellow fever vaccine early in their pregnancies were examined for malformations [1]. There was no increased risk of major malformations found. However, there was an increased risk for minor malformations (e.g., pigmented nevi) but the authors suggested that the finding could have resulted from assessment bias. The second study involved the same mother-child cohort and it did not find an increased risk of fetal death (7.4/1,000 in vaccinated women versus 18.5/1,000 unvaccinated women in the general population) among 441 women inadvertently vaccinated early in their pregnancy [2]. These findings do not support an earlier study that suggested a potential increased rate of spontaneous abortions among pregnant women who received the vaccine [relative risk of 2.3 (95% confidence intervals 0.7-8.0)] [3].

The second study also examined the rates of yellow fever virus IgG antibodies formed in pregnant women and found that 98% of 433 women vaccinated predominantly in the first trimester developed IgG antibodies [2]. These findings differ from that of a previous study which found only 39% of 101 pregnant women receiving yellow fever vaccine predominantly in their third trimester had evidence of seroconversion to yellow fever virus [4]. These findings suggest that proportion of women vaccinated during pregnancy who develop antibodies against yellow fever is variable and may be related to trimester in which they received vaccine.

Recommendations: [*Maintain wording from 2003 position paper*] On theoretical grounds, [yellow fever] vaccine is not recommended during pregnancy. However, pregnant women may be vaccinated during epidemics when the risk of yellow fever virus transmission may be very high.

References

1. Cavalcanti DP, et al. Early exposure to yellow fever vaccine during pregnancy. Trop Med Int Health. 2007; 12: 833-837.
2. Suzano CE, et al. The effects of yellow fever immunization (17DD) inadvertently used in early pregnancy during a mass campaign in Brazil. Vaccine. 2006; 24: 1421-1426.
3. Nishioka Sde A, et al. Yellow fever vaccination during pregnancy and spontaneous abortion: a case-control study. Trop Med Int Health. 1998; 3: 29-33.
4. Nasidi A, et al. Yellow fever vaccination and pregnancy: a four-year prospective study. Trans R Soc Trop Med Hyg. 1993; 87(3): 337-339.

Use of yellow fever vaccine in lactating women

Key Findings

- Three infants less than 6 weeks of age developed encephalitis as a result of infection with yellow fever vaccine virus potentially transmitted to them via breastfeeding from their recently-vaccinated mothers.
- Potential risk of transmission may vary depending on whether mothers are vaccinated for the first time or have been previously vaccinated.

Language below is from the Weekly Epidemiological Record (No. 30, 2010, 85, 285–292) that summarized the GACVS Meeting from June 2010 where the use of yellow fever vaccine and breastfeeding was reviewed [1].
The [GACVS] reviewed recent data suggesting that 3 neonates (aged 10 days, 23 days and 5 weeks) developed encephalitis as a result of infection with yellow fever vaccine virus transmitted to them from their recently-vaccinated mothers. All 3 infants were being breastfed, but the mode of transmission has not been established. All 3 mothers had received the vaccine for the first time during the infant's first month of life. Further research is needed to quantify the potential risk of transmission of yellow fever vaccine virus from mothers to infants, including the possibility of transmission through breast milk.

Mass vaccination campaigns being conducted in West Africa provide an opportunity to conduct studies that will clarify these issues. Such studies might test breast milk from vaccinated mothers for the presence of vaccine virus, and test infants for evidence of seroconversion to the vaccine virus. The potential risk of transmission may vary depending on whether mothers are vaccinated for the first time or have been previously vaccinated.

In areas where yellow fever is endemic, or during outbreaks, the Committee believes that the benefits of vaccinating nursing mothers are likely to far outweigh the risk of potential transmission of vaccine virus to infants; the Committee also believes that the benefits of breastfeeding far outweigh the alternatives for infant feeding. Nursing mothers who are considering travel to endemic areas should be counseled regarding the benefits and potential risks of vaccination. Vaccination is recommended if vaccination is indicated for a breastfeeding woman and travel cannot be avoided or postponed.

