



Advancing vaccine development and manufacture in Africa  
24 – 25 September 2018, Freetown, Sierra Leone

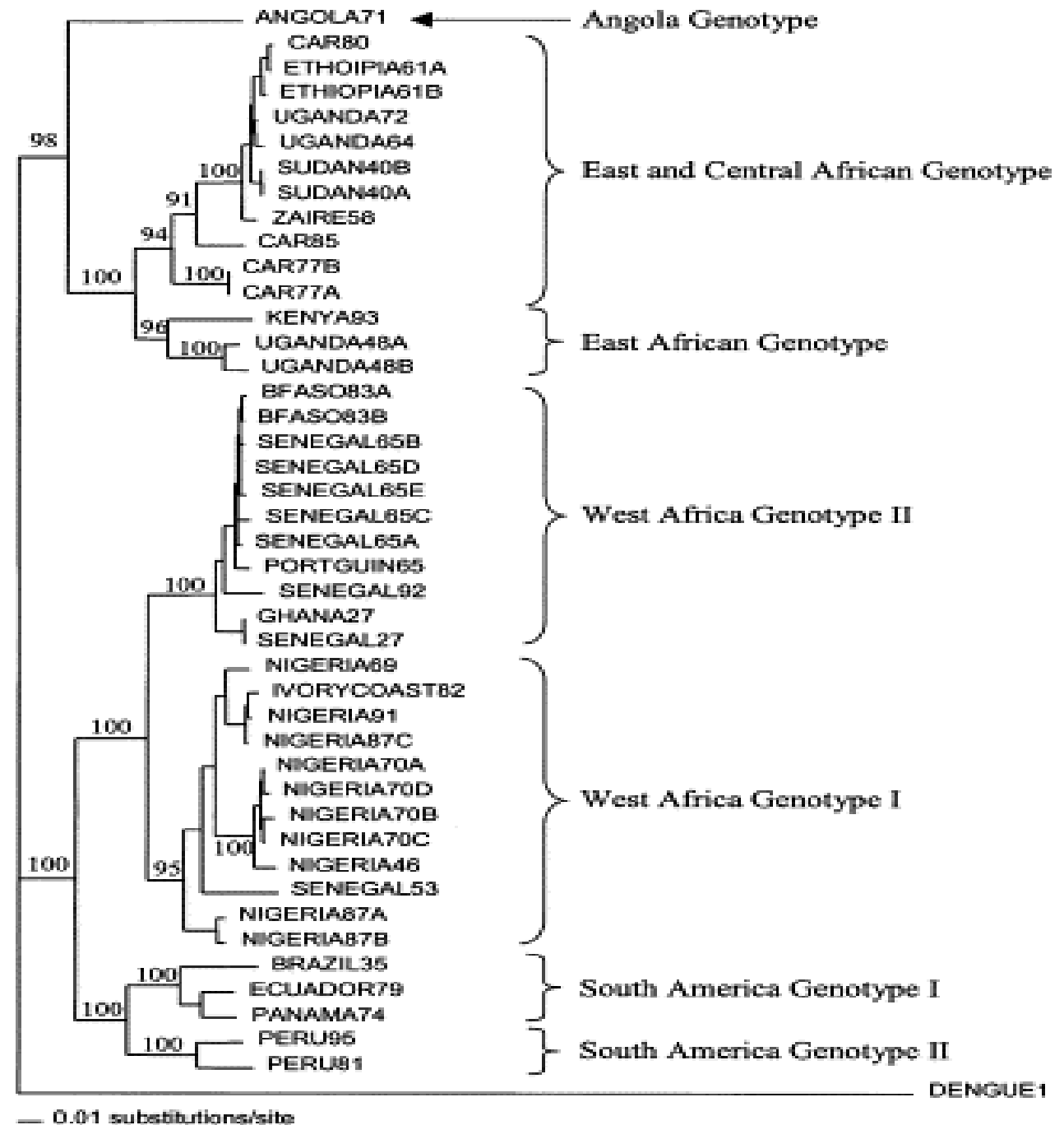
**YELLOW  
FEVER**

# **Yellow Fever – The Virus**

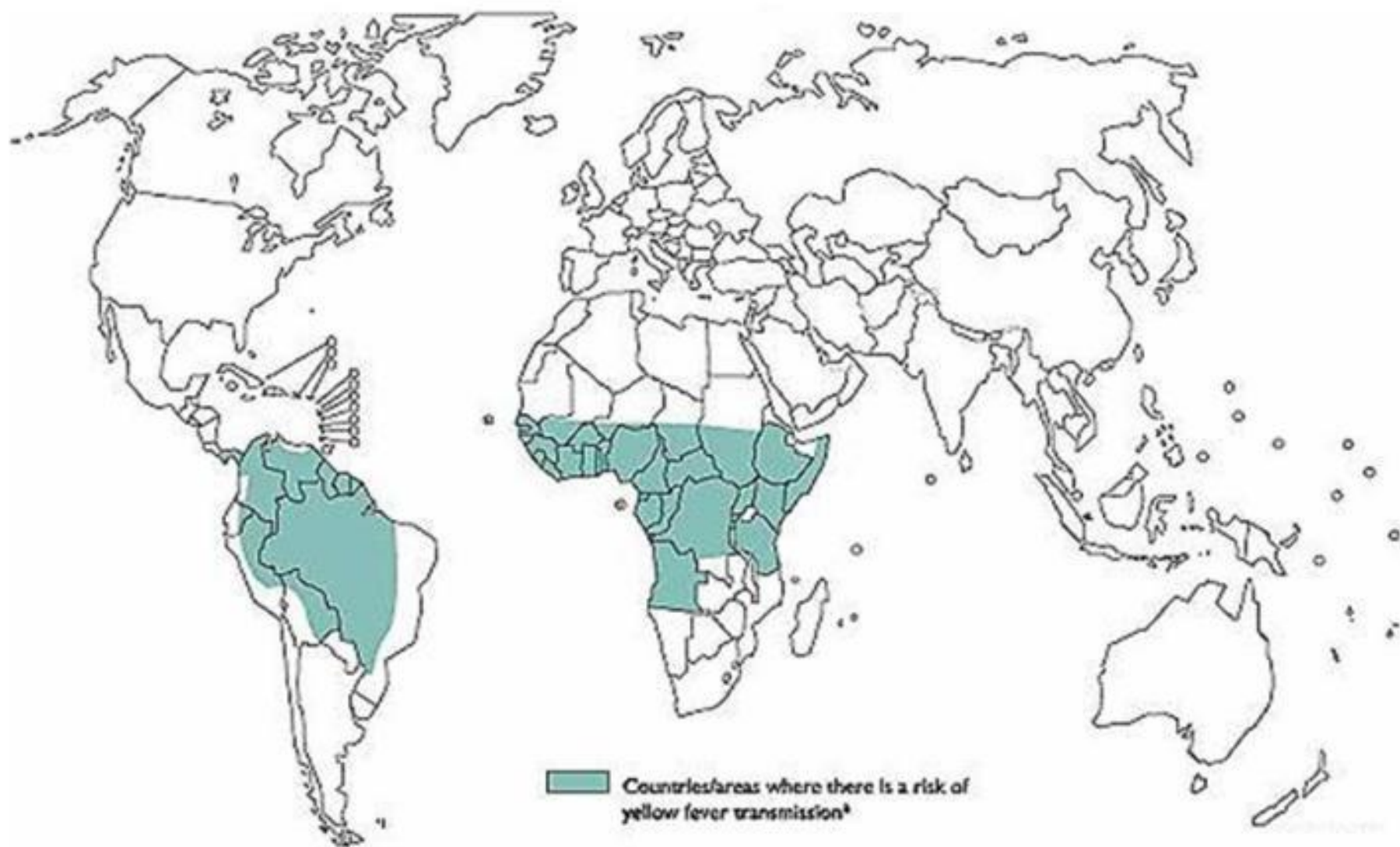
- **An Arthropod-borne virus “arbovirus” - diverse group of viruses transmitted by arthropods between vertebrate hosts**
- **Vertebrate hosts of YF are monkeys and man**
- **Prototype member of the over 70 related *Flaviviruses* of the *Flaviviridae* family, including DEN, JE, BAN, WESS, WN, ZIKA**
