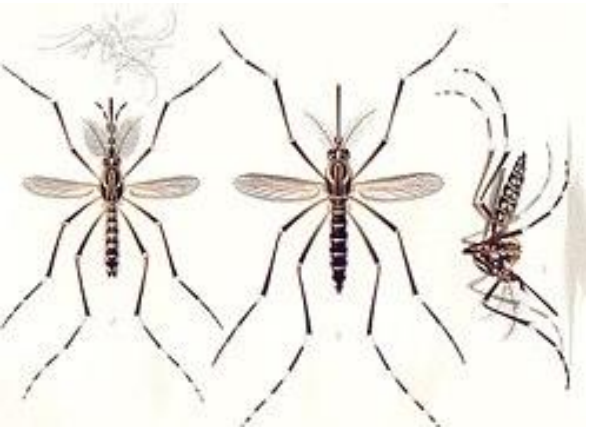
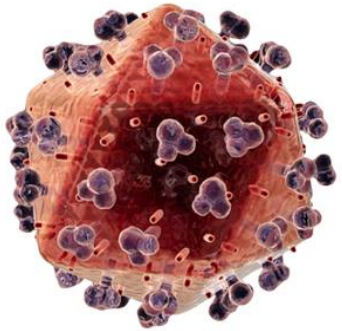
CHU Saint-Pierre
UMC Sint-Pieter

INFECTIOUS DISEASES
DEPARTMENT
AIDS REFERENCE CENTRE

ULB UNIVERSITÉ LIBRE DE BRUXELLES

Yellow fever vaccination in HIV patients



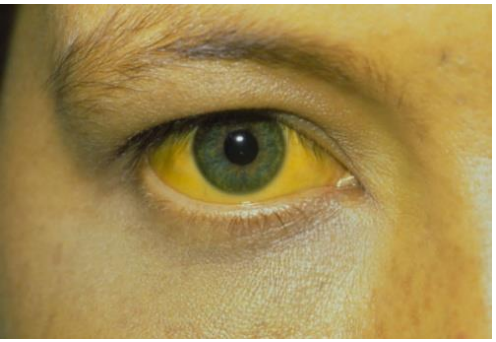


Dr Ch. MARTIN

Travel & Vaccine Clinic

CHU Saint-Pierre, Brussels

Yellow Fever



- Incubation: 3-6 days
- Symptoms: asymptomatic, flu symptoms, mild → icteric haemorragic fever
- Mortality: CRF 20-60% of severe cases
- 200 000 severe cases/y, 30 000 deaths/y
- Endemic in 44 countries (900 x 10^6)
- 90% in Africa
- Transmission by *Aedes*/*Haemagogus* spp (day biting mosquitoes)
- No treatment

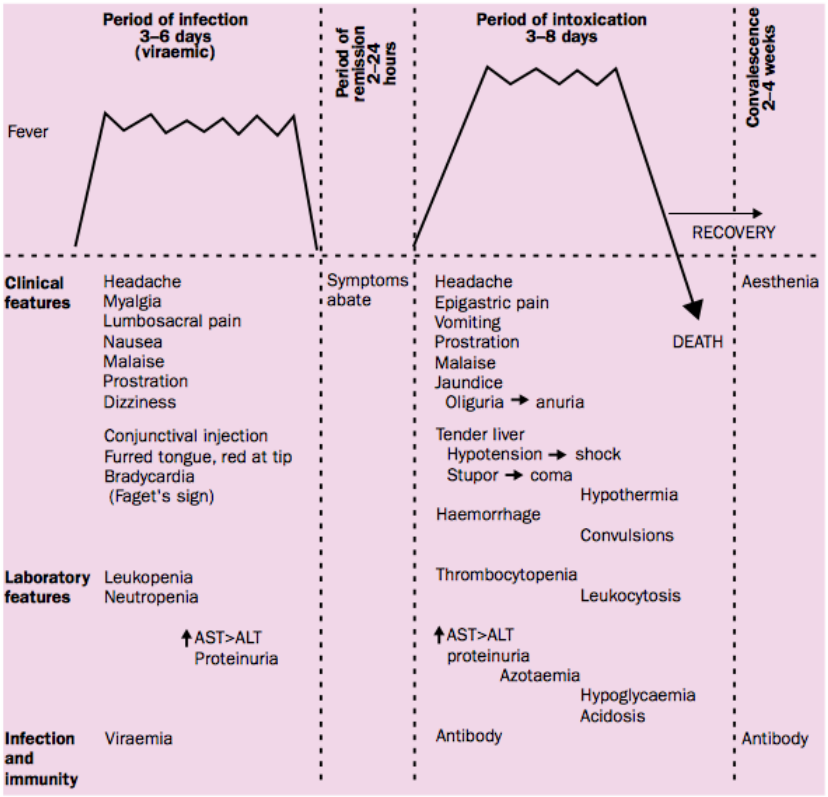
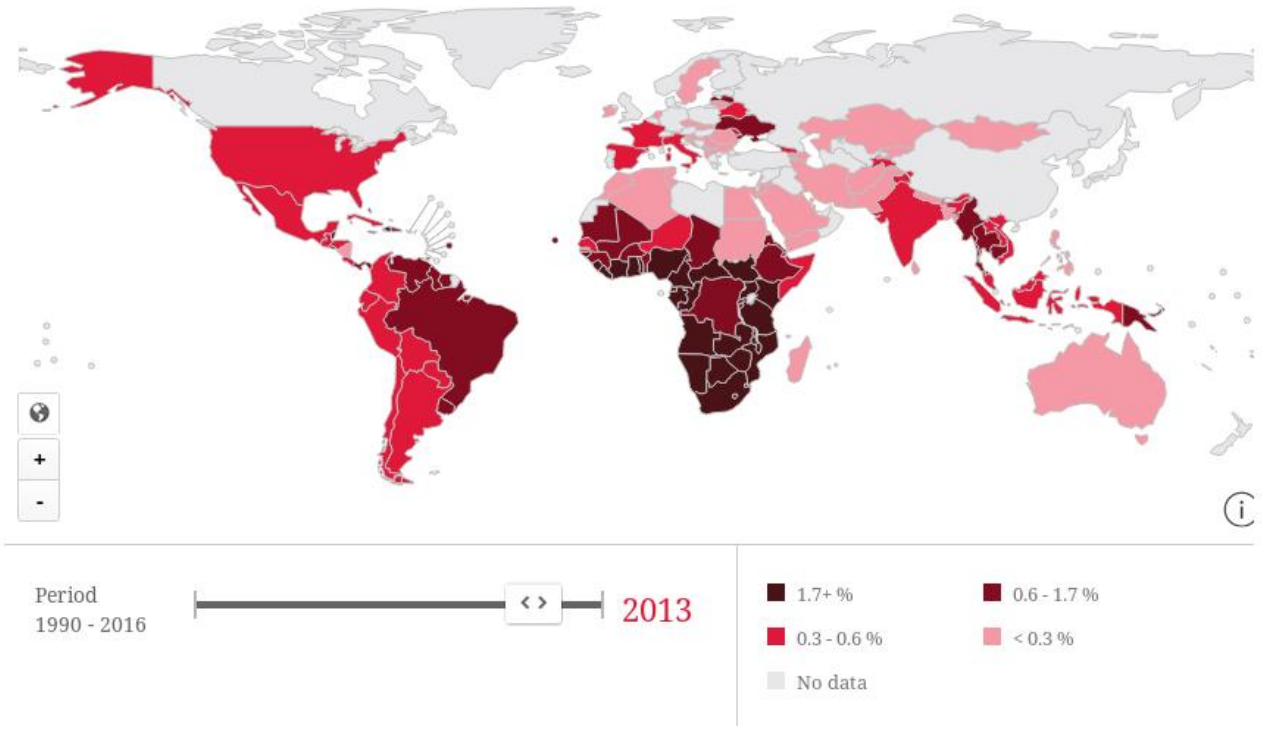


