Yellow Fever: where are we up to now?

Travel Medicine Seminar: 20 years later

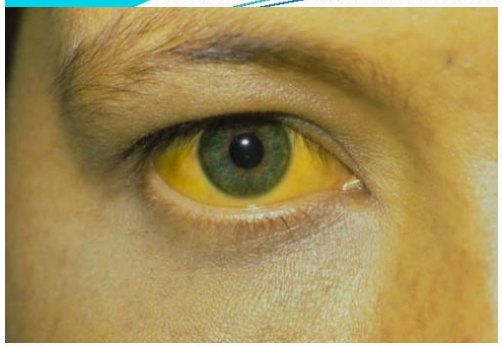
19 nov 2015

Dr Ch. Martin

Infectious Diseases

CHU Saint-Pierre, Brussels

Yellow Fever



- Incubation: 3-6 days
- Symptoms: asymptomatic, flu symptoms, mild → icteric haemorragic fever
- Mortality: 20-60%
- 170 000 severe cases/y, 30 000 deaths/y
- Endemic in 44 countries
- 90% in Africa
- Transmission by *Aedes*/*Haemagogus* spp (day biting mosquitoes)

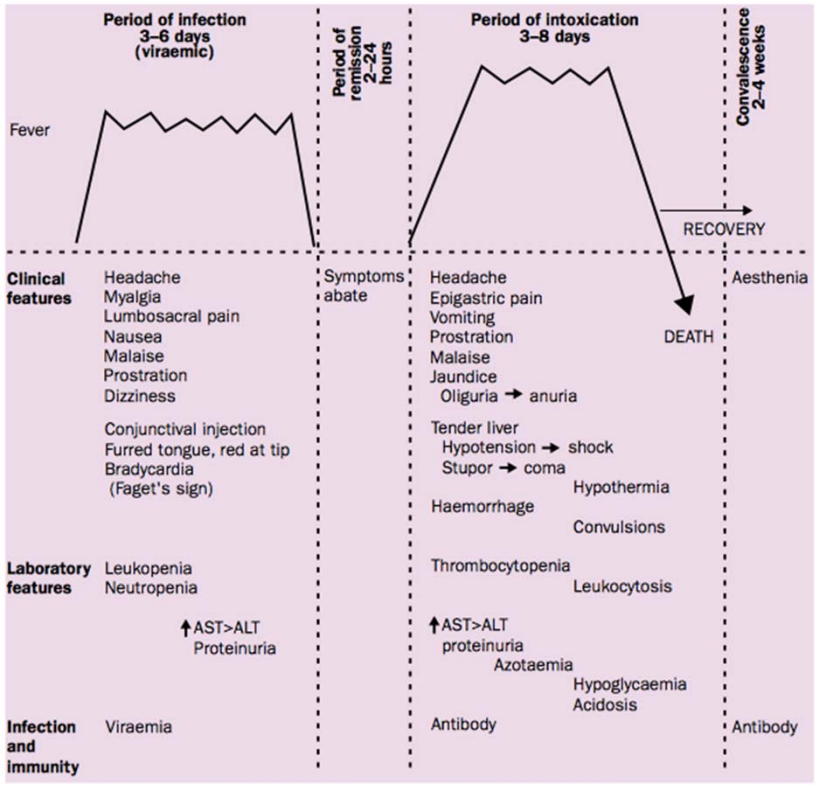
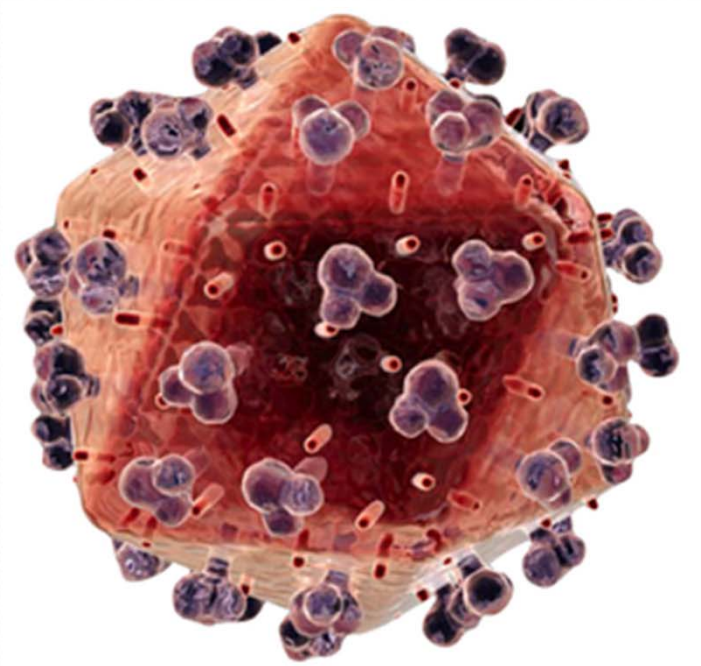
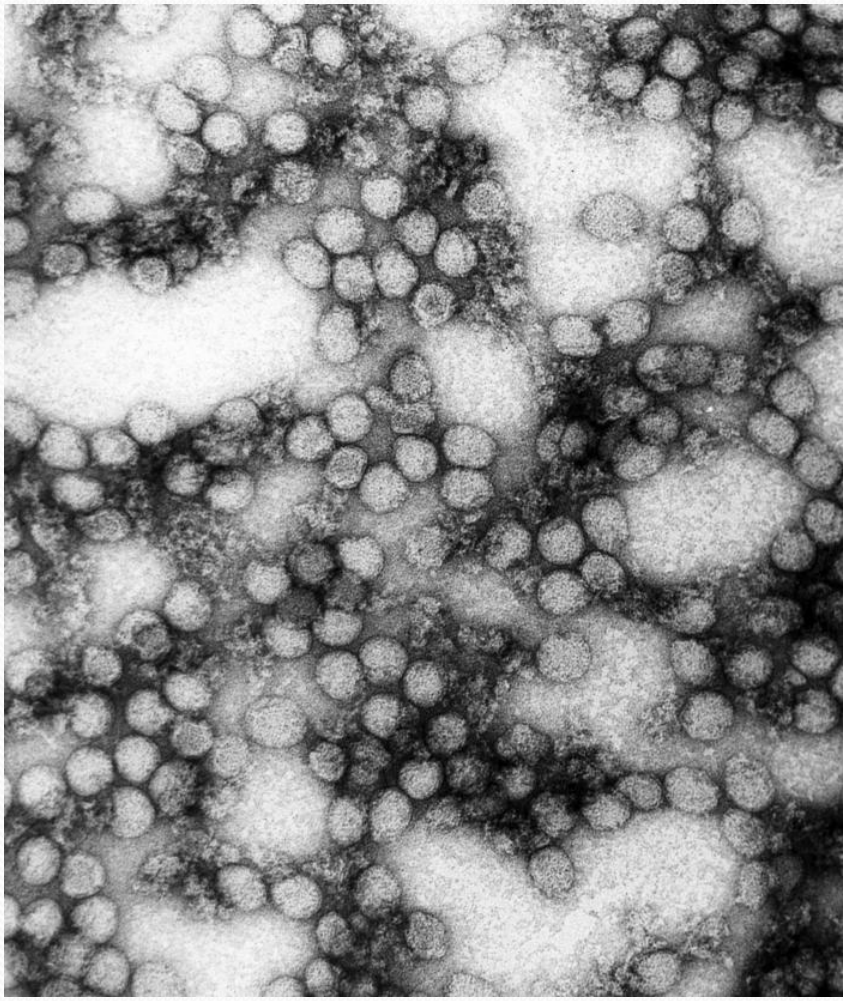


Figure 4. Stages of yellow fever infection, showing the major clinical and laboratory features of the disease.

