Yellow fever vaccine: Evidence review with respect to the duration of protection and vaccine safety in special populations

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Overview

- Need for booster dose every 10 years to maintain protection against yellow fever (YF)
- Safety of YF vaccine in selected special populations
  - Persons aged 60 years and older
  - HIV-infected persons
  - Persons with other immunocompromising conditions
  - Pregnant women
  - Lactating women

YF vaccine

Booster dose

History of YF vaccine immunity

- No YF vaccine efficacy studies have been performed
- Several observations supported protective effect
  - Reduction in laboratory-acquired infection in vaccinated workers
  - YF only noted in unvaccinated persons in South America following vaccine introduction
  - Disappearance of cases in outbreaks when campaign conducted
  - Protection of monkeys against virulent virus challenge by neutralizing antibodies generated in response to vaccination
- Monkey studies have established $\log_{10}$ neutralization index (LNI) of >0.7 correlates with protection[1]
  - Correlates using more common plaque reduction neutralization test (PRNT) not established

1. Mason. Appl Microbiol. 1973; 25: 539.

YF vaccine immunity and booster dose

- 80-100% of vaccinated persons in clinical trials develop neutralizing antibodies within 10 days
- >99% of vaccinated persons develop neutralizing antibodies at 28 days post vaccination
- 10 year booster dose interval established in 1965
  - Based on 2 studies documenting majority of recipients with neutralizing antibodies at least 10 years post vaccination

Findings of systematic review on duration of YF antibodies following vaccination

- Six additional studies published since booster dose interval established

Year	# of subjects	Population	Time since YF vaccine	Testing	Findings
1981	116	US military (travelers)	30-35 years	$PRNT_{90}$	78% with titers; varied by service (60-97%)
1988	5	Travelers	10 years	$PRNT_{90}$	100% detectable titers
1999	59	Travelers	11-38 years	$PRNT_{90}$	75% titer ≥ 10
2008	19	Endemic	5-24 years	$PRNT_{75}$	68% titer ≥ 10
2011	20	Endemic	10 years	$PRNT_{50}$	100% titer ≥ 20
2011	84	Travelers	1-60 years	$PRNT_{80}$	95% titer ≥ 10; 93% 10-19 years; 87% ≥ 20 years

$PRNT_n$ = Plaque reduction neutralization testing where the reciprocal of the highest serum dilution at which n% of virus is inhibited

Findings of systematic review on YF vaccine failures

- Since 1930s, only 12 YF disease cases noted in recipients of 600 million doses of vaccine
- Ten cases lacked confirmatory laboratory data
  - Three lacked any laboratory data
  - Seven had inadequate laboratory data
- Two cases were in persons receiving YF vaccine <2 weeks before disease onset
- All cases developed disease ≤5 years after YF vaccination

Summary of systematic review findings on YF vaccine booster dose

- High proportion (>90%) of vaccine recipient with neutralizing antibodies ≤20 years of vaccination
- In persons vaccinated >20 years previously, ~80% have detected neutralizing antibodies
  - Neutralizing antibodies detected as long as 60 years post vaccination
- All vaccine failures were within 5 years post vaccination (primary failures*)
- No secondary vaccine failures* noted

*Primary vaccine failure = failure to seroconvert after vaccination; secondary vaccine failure = loss of protection after initial seroconversion.

Is there evidence that a booster dose is required in immunocompetent individuals to ensure long-term protection? GRADE: Quality assessment

		Rating	Adjustment to rating
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**

[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.

Is there evidence that a booster dose is required in immunocompetent individuals to ensure long-term protection? GRADE: Summary and conclusions

- Confidence in estimate of effect on outcome is limited
- Observational studies attest effectiveness of vaccine
- Health persons rarely fail to develop neutralizing antibodies
  - Titers found in vast majority >10 years after vaccination despite some time dependent waning
- Only 12 cases of vaccine failure reported
- There is no demonstrated need for booster dose every ten years in immunocompetent persons

Additional Working Group considerations on YF vaccine booster data

- Systematic review suggest immunity following YF vaccination is life-long and secondary vaccine failures do not occur
- YF disease noted only in unvaccinated persons during outbreaks
- Data suggest role innate and cell-mediated immunity in initial and memory immune response

Working Group issue and concerns with YF vaccine booster dose data

- Different PRNT levels used in published studies
- Lack of understanding of protective immunity
  - Neutralizing antibodies associated with protective immune response
  - Significance of innate and cell-mediated immunity not known
- Natural boosting likely to occur in endemic areas
  - Role of boosting with related flaviviruses not know
- Limited data suggest children <2 years may have lower seroconversion rates following single dose