Figure 4. Stages of yellow fever infection, showing the major clinical and laboratory features of the disease.

HIV: epidemiology



- 35 millions people infected worldwide
  - 25 millions infected patients in SSA
- 1.5 million infected patients in Latin America

(UNAIDS, 2013)

Yellow Fever: a zoonose

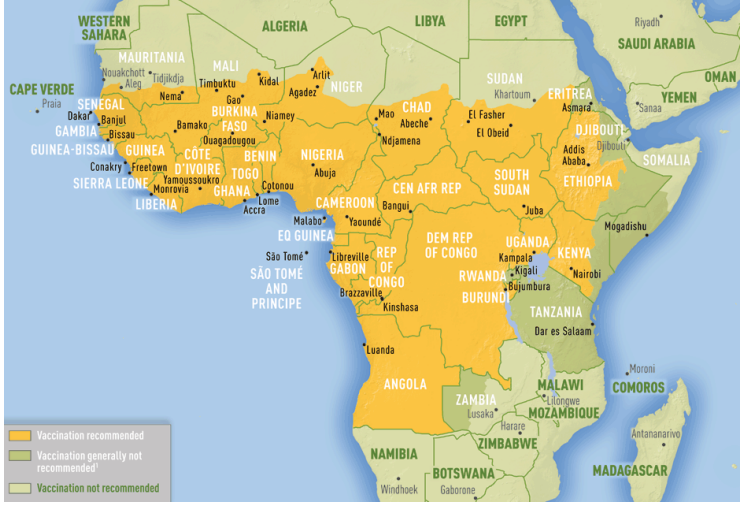
- Reservoir: human and non-human primates

- **Sylvatic** (jungle): mosquitoes of forest canopy
  →non human primates, accidentally → humans (occupational, recreational)

Spillover in population ~~Herd immunity~~

- **Intermediate**: wild and peridomestic *Aedes* → monkeys, human
- **Urban**: viremic human → *Aedes aegyptii* → human

Outbreaks Herd immunity



High HIV prevalence
Frequent natural boost

Africa

- Sylvatic, intermediate and urban
- Immunity accumulates with age → mostly infants and children
- 90% infections
- Herd immunity

Immunized once in a lifetime
Rare natural boost

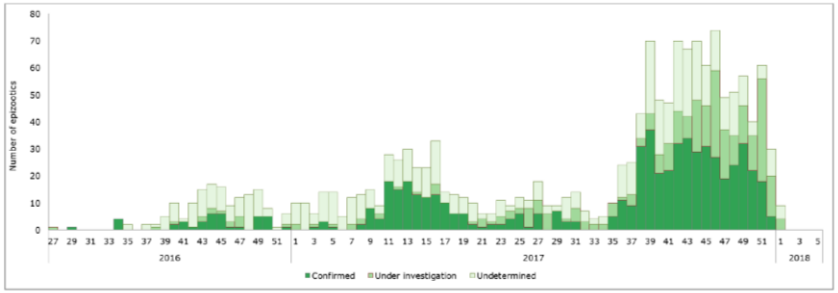
America

- Sylvatic mostly
- Mostly young adults (occupational)
- 10x less risk
- ~~Herd immunity~~