Yellow fever virus

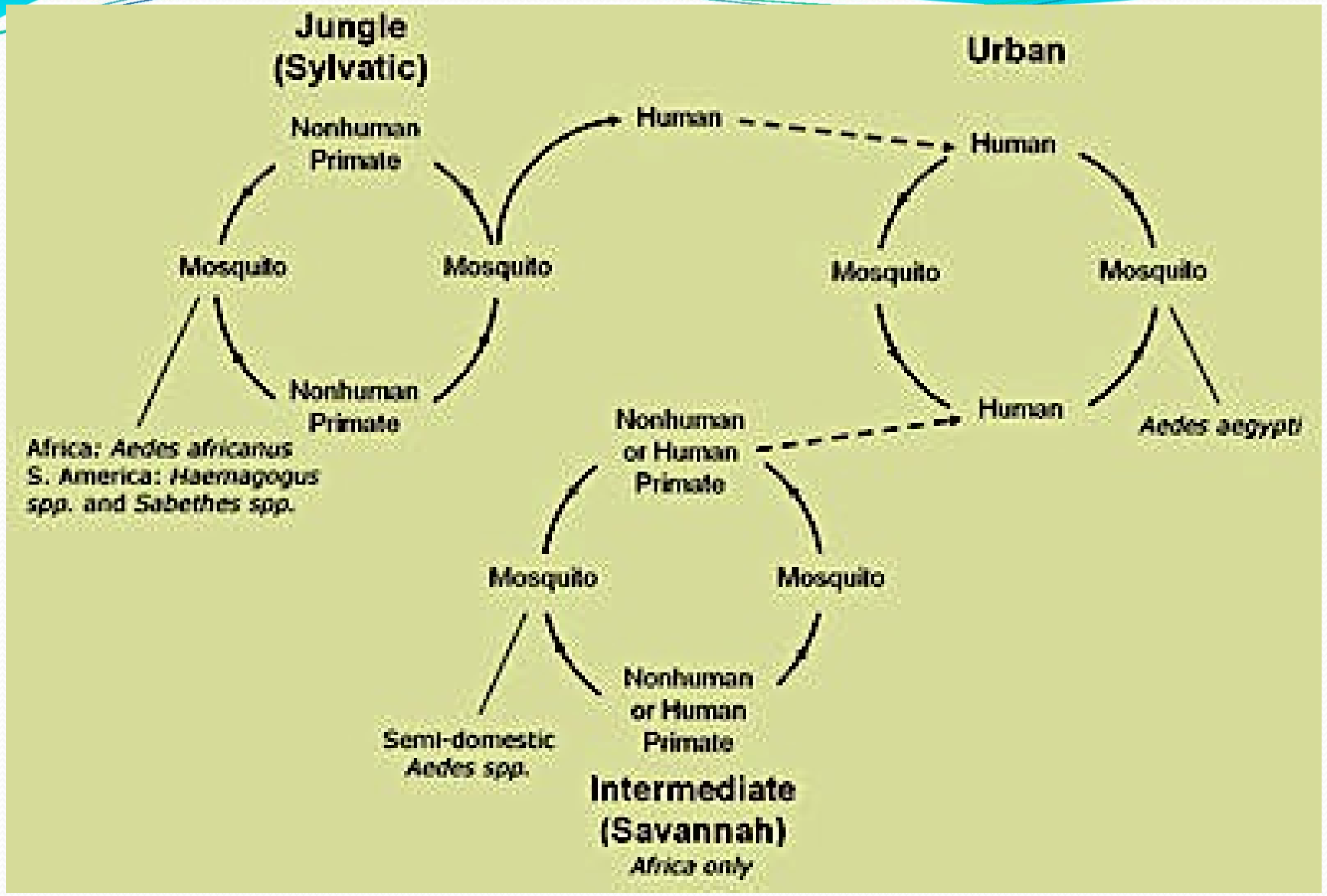




Single stranded RNA
Gender *Flavivirus,* enveloped
7 genotypes

Yellow Fever: a zoonose

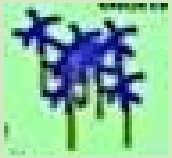
- Reservoir: human and non human primates
- **Sylvatic** (jungle): mosquitoes of forest canopy →non human primates, accidentally → humans (occupational, recreational)
  ~~Herd immunity~~
- **Intermediate**: wild and peridomestic *Aedes* → monkeys, human Africa only
- **Urban**: viremic human → *Aedes aegyptii* → human
  Outbreaks Herd immunity


Jungle
(Sylvatic)
Urban
Nonhuman
Primate
Human
Human
Mosquito
Mosquito
Mosquito
Mosquito
Nonhuman
Primate
Human
Nonhuman
or Human
Primate
Africa: Aedes africanus
S. America: Haemagogus
spp. and Sabethes spp.
Aedes aegypti
Mosquito
Mosquito
Nonhuman
or Human
Primate
Semi-domestic
Aedes spp.
Intermediate
(Savannah)
Africa only

YF transmission patterns

Sylvatic YF

Monkeys



Jungle mosquitoes

Intermediate YF

Human in transition (emergence) zone

Humans in City

Aedes aegypti

Urban YF

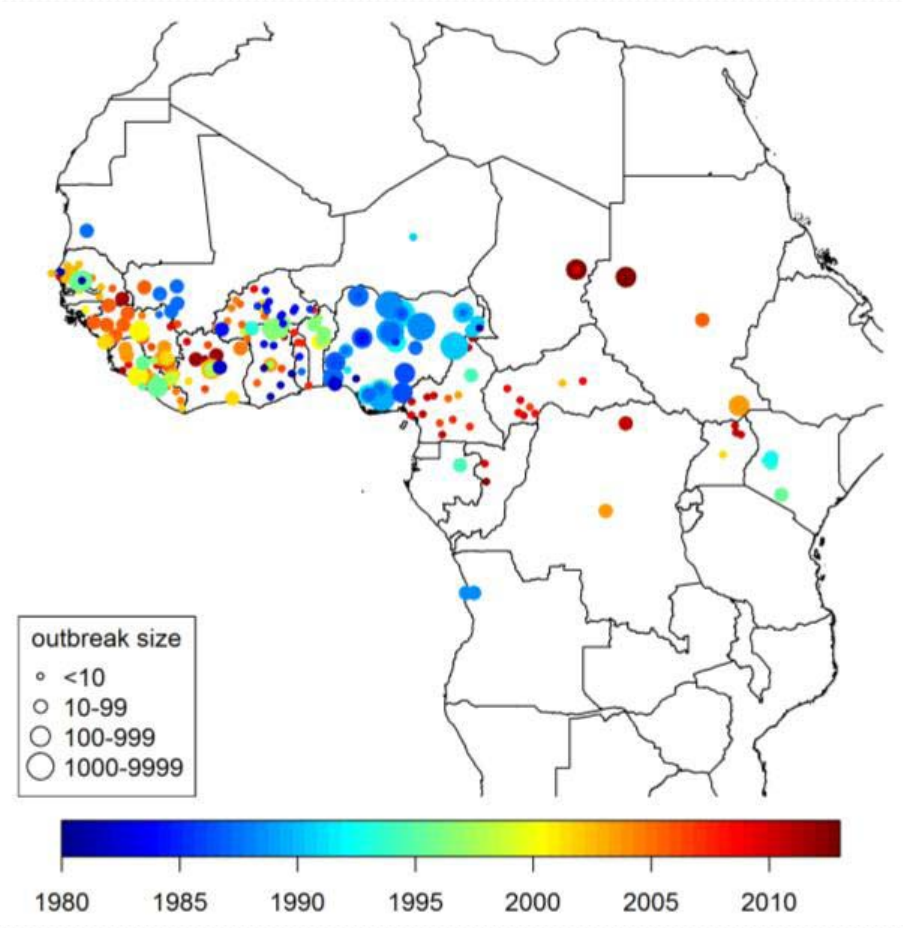
Africa

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

America

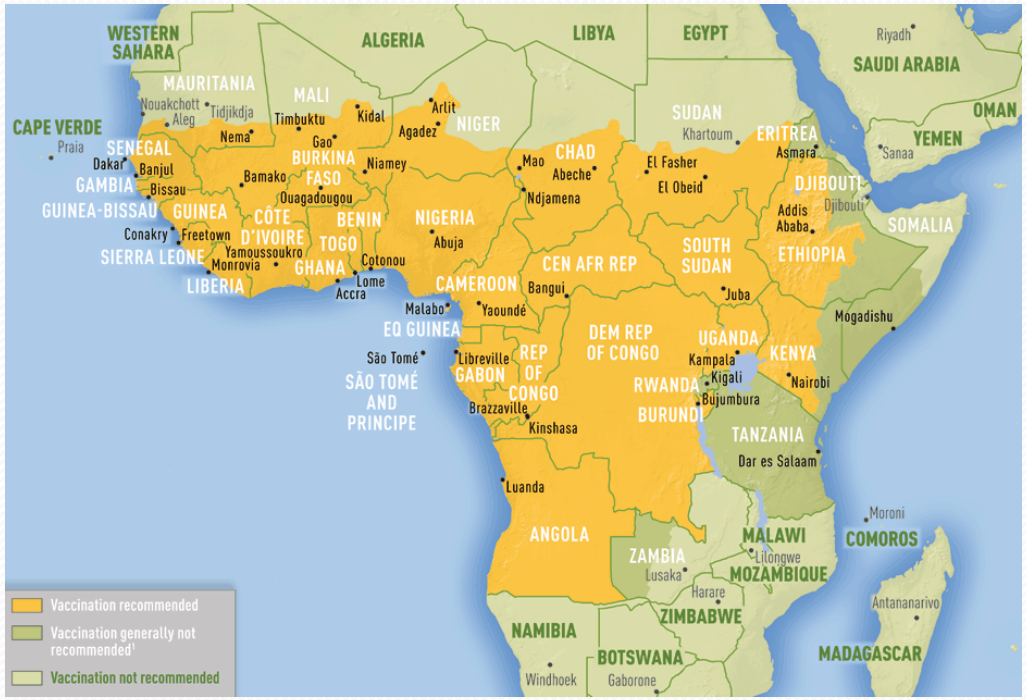
- Sylvatic mostly and sometimes urban
- Mostly young adults (occupational)
- 10x less risk
- ~~Herd immunity~~

