GRADE and Work Group conclusions regarding YF vaccine booster doses

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Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) steps

- Develop policy question
- Identified and ranked importance of outcomes
- Searched and reviewed of published and unpublished data
- Summarized evidence for critical outcomes
- Evaluated quality of evidence for outcomes
- Assessed values related to options and outcomes
- Reviewed health economic data
- Considerations for formulating recommendations
- ACIP recommendations and GRADE category

Primary policy question

- 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

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Outcome measure ranking and inclusion for YF vaccine booster doses

	Importance	Include in evidence profile	Data Available
Benefits			
Vaccine efficacy	Critical	Yes	No
Vaccine effectiveness	Critical	Yes	Yes
Seroprotection	Critical	Yes	No
Seropositivity	Critical	Yes	Yes
Harms			
Serious adverse events	Critical	Yes	Yes
Viscerotropic disease	Critical	Yes	Yes
Neurologic disease	Critical	Yes	Yes
Anaphylaxis	Important	No	--
Systemic adverse events	Important	No	--

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Evidence retrieval

- Performed systematic search and review of published literature
  - Identified 32 studies that reported primary data relevant to critical outcomes
- Reviewed unpublished data
  - Data from Brazil Ministry of Health (MOH) on duration of immunity and vaccine failures
  - VAERS reports for YF vaccine administered from Jan 2007 – Dec 2013
  - CDC Arboviral Disease Laboratory data on antibody titers in vaccine recipients ≥10 years post vaccination

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Vaccine effectiveness measured by vaccine failures reported following YF vaccination, 1940-2013

Population	Type	No. of cases	Lab confirmed	Timing post vaccination
Non-endemic	Obs	3	0	15-16 months
Non-endemic	Obs	1	0	4 years
Non-endemic	Obs	1	0	5 years
Endemic	Obs	6	0	Unknown[1]
Endemic	Obs	7	7	10 days-10 years (5), 20 years, 27 years

Obs = observational study; [1]Exact timing unknown but dose given in last 10 years

Summary of YF vaccine effectiveness data

- 18 vaccine failures among over >540 million doses of YF vaccine delivered
  - Limited laboratory data to support diagnosis of YF
- 16 (89%) of vaccine failures occurred in persons receiving YF vaccine dose in last 10 years
- Two vaccine failures occurred ≥10 years from last YF vaccine dose (20 and 27 years)

Seropositivity at ≥10 years following YF vaccination - 1

Population	Type	Seropositivity criteria	Years post vaccination	Seropositive No.	(%)
Endemic	Obs	Mouse protection	10	156/202	(77)
Endemic	Obs	$PRNT_{50}$ ≥20	10	20/20	(100)
Non-endemic	Obs	$PRNT_{90}$ ≥10	≥10	5/5	(100)
Endemic	Obs	$PRNT_{80}$ ≥10	≥10	19/19	(100)
Endemic	Obs	$PRNT_{50}$ ≥10	10-18	307/329	(93)
Non-endemic	Obs	Mouse protection	10-15	24/24	(100)
Endemic	Obs	Mouse protection	12	76/79	(96)

PRNT = plaque reduction neutralization test; PRNTx is the reciprocal of the highest serum dilution at which x% of virus is inhibited.

Seropositivity at ≥10 years following YF vaccination - 2

Population	Type	Seropositivity criteria	Years post vaccination	Seropositive No.	(%)
Non-endemic	Obs	Mouse protection	17	105/108	(97)
Endemic	Obs	$PRNT_{75}$ ≥10	10-24	13/19	(68)
Non-endemic	Obs	$PRNT_{90}$ ≥10	11-38	38/51	(75)
Non-endemic	Obs	$PRNT_{80}$ ≥10	10-60	80/84	(95)
Non-endemic	Obs	$PRNT_{90}$ ≥10	10-69	68/81	(84)
Non-endemic	Obs	$PRNT_{90}$ ≥2	30-35	91/116	(78)

PRNTx is the reciprocal of the highest serum dilution at which x% of virus is inhibited