Working Group Discussion and Conclusions
The working group reviewed the available literature, which included published case reports for each of the cases reviewed by GACVS [2, 3, 4]. The working group agreed with GACVS' assessment, recommendations, including the call for more study on yellow fever vaccine use among breastfeeding women.

Recommendations: *[Per GAVCS]* In areas where yellow fever is endemic, or during outbreaks, the benefits of vaccinating nursing mothers are likely to far outweigh the risk of potential transmission of vaccine virus to infants. Nursing mothers who are considering travel to endemic areas should be counseled regarding the benefits and potential risks of vaccination. Vaccination is recommended if vaccination is indicated for a breastfeeding woman and travel cannot be avoided or postponed.

References

1. World Health Organization. Global Advisory Committee on Vaccine Safety, 16–17 June 2010: Yellow fever vaccine and breastfeeding. Wkly Epidemiol Rec. 2010; 85 (30): 285–292.

2. Centers for Disease Control and Prevention. Transmission of yellow fever vaccine virus through breast-feeding — Brazil, 2009. MMWR. 2010; 59(5): 130-132.
3. Kuhn S, et al. Case report: probable transmission of vaccine strain of yellow fever virus to an infant via breast milk. CMAJ. 2011; 183(4): E243-E245.
4. Traiber C, et al. Infant meningoencephalitis caused by yellow fever vaccine virus transmitted via breast milk. J Pediatr (Rio J). 2011; 87(3): 269-272.

Co-administration of yellow fever and other vaccines

Key Findings

- Co-administration of yellow fever vaccine and other vaccines typically has no impact on safety.
- Co-administration of yellow fever vaccine and other vaccines generally elicits a good immune response to yellow fever; notable exception is combined measles, mumps, and rubella vaccine.
- Additional co-administration studies are needed yellow fever vaccine with several vaccines where co-administration data are lacking or incomplete.

Data were reviewed by the working group from both published and unpublished literature regarding the safety and immunogenicity of yellow fever vaccine when co-administered (given on the same day but in different locations and in different syringes) with other vaccines. Yellow fever vaccine co-administration has been studied for at least unique 17 antigens (Table 9). Twenty-eight published articles or abstracts on the co-administration of yellow fever vaccine were identified since 1964, which includes articles on the co-administration with 10 inactivated vaccines and 10 live-attenuated vaccines (*see more specific report on web for more details*). There are also several (n=11) available vaccines for which there are no co-administration data available (Table 9).

Based on the available data for inactivated vaccines (Table 10), there are no safety concerns with the co-administration of yellow fever vaccine and inactivated vaccines. Immunogenicity for most vaccines appears not to be compromised when yellow fever vaccine is co-administered with inactivated vaccines. Potential limitations of the studies include: 1) most studies were conducted several decades ago, using different vaccine preparation than what might be currently available; 2) individual studies often contained low number of subjects; 3) studies do not include all potential targeted populations (e.g., children or adults); and 4) no studies were performed in special populations.

Based on the available data for co-administration of yellow fever vaccine with other live-attenuated vaccines (Table 11), there are no safety concerns with co-administration with most vaccines. However, data from two studies on the co-administration of yellow fever vaccine and a dengue chimeric vaccine based on the yellow fever vaccine backbone found increased rates of both systemic and local adverse events [1, 2]. Although there was no increase in serious adverse events noted, there was limited power to detect serious AEFIs. Immunogenicity for most vaccines is also not compromised when yellow fever vaccine is co-administered with other live-attenuated vaccines. The most notable exception was with the co-administration of yellow fever vaccine and the combined measles, mumps, and rubella vaccine (MMR) to children 12-23 months of age [3]. The study found a significant decrease in the seroconversion rates and geometric mean titers obtained against yellow fever, mumps, and rubella when the vaccines were co-administered versus administered 28 days apart; no decreases were noted in the immune response to measles. Another exception was from a study involving persons who received yellow fever vaccine one year before the chimeric tetravalent dengue vaccine based on the yellow fever vaccine backbone [4]. The study found an initial delay in the antibody response to dengue 1 among yellow fever vaccine-primed persons. Potential limitations of the studies on the co-administration of yellow fever vaccine and live vaccines are similar to those noted for inactivated vaccines.