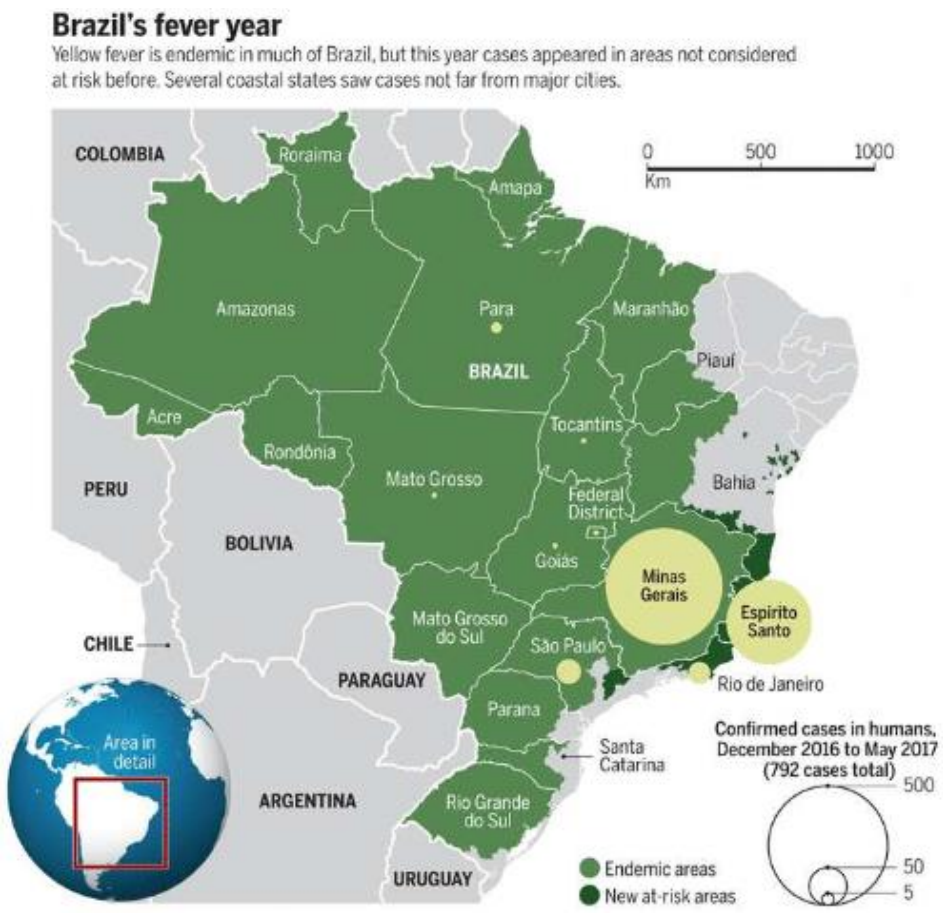
Monitoramento do Período Sazonal da Febre Amarela
Brasil – 2017/2018

MONITORAMENTO DA SITUAÇÃO EPIDEMIOLÓGICA DA FEBRE AMARELA NO BRASIL	
Período de monitoramento: 01/07/2017 a 30/06/2018	**Atualização:** 08/01/2018
Epizootias em PNH notificadas: 2.296 **358 confirmadas** 687 em investigação 790 indeterminadas 461 descartadas	**Casos humanos notificados: 381** **11 confirmados (4 óbitos)** 92 em investigação 278 descartados
Anexo: Glossário	

Figure 2. Distribution of reported epizootics per EW according to classification. São Paulo state, EW 27 of 2016 to EW 1 of 2018.



Source: Data published by the São Paulo State Health Secretary and reproduced by PAHO/WHO



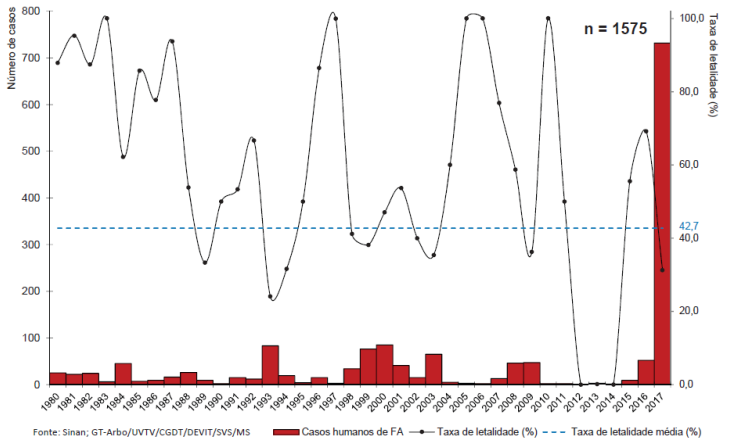


FIGURA 1 • Série histórica do número de casos humanos confirmados para FA e a letalidade, segundo o ano de início dos sintomas, Brasil, 1980 a junho de 2017.

Nigeria

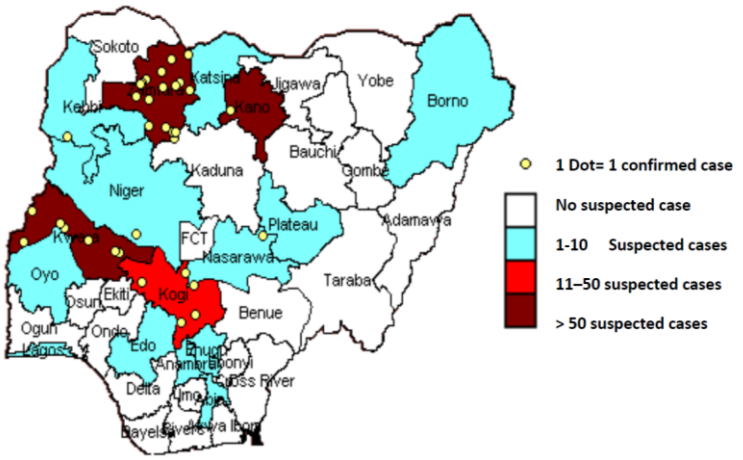


Figure 2: Map of Nigeria showing states with suspected/confirmed cases of yellow fever, as at 2nd January, 2018