Summary of seropositivity data at ≥10 years following YF vaccination

- 13 observational studies with immunogenicity data for 1,137 persons ≥10 years post vaccination
- 88% (1,002) were seropositive at ≥10 years post vaccination
  - When study size differences and variability between studies is accounted for, estimate of seropositivity is 92% (95%CI 85%-96%)
- 80% (131/164) persons were seropositive at ≥20 years post vaccination
  - Estimate of seropositivity is 80% (95%CI 74%-86%)

Serious adverse events following YF vaccination by dose type

Population	Reporting Period	Type	Doses (x1,000)	Number of cases by dose type		
				Primary	Booster	Unknown
Non-endemic	2007-2013	Obs	3,115	96	11	0
Both	1993-2010	Obs	276,000	-	-	805
Non-endemic	1991-2001	Obs	273	-	-	7
Non-endemic	2003-2006	Obs	903	54	1	0
Non-endemic	1990-2002	Obs	9,600	13	2	32
Endemic	2008-2009	Obs	1,940	24	-	9
Endemic	2007-2010	Obs	38,009	-	-	164
Endemic	1999-2005	Obs	500	-	-	24
Endemic	2001	Obs	2,600	-	-	13

Summary of serious adverse events data

- 9 observational studies from manufacturers and national surveillance data
  - 333 million doses of vaccine administered; 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

Viscerotropic disease following YF vaccination by dose type

Population	Reporting Period	Type	Doses (x1000)	Number of cases by dose type		
				Primary	Booster	Unknown
Both	1993-2010	Obs	276,000	4	1	7
Non-endemic	2003-2006	Obs	903	6	-	-
Non-endemic	1990-2002	Obs	9,600	8	-	-
Non-endemic	1991-2003	Obs	3,046	-	-	4
Endemic	2008-2009	Obs	1,940	12	-	-
Endemic	2007-2010	Obs	38,010	-	-	5
Endemic	1999-2009	Obs	107,649	-	-	20
Endemic	2007	Obs	42	-	-	5

Summary of viscerotropic disease data

- 8 observational studies from manufacturers and national surveillance data
  - 437 million doses of vaccine administered; unknown how many doses administered as boosters
- 72 subjects reported viscerotropic disease following YF vaccination
  - 57% (41) of subjects with unknown vaccination type
- 3% (1/31) of subjects where their dose type was known occurred following YF booster dose

Neurologic disease following YF vaccination by dose type

Population	Reporting Period	Type	Doses (x1000)	Number of cases by dose type		
				Primary	Booster	Unknown
Both	1993-2010	Obs	276,000	10	1	13
Non-endemic	2003-2006	Obs	903	6	-	-
Non-endemic	1990-2002	Obs	9,600	10	-	-
Non-endemic	1991-2003	Obs	3,046	-	-	4
Endemic	2009-2012	Obs	30,746	59	2	-
Endemic	2008-2009	Obs	1,940	12	-	-
Endemic	2007-2010	Obs	38,009	-	-	6
Endemic	2000-2008	Obs	101,564	-	-	85

Summary of neurologic disease data

- 8 observational studies from manufacturers and national surveillance data
  - 462 million doses of vaccine administered; unknown how many doses administered as boosters
- 218 subjects reported neurologic disease following YF vaccination
  - 50% (108) of subjects with unknown vaccination type
- 3% (3/110) of subjects where their dose type was known occurred following YF booster dose

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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

Limitations and evidence type for benefits of YF vaccine booster doses

	Vaccine effectiveness	Seropositivity
Design (# studies)	Obs (5)	Obs (13)
Risk of bias	Yes[2]	Yes[4]
Inconsistency	No serious	No serious
Indirectness	Yes[3]	Yes[5]
Imprecision	No serious	No serious
Evidence type[1]	4	4

[1] Other criteria considered included publication bias, strength of association, dose response, or direction of all plausible confounding would reduce the effect

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

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

[4] Risk of bias in those who were tested for long-term seropositivity

[5] Indirectness due to different population (majority of data are from endemic areas); no efficacy data are available, no correlate of protection established for the assays used to assess immunity, and different assays and antibody levels were used to assess either seropositivity or ”seroprotection”

Limitations and evidence type for harms of YF vaccine booster doses

	Serious adverse events	Viscerotropic disease	Neurologic disease
Design (# studies)	Obs (9)	Obs (8)	Obs (8)
Risk of bias	No serious	No serious	No serious
Inconsistency	No serious	No serious	No serious
Indirectness	Yes[2]	Yes[2]	Yes[2]
Imprecision	No serious	No serious	No serious
Evidence type[1]	4	4	4

[1] Other criteria considered included publication bias, strength of association, dose response, or direction of all plausible confounding would reduce the effect

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

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

- Additional policy question created for special populations whose initial immunologic response to YF vaccine may be suboptimal
- 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)?