Figure 1: Outbreaks of yellow fever between 1980 and 2012. Legend: Colours indicate the year of the outbreak, symbol sizes the approximate number of reported cases.



Source: WHO.int

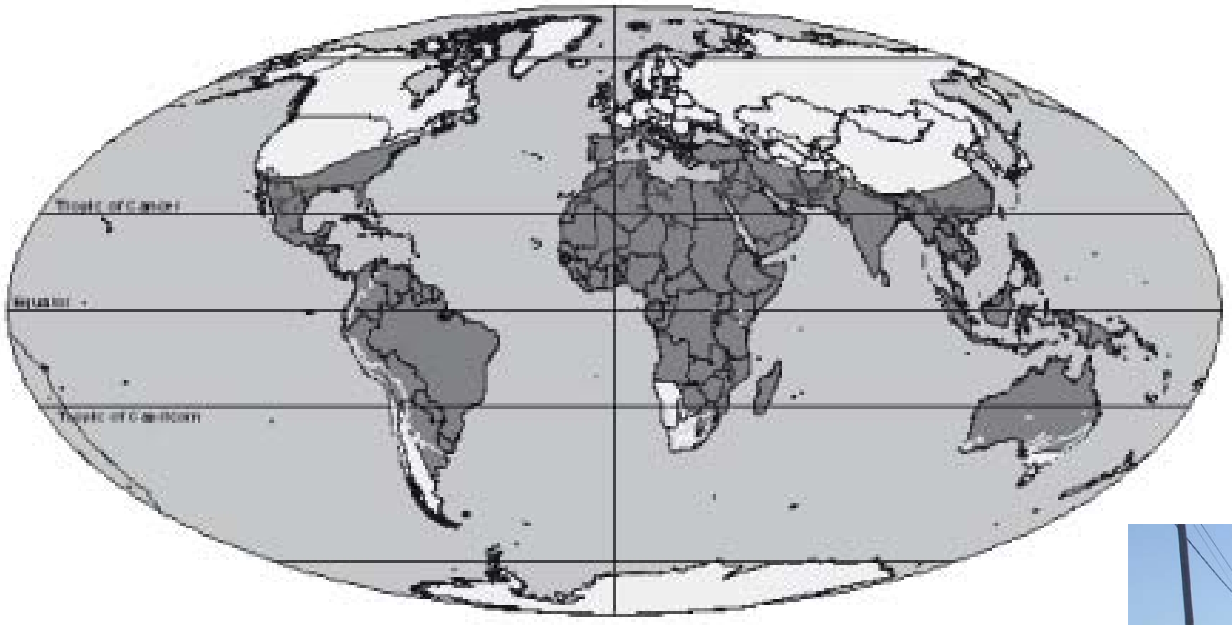
CDC Yellow Book 2015



Mid 20th century

FIGURE 1

Historical distribution of *Aedes aegypti*



Eurosurveillance 2010

Aedes aegypti

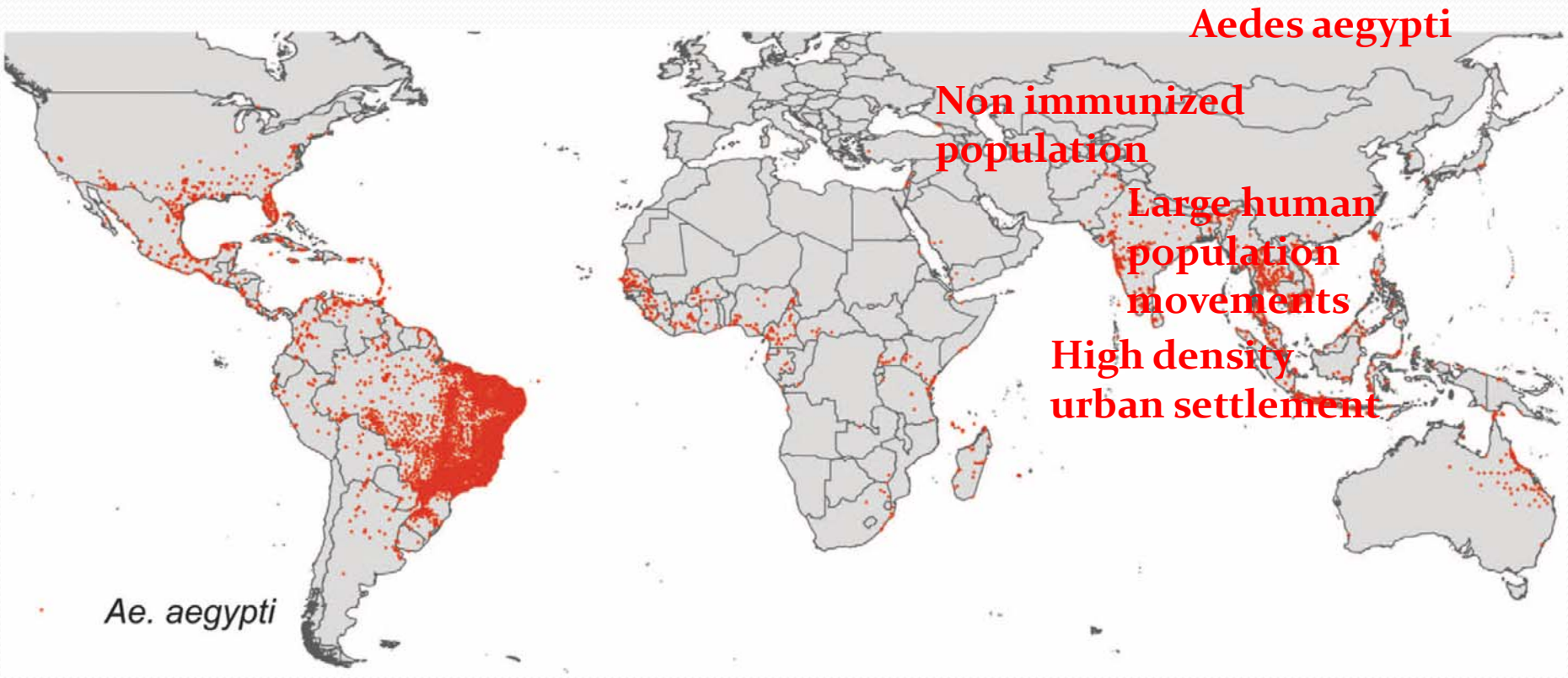
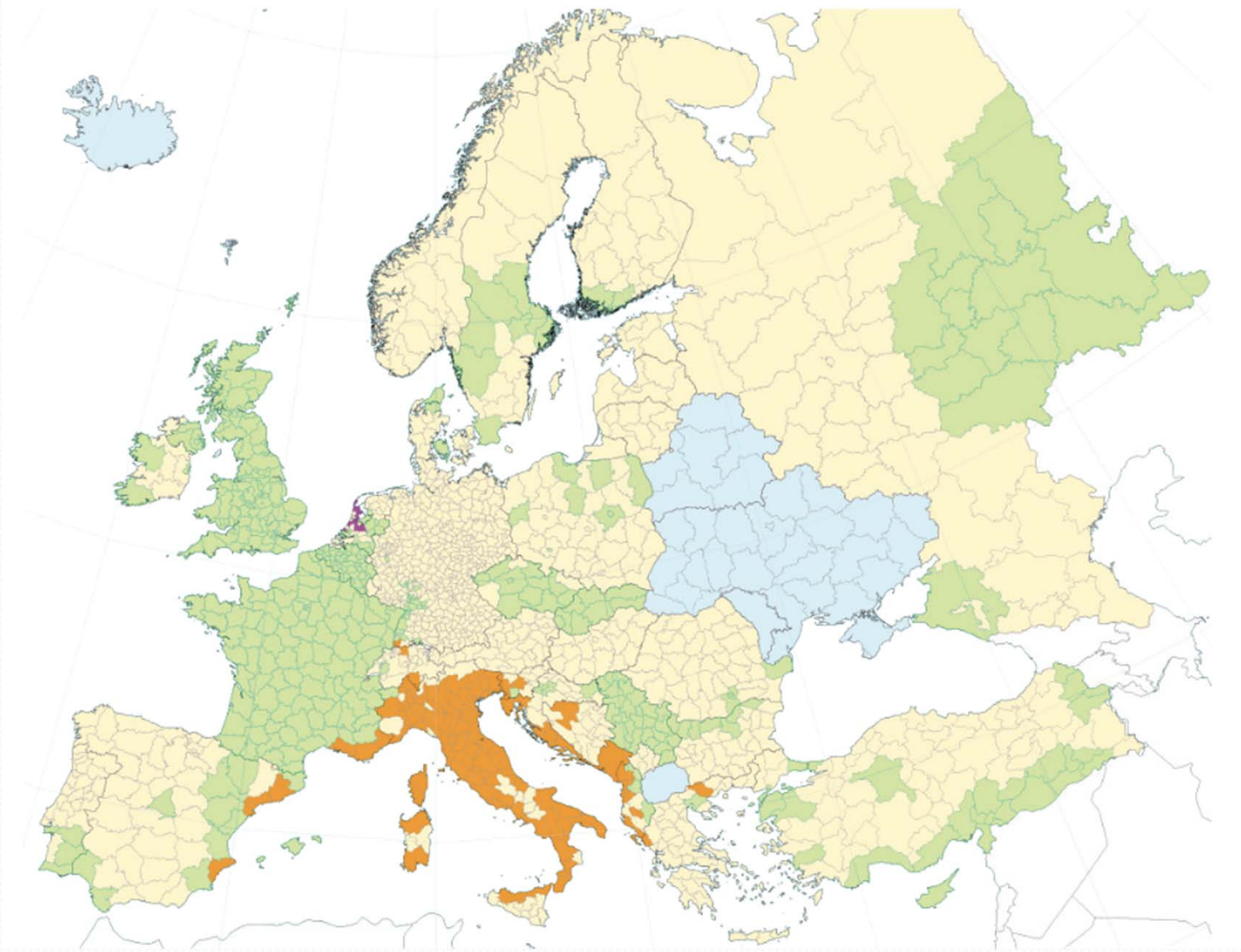