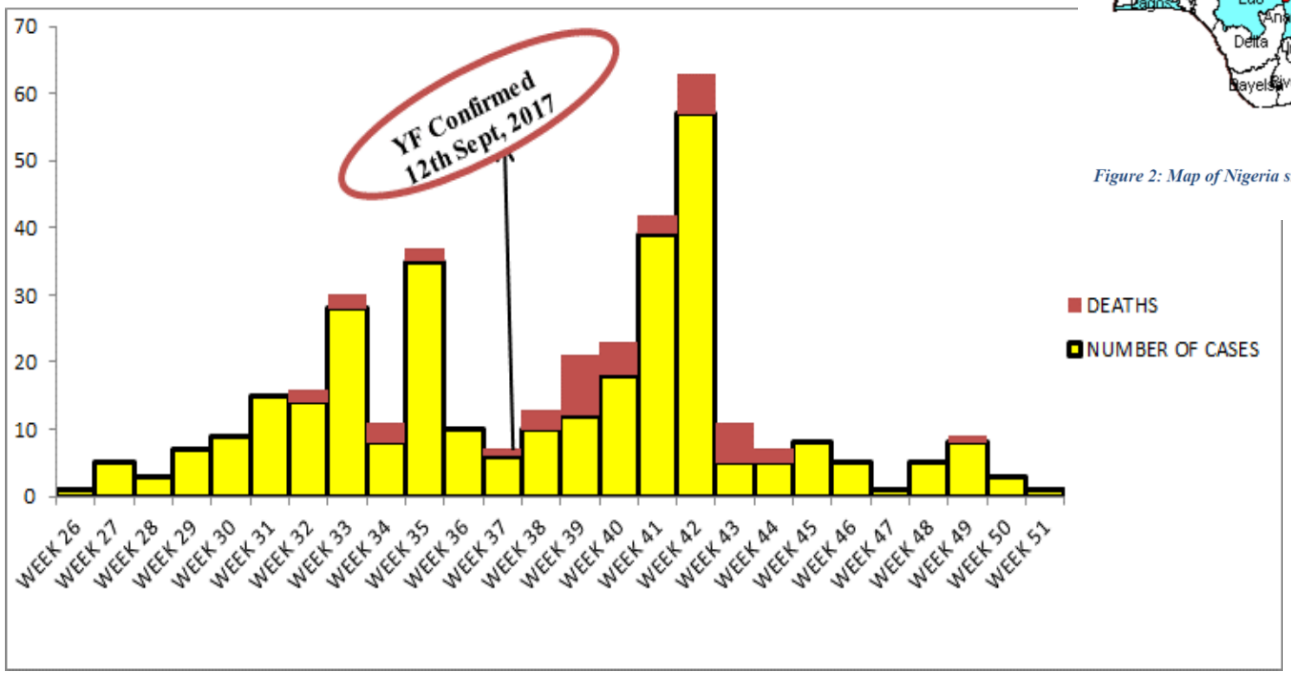
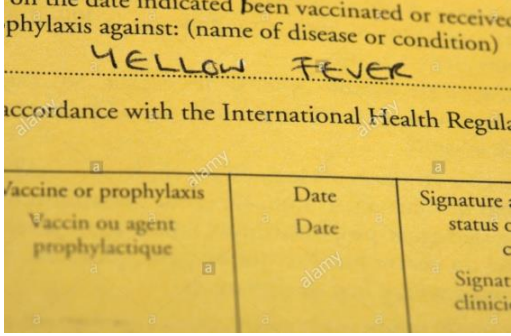


Figure 1: Epidemic curve of suspected / confirmed cases of yellow fever in Nigeria as at 2nd January, 2018

YF vaccine



- 1936- live attenuated vaccine with 17D strain
- >600 million doses worldwide
- 80% protective levels of neutralizing Ab after 10 days, >99% by day 28
- Neutralizing ab (NT) ~ proxy for protective immunity/ cut-offs?
- « Data on the long-term immunity induced by YFV, which should guide vaccination policy, are still scarce » (Collaborative group on YFV, *Vaccine* 2014)


O updates
عربي 中文 English Français Русский Español
World Health Organization
Health topics Data Media centre Publications Countries Governance About WHO
Search
International travel and health
International travel and health
Disease information
Vaccines
Other travel health risks
General precautions
Mode of travel considerations
World – Yellow fever vaccination booster
5 June 2014 - Currently, the IHR stipulate that vaccination with an approved yellow fever vaccine provides protection against infection for 10 years, and that the certificate of vaccination or re-vaccination is accordingly valid for 10 years. Requiring the certificate from travellers is at the discretion of each State Party, and it is not currently required by all countries (see country list, 2014 update: http://www.who.int/ith/ITH_country_list.pdf)
The WHO World Health Assembly in May 2014 adopted an amendment to Annex 7 of the International Health Regulations (2005) (IHR), which stipulates that the period of protection afforded by yellow fever vaccination, and the term of validity of the certificate will change from 10 years to the duration of the life of the person vaccinated.
This change will enter into force legally in June 2016. Until then the current IHR text on yellow fever vaccination and certificates continues to apply, and some countries may continue to request proof of vaccination or a booster within the last 10 years from travellers.
Starting with the online 2015 ITH edition, WHO will report on the status of yellow fever vaccination requirements for countries.
Share
Print
Adopted by World Health Assembly (WHA) in May 2014

Duration of post-vaccination immunity against yellow fever in adults

Collaborative group for studies on yellow fever vaccines[1]

Vaccine 32 (2014) 4977–4984

- HIV(-), non-endemic zone in Brazil, primovaccination only, excluded baseline + sero, cross-sectionnal design, real life, $PRNT_{50}$
- 691 pts