Working Group Discussion and Conclusions

In reviewing available data, the working group found that co-administration of yellow fever vaccine and other vaccines typically have no impact on safety and generally elicit a good immune response to yellow

fever vaccine. A notable exception is the co-administration of MMR vaccine and yellow fever vaccine where immune response is decreased to several antigens when they are co-administered versus administered 28 days apart. The working group suggests additional studies are needed on the co-administration of yellow fever vaccine and vaccines that are likely to be given at the same time as yellow fever vaccine and where there are no, limited, or conflicting data. Priority co-administration studies identified by the group include:

1. MMR vaccine – Only study performed showed decrease immune response to several antigens [3]. MMR will be increasing used in yellow fever endemic countries and based on current timing of measles vaccine, these vaccines will be co-administered.
2. Meningococcal A or quadrivalent meningococcal vaccine – Currently there are no or very limited data on the co-administration with yellow fever vaccine. It is expected that yellow fever and meningococcal vaccines will be co-administered in the EPI of several African countries where both diseases are endemic or prone to causing epidemic disease. *Note: One study has been conducted but the results are currently pending.*
3. Other considerations: Haemophilus influenzae b (Hib) and pneumococcal vaccines are being increasing used in the EPI and final doses in the series for these vaccines may coincide with yellow fever vaccine delivery. Malaria and dengue vaccines are in development but once available are likely to be used in the same populations (endemic and travelers) and may be co-administered with yellow fever vaccine.

Recommendations: Currently available data suggest that there is minimal impact on the reactogenicity and immunogenicity when yellow fever vaccine is co-administered with other vaccines. One notable exception is the co-administration of yellow fever vaccine and MMR vaccine in young children, where immunogenicity appears to be compromised against several antigens. Additional studies are warranted on the co-administration of yellow fever vaccine and other vaccines, in particularly MMR and meningococcal A vaccines.

References

1. Poo J, et al. Live-attenuated tetravalent dengue vaccine in dengue-naïve children, adolescents, and adults in Mexico City. Pediatr Infect Dis. 2011; 30: e9-e17.
2. Guirakhoo F, et al. Live attenuated chimeric yellow fever dengue type 2 (ChimeriVax-DEN2) vaccine: phase I clinical trial for safety and immunogenicity: effect of yellow fever pre-immunity in induction of cross neutralizing antibody responses to all 4 dengue serotypes. Hum Vaccin. 2006; 2: 60-67.
3. Nascimento Silva JR, et al. Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps, and rubella. Vaccine. 2011; 29: 6327-6334.
4. Qiao M, et al. Priming effect on dengue and yellow fever vaccination on the immunogenicity, infectivity, and safety of a tetravalent dengue vaccine in humans. Am J Trop Med Hyg. 2011; 85: 724-731.

Table 9: Vaccines either studied or available for co-administration with yellow fever vaccine listed by whether data are present on co-administration

Data present		*No data available*
Inactivated Vaccines	***Live (attenuated) vaccines***	
Cholera*	Bacillus Calmette-Guérin (BCG)	Anthrax
Diphtheria	Cholera*	Haemophilus Influenzae b; Hib
Hepatitis A	*Dengue chimera - recruiting*	Human papillomavirus
Hepatitis B	Measles	Influenza (lv)*
Influenza*	Mumps	Japanese encephalitis (iv)*
Meningococcal - *recruiting*	Japanese encephalitis chimera*	*Malaria - recruiting*
Polio*	Polio*	Pneumococcal
Pertussis	Rubella	Rabies
Tetanus	Smallpox	Rotavirus
Typhoid*	Typhoid*	Tick-borne encephalitis
		Varicella/Zoster

* Both live and inactivate forms of vaccine; Abbreviations: iv = inactivated viral; lv = live viral; *Italic* indicate vaccines not yet licensed; ClinicalTrials.gov was used to determine if there were on-going studies and are indicated with "recruiting"

Table 10: Immunogenicity and reactogenicity of yellow fever (YF) vaccine and inactivated vaccines

