Summary of GRADE, consideration for special populations, and proposed recommendations for YF vaccine booster doses

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Primary policy question for GRADE

- Should booster doses of YF vaccine every 10 years continue to be recommended for healthy travelers and laboratory workers?
  - Population: Healthy travelers and laboratory workers
  - Intervention: Remove current recommendation for booster doses
  - Current option: Continue current recommendation for booster doses of YF vaccine

Outcome measures assessed for YF vaccine booster doses

- Benefits included vaccine efficacy, seroprotection, vaccine effectiveness, and seropositivity
  - No data for vaccine efficacy or seroprotection
- Harms included serious adverse events, viscerotropic disease, and neurologic disease

YF vaccine effectiveness data

- 18 vaccine failures among >540 million doses of YF vaccine delivered
- 2 (11%) of vaccine failures occurred ≥10 years from last YF vaccine dose (20 and 27 years)

Seropositivity data at ≥10 years following YF vaccination

- 13 observational studies with immunogenicity data for 1,137 persons ≥10 years post vaccination
- Estimate of seropositivity is 92% (95%CI 85%-96%) using random effects model

Seropositivity data at ≥20 years following YF vaccination

- 3 observational studies with immunogenicity data for 164 persons ≥20 years post vaccination
- Estimate of seropositivity is 80% (95%CI 74%-86%) using random effects model

Serious adverse events data

- 9 observational studies including 333 million doses of vaccine distributed
  - Unknown how many doses administered as boosters
- 1,255 subjects reported a serious adverse event following YF vaccination
  - 84% (1,054) of subjects with unknown vaccination type
- 7% (14/201) of subjects where their dose type was known occurred following YF booster dose
- Data were similar for YF vaccine-associated viscerotropic and neurologic disease

Initial evidence type used for GRADE

1 = Randomized control trials (RCTs) or overwhelming evidence from observational studies

2 = RCTs with important limitations or exceptionally strong evidence from observational studies

3 = Observational studies or RCTs with notable limitations

4 = Clinical experience, observational studies with important limitations, or RCTs with several major limitations

Overall quality of evidence for YF vaccine booster doses

Outcome	Study Design (# studies)	Evidence Type	Overall evidence
Vaccine effectiveness	Obs (5)	4	4
Seropositivity	Obs (13)	4	
Serious adverse events	Obs (9)	4	
Viscerotropic disease	Obs (8)	4	
Neurologic disease	Obs (8)	4	

Additional policy question

- Should booster doses of YF vaccine every 10 years continue to be recommended for travelers and laboratory workers who had a precaution to vaccination that might have negatively impacted their immune response to their primary dose of YF vaccine (e.g., pregnancy, asymptomatic HIV infection, or age 6-8 months)?
  - Population: Travelers or laboratory workers who have a precaution to vaccination that might negatively impact their immune response to their primary dose of YF vaccine
  - Intervention: Remove current recommendation for booster doses
  - Current option: Continue current recommendation for booster doses of YF vaccine

Immunogenicity of YF vaccine in pregnant women

- 39% (32/83) of pregnant women vaccinated during their third trimester seroconverted
  - Compared to 94% (89/95) of general population
- 98% (425/433) of pregnant women vaccinated during first trimester developed YF-virus specific antibodies

Summary and consideration of immunogenicity of YF vaccine in pregnant women

- Proportion of pregnant women who develop antibody titers following YF vaccination is variable
- Data indicate lack of initial seroconversion in some pregnant women
- Work Group suggests revaccinating one time prior to next at risk travel

Consideration of immunogenicity of YF vaccine in hematopoietic stem cell transplant (HSCT) recipients

- Most HSCT recipients become seronegative to live viral vaccine antigens post transplantation
- IDSA guidelines recommend readministering live viral vaccines (i.e., MMR, Varicella) post transplant when no longer immunosuppressed
- Work Group suggests revaccinating HSCT recipients one time prior to next at risk travel as long as they are immunocompetent

Immunogenicity of YF vaccine in HIV-infected individuals

- 17% (3/18) HIV-infected children had YF virus-specific antibodies 10 months post vaccination
  - Compared to 74% (42/57) age and nutritionally matched children
- 83% (65/78) HIV-infected travelers had YF virus-specific antibodies one year post YF vaccination
  - Compared to 97% (64/66) uninfected controls
- 77% (54/70) HIV-infected travelers had YF virus-specific antibodies 1-10 years post vaccination
  - Compared to 88% (81/92) uninfected controls