- **YF virus is also classified as a hemorrhagic fever virus, because major bleeding with hematemesis and melena occur in some cases**

# Yellow Fever – The Virus

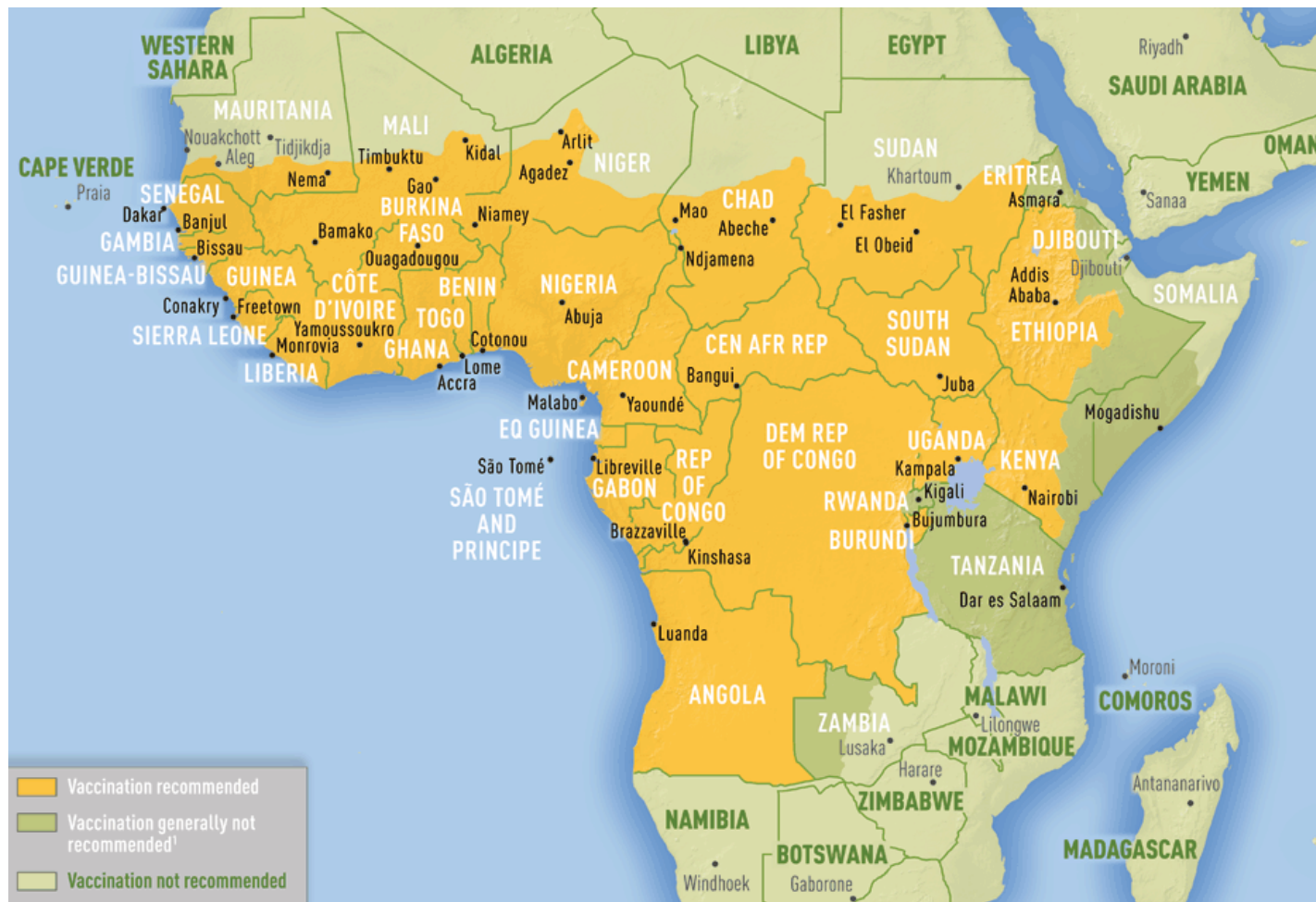
- Single serotype, with antigenic differences between strains
- African and American strains are distinguishable by lab techniques and pathogenicity for laboratory mice
- 2 genotypes in Africa, with 1, or 2 in the Americas



## Areas at risk of Yellow Fever transmission



\* Either yellow fever has been reported or the presence of vectors and animal reservoirs creates a potential risk of infection (considered to be endemic areas).



