9th National Seminar on Travel Medicine

17 November 2011

Dengue and yellow fever vaccines: what's new?

14.50-15.15

Dengue and yellow fever vaccines: what's new?

Prof Y.Van Laethem Travel Clinic CHU St Pierre-Brussels

Dengue and yellow fever vaccines: what's new?

Y.Van Laethem

Travel Clinic

CHU St Pierre-Brussels

Dengue fever vaccines in the pipeline

A dream makes true.....

The problem

- Dengue fever is the most frequent arbovirose

  +/- 100 million cases/year

  mostly South East Asia

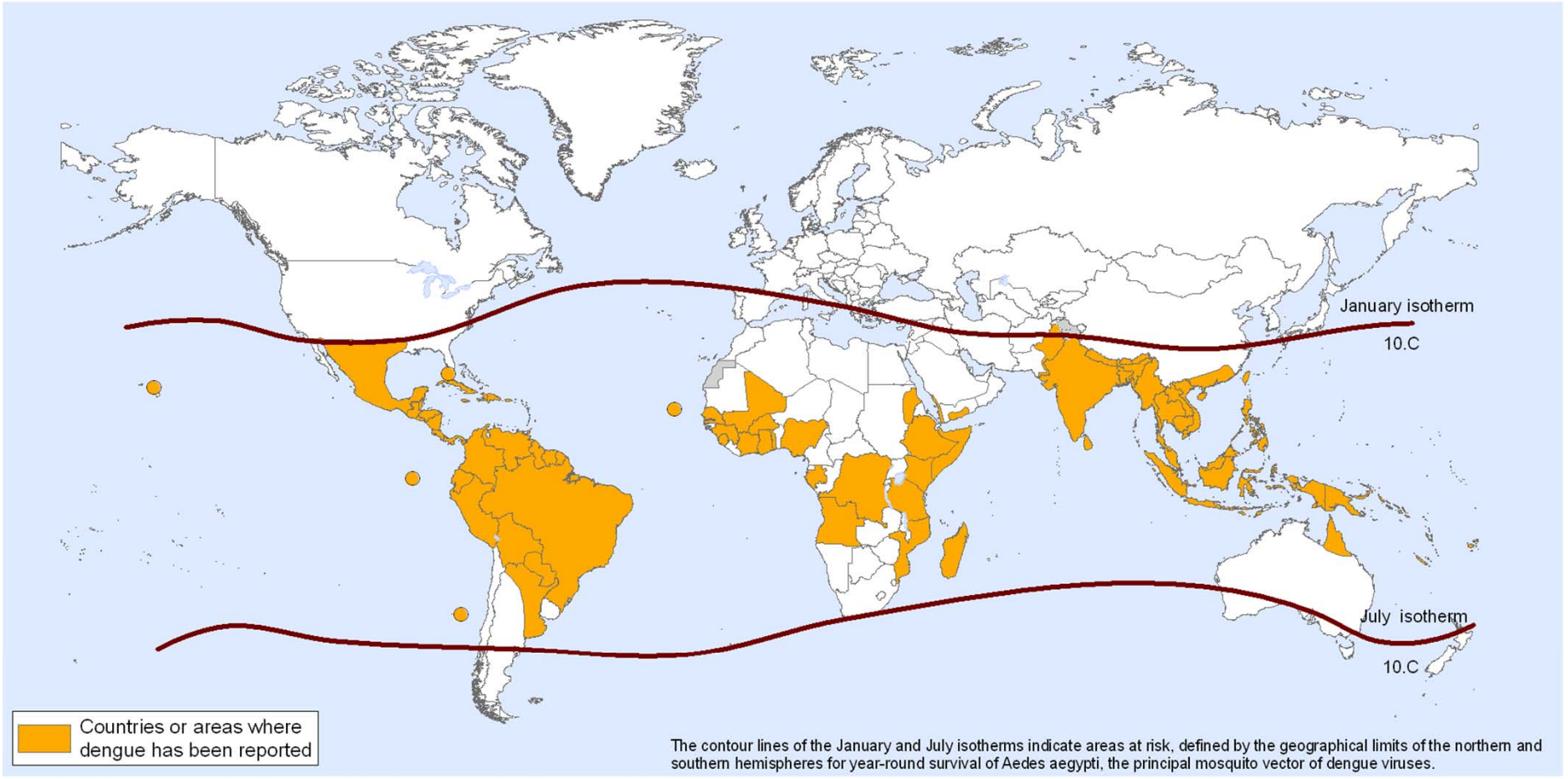
  Linked to increasing urbanisation

  climate modifications..??

  allowing Aedes sp. to a larger geographic distribution

  breed on more patients

Dengue, countries or areas at risk, 2010



The contour lines of the January and July isotherms indicate areas at risk, defined by the geographical limits of the northern and southern hemispheres for year-round survival of Aedes aegypti, the principal mosquito vector of dengue viruses.

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

Epidemilogy of dengue fever

- **2,5 to 3,5 billion people are at risk**

  (we recently commemorate the 7 billionth earth inhabitant….)