Summary of key findings on YF vaccine booster doses

- No efficacy studies performed; neutralizing antibodies used as surrogate
- Current booster dose recommendation of every 10 years from IHR in 1965 and based on limited data
- Majority of vaccine recipients develop antibody titers and will maintain titers for several decades, possibly life-long
- Very few primary vaccine failures reported; no secondary vaccine failures reported
- Both innate and cell-mediated immunity contribute to initial and memory immune response

Recommendations on YF vaccine booster doses

Based on currently available data, a single dose of YF vaccine appears to confer life-long protective immunity against YF disease.

A booster dose of YF vaccine is not needed to maintain immunity.

Further research 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.

Use of YF vaccine in

Persons aged 60 years and older

Background on YF vaccine use in persons aged ≥ 60 years

- Several studies found higher rates of serious AEFIs, both YEL-AVD and YEL-AND, in travelers aged ≥ 60 years[1,2,3]
- Systematic review performed of travelers and endemic populations
  - Used Brighton viscerotropic case definition published in 2012
  - Recalculated reporting rates (RR) and established reporting rate ratios (RRR)

1. Martins et al. Emerg Infect Dis. 2001; 7: 945; 2. Khromava et al. Vaccine. 2005; 23: 3256; 3. Lindsey et al. Vaccine. 2008; 26: 6077.

Findings of systematic review of serious AEFIs rates persons aged ≥ 60 years[1]

- Crude number of YEL-AVD cases in ≥ 60 years (n=19) is higher than all other age groups (n=24)
- Re-calculated RR and RRR among travelers remained statistically elevated
  - RRR ≥ 65 years = 47 (95%CI 5-454)[2]
  - RRR ≥ 60 years = 34 (95%CI 4-295)[3]
- Limited data in endemic populations; RR and RRR not elevated (RRR ≥ 60 years = 2.6 [95%CI 0.6-8.5])[4]

1. Rafferty et al. Manuscript online; 2. Martin et al. Emer Infect Dis. 2001; 7: 945; 3. Khromava et al. Vaccine. 2005; 23: 3256; 4. de Menezes Martins et al. Procedia Vaccinol. 2010; 2: 178.

Is there evidence that *travelers* aged ≥ 60 years are at increased risk for serious AEFIs? GRADE: Quality assessment

		Rating	Adjustment to rating
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**

[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).

Is there evidence that *travelers* aged ≥ 60 years are at increased risk for serious AEFIs? GRADE: Summary and conclusions

- Confidence in estimate of effect on outcome is limited
- Age-related tendencies showing association between higher rates of serious AEFIs in travelers can be seen
- Evidence to support association between older age and YEL-AVD in travelers is limited
- Further research is needed to support hypothesis

Is there evidence that persons aged ≥ 60 years in *endemic areas* are at increased risk for serious AEFIs? GRADE: Quality Assessment

		Rating	Adjustment to rating
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**

[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).

Is there evidence that persons aged ≥ 60 years in *endemic areas* are at increased risk for serious AEFIs? GRADE: Summary and conclusions

- Confidence in estimate of effect on outcome is limited
- Age-related tendencies between YEL-AVD and older age in endemic settings can be seen
- Evidence to support association between older age and YEL-AVD in endemic populations is limited
- Further research is needed to support hypothesis

Potential mechanism of increased rates of serious AEFIs in persons aged ≥ 60 years

- Likely secondary to fact that travelers are immune naïve to YF virus or related viruses
  - Primary vaccine recipients develop transient viremia following vaccination; normally not seen with booster doses
- More frequent and higher viremia and slower antibody response seen in vaccinated naïve elderly compared to younger naïve persons[1]

1. Roukens et al. PLoS One. 2011; 6: e27753.

Summary of key findings on use of YF vaccine in persons aged ≥ 60 years

- Higher risk of serious AEFIs in persons aged ≥ 60 years compared to younger persons receiving vaccine for travel
- Insufficient data from endemic area to determine if risk is higher
- Risk may correlate to higher RNA replication and slower immune response in older persons

Recommendations on use of YF vaccine in persons aged ≥ 60 years

Based on currently available data, it is advisable to recommend caution in vaccinating persons aged ≥ 60 years if they have not been previously vaccinated.