# YELLOW FEVER IN AFRICA

&



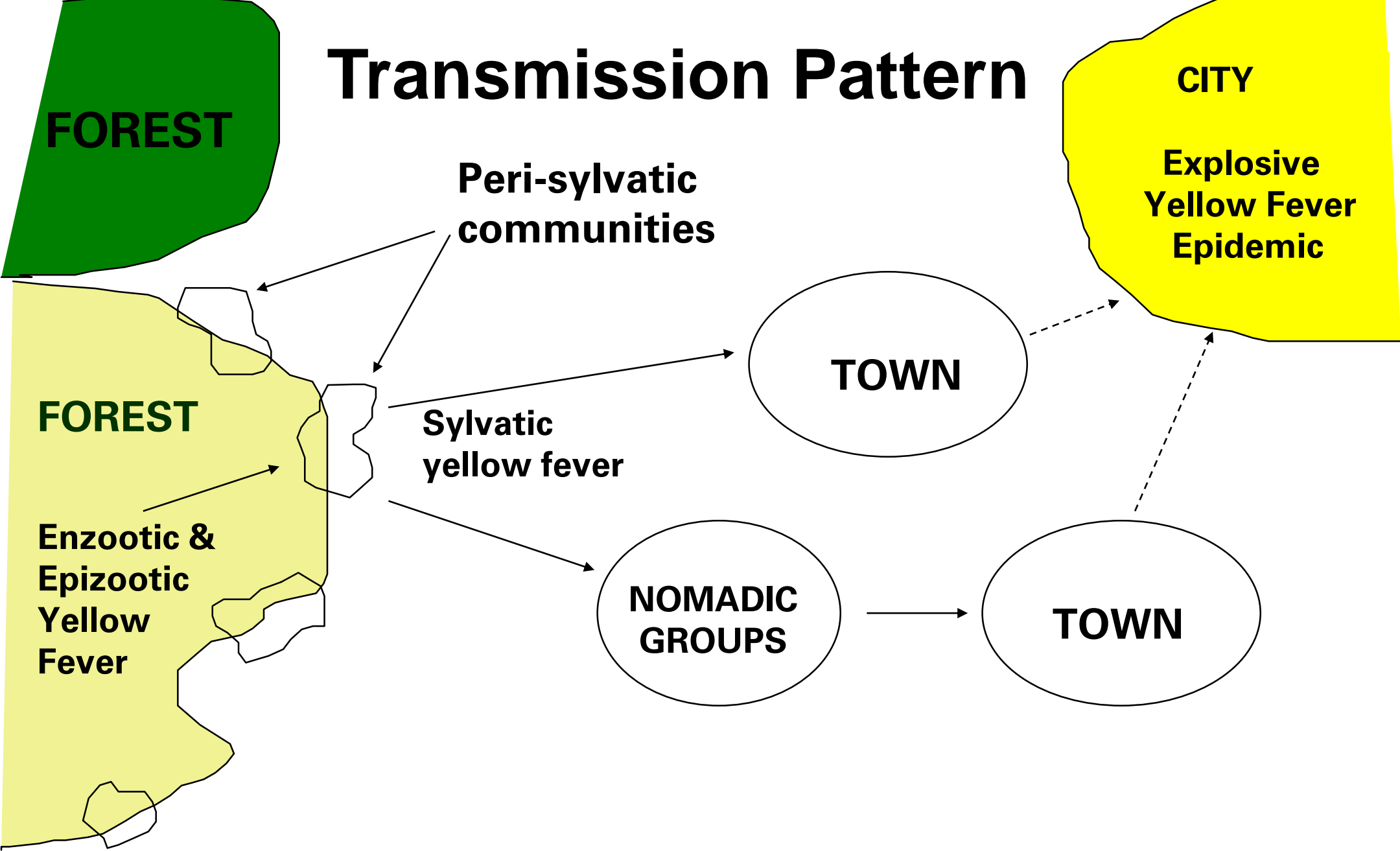
# SOUTH AMERICA

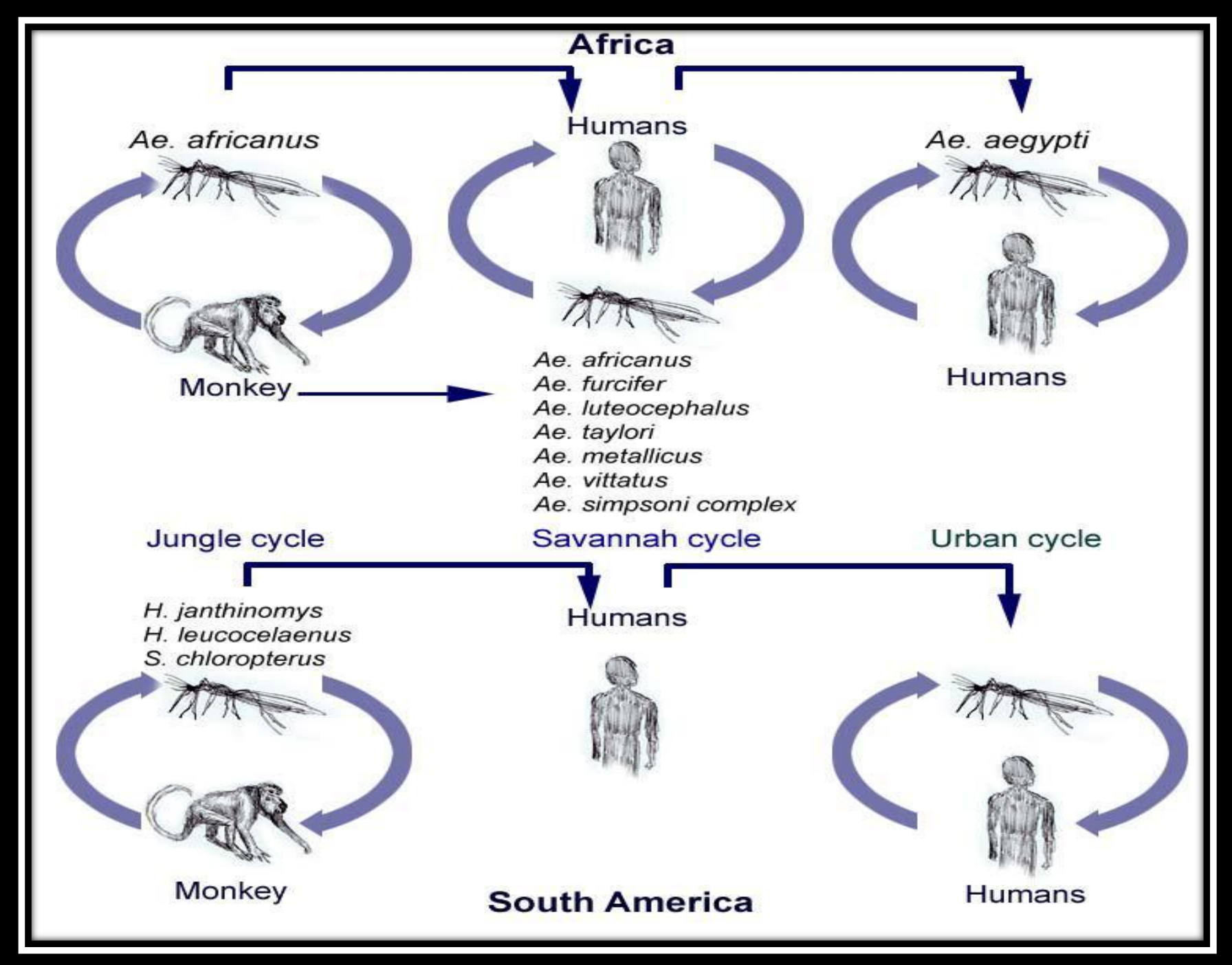
# **Yellow Fever:**

## **Incidence & Geographical Distribution**

- **No report of YF in Asia**
  - ***Non-introduction of YF to Asia***
  - ***Low viremia in infected humans***
  - ***Cross protection due other flavivirus infections (DEN, JE etc)***
  - ***Low vector competence (Ae. albopictus)***