- **50 to 100 million cases/y:**

  50% in adults, predominantly overt: Dengue Fever
  in older one/preexisting condition: →more severe

  50 % in children: predominantly mild/silent

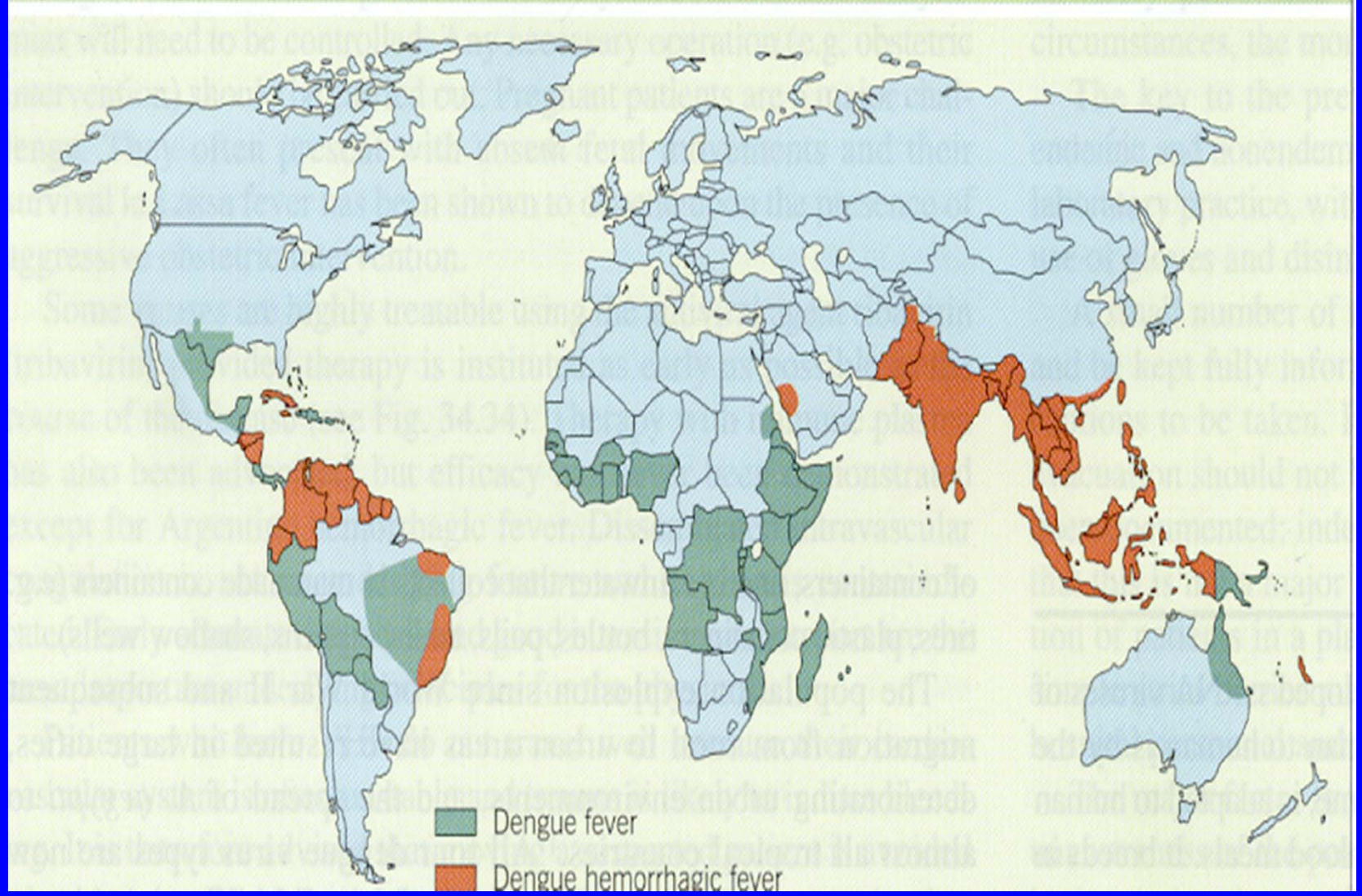
  leading to +/- 20.000 death/y

  !Not the same epidemiology everywhere (S America:older)

- More frequent cause of fever in travellers (3X malaria)/ hospit for fever when coming back from Asia

Peters and Pasvol: Atlas of Tropical Medicine and Parasitology 6th edition © 2006 Elsevier Ltd

GEOGRAPHIC DISTRIBUTION OF DENGUE



Dengue fever

- Single RNA virus of the genus Flavivirus
  (as YF , JE, several VHF,…)
- Protein E is the main target for neutralizing Ab
- In endemic countries, 40-90% of the population has Ab against dengue
- ≥ 2 infections with ≠ serotypes induce protection against severe dengue
  ≡ Ab directed at epitopes expressed by all 4 dengue viruses

Immunity

- **Homologous immunity**: lifelong, but only 70% homology
- **Heterologous immunity**: only for a few months

and « *immune enhancement* », due to

-a new(2d,3th,…) infection

-linked to a new serotype interacting with non neutralizing Ab to the 1st strain

leading to more severe forms (→ DHF/DSS)

10-100 x more frequently than a 1st infection

→ **2-4% of secondary dengue infections are hospitalized**

< Immunological storm (Il-10,…) ,AFTER viremia,due to :

-3x increase in infected mono/macrophages(↑uptake)

-10x increase in virus production/infected cell

Challenges for a vaccine

- **No animal model (monkeys are infected but a Σ)**
- **No known true correlate of protection**

  Yes, neutralizing Ab seems to be indicator of protection

  BUT

  Absolute titer:??
- Need to build immune response against (the) 4 (2?) serotypes
- Whole killed virus is not protective….
- Avoiding immune enhancement !