Figure 2. Map of occurrence points for Ae. aegypti

Kraemer, M. U. G. et al. The global compendium of Aedes aegypti and Ae. albopictus occurrence. Sci. Data 2:150035 doi: 10.1038/sdata.2015.35 (2015).

FIGURE 2

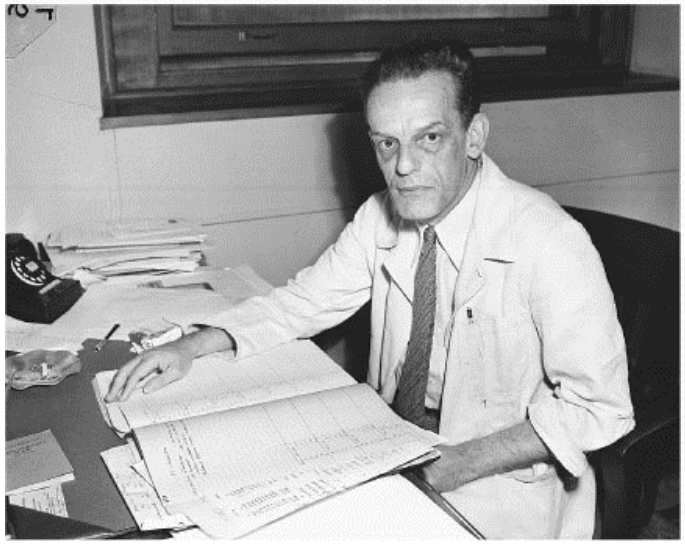
Current (2009) distribution of *Aedes albopictus* in Europe by administrative unit



Source: EuroSurveillance 2010

YF vaccine

- Available for >80 years (‘30)
- Live attenuated vaccine with 17D strain of YF virus, currently derived from wild type Ghana 1927
- >600 million doses worldwide
- Max Theiler (Rockefeller Institute): Nobel Prize 1951



Vaccine Efficacy?

- reduction of laboratory-associated infections in vaccinated workers
- observation following initial use of the vaccine in Brazil and other South American countries that YF only occurred in unvaccinated people
- rapid disappearance of cases during vaccination campaigns initiated during YF epidemics
- protection of rhesus monkeys against virulent yellow fever virus by neutralizing antibodies generated in response to YF vaccination

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No human efficacy study with YF vaccine

Protective efficacy

- Neutralizing Ab ~ best proxy for protective immunity
- 80% protective levels of neutralizing Ab after 10 days
- >99% by day 28

APPLIED MICROBIOLOGY, Apr. 1973, p. 539–544.

Vol. 25, No. 4
Printed in U.S.A.

Yellow Fever Vaccine: Direct Challenge of Monkeys Given Graded Doses of 17D Vaccine

RICHARD A. MASON, NICOLA M. TAURASO, RICHARD O. SPERTZEL, AND ROBERT K. GINN[1]

Laboratory of Virology and Rickettsiology, National Institutes of Health, Bethesda, Maryland 20014, and U.S. Army Medical Research Institute of Infectious Diseases, Frederick, Maryland 21701

Received for publication 28 December 1972

Side effects

• Anaphylaxis (eggs/gelatine)	• 1,8/100 000 doses
• YEL-AND: conglomerate of clinical syndroms (meningoenceph., GBS, ADEM, cranial n. palsy, …) - 3-28 days post-vaccine - Historically infants, now cases reports all ages	• Primary vaccination • Rarely fatal • 0,8/100 000 doses 60-69 y: 1,6/100 000 dos ≥70 y: 2,3/100 000 dos
• YEL-AVD: similar to wild disease - 0-8 days post-vaccine - >65 cases reported since 2001	• Primary vaccination • 60% CFR • 0,4/100 000 doses 60-69 y: 1/100 000 doses ≥70 y: 2,3/100 000 doses

Aims of YF vaccination

- Personale protection for resident/traveller in endemic/epidemic zone
- Prevent international spread via importation of virus by viremic travellers in a zone where vectors are present

→ International Health Regulations 2005

Both must be considered!

Strengthening health security by implementing the International Health Regulations (2005)

Core functions of the IHR

In today's connected world, health security is a global issue. We must all protect ourselves, and each other, from threats like infectious diseases, chemical and radiological events. That is why 196 countries have agreed to work together to prevent and respond to public health crises. The agreement is called the International Health Regulations, or IHR (2005), and WHO plays the coordinating role. Through the IHR, WHO keeps countries informed about public health risks, and works with partners to help countries build capacity to detect, report and respond to public health events.

WHO's work in coordinating IHR implementation is led by the Department of Global Capacities Alert and Response (GCR).

Note regarding the issuance of International Certificate Of Vaccination Or Prophylaxis

As of 15 June 2005, under the International Health Regulations (2005) (IHR (2005)), all States Parties are required to issue and accept a new **International Certificate Of Vaccination Or Prophylaxis** (IHR (2005)Annex 6), replacing the **International Certificate Of Vaccination Or Revaccination Against Yellow Fever.**

The WHO Secretariat is aware that a number of States have indicated that they may not be in a position to implement these new Certificate requirements immediately as of 15 June 2007, and will potentially continue for a limited period to issue/utilize the version of this certificate previously authorized under the IHR (1969).

The WHO Secretariat is not authorized under the Regulations to modify the provisions of, or grant extensions or exceptions, to these requirements of the IHR (2005). At the same time, in order to minimize potential short-term disruptions to international travel, States Parties may consider continuing to recognize and accept Certificates issued using the format required by the IHR(1969) for a limited time period of 6 months.