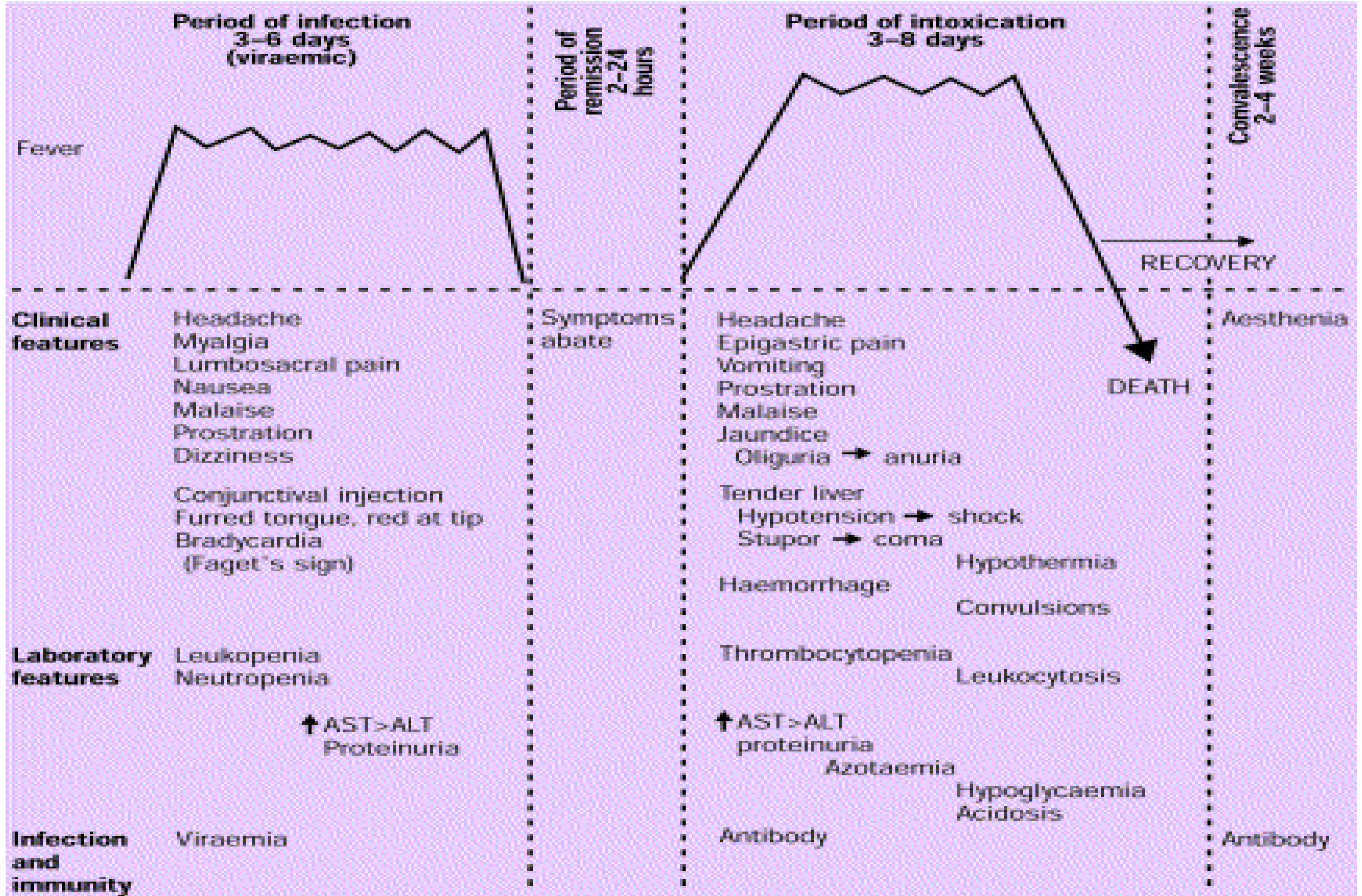
# Transmission Pattern





# **Characteristics of Yellow Fever Disease**

- 3-7 day incubation with an acute onset: initial malaria-like**
- Runs a mild to fatal course, remission in 4-5 days, death 7-10 days**
- Hepato-renal & neurotropic with/out haemorrhage; mortality as high as 20-50% in hepato-renal disease.**



**Period of infection**  
3-6 days  
(viraemic)

**Period of remission**  
2-24  
hours

**Period of intoxication**  
3-8 days

**Convalescence**  
2-4 weeks

Fever

RECOVERY

DEATH

**Clinical features**

Headache  
Myalgia  
Lumbosacral pain  
Nausea  
Malaise  
Prostration  
Dizziness  
  
Conjunctival injection  
Furred tongue, red at tip  