Vaccines against Dengue

- **At least 10 vaccines in** early clinical or preclinical stage of **development.**

  Live attenuated , DNA ,recombinant subunit,....

- **The only one reaching Phase 3** clinical trial:

  the tetravalent Sanofi Pasteur **live attenuated**

Chimeri Vax

Vaccin dengue Sanofi Pasteur

- **Chimeri Vax:**

chimeric vaccine , produced on Vero cells

≡ based on the 17D YFV backbone, wherein 2 genes (prot E and prM) are replaced by genes of **each** dengue serotypes ≡ the 4 strains

→a « YF life atten.virus » expressing outside Dengue Ag

-Genetically stable, no possible reversion

-Very unlikely natural recombinaison(in flaviviruses)

-Very low viremia, not transmitted to/by mosquitos

-No hepato or neurotropism (monkeys)

Chimeri Vax

- Supplied as powder with solvant
- Storage :+5°, but seems thermostable 1 month at 25 ,°
  1 week at 37° and 6 h after reconstitution
- 0,5 ml, SC
- 3 injections at O-6-12 months

Chimeri Vax

- **Several trials performed in**:

  -S. America: Mexico, Honduras,Colombia,Peru, Brazil

  -Asia: India, Thailand, Malaysia ,Vietnam ,Phillipines Singapore, Indonesia ,Australia

  Tolerability (on 6000 patients): similar to placebo

  No problems after≥ 2 injections/ in subjects already in contact with a flavivirus

  No « Dengue-like syndrom »

  Immunogenicity: (based empirically on GMT of 1/10)

  OK , ≡ from 2 y to 45 y, also if already YF vaccinated

Chimeri Vax: efficacy trial in 4-11 y old Thai children

- In 57 schools: 2668 dengue vaccines/1334 placebo
- To assess the efficacy after 3 inj. in preventing:
  - -symptomatic virologically confirmed dengue
  - -due to any of the 4 serotypes
  - -regardless of the severity
- Third vaccination completed 2/2011
- First efficacy results:end 2012 Expect to licence by 2014

NB: Additional F. up < all febrile illness that requires hospitalisation →3 y after end of vaccination

Challenges

- **Safety:**

  -4/2011: no evidence to suggest a safety concern

  - long term surveillance needed at least in the early adopting countries

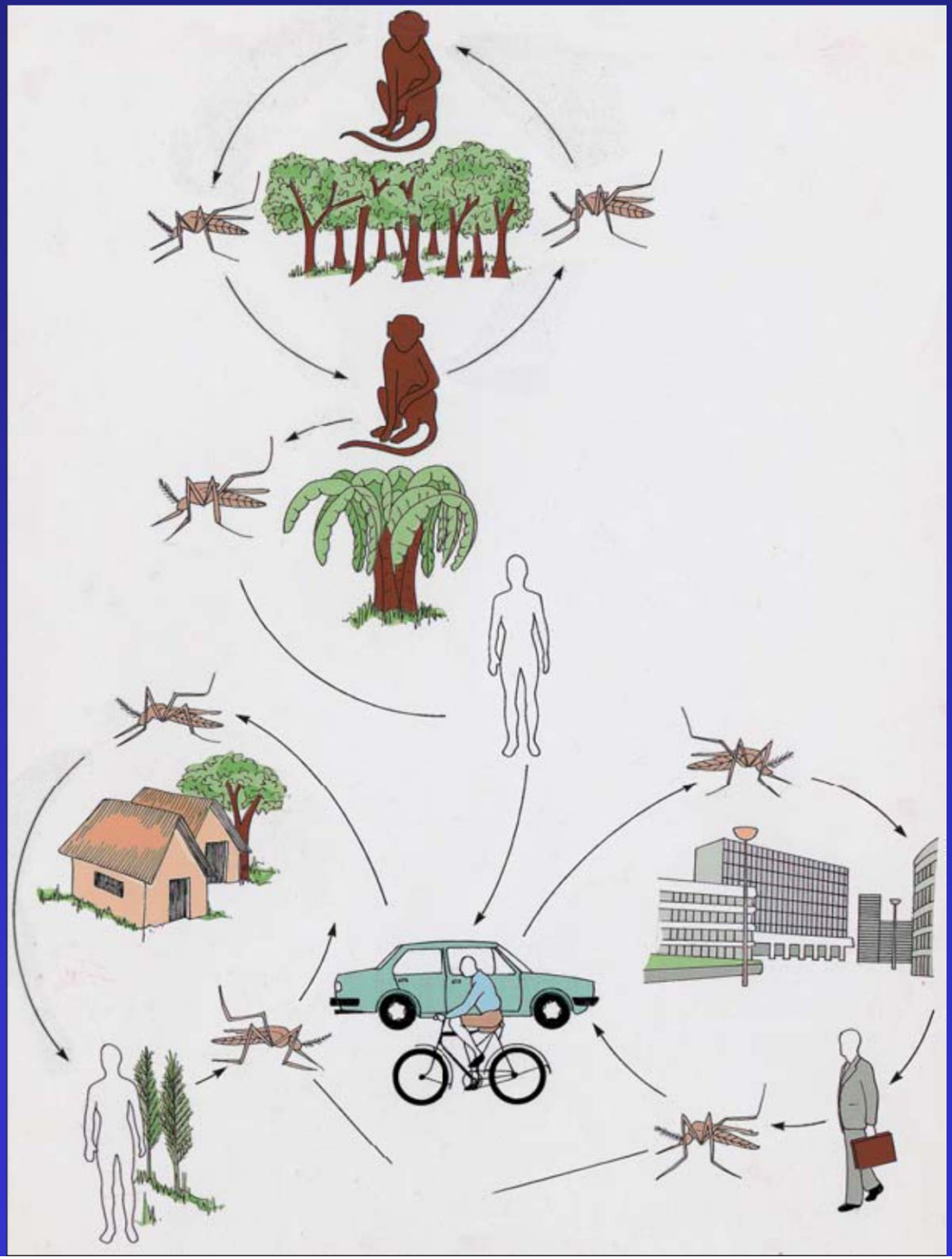
and a dream comes true…????