Risk-benefit assessment for YF vaccination should be performed for any person aged ≥ 60 years who has not been vaccinated but for whom the vaccine is recommended.

Further research is needed to better quantitate risk for vaccine recipients aged ≥ 60 years who reside in or near YF endemic areas.

Use of YF vaccine in

HIV-infected persons

GAVCS review of use of YF vaccine in HIV-infected persons

- GAVCS discussed use of YF vaccine in persons with HIV-infection in December 2010[1]
- Reviewed data from recent mass vaccination campaigns in West Africa
  - Few HIV-positive persons identified among those with serious AEFIs in areas with HIV prevalence of 1-5%
  - No clear risk identified that precludes use of YF vaccine in HIV-infected persons
- No change to WHO recommendations; further data are needed

1. WHO. Wkly Epidemiol Rec. 2011. 86: 37.

Working Group review of YF vaccine use in HIV-infected persons

- Additional data from large preventive campaigns in Africa did not suggest safety concerns
- Recent data suggest immune response wanes more rapidly in HIV-infected persons[1]
  - 83% (68/78) of infected persons had YF antibodies at one year versus 97% (64/66) uninfected controls
- Mechanism of diminished response not clear but correlated to HIV RNA levels and CD4+ counts[2]

1. Veit et al. Clin Infect Dis. 2009; 48: 659; 2. Veit et al. HIV Ther. 2010; 4: 17.

Recommendations on use of YF vaccine in HIV-infected persons

- Maintain wording from 2003 position paper

  YF vaccine is contraindicated for severely immunocompromised persons, including persons with AIDS or CD4+ counts < 200 cells/mm^3.

  YF 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-infected persons.

Use of YF vaccine in

Persons with immunocompromising conditions (other than HIV)

Data on YF vaccine use in persons with immunocompromising conditions

- Data for YF vaccine exist only for case reports or case series
- YF vaccine is contraindicated based on historical experience with live vaccines
- Only condition associated with increased risk of serious AEFIs is thymus disease
  - 4 (17%) of initial 23 YEL-AVD cases were noted in persons who underwent thymectomies for thymomas[1]

1. Barwick. Lancet. 2004; 364: 936.

Consideration of immunocompromising conditions as related to YF vaccination

- Previous recommendations state vaccine should not be given in persons with immunocompromising conditions
  - No clear description of conditions to which this applies
- List of conditions considered immunocompromising by working group
  - Severe primary immunodeficiency (e.g., IgG or T cell)
  - Thymus disorder
  - Symptomatic HIV or CD4+ count < 200 cells/mm^3
  - Malignant neoplasm undergoing treatment
  - Recent (<2 years) hematopoietic stem cell transplant
  - Immunosuppressive or immunomodulatory drugs
  - Current or recent radiation therapy targeting immune cells

Recommendations on use of YF vaccine in persons with immunocompromising conditions

- Maintain wording from 2003 position paper but further clarify immunocompromising conditions

  Contraindications against YF vaccination include severe immunodeficiency.

  Conditions and treatments that would be considered severely immunocompromising include: certain primary immunodeficiencies, thymus disorder, symptomatic HIV-infection or CD4+ counts < 200 cells/mm^3, malignant neoplasms undergoing treatment, recent hematopoietic stem cell transplantation, drugs with known immunosuppressive or immunomodulatory properties, and current or recent radiation therapy targeting immune cells.

Use of YF vaccine in

Pregnant women

Data on YF vaccine use in pregnant women: Impact on pregnant women and fetus

- Since 2003, one study published on 433 women administered YF vaccine earlier in pregnancy[1]
- No increase rate of fetal death observed
  - 7.4 per 100,000 in vaccinated women vs 18.5 per 100,000 in unvaccinated women
  - Previous study found potential increase risk (relative risk 2.3 [95%CI 0.7-8.0])[2]
- 98% of women generated YF IgG antibodies
  - Previous study that found 39% of pregnant women (n = 101) given vaccine in third trimester seroconverted[3]

1. Suzano et al. Vaccine. 2006; 24: 1421; 2. Nishioka et al. Trop Med Int Health 1998; 3: 29; 3. Nasidi et al. Tran Roy Soc Trop Med Hyg. 1993l 87: 337.