Time from vaccine	Seropositivity rate % (range)	GMT (mUI/ml) (range)
30-45 days	93 (88-96)	8,8 (7,0-10,9)
1-4 y	94 (88-97)	3 (2,5-3,6)
5-9 y	83 (74-90)	2,2 (1,7-2,8)
10-11 y	76 (68-83)	1,7 (1,4-2,0)
≥ 12 y	85 (80-90)	2,1 (1,7-2,5)

- GMT slowly decreasing with time ***mostly and sharply*** at 1-4 years post-YFV, as already described in other studies

What is difficult in studies about YFV

- Differences in YF vaccines
- Differences in vaccinees: age, health conditions
- Cross-sectionnal (no RCT), **small samples**
- **Baseline seroprevalence**
- **Number of YFV received**
- Potential natural boosting by wild virus/ other flavivirus and how often?
- Vaccination procedures: conservation, administration, clinical trials or **real life**
- Laboratory methods in for Ab, positivity cut-offs
- PRNT: heterogeneous, sometimes not so reproductible
- Role of cellular immunity: conflicting data
- Immune activation in African patients
- What is acceptable as vaccine failure? Depending on kind of travel/country where pt live/…
- Need for herd immunity or not, recommendations for travelers versus resident
- …

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 [11]					with protective antibody titers; 5 years mean LNI† 3.9, range -4.4; 16-19 years mean LNI 4.2, ge 2.6-5.0
Poland - 1981 [12]	116	Traveler population; Adult U.S. military	30-35 years	$PRNT_{90}$	116 (78%) with detectable PRNT iter (≥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

NO CLEAR CUT-OFF FOR DEFINITION OF PROTECTION

Source: Background paper on YF vaccine/ WHO 2013

Role of cellular immunity

- Role of CD4+ as “helper” (→ Ab): peak 7-14d
- CD8+: expansion 14-30d *correlated to YF viral load* → memory cells (25y)
- Unclear if cellular response would work in challenge with wild YF in humans / conflicting (and few human) data

Watson and Klimstra « T-cell mediated immunity towards YF virus » *Viruses* 2017
Amanna and Slifka «Questions regarding the safety and duration of immunity following live yellow fever vaccination » *Expert Rev Vaccines* 2016

Why are we worried for HIV-infected patients?

- Accelerated decay in Ab : 17-23% within 10 y (secondary failures) in a meta-analysis based on 3 retrospective studies
- Uncontrolled HIV viral load is deleterious for immune response to the following vaccines: YF, HAV, HBV, JE, Flu, Pneumo, VZV
- Low/ dysfunctionnal CD4
- Data on Immune activation

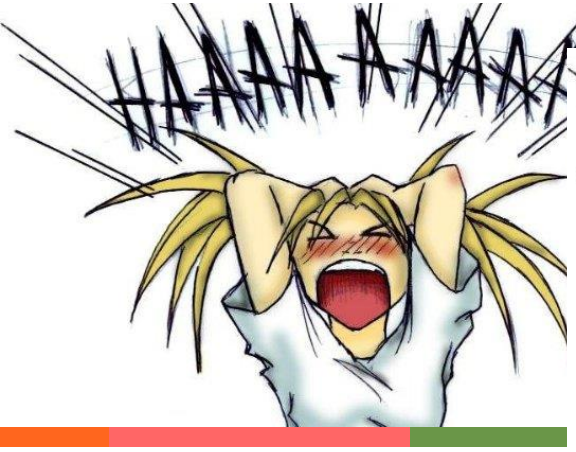
Pacanowski et al. *JAIDS* 2012
Kerneis et al. *Clin Infect Dis* 2014 A meta-analyse of long-term immune response in HIV patients
Muyanja et al. *J Clin Invest* 2014

Pending questions in HIV-infected patients

- Is worse immune response to vaccination in HIV patients only leading to *primary failure* (Ab quality, AB titers, seroconversion rate) or *secondary failure* (duration of protection) or both?
- Are « current patients » similar to HIV (-) patients?
- Would a/several booster(s) be effective?
- When would a booster be necessary?

Specificities of HIV studies

- YF vaccine before/after HIV infection
- CD4/HIV VL/ ART at time of vaccination, at NT determination
- Pre-HAART era/ beginning of HAART era/early (full) HAART era
- Parameters of Immune activation



- Only 3 cohort studies including one in children in pre-HAART era (no RCT)
- Only observationnal (high risk for bias)
- Total= 484 patients
- Quality of evidence: low to very low for all outcomes

- Pacanowski et al. *JAIDS* 2012

- Prospective 364 pts
- 124 pts immunized before/ 240 immunized **after HIV diagn**
- 98% protected within a year/ 92% after 10 years
- Before HIV: x1.12 vaccine failure /year delay
- After HIV: OR 3.73 / log10 **VL** for vaccine failure in primovaccinated
- Trend to **GMT decreasing** with time associated with **detectable/higher VL, duration of indetectability**

- Veit et al. *CID* 2009:

- Retrospective 102 pts
- Compared to 209 HIV (-)
- **Seroconversion**: 17% non protected versus 3% p=0.01 (19% if primovaccinated)
- Higher NT associated to high **CD4**, low **VL**, females
- Decay pattern within 10 y: similar HIV (-) with **most Ab loss within 5 y**