Additional policy question consideration

- Very limited data related to special populations whose immune response to YF vaccine may be suboptimal
- Work group decided not to perform GRADE
- Immunogenicity data reviewed for pregnant women, HIV-infected persons, and young children

Immunogenicity of YF vaccine in pregnant women

- Proportion of pregnant women who develop antbody titers is variable
- 39% (40/101) of pregnant women vaccinated during their third trimester seroconverted
  - Compared to 92% of general population
- 98% (425/433) pregnant women vaccinated during first trimester developed YF-virus specific antibodies

Immunogenicity of YF vaccine in HIV-infected individuals

- 83% (65/78) HIV-infected persons had YF virus-specific antibodies one year post YF vaccination
  - Compared to 97% (64/66) uninfected controls (p=0.01)
- 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

Seroconversion rates following primary dose of YF vaccine in children aged 6-36 months

Age in months	Type	Other vaccines	Assay used	Seroconversion No.	(%)
12-23	RCT	MMR	$PRNT_{90}$	765/922	(83)
9-36	RCT	None	LNI	317/342	(93)
9	RCT	Measles	PRNT	228/294	(78)
6-12	Obs	Measles	ELISA	376/400	(94)
6-10	Obs	Measles	$PRNT_{80}$	131/139	(94)
6-9	RCT	Measles	HIA	122/135	(90)
6-24	RCT	Measles	PRNT	159/167	(95)
9-36	Obs	Several	$PRNT_{90}$	170/183	(93)
9-36	Obs	HepB, Measles	$PRNT_{90}$	165/172	(96)

LNI = $\log_{10}$ neutralization index; ELISA = enzyme linked immunosorbent assay; HIA = hemagglutination inhibition assay

Summary of immunogenicity of YF vaccine in young children

- Nine studies with immunogenicity data on children aged 6-36 months in endemic areas
- 88% (2,433/2,754) children seroconverted one to two months post YF vaccination
- Very limited long-term immunogenicity data available for children

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YF among travelers from non-endemic areas

- From 1970-2013, 10 YF cases reported in travelers from United States (3) and Europe (7)
  - Nine were unvaccinated; 8 (89%) died
  - One traveler received YF vaccine 5 years before traveling to West Africa and developing YF; survived
- YF vaccine available since 1930s, unknown how many cases prevented due to vaccination
- Vaccination coverage rates for persons traveling YF endemic area is 91-93%

YF vaccine considerations for U.S. travelers

- Risk of YF disease and death in unvaccinated traveler for 2 week stay
  - West Africa: 50 and 10 per 100,000 population
  - South America: 5 and 1 per 100,000 population
- Risk of YF varies based on location, duration, season, and activities
- Risk of YF will be lower in persons receiving at least one dose of YF vaccine ≥10 years previously

Additional Work Group considerations regarding disease risk in U.S. population

- Work group considered persons who might be at higher risk of exposure to YF virus
  - Locaton – YF disease risk in West Africa estimated to be 10 times higher than South America
  - Duration of travel – longer travel (e.g., months to years) likely to increase risk of disease
  - Type of exposure – more consistent exposure to virulent virus among laboratory workers
- Minimal to no data to support these considerations of risk

Values considered by Work Group

- YF is a severe disease with substantial mortality
- No specific treatment
- Safe and effective vaccine is available
  - Low probability of serious adverse event with revaccination
- Vaccine prevents importation or spread of YF virus
- Vaccine is expensive

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Considering cost of YF vaccine for travelers

- No data on cost-effectiveness of vaccinating travelers with either primary or booster doses
- Providing YF vaccine to all travelers going to endemic areas would not be cost-effective
  - Large number of travelers to endemic areas (~3 million/year)
  - Risk of YF disease for vaccinated travelers (less than 5-50 cases per 100,000 population)
  - Cost of YF vaccine ($150-350)