Please note the International Certificate Of Vaccination Or Revaccination Against Yellow Fever is valid for a period of 10 years and this is not affected by the entry into force of the IHR(2005). Such certificates remain valid proof of vaccination against yellow fever and do not need to be replaced by new certificates during their period of validity.

Source: www.who.int

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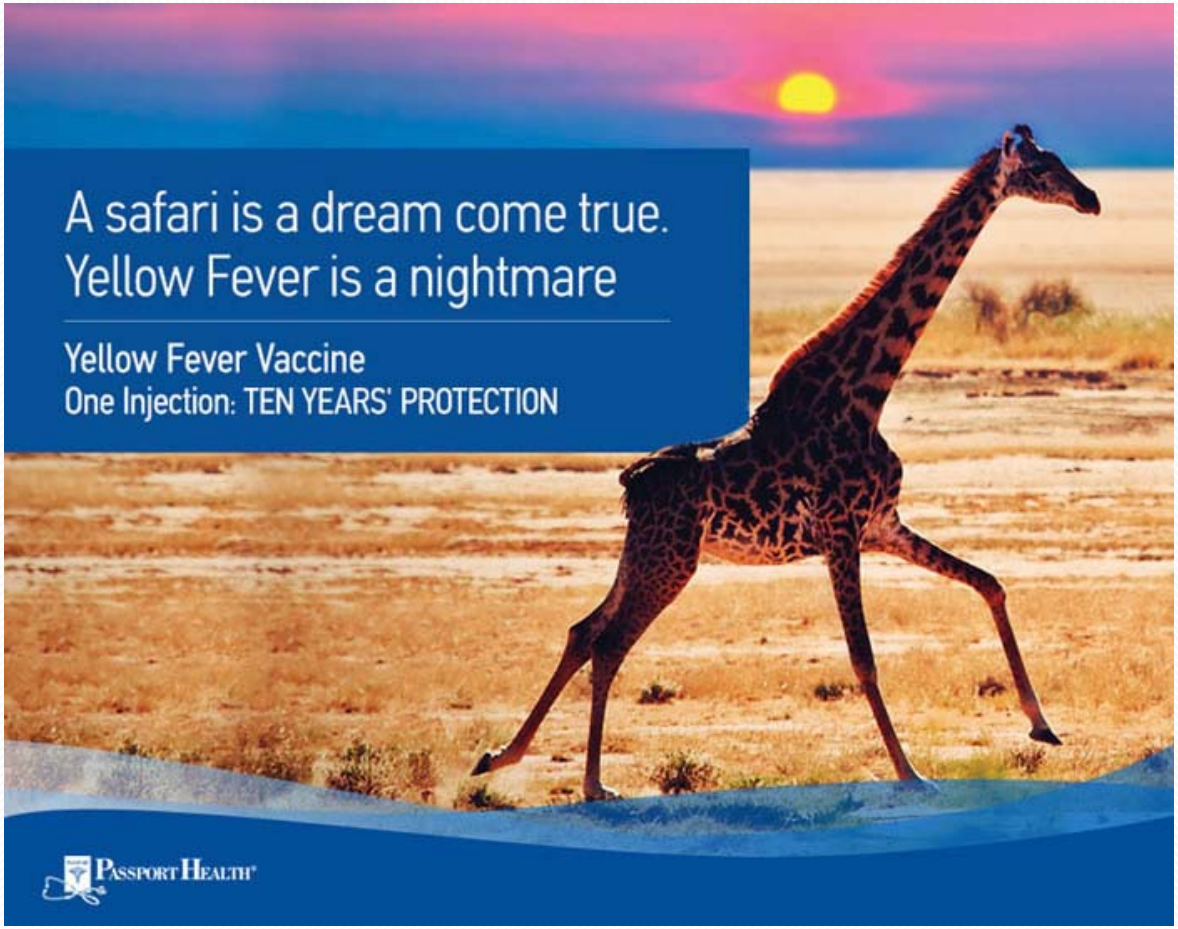
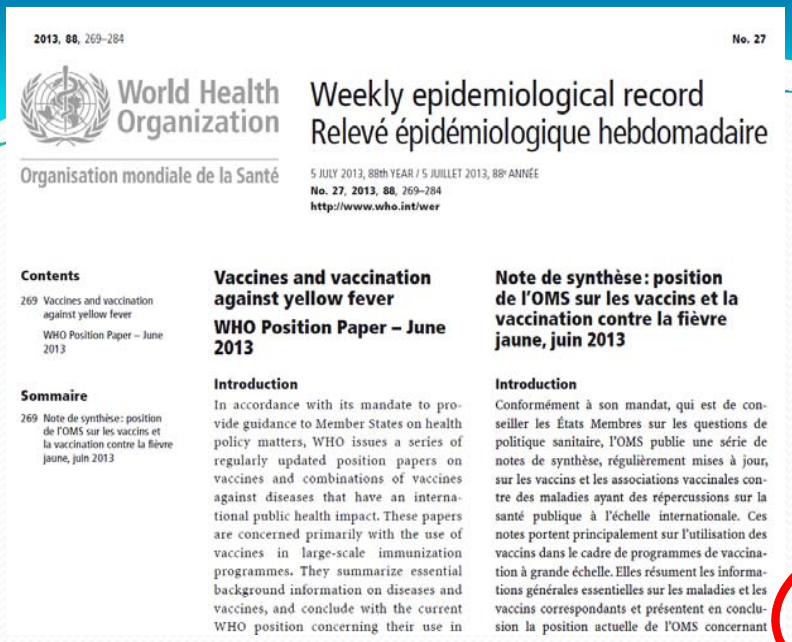
Adopted by World Health Assembly (WHA) in June 2007

Source: www.who.int

WHO 2013


A safari is a dream come true.
Yellow Fever is a nightmare
Yellow Fever Vaccine
One Injection: TEN YEARS' PROTECTION
PASSPORT HEALTH



2013, 88, 269–284 No. 27

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

5 JULY 2013, 88th YEAR / 5 JUILLET 2013, 88e ANNÉE
No. 27, 2013, 88, 269–284
http://www.who.int/wer

Contents

Sommaire

Vaccines and vaccination against yellow fever

WHO Position Paper – June 2013

Introduction

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes. They summarize essential background information on diseases and vaccines, and conclude with the current WHO position concerning their use in

Note de synthèse: position de l'OMS sur les vaccins et la vaccination contre la fièvre jaune, juin 2013

Introduction

Conformément à son mandat, qui est de conseiller les États Membres sur les questions de politique sanitaire, l'OMS publie une série de notes de synthèse, régulièrement mises à jour, sur les vaccins et les associations vaccinales contre des maladies ayant des répercussions sur la santé publique à l'échelle internationale. Ces notes portent principalement sur l'utilisation des vaccins dans le cadre de programmes de vaccination à grande échelle. Elles résument les informations générales essentielles sur les maladies et les vaccins correspondants et présentent en conclusion la position actuelle de l'OMS concernant

The papers have been reviewed by external experts and WHO staff, and are reviewed and endorsed by the WHO Strategic Advisory Group of Experts on Immunization (SAGE).[1] The position papers are designed to be used mainly by national public health officials and managers of immunization programmes but may also be of interest to international funding agencies, vaccine manufacturers, the medical community, the scientific media, and the public. A description of the processes followed for the development of vaccine position papers is available at http://www.who.int/immunization/position_papers/position_paper_process.pdf

This updated position paper on yellow fever (YF) vaccines and vaccination replaces the previous 2003 WHO position paper and summarizes recent developments in the field.

Ces notes ont été examinées par des experts externes et des membres du personnel de l'OMS et sont approuvées par le Groupe stratégique consultatif d'experts sur la vaccination (SAGE).[1] Elles sont principalement destinées aux responsables nationaux de la santé publique et aux administrateurs des programmes de vaccination, mais peuvent aussi intéresser les agences de financement internationales, les fabricants de vaccins, la communauté médicale, les médias scientifiques et le public. Le lecteur trouvera une description du processus suivi pour élaborer les notes de synthèse résumant la position de l'OMS à l'adresse: http://www.who.int/immunization/position_papers/position_paper_process.pdf

La présente note de synthèse actualisée sur les vaccins et la vaccination contre la fièvre jaune (FJ) remplace la note antérieure de 2003 et résume les faits récents dans le domaine.