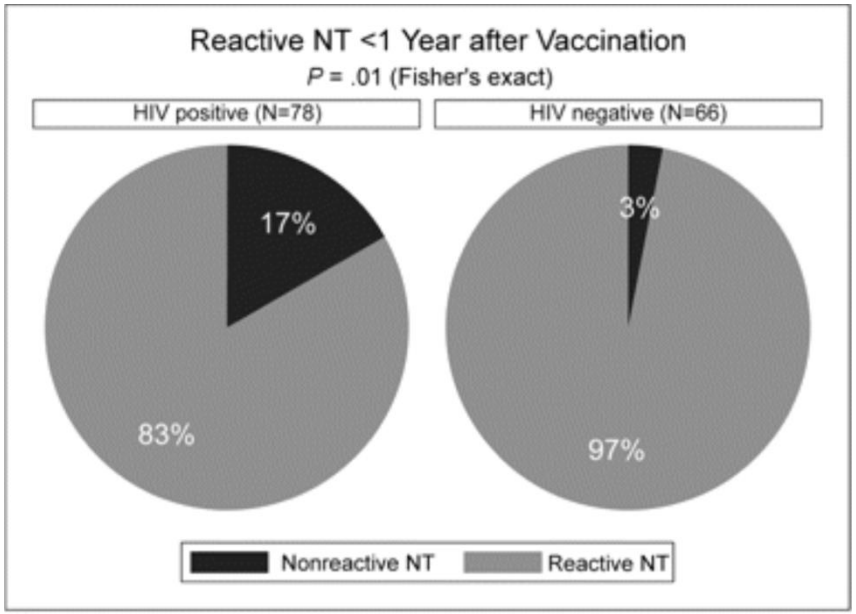
Veit et al. *Clin Infect Dis* 2009

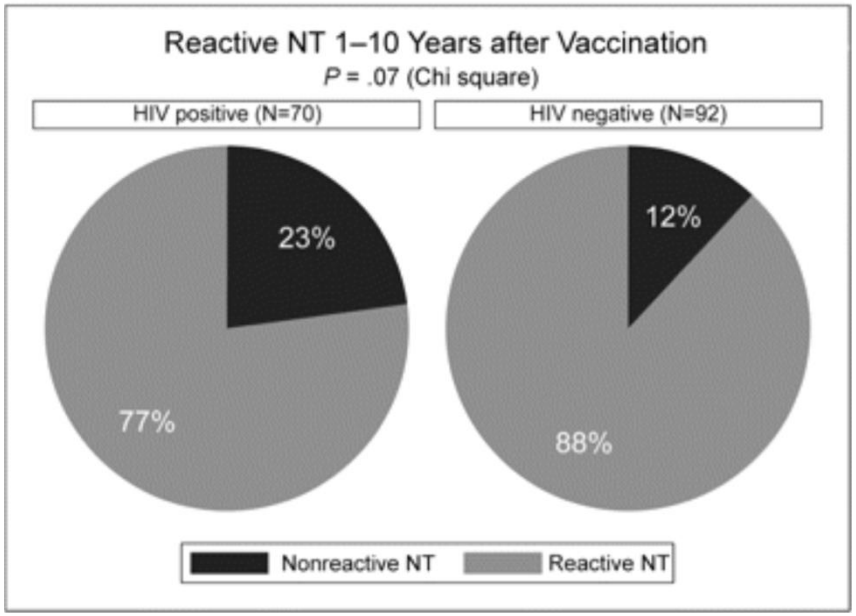
- Swiss HIV Cohort, retrospective study
- 102 pts HIV+ who received YFV when already HIV
- 40% <SSA, 17% ≥2 YFV, 7% AIDS
- Comparison to historical HIV (-) pts