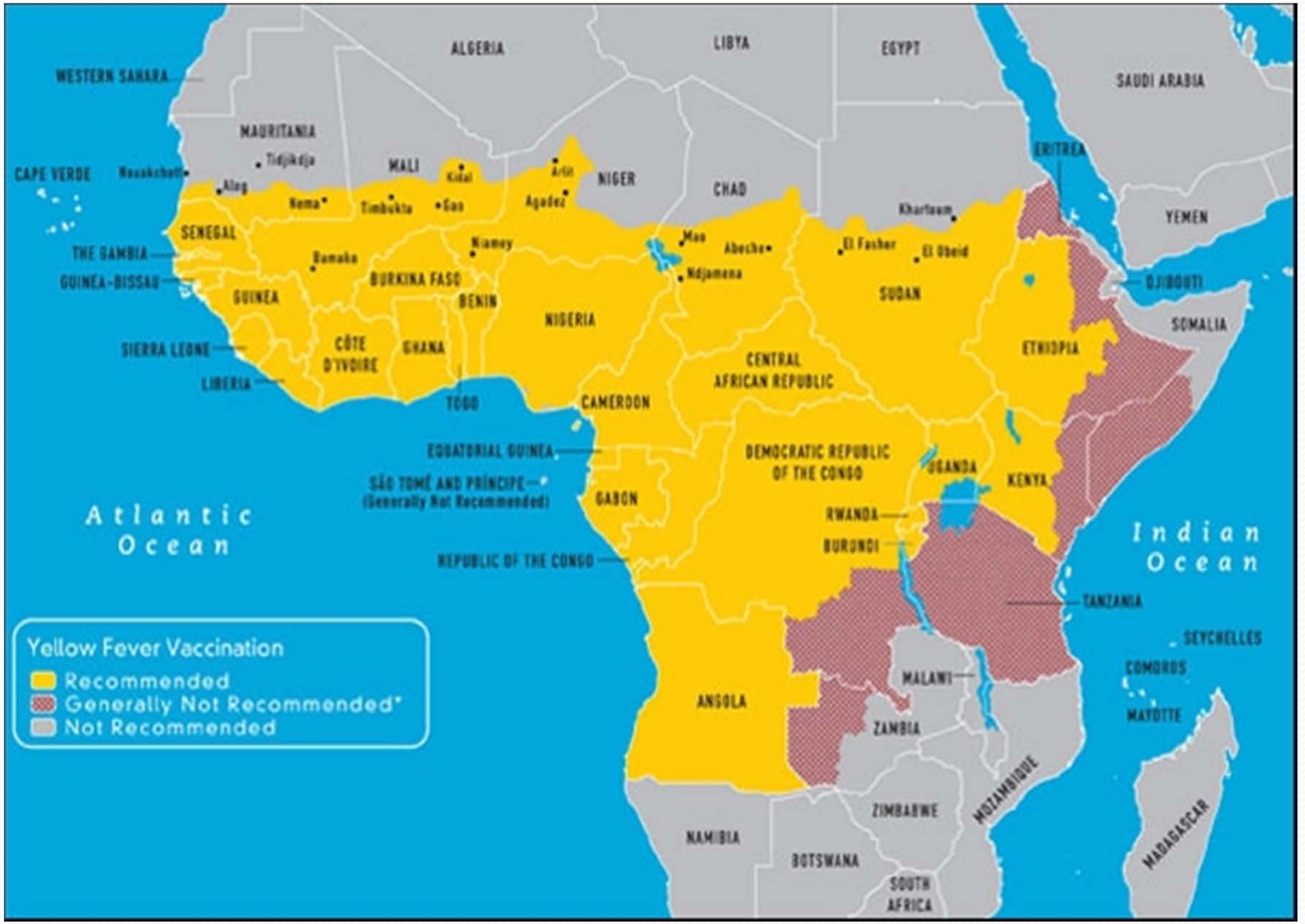
At least 3 factories (300 million euros) have been already build ….