Data on YF vaccine use in pregnant women: Impact on infants

- Since 2003, one study published in 304 infants born to women vaccinated early in pregnancy[1]
- No risk of major malformation
- Increased risk of minor skin malformations (e.g., pigmented nevi)
  - Observation impacted by assessment bias

1. Cavalcanti et al. Trop Med Int Health. 2007; 12: 833.

Recommendations on use of YF vaccine in pregnant women

- Maintain wording from 2003 position paper

  On theoretical grounds, YF vaccine is not recommended during pregnancy.

  However pregnant women may be vaccinated during epidemics when risk of YF virus transmission may be very high.

Use of YF vaccine in

Lactating women

Data on use of YF vaccine in lactating women and their infants

- Three cases of encephalitis identified in infants whose mothers received YF vaccine[1,2,3]
  - All mothers were YF vaccine naïve
  - All infants less than 6 weeks when mother vaccinated (10 days, 23 days, and 5 weeks old)
  - All infants exclusively breastfed and not vaccinated
- YF IgM antibodies with confirmatory neutralizing antibodies recovered in CSF for all infants
- One infant with YF vaccine viral RNA in CSF

1. CDC. MMWR. 2010; 59: 130.; 2. Kuhn et al. CMAJ. 2011; 183: E243; 3. Traiber et al. J Pediatr (Rio J). 2011; 87: 269.

GAVCS review of use of YF vaccine in lactating women and their infants

- Details of three cases reviewed by GAVCS in June 2010
- Concluded for lactating women in endemic areas
  - Benefits of vaccination outweigh risk of disease
  - Benefits of breastfeeding far outweigh alternatives
- Concluded for lactating women in non-endemic areas (i.e., travelers)
  - Counsel regarding benefits and risk of vaccination
  - Given vaccine if travel cannot be avoided

Recommendations on use of YF vaccine in lactating women

- Use GAVCS language

  In areas where YF is endemic, or during outbreaks, the benefits of vaccinating mothers are likely to far outweigh the risk of potential transmission of vaccine virus to infants.

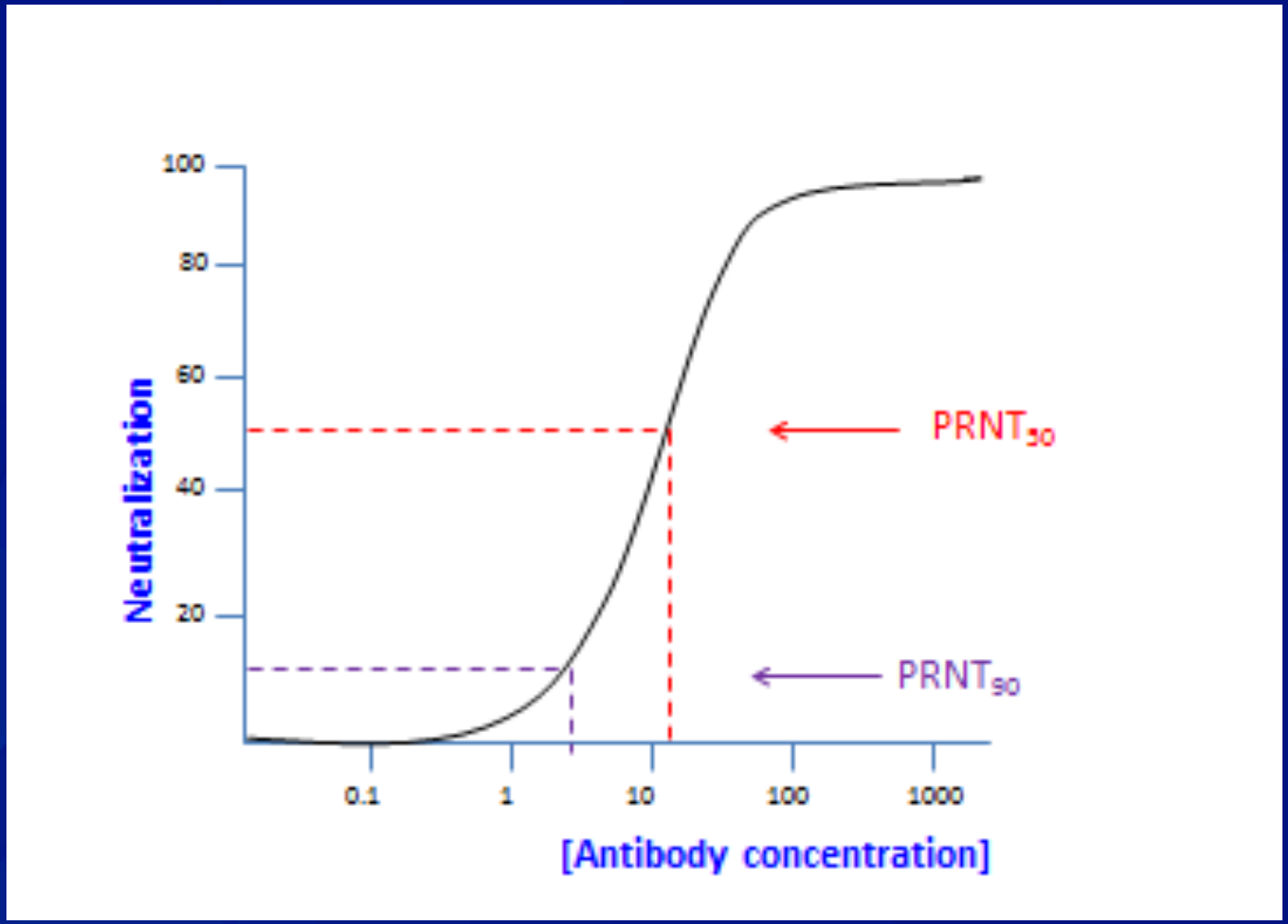
  Nursing mother who are considering travel to endemic areas should be counseled regarding the benefits and potential risks of vaccination.