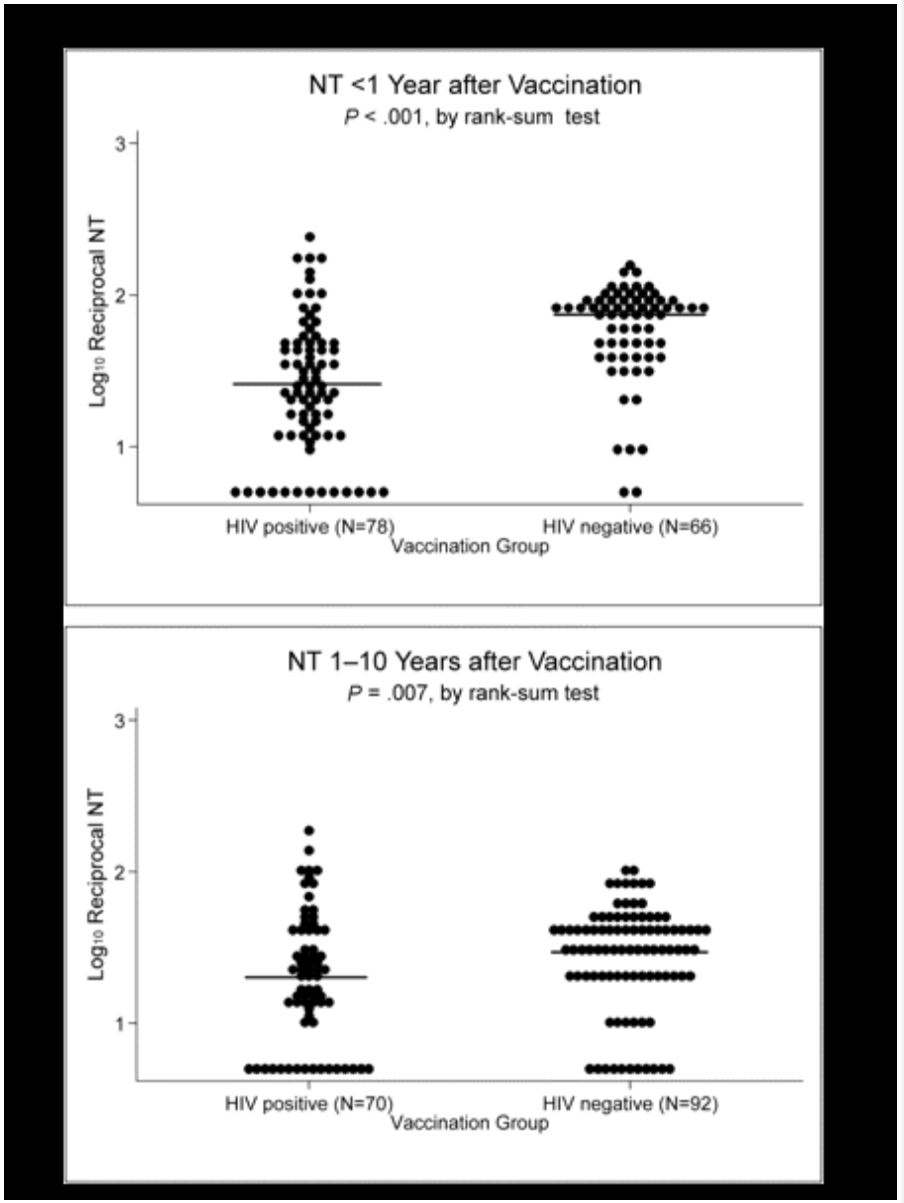
→ seroconversion 83% versus 97%

→ less NT Ab than HIV(-) RF CV<20, CD4↑

→ 11 seroconverters lost Ab within 5 y







From: Immunogenicity and Safety of Yellow Fever Vaccination for 102 HIV-Infected Patients

Clin Infect Dis. 2009;48(5):659-666. doi:10.1086/597006

- 34 pts HIV(+) ART-treated (at inclusion) vs 58 pts HIV (-)
- Only primovaccination
- 88% received YFV after HIV diagnosis

- GMT lower in HIV pts (ajusted to sex/age/delay) p=0.024
- Associated with **delay since YFV↑ and CD4/CD8 ratio** after ajustment

Avelino-Silva et al. *JAIDS* 2016

Veit et al. *Clin Infect Dis* 2017

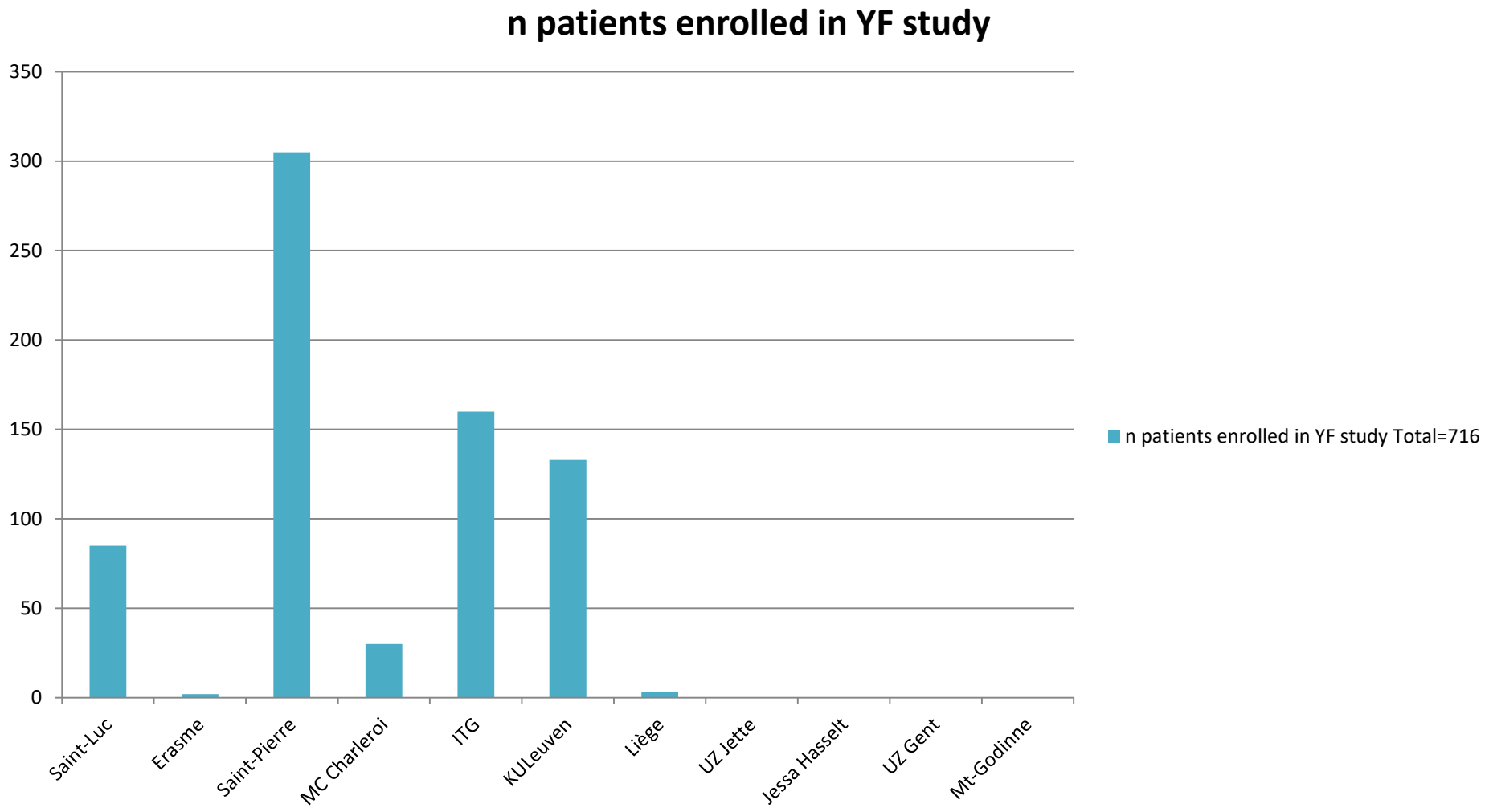
- 247 pts < Swiss HIV Cohort
- Primovaccination after HIV diagnosis