Vaccines[*]	# of Studies	Years studies published	# of subjects (type)[†]	Immune Response YF Vaccine[‡]	Reactogenicity[¶]	Immune Response Other Vaccine[‡]
Cholera	2	1973, 1986	500 A predominantly	50%	+	50%
Diphtheria	3	1973, 1986 (2)	800 A/C	+	+	+
HepA	5	1993, 1996 (2), 1997, 1999	650 A only	+	+	90%
HepB	2	1986 (2)	400 C only	75%	+	+
Influenza	1	1993	65 A only	+	Not assessed	78-80%
Meningococcal	1[§]	1996	Unknown A only	(+)	(+)	(+)
Pertussis	1	1973	550 C only	+	+	+
Polio	2	1986 (2)	450 A/C	+	+	Not assessed
Tetanus	4	1973 (2), 1986 (2)	1405 A/C	+	+	50%
Typhoid	3[§]	1996, 1997, 2002	360 A only	+	+	+

[*] Listed by antigen component rather than specific vaccines; the specific vaccine and manufacturer often varied between studies;

[†] type of subjects: A=adults; C=children (definition of children variable by study but typically less than 18 years of age);

[‡] + = No difference between co-administration immune response and immune response administered non-simultaneously or in some cases seroconversion rates of higher than 90% for participants receiving co-administered vaccines, ##% indicates the decrease from vaccines administered "alone" or proportion that showed seroconversion, ( ) = specific data not given;

[¶] + No impact on safety profile when co-administered, ( ) = specific data not given;

[§] Indicates that at least one of the studies was a published abstract from a meeting rather than data from a full manuscript

Table 11: Immunogenicity and reactogenicity of yellow fever (YF) vaccine and other live-attenuated vaccines

Vaccines[*]	# of studies	Year studies published	# of subjects (type)[†]	Immune Response YF Vaccine[‡]	Reactogenicity[¶]	Immune Response Other Vaccine[‡]
BCG	1	1973	600 C only	+	+	(+)
Cholera	1	1997	150 A only	+	+	+
Dengue Chimeric	3	2006 (2), 2011	217 A/C	(+)	(-)	+
JE Chimeric	2	2003, 2010	120 A only	(+)	+	50%
Measles (Only)	8	1973 (2), 1986, 1989, 1990, 1991, 1996, 1999	2000 C only	+	+	+
MMR	1	2011	1828 C only	-	+	66%
Polio	2	1984, 1986	440 A only	+	+	Not assessed
Smallpox	4	1964, 1972, 1973 (2)	2000 A/C	+	+	(+)
Typhoid	2[§]	1996, 1997	150 A only	+	+	+

[*] Listed by antigen component rather than specific vaccines; the specific vaccine and manufacturer often varied between studies;
[†] type of subjects: A=adults; C=children (definition of children variable by study but typically less than 18 years of age);
[‡] + = No difference between co-administration immune response and immune response administered non-simultaneously or in some cases seroconversion rates of higher than 90% for participants receiving co-administered vaccines, - = Statistically significant decrease in the immune response when vaccines is co-administered, ##% indicates the decrease from vaccines administered "alone" or proportion that showed seroconversion, ( ) = specific data not given;
[¶] + No impact on safety profile when co-administered, - Significant impact (worsening) of the safety profile when co-administered, ( ) = specific data not given;
[§] Indicates that at least one of the studies was a published abstract from a meeting rather than data from a full manuscript

Impact of vaccination strategies on the control of yellow fever

Key Findings

- Data from yellow fever endemic countries support the combined use of yellow fever vaccine through Expanded Program on Immunization (EPI) and mass vaccination campaigns as an effective approach to prevent yellow fever and control outbreaks of the disease.
- There is a continued need to improve and strengthen yellow fever disease surveillance and improve vaccination coverage.
- Current yellow fever vaccination strategies are cost-effective and the costs do not vary substantially between the various strategies (e.g., EPI, preventive, or reactive campaigns).
- Vaccine supply issues need to be considered when determining the optimal vaccination strategies.

The WHO-recommended control strategy for yellow fever centers on preventing, detecting and controlling outbreaks [1, 2]. This strategy includes ensuring the quality and sensitivity of the epidemiological surveillance system for yellow fever and delivery of yellow fever vaccine through systematic organized programmes, such as the EPI, or mass prevention and response campaigns.