  Vaccination is recommended if vaccination is indicated for a breastfeeding women and travel cannot be avoided or postponed.

Discussion

"*It is perhaps not too much to hope that it will eventually be found that the immunity following yellow fever vaccination is life-long*."
Stated by A.F. Mahaffy at the African Seminar on Yellow Fever held in Kampala, Uganda in 1953 (in Yellow Fever Vaccine Monograph, WHO, Geneva 1956)

Neutralization versus antibody concentration



Slide from Alan Barrett, UTMB, Galveston, TX, USA

Yellow fever vaccine response in children - 1

Year	# of subjects Other vaccines	Age Location	Testing and time points	Findings
2011	906 MMR	12-23mo Brazil	$PRNT_{50}$; 30 days post vaccination	82.8% seroconverted (95%CI 80.2-85.2)
2008	22 <16 yo 78 ≥ 16 yo* None	All Colombia	$PRNT_{75}$; 3-24 months post vaccination	91% children with titer ≥ 10 vs 90% adults
2005	981 (652 Arilvax; 329 YF-VAX) None	9mo-10yo Peru	$PRNT_{50}$; 31 days post vaccination	94% seroconversion (95% Arilvax; 91% YF-VAX)
1999	294 Measles	9mo Brazil	PRNT; one month	67.9-84.6% seroconversion
1996	1177 Measles	6-12mo Nigeria	ELISA; one month	87-97% seroconversion
1990	319 Measles	6-10mo Cameroon	$PRNT_{80}$; one month	93-94% seroconversion

* Of those with proof of vaccination (lower in persons lacking proof of vaccination 69% in children <15 years)

Yellow fever vaccine response in children - 2

Year	# of subjects Other vaccines	Age Location	Testing and time points	Findings
1989	410 Measles	6-9mo; Ivory Coast	HI/PRNT; one month	88-92% seroconversion
1988	453 Measles	6-24mo Mali	PRNT; one month	93-96% seroconversion
1986	226 HepB, DPT, measles	9-36mo Senegal	$PRNT_{90}$; one month	92-94% seroconversion
1986	176 HepB	9-36mo Senegal	$PRNT_{90}$; one month	95-96% seroconversion
1973	334 DPT, Smallpox, Measles	6-24mo Nigeria	$PRNT_{90}$; three months	95-96% seroconversion
1973	600 BCG, smallpox, measles, tetanus	1-5yo Cameroon	HI; 60 days post vaccination	84-86% seroconversion

Yellow fever vaccine response in children - 3

Year	# of subjects Other vaccines	Age Location	Testing and time points	Findings
1962	545 Measles, smallpox	4-54mo Burkina Faso	Mouse protection; one month	85-97% seroconversion
1952	57 <16 years 145 ≥ 16 years None	All Uganda	Mouse protection assays; 9 years post vaccination	63% children vs 83% adults; Variable by location
1949	126 <15 years 224 ≥15 years None	All Uganda	Mouse protection; 6 years post vaccination	81% children vs 88% adults
1945	150 <15 years 150 ≥15 years None	All Uganda	Mouse protection; 3 years post vaccination	94% children versus 93% adults