New yellow fever vaccine

Do we need it?

Could we trust it?




WESTERN SAHARA
ALGERIA
LIBYA
EGYPT
SAUDI ARABIA
MAURITANIA
Tidjikdja
MALI
Kidal
Arlit
NIGER
CHAD
ERITREA
CAPE VERDE
Nouakchott
Aleg
Nema
Timbuktu
Gao
Agadez
Khartoum
YEMEN
SENEGAL
Niamey
Mao
Abeche
El Fasher
El Obeid
THE GAMBIA
Bamako
Ndjamena
GUINEA-BISSAU
BURKINA FASO
SUDAN
DJIBOUTI
GUINEA
BENIN
NIGERIA
SOMALIA
SIERRA LEONE
CÔTE D'IVOIRE
GHANA
ETHIOPIA
CENTRAL AFRICAN REPUBLIC
LIBERIA
TOGO
CAMEROON
EQUATORIAL GUINEA
DEMOCRATIC REPUBLIC OF THE CONGO
UGANDA
KENYA
SÃO TOMÉ AND PRÍNCIPE (Generally Not Recommended)
GABON
RWANDA
BURUNDI
Atlantic Ocean
Indian Ocean
REPUBLIC OF THE CONGO
TANZANIA
SEYCHELLES
COMOROS
MALAWI
ANGOLA
MAYOTTE
ZAMBIA
ZIMBABWE
MOZAMBIQUE
NAMIBIA
BOTSWANA
MADAGASCAR
SOUTH AFRICA
Yellow Fever Vaccination
Recommended
Generally Not Recommended*
Not Recommended


Panama Canal Zone
Cartagena
Santa Marta
PANAMA
Caracas
TRINIDAD AND TOBAGO
GUYANA
SURINAME
FRENCH GUIANA
Atlantic Ocean
Maturin
VENEZUELA
PanamaCity
Medellín
Bogotá
Cali
COLOMBIA
Quito
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Belo Horizonte
Pacific Ocean
Tarija
Iguassu Falls
PARAGUAY
Rio de Janeiro
São Paulo
Salta
CHILE
Resistencia
ARGENTINA
URUGUAY
Yellow Fever Vaccination
Recommended
Generally Not Recommended*
Not Recommended
Falkland Islands