Protection appears to last at least 20–35 years and probably for life. A systematic review has identified 6 studies indicating that a high proportion of vaccine recipients (>90%) have detectable levels of serum neutralizing antibodies up to 20 years post YF vaccination.[20] In a study of antibody levels in US World War II veterans, it was found that >80% had neutralizing antibodies 30–35 years after a single dose of YF vaccine.

Since the introduction of YF vaccination in the 1930s,

La protection conférée semble durer au moins 20 à 35 ans et se prolonge probablement tout au long de la vie. Une revue systématique a identifié 6 études indiquant qu'une forte proportion des personnes ayant reçu le vaccin (>90%) présentaient des titres détectables d'anticorps neutralisants dans le sérum jusqu'à 20 ans après la vaccination contre la FJ.[20] Une étude a examiné les titres d'anticorps chez des vétérans américains de la deuxième guerre mondiale et constaté que >80% d'entre eux étaient porteurs d'anticorps neutralisants 30 à 35 ans après l'administration d'une dose unique de vaccin antiamaril.

Depuis l'introduction de la vaccination contre la FJ dans les an-

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

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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.


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World Yellow fever vaccination booster
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Adopted by World Health Assembly (WHA) in May 2014

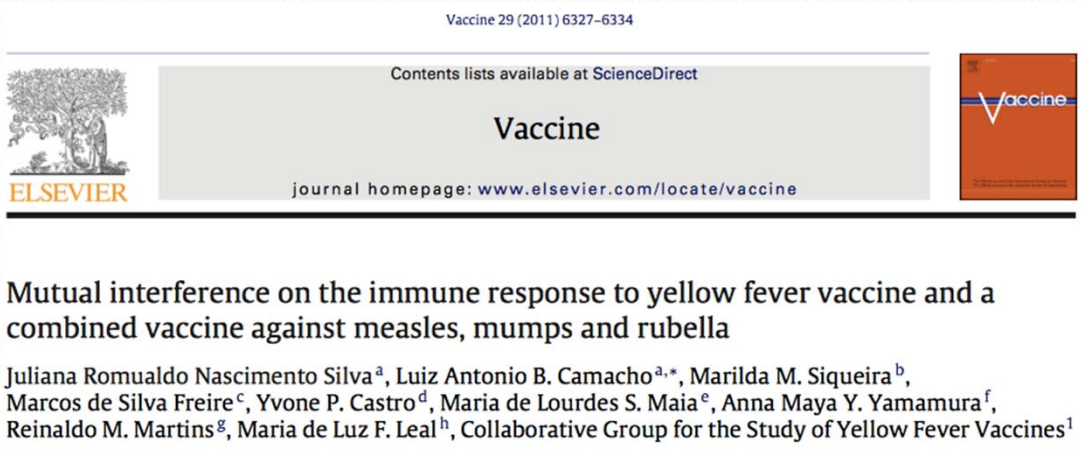
ANNEX 1

Countries[1] with risk of yellow fever transmission[2] and countries requiring yellow fever vaccination

Country	Country with risk of yellow fever transmission	Country requiring yellow fever vaccination for travellers[3]		Country statement for yellow fever vaccination certificate validity[3]
		arriving from countries with risk of yellow fever transmission (age of traveller)	from all countries (age of traveller)	
Afghanistan		Yes		Not communicated
Albania		Yes (> 1 year)		Not communicated
Algeria		Yes[4] (> 1 year)		Life
Angola	Yes		Yes (> 9 months)	Life
Antigua and Barbuda		Yes (> 1 year)		Not communicated
Argentina	Yes			Not applicable
Australia		Yes[4] (> 1 year)		10 years
Bahamas		Yes[4] (> 1 year)		Life
Bahrain		Yes[4] (> 9 months)		Life
Bangladesh		Yes (> 1 year)		Not communicated
Barbados		Yes[4] (> 1 year)		Not communicated
Belize		Yes (> 1 year)		Not communicated
Benin	Yes		Yes (> 1 year)	Not communicated
Bhutan		Yes[5]		Not communicated
Bolivia, Plurinational (State of)	Yes	Yes[4] (> 1 year)		Not communicated
Botswana		Yes[5] (> 1 year)		10 years

(Re) vaccination?

- No medical record
- immune depression incl. HIV
- Pregnancy (depending trimester?)
- Malnutrition (definition?)
- Infant, child< 2 years old
- Co administration MMR vaccine



Vaccine 29 (2011) 6327–6334

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

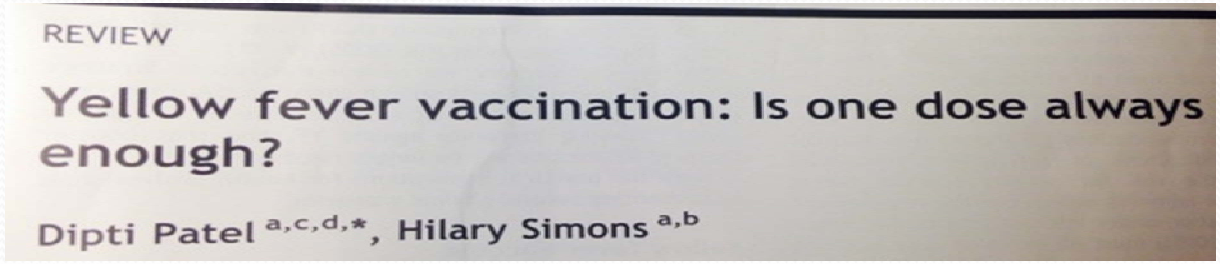
Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps and rubella

Juliana Romualdo Nascimento Silva[a], Luiz Antonio B. Camacho[a,*], Marilda M. Siqueira[b], Marcos de Silva Freire[c], Yvone P. Castro[d], Maria de Lourdes S. Maia[e], Anna Maya Y. Yamamura[f], Reinaldo M. Martins[g], Maria de Luz F. Leal[h], Collaborative Group for the Study of Yellow Fever Vaccines[1]

Don’t forget!

- Revaccination → no risk for YEL-AVD or YEL-AND
- If weak Ab titers → boosting
- More studies…

What is debatable



REVIEW

Yellow fever vaccination: Is one dose always enough?

Dipti Patel [a,c,d,*], Hilary Simons [a,b]

Yellow fever revaccination guidelines change – a decision too feverish?

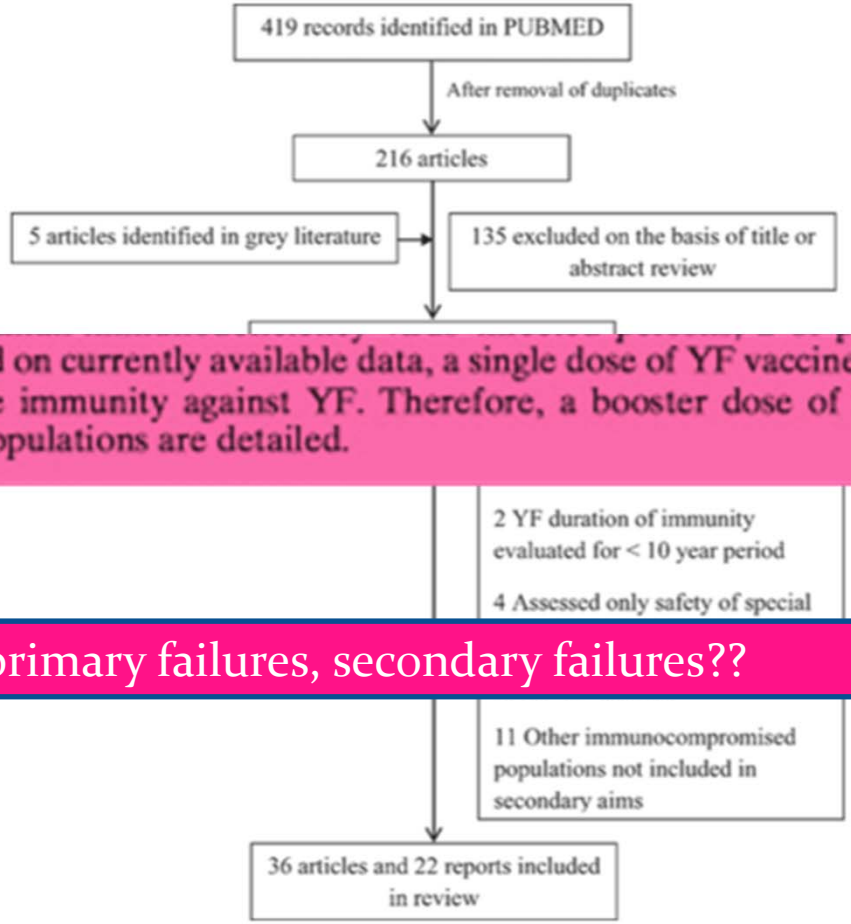
M. P. Grobusch[1], A. Goorhuis[1], R. W. Wieten[1], J. D. M. Verberk[1], E. F. F. Jonker[2], P. J. J. van Genderen[3] and L. G. Visser[2]

Clinical Microbiology and Infection, Volume 19 Number 10, October 2013

Am. J. Trop. Med. Hyg., 89(3), 2013, pp. 434–444
doi:10.4269/ajtmh.13-0264

Review Article: Efficacy and Duration of Immunity after Yellow Fever Vaccination: Systematic Review on the Need for a Booster Every 10 Years

Eduardo Gotuzzo, Sergio Yactayo, and Erika Córdova*



malnourished children. Based on currently available data, a single dose of YF vaccine is highly immunogenic and confers sustained life-long protective immunity against YF. Therefore, a booster dose of YF vaccine is not needed. Special considerations for selected populations are detailed.