- 83% with VL<400 cop/ml
- med CD4=536/mm^3

Overall	
- baseline sero+	46% (!)
- 1 year	95%
- 5 years	86%
- 10 years	75%

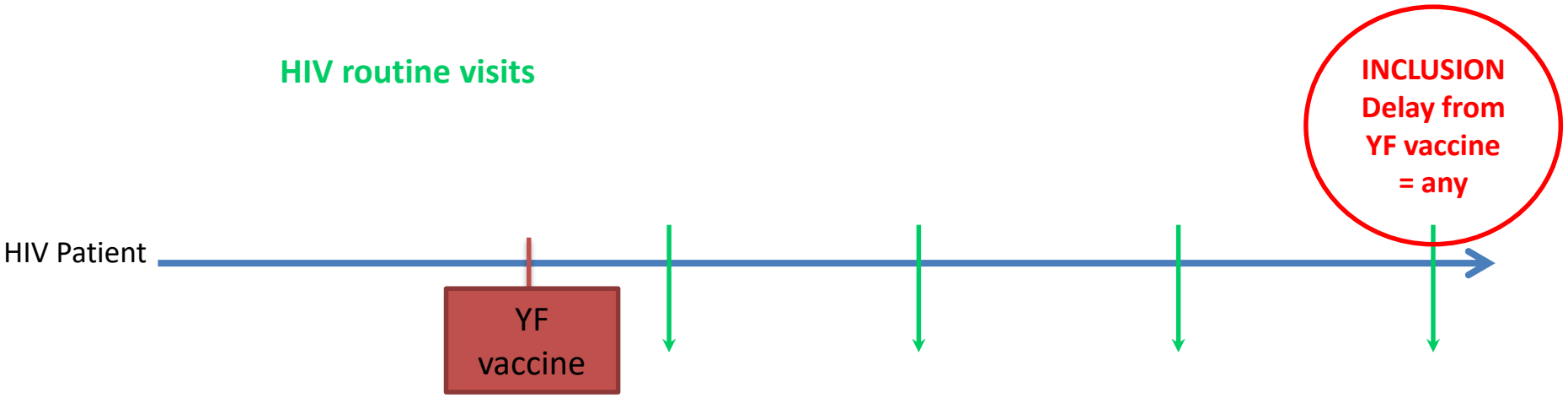
VL<400 cop/ml	
- baseline sero+	46% (!)
- 1 year	99%
- 5 years	99%
- 10 years	100%

As of 22/01/2018: Total 716 patients



STUDY DESIGN

Any timepoint after vaccination was accepted for inclusion



Retrospective plasma in the year before YFV (baseline seroprevalence)

Retrospective plasma within 1 year of YFV (YF seroconversion)

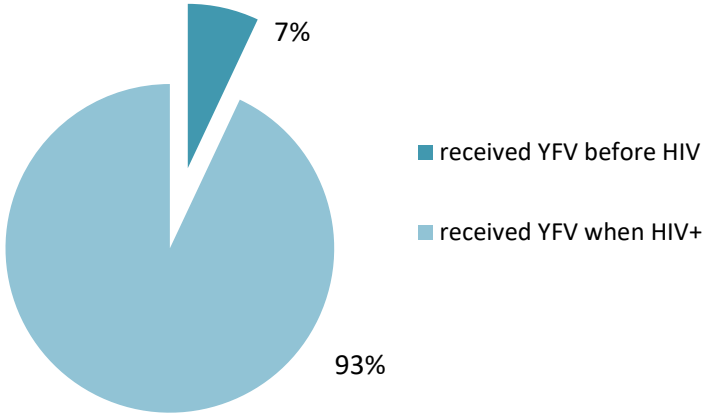
Timepoint 0

Timepoint 1

Timepoint 2

First results of YF study: preliminary!

- N= **230 patients**
- Age: med 43 y F 56%
- HIV mode acq: Ht 75% MSM 19%



- From SSA 75%

>10 y in YF endemic countries: 84% pts/ travel 1 mo (med 3x)

Immunovirological parameters

- At time of vaccination

  - med CD4 564/mm³
  - med HIV VL<20
  - nadir CD4 230/mm³

- But… nadir CD4<200: 41%

  AIDS event in 20% (mostly before YFV)

- At NT determination

  -med CD4 650
  -med HIV VL <20

- Med time between YFV and Ab determination « delay » : 63 mo (3-455)
- Med time with ART during delay: 100%

Results and analysis

- **Risk factors for non-protection:**
  - **YFV before or *after* HIV diagnosis** — **p= 0.0283**
  - **Age/ Sex/ ethnicity/ HIV acquisition mode** — **p=NS**
  - **Med CD4 at time of vaccination** — **p=0.0386**
  - **Cat CD4 at time of vaccination>500 versus <500/mm³** — **p=NS**
  - **Med CV at time of vaccination** — **p=0.0008**
  - **Cat CV at time of vaccination <50 versus >50/ml** — **p=0.02**
  - **Nadir CD4** — **p= NS**
  - **Immunovirological parameters at NT determination** — **p=NS**
  - **Time under ART during delay YFV-NT determination** — ***p<0.0001***

Missing…

- Very partial results
- Baseline seroprevalence (before YFV)
- Early seroprevalence (in the first year after YFV)
- Estimation of YFV number in each patient
- …

- Be careful in primovaccination: at least two vaccines will be needed (measles-like?)
- Delay before booster? Probably ≤ 5 years (1 year like pregnant women, children<2 and other LAV?)
- HIV VL controlled for vaccination/ max ART duration → early and universal ART
- Role of immune activation?
- « current » HIV patients ≠ patients HIV (-)?
- After 2 vaccines: ? Data needed

Take Home Messages