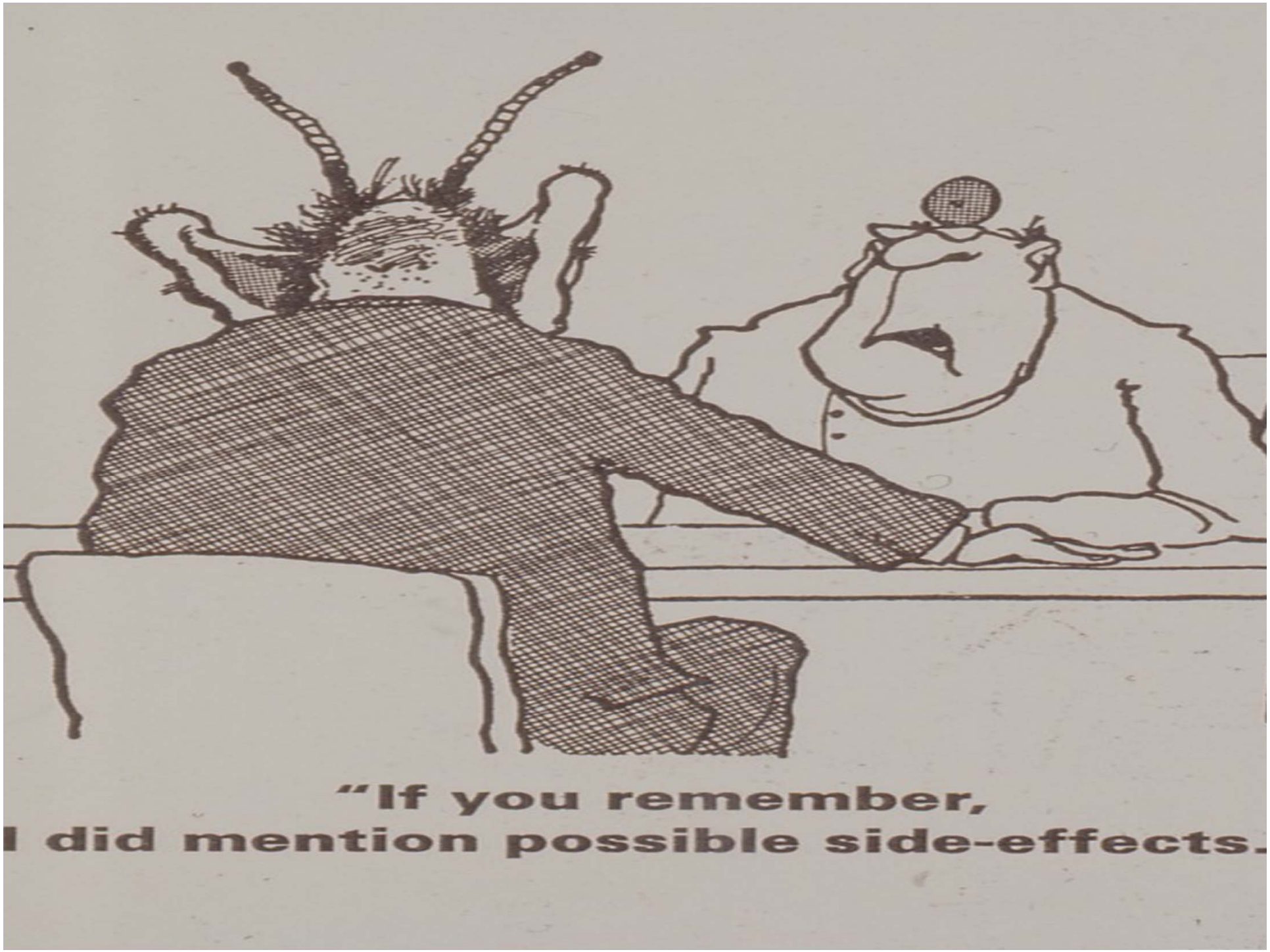
Yellow fever

- +/_ 200.000 cases/y and 20.000 deaths/y
- No specific therapy

  →Only possibility : vaccination
- 17D YFVaccine used since 1937;

  > 500 million vaccinated
- Cheap (< 1 $),very active (100%?) after 1 dose
- Inducing Th1-Th2 answer, with neutralizing Ab, cellular immunity and memory B cells…

  → What else !


"If you remember,
I did mention possible side-effects.

And 2001….

- **In addition to**
  - anaphylaxis: 1,8/100.000 (egg protein and gelatin)
  - YEL-AND: 0,8-9,9 / 100.000 († 1,5%)

  → **First description of**

  YEL-AVD: 0,4-7,9 / 100.000 († 63%) Mean age 47

  25 travellers/41 in mass campaign in the country in South America

  Always in primovaccination

  Not reported in Africa

And 2001…

- **YEL-AVD**: not linked to mutation but
  host factors: genetic
  immunosenescence…
- **Major CI:**

  - corticosteroids > 15 d AND > 20 mg predn./d
  - immunomodulating drugs (including monoclonal Ab)
  -chemotherapy/major radiotherapy,…
  - pregnant woman
  -CD4 < 200 (HIV or other T cell immunodeficiencies)
  -thymectomy or « thymus- related »pathologies
  -**age: to consider if > 65/70 y**

Is it time for a new YF vaccine?

Vaccine 2010 EB Hayes

- **Why not?**

  In addition to previous problems:

  -encephalitis in children acquiring the virus through breastfeeding (MMWR 2010)

  - increase relapse rate following YF vaccination in patients with MS (Farez, Arch Neurol 10/2011)

  - mutual interference on the immune response to YF vaccine and MMR vaccine(Nascimento Silva,Vaccines 2011)

  simultaneous administation leading to lower Ab (seroconversion and/or GMT) for rubella/YF

Inactivated cell culture vaccine against YF

Monath, Vaccine 2010 and NEJM 2011

- **XRX-001** : investigational YF vaccine

  Has been shown immunogenic in

  mice ,hamsters and monkeys

  and protect against lethal challenge

  in small animals

- ***Phase 1 study recently published***:

  DBPC study in 60 healthy adult subjects

  < Safety and immunogenicity

XRX-001 phase 1 study (NEJM 2011)

- Whole –virus inactivated with β propionolactone
- Produced in Vero cell cultures
- Adsorbed to alum

→Injection at Do and D 21 of 4,8 or 0,48 µg Ag

-Neutralizing Ab in 100% >< 88%

- > 90% of those receiving 4,8µg have titers > 1/40

(exceeding the minimum protective level estimated at 1/10 to 1/20)