Bradycardia  
(Faget's sign)

Symptoms abate

Headache  
Epigastric pain  
Vomiting  
Prostration  
Malaise  
Jaundice  
Oliguria → anuria  
  
Tender liver  
Hypotension → shock  
Stupor → coma

Aesthenia

**Laboratory features**

Leukopenia  
Neutropenia  
  
↑AST > ALT  
Proteinuria

Haemorrhage  
  
Thrombocytopenia  
Leukocytosis

Hypothermia

Convulsions

↑AST > ALT  
proteinuria  
Azotaemia

Hypoglycaemia  
Acidosis

**Infection and immunity**

Viraemia

Antibody

Antibody

# **YELLOW FEVER**

## **THE RECURRING PLAGUE**

- **Brief historical overview of Yellow Fever**

- **Current Yellow Fever outbreaks**

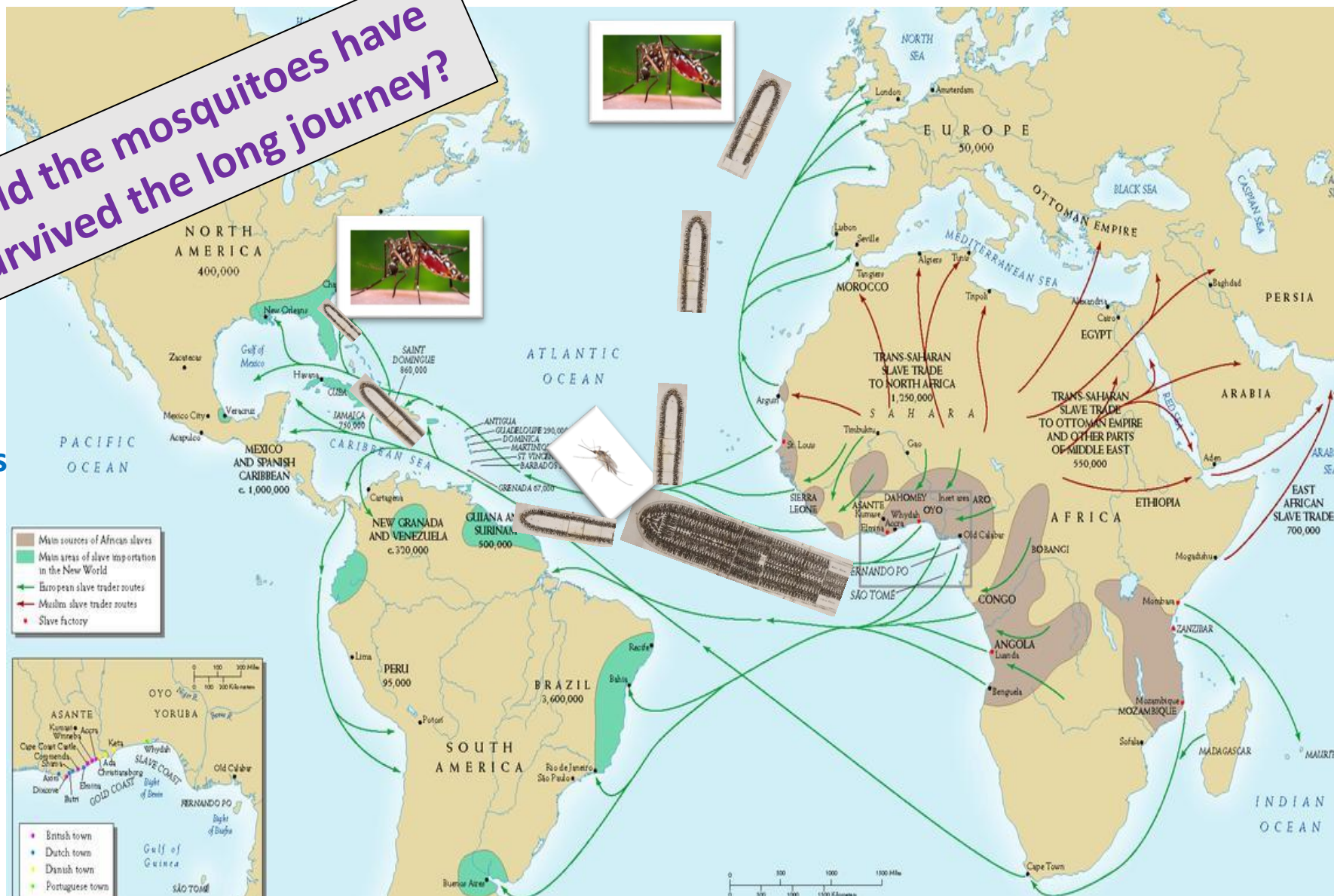
- **Impact of Yellow Fever outbreaks globally**