Cost-effectiveness analysis for GRADE

- Travel vaccines are usually paid for by travelers themselves
- Not covered by most private insurance and not included in Vaccine for Children (VFC)
- Work Group decided not to perform cost-effectiveness study of YF vaccine booster doses

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Potential recommendations

- A booster doses of YF vaccine every 10 years is recommended for travelers and laboratory workers.
- A single dose of YF vaccine is sufficient to confer sustained life-long protective immunity against YF disease; a booster dose is not necessary. [WHO SAGE recommendation]
- Booster doses are no longer recommended for most travelers or laboratory workers. However, booster doses are recommended for certain persons at risk for exposure to YF virus.

Considerations for formulating recommendations

- 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 soon be antiquated (IHR to be updated in June 2016)
  - "IHRs require revaccination at intervals of 10 years to booster antibody titers"

Work Group conclusions and recommendations

- Single dose of YF vaccine provides long-lasting protection in most travelers
- Work Group proposes to no longer recommend booster doses of YF vaccine for most travelers
- Based on limited data, Work Group would recommend YF vaccine booster doses for certain persons
  - At increased risk of exposure to YF virus
  - Whose immune response to their previous dose might have been compromised due to an existing condition at time of vaccination

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Recommendation for ACIP consideration (1 of 4)

"Booster doses are no longer recommended for most travelers or laboratory workers (Recommendation category A)."

Recommendation for ACIP consideration (2 of 4)

"However, based on limited data, a YF vaccine booster dose is recommended for certain persons either at increased risk of exposure to YF virus or whose immune response to their previous dose might have been compromised due to an existing condition at the time of vaccination (Recommendation category A)." OR

"However, based on limited data, a YF vaccine booster dose may be considered for certain persons either at increased risk of exposure to YF virus or whose immune response to their previous dose might have been compromised due to an existing condition at the time of vaccination (Recommendation category B)."

Recommendation for ACIP consideration (3 of 4)

Booster doses for:

"Travelers who received their last dose of YF vaccine ≥10 years previously and plan to stay in an endemic area for a prolonged period (e.g., months or longer) or plan to travel to a highly endemic area (e.g., rural West Africa)"

Alternative: remove examples in parenthesis as based on limited data

"Laboratory workers who routinely handle infectious YF virus and who have no detectable YF virus-specific neutralizing antibody titers or who received their last dose of YF vaccine ≥10 years previously and for whom YF virus-specific neutralizing antibody titers are unavailable."

Recommendation for ACIP consideration (4 of 4)

Booster doses for:

“Persons who received their last dose of YF vaccine ≥10 years previously and who had, at the time of their last vaccination, a condition that might have compromised their immune response to that dose (e.g., age <1 year, pregnancy, or HIV infection)”

“Persons who had an intervening condition, since their last dose of YF vaccine, that might have a substantial impact on their memory immune response (e.g., bone marrow transplantation)”

Further study

- Assess neutralizing antibody levels ≥10 years post initial vaccination in travelers
- Evaluate amnestic immune response to re-vaccination in person without detectable antibodies
- Determine seroprotective level of antibodies using PRNT, correlating to LNI ≥0.7
- Establish role of vaccine-induced cell-mediated immunity in long-term protection against YF
- Assess neutralizing antibody levels among persons with suboptimal immune response to YF vaccine

Next steps

- Questions and discussion
- Vote on no longer recommending booster doses for most travelers
- Vote on whether to recommend or consider YF vaccine booster doses in certain persons
- No VFC vote

JE and YF Vaccines Work Group Members

ACIP members

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Lorry Rubin

Liaison representatives

Cody Meissner (AAP)

Robert Schechter (AIM)

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Back-up Slides

Alternative recommendation wording

A single dose of YF vaccine may provide long-lasting protection and booster doses are not routinely recommended for all travelers or laboratory workers.

However, a YF vaccine booster dose is recommended for certain persons at risk for exposure to YF virus, particularly those with long stays or travel to highly endemic areas, and persons that were pregnant, age <1 year, or had HIV infection at the time of their initial vaccination.

SAGE PICO and Question

- **Population : Immunocompetent individuals**
- **Intervention :** Primary YF 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?