Yellow fever vaccination in routine EPI

Immunization against yellow fever through EPI is an effective strategy for disease control [1]. Significant progress had been made since 1998 when WHO and UNICEF recommended introducing yellow fever vaccine into the routine immunization schedule of countries considered to be at risk. By 2008, 23 of the 33 yellow fever endemic countries in the African Region and 9 of the 13 endemic countries in American Region were offering yellow fever vaccine through EPI. Although gap between coverage of yellow fever vaccine and measles vaccine is decreasing, EPI coverage rates have varied by country and in certain countries is <50% [1]. One major limitation to the EPI coverage has been shortages of the vaccine [1, 2].

Preventive mass vaccination campaigns

Immunization against yellow fever through EPI requires several years to raise population immunity to a level that is sufficient to prevent outbreaks. To obtain faster and broader population coverage, routine (EPI) immunization may be complemented by preventive mass immunization campaigns. This combined strategy (routine EPI plus preventive campaigns) has proved to be highly effective in reducing the mortality and morbidity associated with yellow fever and reducing the risk of outbreaks [1, 2]. A good example of this approach has been in The Gambia that had several large outbreaks of yellow fever disease including one in 1978 when 271 cases and 63 deaths were reported [3]. Estimations from subsequent studies suggested that there were likely more than 8,000 cases and 1,700 deaths in the 1978 outbreak. Following this outbreak a mass campaign vaccination targeting the whole country was conducted with a vaccine coverage > 95%. Starting in 1979, yellow fever vaccine was introduced into the EPI for children > 9 months. In 2009, 96% coverage was reported. Despite ongoing risk that has been documented through unvaccinated travelers to Gambia becoming ill with yellow fever, no autochthonous cases have been reported in the country since 1978.

In 2005, the GAVI Alliance invested US$ 58 million to decrease the risk of yellow fever epidemics in Africa by vaccinating millions of people in 12 African countries (Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Ghana, Guinea, Liberia, Mali, Nigeria, Senegal, Sierra Leone and Togo) [1]. To date 11 of the original 12 countries as well as Central Africa Republic have undergone preventive mass vaccination campaigns. Nigeria is the only remaining country to have a preventative mass vaccination campaign mostly due to larger than anticipated vaccine needs. The country is currently scheduled to undergo a mass vaccination campaign from 2013-2016. The same preventive mass vaccination campaign strategy has been used as well in the American Region, namely in Bolivia, Brazil, and Peru. As was seen with The Gambia, there have been no outbreaks reported in areas receiving preventive campaigns.

Reactive mass vaccination campaigns

Reactive mass vaccination campaigns have been successful in the past years at controlling outbreaks of yellow fever disease in places with inadequate vaccination coverage [1]. There is currently an emergency vaccine stockpile of roughly 6 million doses funded by the GAVI Alliance, which allows for a more effective response to outbreaks. Since 2007, the vaccine stockpile has been used by a number of countries that experienced an outbreak of the disease in areas where the disease has been silent for decades, such as Southern Brazil, Paraguay, Sudan, and Uganda. In each instance, no subsequent cases of the disease were noted among vaccinated persons following the reactive campaigns. However, with the outbreaks in Brazil and Paraguay in 2008, the vaccine stockpile was depleted by February of that year. Although the stockpile was eventually restocked in the following months, this situation stressed the need for countries to: 1) continue to optimize their current vaccine coverage in populations at risk; and 2) develop a national stock of vaccine in areas where significant proportions of their population are outside the endemic area and therefore are unvaccinated (e.g., the Americas).

Cost-effectiveness of the various vaccination strategies

Following a review of the various vaccination strategies that are available, the working group assessed the cost of each strategy to determine if any of the strategies are more cost-effective or cost-prohibitive. Although older data suggest differential costs between EPI and reactive (outbreak control) vaccination strategies, current available data suggest that cost per dose of yellow fever vaccine is similar for various strategies. Cost was estimated to be approximately US$ 0.67/dose for each strategy but the breakdown of cost (e.g., cold chain, vaccine price) varied based on strategy. Given these data, it was decided that vaccine utilization strategies should be driven by factors other than cost (e.g., vaccine availability).