- **What Future for Yellow Fever?**

# Brief historical overview of Yellow Fever

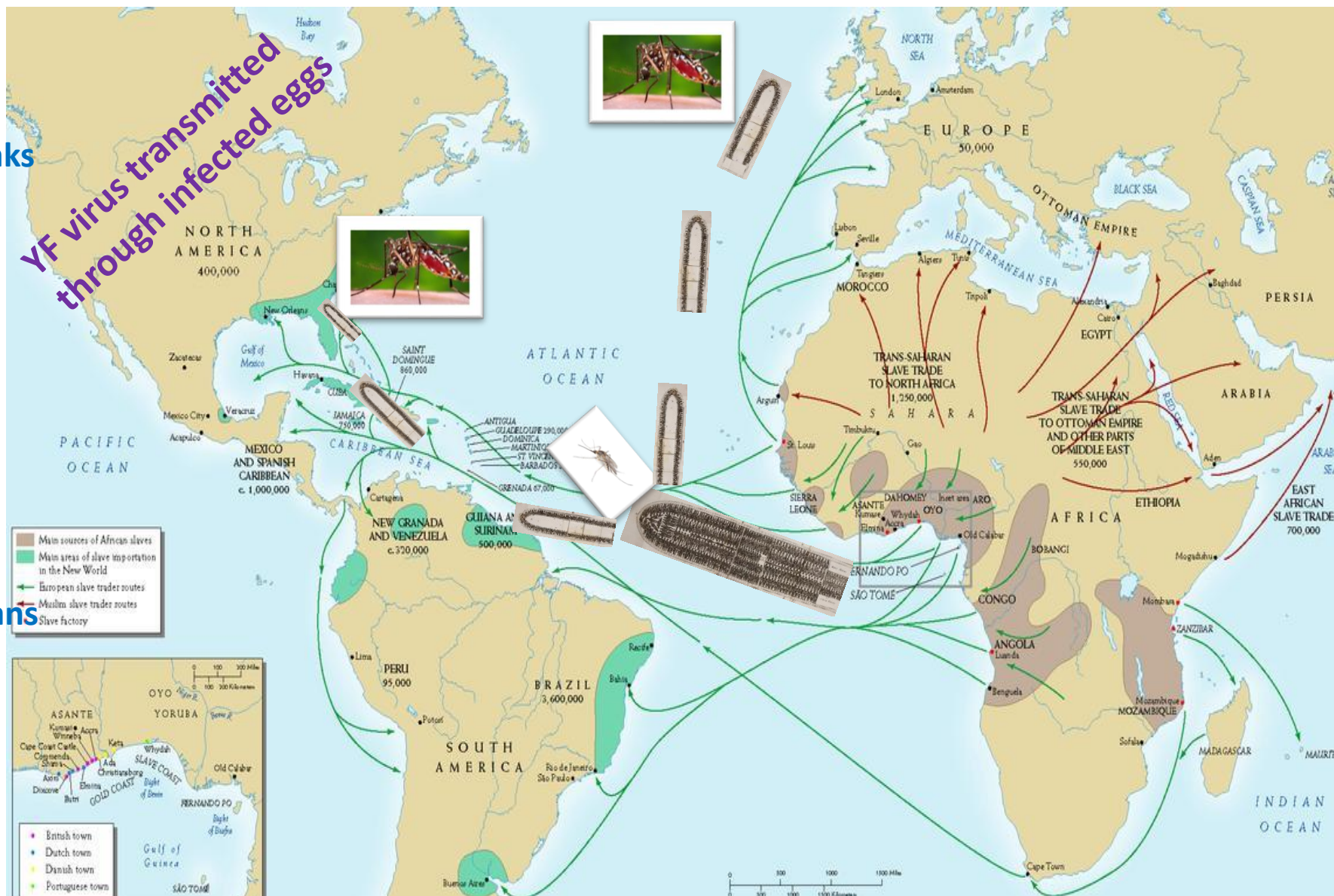
- 3000 BC – Africa
- 1526-1867 – Slave trade
- 1648 – Maya Manuscript
- 1668-1699 - First wave, YF outbreaks  
US: *New York (1668), Boston (1691)*  
*Charleston (1699)*
- 1700-1730 – Europe: Spain, French/  
English sea ports
- 1768 – Senegal \*St. Louis
- 1842-1878 - F. Po, Gambia

Could the mosquitoes have survived the long journey?