Summary and consideration of immunogenicity of YF vaccine in HIV-infected individuals

- Data indicate HIV-infected persons less likely to have sustained YF virus-specific antibody titers following vaccination
- Work Group suggests continuing doses of YF vaccine every 10 years

Immunogenicity of YF vaccine in young children

- 12 studies with immunogenicity data on 4,675 children aged 4 months to 10 years in endemic areas at one to two months post vaccination

- Estimate of seroconversion rate is 93% (95% CI 88%-96%) using random effects model
  - 88% when study size differences and variability between studies was not accounted for

Seroconversion rates for children by age groups

Age group	Number of studies	Estimated seroconversion*	(95% CI)
≥9 months	11	92%	(86%-96%)
<9 months	4	95%	(91%-98%)

Age group	Number of studies	Estimated seroconversion*	(95% CI)
≥12 months	4	89%	(78%-96%)
<12 months	7	93%	(87%-97%)

*DerSimonian-Laird random effects model using the Freeman-Tukey transformation for proportions

Summary and consideration of immunogenicity of YF vaccine in young children

- Estimate for pediatric seroconversion rate was 93% (95% CI 88-96%)
- Adult seroconversion rate of 98% for all populations; 97% from endemic areas
- No clear age difference in seroconversion rates
- COID concluded young children were not immunologically different from adults in their response to YF vaccine

Additional considerations regarding persons at higher risk for YF virus exposure

- Higher risk locations for YF virus exposures
  - West Africa during peak transmission season; disease risk ~10 times higher than South America
  - Areas with ongoing outbreak
  - Regular exposure to wild-type YF virus in laboratory
- Travel with long periods (e.g., months to years) likely to increase risk of disease

Summary of YF vaccine booster dose data and considerations

- Very few vaccine failures noted following YF vaccine
- Most (92%) vaccine recipients are seropositive at ≥10 years post vaccination
- Serious adverse events are uncommon following booster doses of YF vaccine
- High value placed on preventing serious disease with no treatment and poor outcome
- Current statement in ACIP recommendations will no longer be relevant when IHR updated in June 2016

Work Group conclusions

- Single dose of YF vaccine provides long-lasting protection in most travelers
- No longer recommend booster doses of YF vaccine for most travelers
- Recommend YF vaccine booster doses for persons who immune response to previous dose might have been compromised
- Consider YF vaccine booster doses for persons in higher-risk setting for exposure to YF virus

Recommendation for most travelers

"A single dose of yellow fever vaccine provides long-lasting protection and is adequate for most travelers." (Recommendation category A)

Recommendation for certain populations

"Additional doses of yellow fever vaccine are recommended for certain travelers, including:

- Women pregnant when they received their initial dose of yellow fever vaccine should receive one additional dose of yellow fever vaccine prior to their next travel that puts them at risk for yellow fever virus infection.
- Individuals who received a hematopoietic stem cell transplant after receiving a dose of YF vaccine and who are sufficiently immunocompetent to be safely vaccinated should be revaccinated prior to their next travel that puts them at risk for yellow fever virus infection.
- Individuals who were HIV-infected when they received their last dose of yellow fever vaccine should receive a dose every 10 years if they continue to be at risk for yellow fever virus infection

Persons being considered for additional doses of yellow fever vaccine should be assessed for contraindications or precautions." (Recommendation category A)

Recommendation for higher-risk settings

"A booster dose may be considered for travelers who received their last dose of YF vaccine at least 10 years previously and who will be in a higher-risk setting based on season, location, activities, and duration of their travel. This would include travelers who plan to spend a prolonged period of time in endemic areas or those traveling to highly endemic areas such as rural West Africa during peak transmission season or areas with ongoing outbreaks." (Recommendation category B)

Recommendation for laboratory workers

"Laboratory workers who routinely handle wild-type yellow fever virus should have yellow fever virus-specific neutralizing antibody titers measured at least every 10 years to determine if they should receive additional doses of the vaccine. For laboratory workers who are unable to have neutralizing antibody titers measured, yellow fever vaccine should be given every 10 years as long as they remain at risk." (Recommendation category A)

Next steps

- Questions and discussion
- Vote on proposed language
- No VFC vote

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