Recommendations: Control strategy for yellow fever should include sound epidemiologic surveillance and delivery of yellow fever vaccine through a complementary and optimized combination of EPI and mass preventive campaigns. Reactive campaigns should be conducted in response to yellow fever outbreaks if there is inadequate vaccination coverage within the population.

References

1. World Health Organization. Update on progress controlling yellow fever in Africa, 2004–2008. Wkly Epidemiol Rec. 2008; 83(50): 450–458.

2. Pan American Health Organization. XVIII Meeting of the Technical Advisory Group (TAG) on Vaccine-preventable Diseases – Final Report 2009. Available at: http://www2.paho.org/hq/dmdocuments/2010/tag18_2009_Final%20Report_Eng.pdf. Accessed on February 4, 2013.
3. World Health Organization. Expanded Programme on Immunization (EPI): Inclusion of yellow fever vaccine in the EPI. Wkly Epidemiol Rec. 1996; 71(24): 181-185.

Summary

Over the last 75 years, yellow fever vaccine has been the most effective means of preventing of yellow fever disease. The vaccine has been proven to be highly immunogenic and a single dose provides long-term protection against yellow fever. However, rare but serious side effects have been observed following the administration of this live attenuated viral vaccine.

The SAGE Working Group on Yellow Fever Vaccine carefully reviewed and weighed all available data regarding the use of yellow fever vaccine to reach the following conclusions and recommendations:

1. Booster dose of yellow fever vaccine is not needed to maintain immunity as a single dose of yellow fever vaccine appears to confer life-long protective immunity against yellow fever disease.
2. Caution should be used in vaccinating pregnant women, lactating women, and persons >60 years of age against yellow fever if they have not been previously vaccinated.
3. Yellow fever vaccine is contraindicated for severely immunocompromised persons, including persons with AIDS or CD4+ counts < 200 cells/mm3, certain primary immunodeficiencies, thymus disorder, malignant neoplasm being trated with chemotherapy , recent hematopoietic stem cell transplantation, drugs with known immunosuppressive or immunomodulatory properties (e.g., high-dose systemic corticosteroids, alkylating drugs, antimetabolites, TNF-α inhibitors, IL-1 blocking agent, or other monoclonal antibodies targeting immune cells), and current or recent radiation therapies targeting immune cells.
4. There is minimal impact on the reactogenicity and immunogenicity when yellow fever vaccine is co-administered with other vaccines. One notable exception is the co-administration of yellow fever vaccine and MMR vaccine.
5. Control strategy for yellow fever should include sound epidemiologic surveillance and delivery of yellow fever vaccine through a combination of EPI, preventive campaigns, and reactive campaigns.

In addition to the conclusions and recommendations above, the working group also noted several areas where additional research is warranted to address critical gaps related to the safety and immunogenicity of yellow fever vaccine (Table 12).

Table 12: Overview of potential studies to be conducted on live attenuated yellow fever (YF) vaccine to address gaps in safety or efficacy of the vaccine that were identified by the SAGE YF working group

Studies are listed below according to the target population where evidence based advice regarding safety and efficacy of YF vaccine are most needed.

Study topics regarding the safety and efficacy of YF vaccine identified by the SAGE YF working group	Studies to be initiated in		
	Developing countries		Developed countries
	YF endemic	YF non endemic	
Transmission of YF vaccine virus by breastfeeding[a]	X		
Efficacy of YF and meningococcal vaccines when co-administered in EPI[b]	X		
Efficacy of YF and combined measles, mumps, and rubella (MMR) vaccines when co-administered in EPI[c]	X		
Efficacy of YF and OPV vaccines when co-administered in EPI[d]	X		
Safety and immunogenicity of YF vaccine in persons with advanced HIV[e]	X		X
Safety of YF vaccine in people ≥60 years[f]	X	X	X
Safety of YF vaccine in people with immunocompromising conditions[g]	X		X
Duration of protective immunity against YF in children[h]	X		
Duration of protective immunity against YF in adults[i]	X	X	X
Development of diagnostic assays for YF outbreaks[j]			X
Evaluation of diagnostic assays for YF outbreaks[j]	X		