- Seropositivity after one dose: 46% >< 13%

But durability/mean GMT most likely < to 17D YFV…

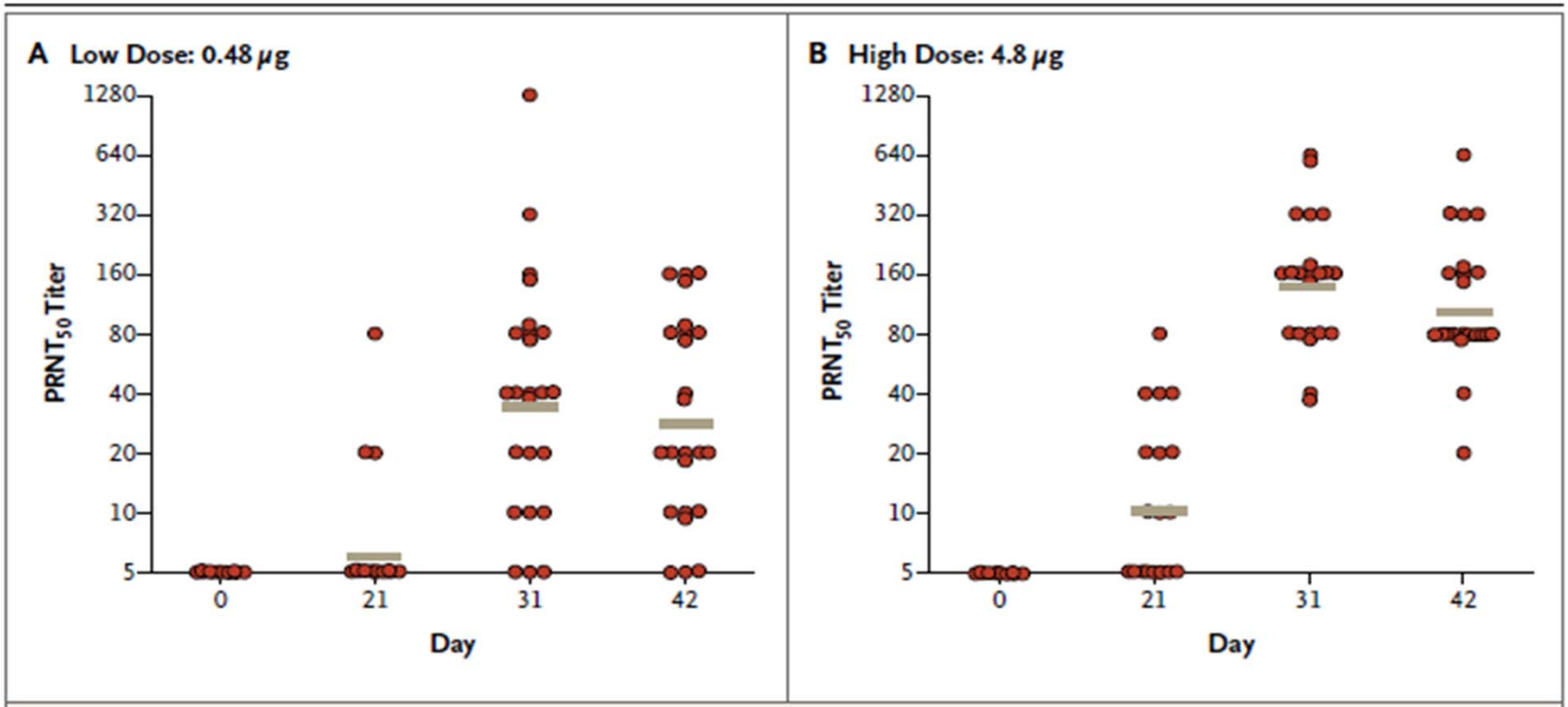


Figure 1. Plaque-Reduction Neutralization Test (PRNT) Titers of Neutralizing Antibody through Day 42 in the Two Vaccination Groups, According to Dose.

Panel A shows data for the low-dose vaccination group, and Panel B data for the high-dose vaccination group. The $PRNT_{50}$ titer is the highest serum dilution inhibiting 50% or more of the plaques. Values for each subject and the geometric mean titers (horizontal gray lines) are shown.