No mention about primary failures, secondary failures??

FIGURE 1. Study selection flow diagram for vaccination against yellow fever (YF).

Duration of post-vaccination immunity against yellow fever in adults

Collaborative group for studies on yellow fever vaccines[1]

Vaccine 32 (2014) 4977–4984

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)

526 adults from non-endemic areas of Southeast Brazil
One dose of YF vaccine
Exclusion of adults with seropositive or inconclusive pre-vaccination serology

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One dose of YF vaccine
Exclusion of adults with seropositive or inconclusive pre-vaccination serology

Am J Hyg. 1948 Jan;47(1):64-70.

Additional observations on the duration of humoral immunity following vaccination with the 17D strain of yellow fever virus.

FOX JP, FONSECA DA CUNHA J, KOSSOBUDZKI SL.

Brazilian vaccinees:

- 87% positive neutralizing Ab titers after 2 years
- 72% positive neutralizing Ab titers after 6 years

Tropical Medicine and International Health

VOLUME 4 NO 12 PP 867–871 DECEMBER 1999

Assessment of IgG antibodies against yellow fever virus after vaccination with 17D by different assays: neutralization test, haemagglutination inhibition test, immunofluorescence assay and ELISA

M. Niedrig[1], M. Lademann[2], P. Emmerich[3] and M. Lafrenz[2]

Table 1 Follow-up of neutralization titre after 17D-vaccination. * = NT titres < 1:10 are considered negative

Years post vaccination	Total number of sera	Number of sera with NT titre ≤ 1:10* (%)	Number of sera with NT titre > 1:10 (%)	Median NT titre of reactive sera
1	66	4 (6.0)	62 (94.0)	1:70
2–10	92	17 (18.5)	75 (81.5)	1:40
11–38	51	13 (25.5)	38 (74.5)	1:40
1–10	158	21 (13.3)	137 (86.7)	1:55
0–38	209	34 (16.3)	175 (83.7)	1:50

Am J Hyg. 1948 Jan;47(1):64-70.

Additional observations on the duration of humoral immunity following vaccination with the 17D strain of yellow fever virus.

FOX JP, FONSECA DA CUNHA J, KOSSOBUDZKI SL.

Brazilian vaccinees:

- 87% positive neutralizing Ab titers after 2 years
- 72% positive neutralizing Ab titers after 6 years

Intraperitoneal protection test in adult mice

Tropical Medicine and International Health

VOLUME 4 NO 12 PP 867–871 DECEMBER 1999

Assessment of IgG antibodies against yellow fever virus after vaccination with 17D by different assays: neutralization test, haemagglutination inhibition test, immunofluorescence assay and ELISA

M. Niedrig[1], M. Lademann[2], P. Emmerich[3] and M. Lafrenz[2]

Table 1 Follow-up of neutralization titre after 17D-vaccination. * = NT titres < 1:10 are considered negative

Years post vaccination	Total number of sera	Number of sera with NT titre ≤ 1:10* (%)	Number of sera with NT titre > 1:10 (%)	Median NT titre of reactive sera
1	66	4 (6.0)	62 (94.0)	1:70
2–10	92	17 (18.5)	75 (81.5)	1:40
11–38	51	13 (25.5)	38 (74.5)	1:40
1–10	158	21 (13.3)	137 (86.7)	1:55
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Épidémiologie / Epidemiology
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October 2011, Volume 104, Issue 4, pp 260-265

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H. Coulange Bodilis, G. Benabdelmoumen, A. Gergely, C. Goujon, M. Pelicot, P. Poujol, P. H. Consigny

84 patients, median age 69 y
Medical contraindication to YF vaccine: 30% age- HIV, neoplasia, IS treatment, AI disease for the rest
Last YF vaccine: 10-60 y before (med 14 y) *how many vaccines?*
Seropositivity rate: 95,2%

Reasons for discrepant results?

- Have received more than one vaccine
- Exposition to disease → natural boosting
- Type of vaccine, substrains of vaccine virus
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- Volunteer profiles
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- Dengue infection influence
- Influence of cellular immune response
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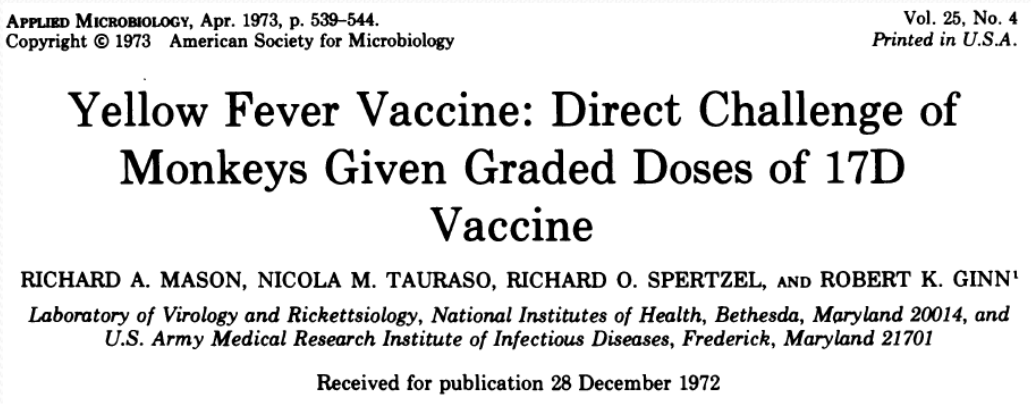
Protective efficacy

- dose-response study conducted in rhesus monkeys → minimal level of neutralizing Ab needed to protect the monkeys against virulent YF virus established with using a log10 neutralization index (LNI) :LNI >0.7 was correlated strongly with protection
- amount of serum needed for LNI testing precludes routine screening among humans → similar test: plaque reduction neutralization test (PRNT) is used



APPLIED MICROBIOLOGY, Apr. 1973, p. 539–544.

Vol. 25, No. 4
Printed in U.S.A.

Yellow Fever Vaccine: Direct Challenge of Monkeys Given Graded Doses of 17D Vaccine

RICHARD A. MASON, NICOLA M. TAURASO, RICHARD O. SPERTZEL, AND ROBERT K. GINN[1]

Laboratory of Virology and Rickettsiology, National Institutes of Health, Bethesda, Maryland 20014, and U.S. Army Medical Research Institute of Infectious Diseases, Frederick, Maryland 21701

Received for publication 28 December 1972

Plaque Reduction Neutralization Test

- Based on the ability of virus specific Ab to inhibit the plaque forming property of virus by x% when plated in semisolid media
- Capacity of immune serum expressed in % neutralization compared

  to non immune serum

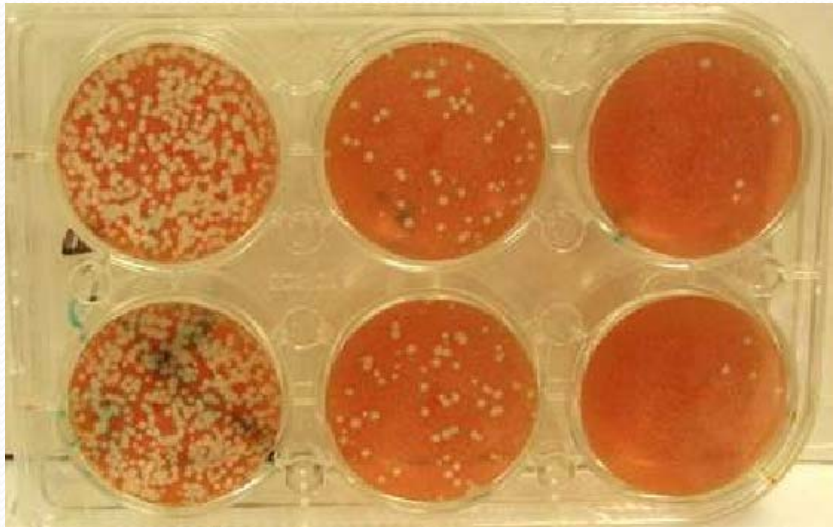


Table 1. Studies documenting long-term immunity following yellow fever (YF) vaccination. *(Adapted from reference 18)*