[a] ***Transmission of YF vaccine virus by breastfeeding.*** Research question(s): Is the YF vaccine virus transmitted by breastfeeding from a vaccinated mother to her baby? How often this transmission does occur and what are the consequences for the baby? Are there any health risks for the baby? Study: An estimated number of 100 breastfeeding mothers in an YF vaccination campaign have to be thoroughly investigated for transmission via breastfeeding.

[b] ***Efficacy of YF and meningococcal vaccines when co-administered in EPI.*** Research question(s): Does the simultaneous administration of YF and meningococcal vaccine in the EPI influence the protective immune response generated against each vaccine? Study: An estimated number of 1000 children in a YF vaccination campaign have to be thoroughly investigated for neutralizing/protective antibodies to get statistically valid data.

[c] ***Efficacy of YF and MMR vaccines when co-administered in EPI.*** Research question(s): Does the simultaneous administration of YF and MMR vaccine in the EPI influence the protective immune response generated against each vaccine? Study: An estimated number of 1000 children in an YF vaccination campaign have to be thoroughly investigated for neutralizing/protective antibodies to get statistically valid data.

[d] ***Efficacy of YF and OPV vaccines when co-administered in EPI.*** Research question(s): Does the simultaneous administration of YF and oral polio vaccine in the EPI influence the protective immune response generated against each vaccine? Study: An estimated number of 1000 children in an YF vaccination campaign have to be thoroughly investigated for neutralizing/protective antibodies to get statistically valid data.

[e] ***Safety and immunogenicity of YF vaccine in persons with advanced HIV***. Research question(s): What is the impact of advanced HIV infection on the safety, magnitude, and duration of immunity following YF vaccination? Study: An estimated number of 200-400 HIV infected persons have to be thoroughly investigated for neutralizing/protective antibodies to get statistically valid data. Since the HIV therapeutic regime has great impact on the quality of the immune system separate studies in developing and undeveloped countries are necessary.

[f] ***Safety of YF vaccine in people ≥60 years.*** Research question(s): Are there higher numbers of serious AEFIs in elderly persons compared to younger persons due to a less competent immune system? Study: This requires continuous notification, analysis and investigation of side effects after YF vaccination. Since the rate of side effects after YF vaccination is in the range of a few cases per thousand vaccinees (1/100,000) the limiting factor to obtain statistically robust data is the total number of YF vaccine administered to people >60 years over the years.

[g] ***Safety of YF vaccine in people with immunocompromising conditions***. Research question(s): Are there higher numbers of serious AEFIs in immunocompromised persons due to a less competent immune system? Study: This

requires continuous notification, analysis and investigation of side effects after YF vaccination. Since the rate of side effects after YF vaccination in immunocompromised is very low and the range of diseases causing immunosuppression is very different it is not possible to give an estimated number of cases to be investigated to get statistically valid data.

[h]***Duration of protective immunity against YF in children***. Research question(s): What is the duration the protection against YF in children receiving YF vaccine in the EPI? Study: An estimated number of 1000 adolescents and adults with a well-documented history of receiving YF vaccine as a child have to be thoroughly investigated for neutralizing/protective antibodies to get statistically valid data.

[i]***Duration of protective immunity against YF in adults***. Research question(s): What is the duration of protection against YF in adults who receive YF vaccine? Study: An estimated number of 200-400 vaccinees with a well-documented YF vaccination have to be thoroughly investigated per time interval for the presence of neutralizing/protective antibodies to get statistically valid data.

[j]***Development and evaluation of diagnostic assays for YF outbreaks*** *(NOTE: topics discussed in the working group but not presented in the background document)*. Research question(s): Which kind of assay provides a sensitive and reliable diagnostic analysis of YF infections in case of a suspected outbreak? Study: An estimated number of 50 – 100 acute YF cases have to be thoroughly investigated for IgM/IgG antibodies and YF RNA detection to get statistically valid data.