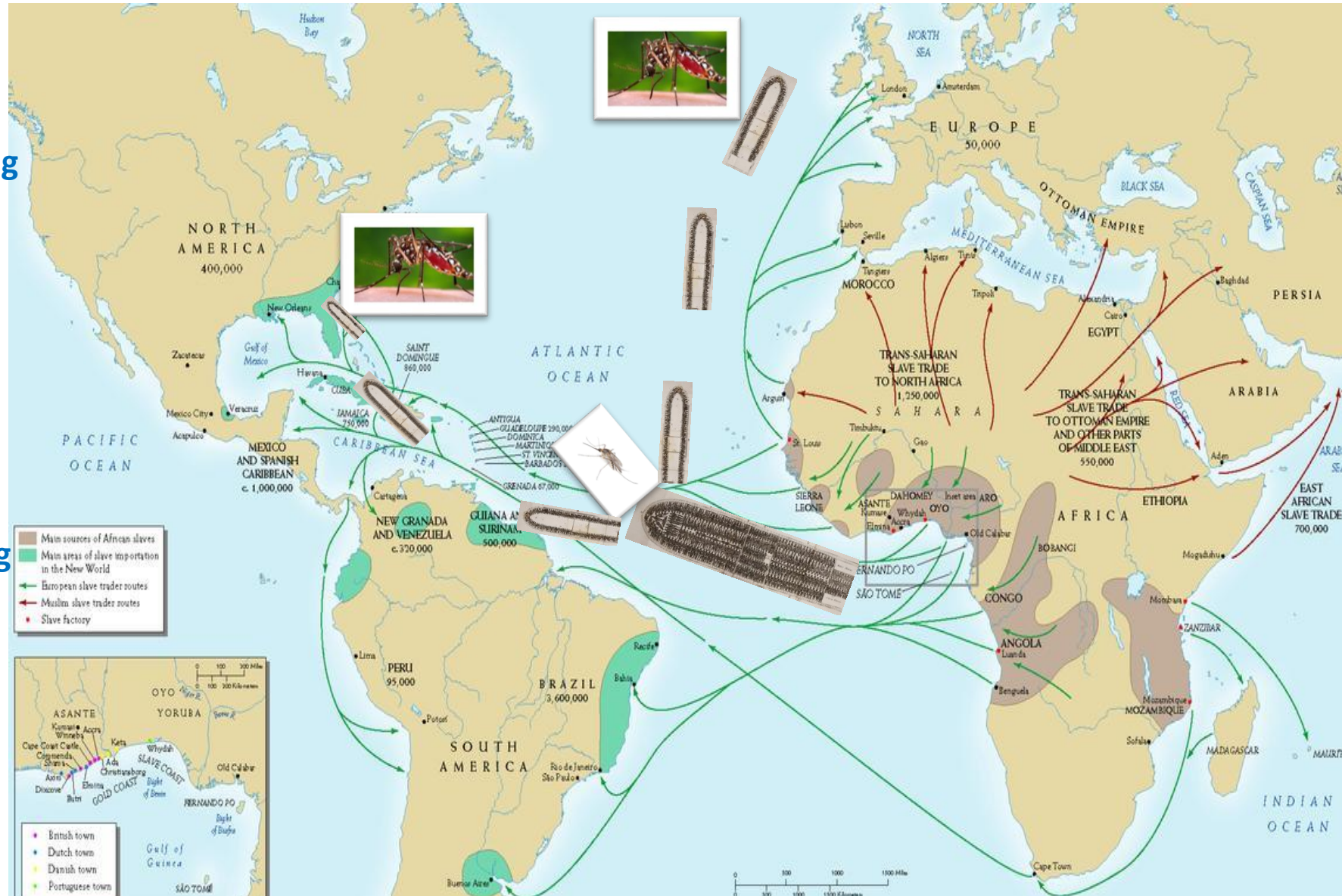
# Brief historical overview of Yellow Fever

- 1793-1878 -2<sup>nd</sup> US wave: YF outbreaks  
*US: Philadelphia (1793), Savannah (1820), New Orleans (1853), Norfolk (1855), Texas & Louisiana (1867), Mississippi (1878)*
- 1790 -1802 - Haiti
- 1848 - Mosquitos as vectors???
- 1900 - Aedes mosquito confirmed
- 1905 - Last US outbreak- New. Orleans
- 1930 - 2 YF vaccines developed: FNV & 17D vaccines
- 1934 - 1953 - YF mass campaigns: S. America (17D) & W. Africa (FNV)



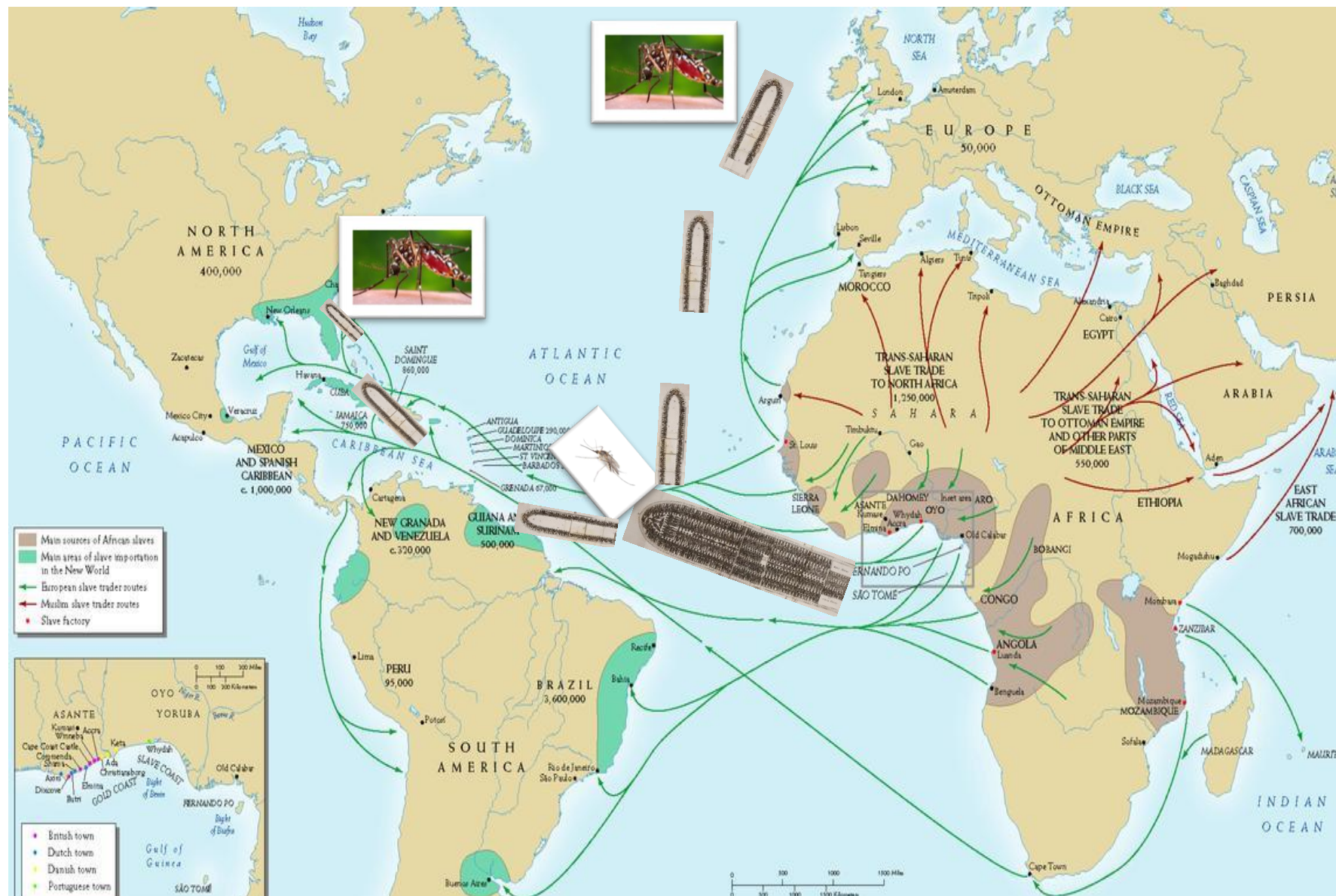
# Brief historical overview of Yellow Fever