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

Source: Background paper on YF vaccine/ WHO 2013

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NO CLEAR CUT-OFF OF ASSAY FOR DEFINITION OF PROTECTION

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Vaccine 32 (2014) 4977–4984

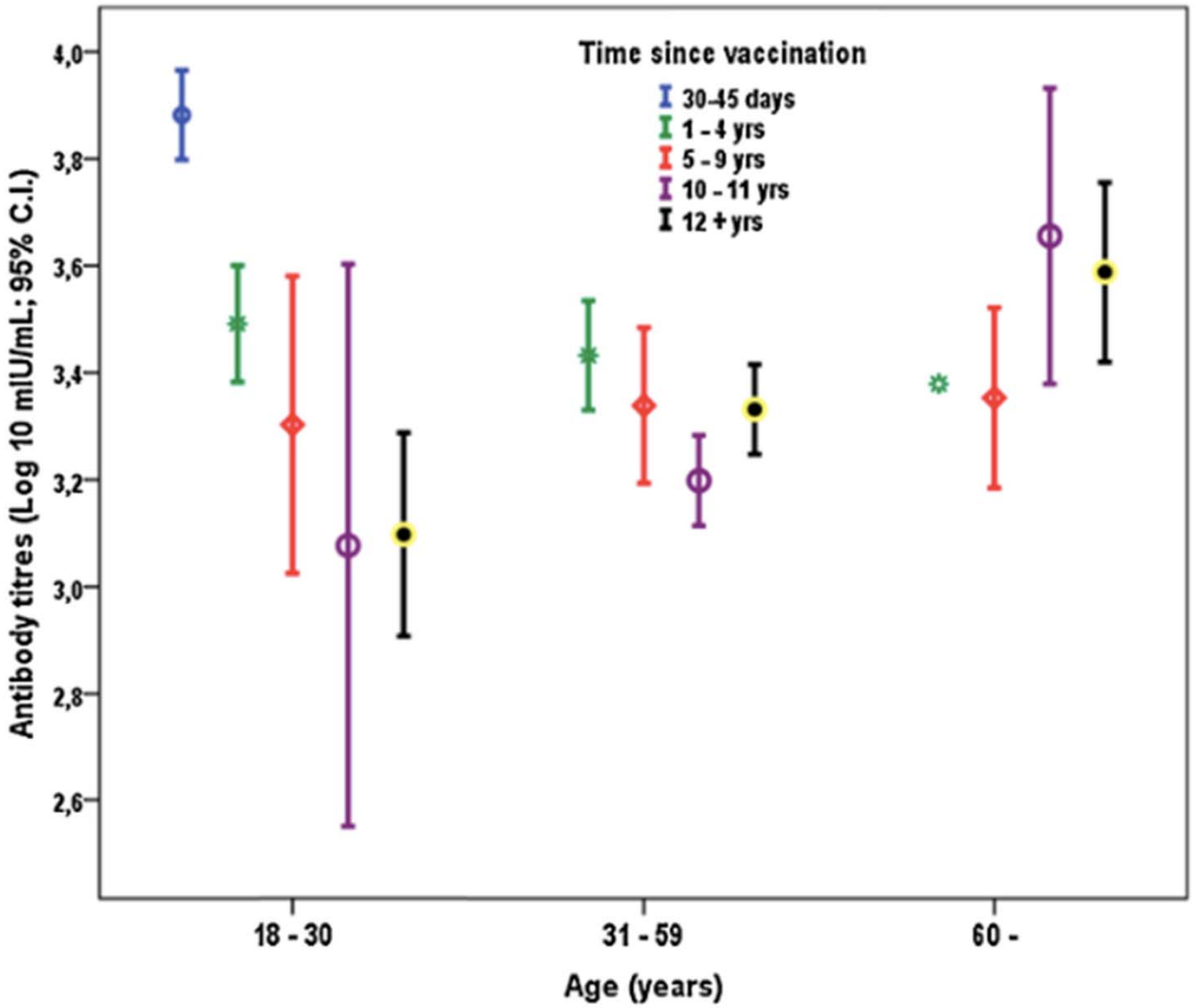

Fig. 3. Mean values at 95% CI of neutralising antibody titres (log_{10} IU/mL) against yellow fever according to the time since vaccination and age.

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Nature Immunology **10**, 116 - 125 (2008)
Published online: 23 November 2008 | doi:10.1038/ni.1688

Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans

Troy D Querec[1,8], Rama S Akondy[1,8], Eva K Lee[2], Weiping Cao[1], Helder I Nakaya[1], Dirk Teuwen[3], Ali Pirani[4], Kim Gernert[4], Jiusheng Deng[1], Bruz Marzolf[5], Kathleen Kennedy[5], Haiyan Wu[5], Soumaya Bennouna[1], Herold Oluoch[1], Joseph Miller[1], Ricardo Z Vencio[5], Mark Mulligan[1,6], Alan Aderem[5], Rafi Ahmed[1] & Bali Pulendran[1,7]

A major challenge in vaccinology is to prospectively determine vaccine efficacy. Here we have used a systems biology approach to identify early gene 'signatures' that predicted immune responses in humans vaccinated with yellow fever vaccine YF-17D. Vaccination induced genes that regulate virus innate sensing and type I interferon production. Computational analyses identified a gene signature, including complement protein C1qB and eukaryotic translation initiation factor 2 alpha kinase 4—an orchestrator of the integrated stress response—that correlated with and predicted YF-17D CD8$^+$ T cell responses with up to 90% accuracy in an independent, blinded trial. A distinct signature, including B cell growth factor *TNFRS17*, predicted the neutralizing antibody response with up to 100% accuracy. These data highlight the utility of systems biology approaches in predicting vaccine efficacy.

Propositions?

- **Adoption of 2 doses schedule?**
- **Increase vaccine interval to 20 years?**

What is missing to get forward

- Define cut-off percentage population protected
- Enhance post-vaccination surveillance to detect failures
- More studies on immune cellular mechanisms in vaccinees without Ab
- Unequivocal PRNT cut-off values + define lower acceptable level
- Further studies in immunocompromised…and immunocompetent!

New YF vaccine?

Vaccine 33 (2015) 4261–4268

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

An inactivated yellow fever 17DD vaccine cultivated in Vero cell cultures

Renata C. Pereira, Andrea N.M.R. Silva, Marta Cristina O. Souza, Marlon V. Silva, Patrícia P.C.C. Neves, Andrea A.M.V. Silva, Denise D.C.S. Matos, Miguel A.O. Herrera, Anna M.Y. Yamamura, Marcos S. Freire, Luciane P. Gaspar*, Elena Caride

Oswaldo Cruz Foundation (FIOCRUZ), Bio-Manguinhos, Avenida Brasil 4365, 21045-900, Rio de Janeiro, RJ, Brazil

- Immunogenicity of inactivated 17DD vaccine in mice
- 3 doses + Al → seroconversion in 7/16
- 100% protected against lethal challenge

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An Inactivated Cell-Culture Vaccine against Yellow Fever

Thomas P. Monath, M.D., Elizabeth Fowler, Ph.D., Casey T. Johnson, D.O., John Balser, Ph.D., Merribeth J. Morin, Ph.D., Maggie Sisti, B.S., and Dennis W. Trent, Ph.D.

- XRX-001: cultivation of Vero cells, inactivated with propiolactone + Al
- double blind placebo controlled study in 60 healthy adult subjects < safety and immunogenicity
- 2 injections D0-D21 of 4.8 or 0.48 µg Ag → neutralizing Ab 100% vs 88%
- Durability? Mean GMT?

Questions?