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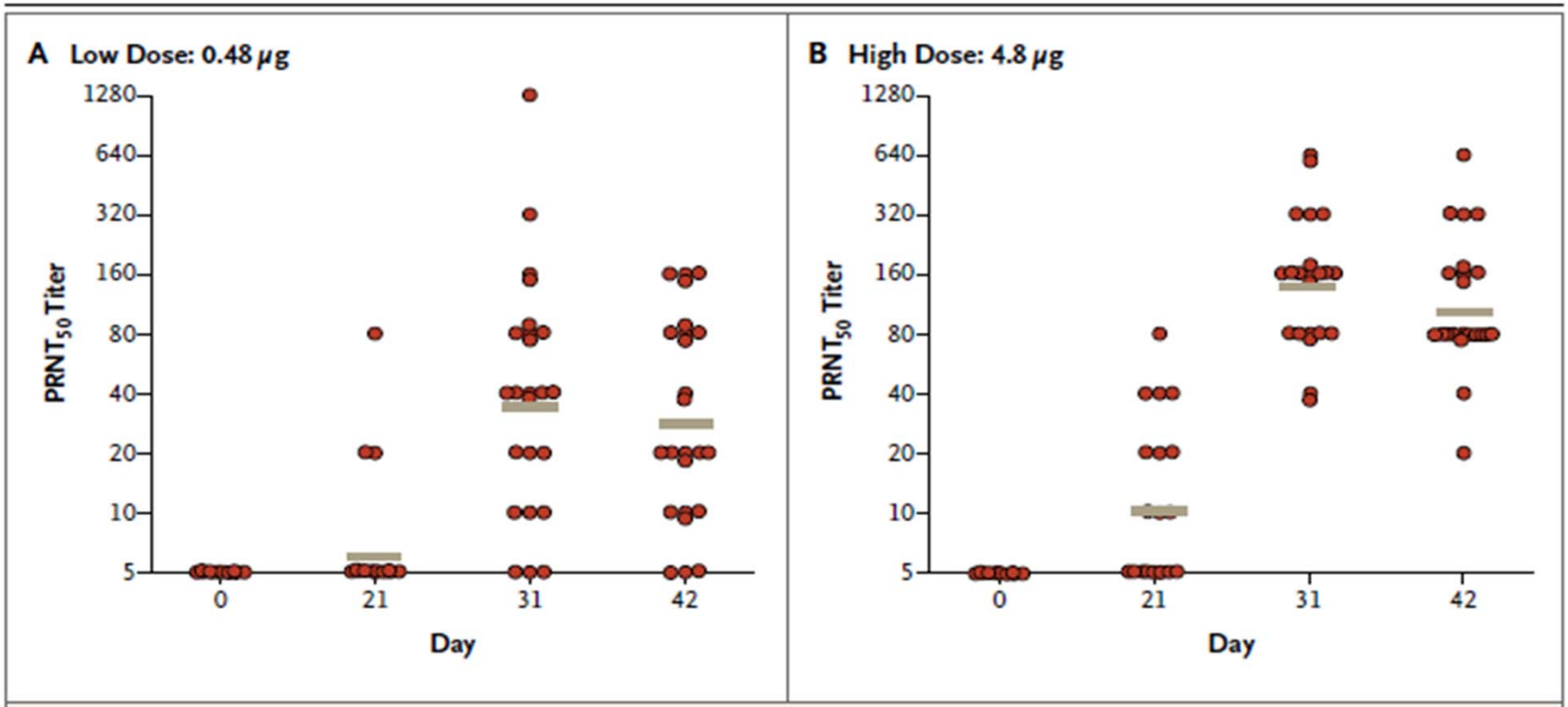

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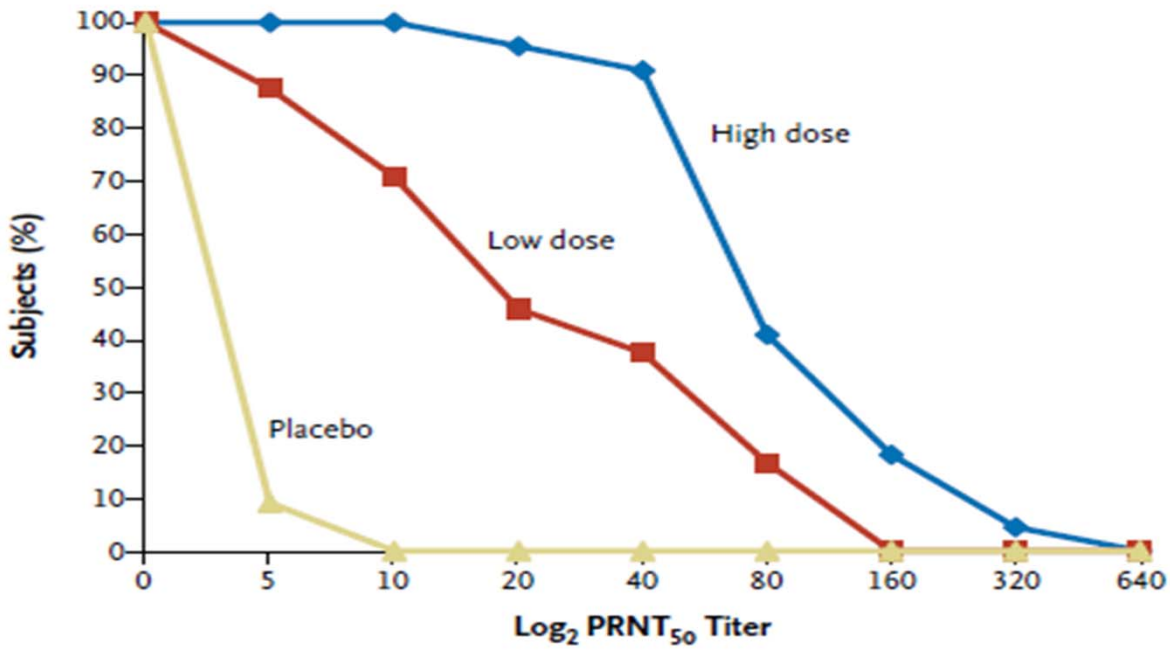

Figure 2. Cumulative Reverse Distribution of Plaque-Reduction Neutralization Test (PRNT) Titers of Neutralizing Antibody at Day 42, According to Study Group.

The $PRNT_{50}$ titer is the highest serum dilution inhibiting 50% or more of the plaques.

2018: Kisses from Iguacu with Chimeri Vax and XRX-001…?