- 1948 – Official YF outbreak reporting by countries to WHO
- 1960-1990 - Major YF outbreaks in W. Africa/Ethiopia/
- 1990-2003 – YF outbreak spreading C. & E. Africa
- 2008-2013 – YF outbreaks escalating in C. & E. Africa, with reduced incidence W, Africa
- 2008-2014 – YF, definite shift to C. & E. Africa



# Brief historical overview of Yellow Fever

- 2015 – WHO declares 1 dose YF vaccine induce life long immunity
- 2016 - Severe urban YF outbreaks in Angola & D.R. Congo,
- Importation/exportation to China, Kenya and Mauritania – self limiting



# **YELLOW FEVER**

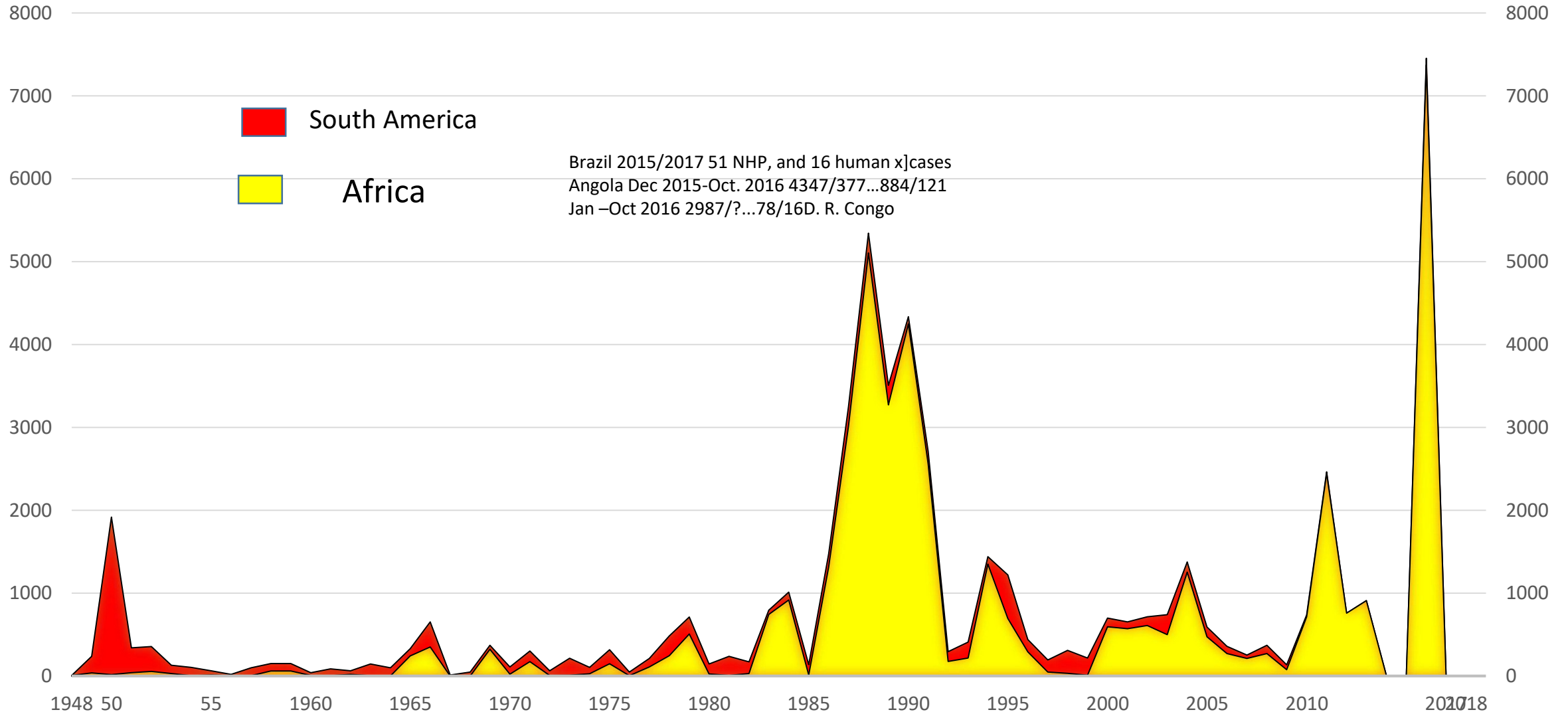
## **THE RECURRING PLAGUE**

- **Brief historical overview of Yellow Fever**

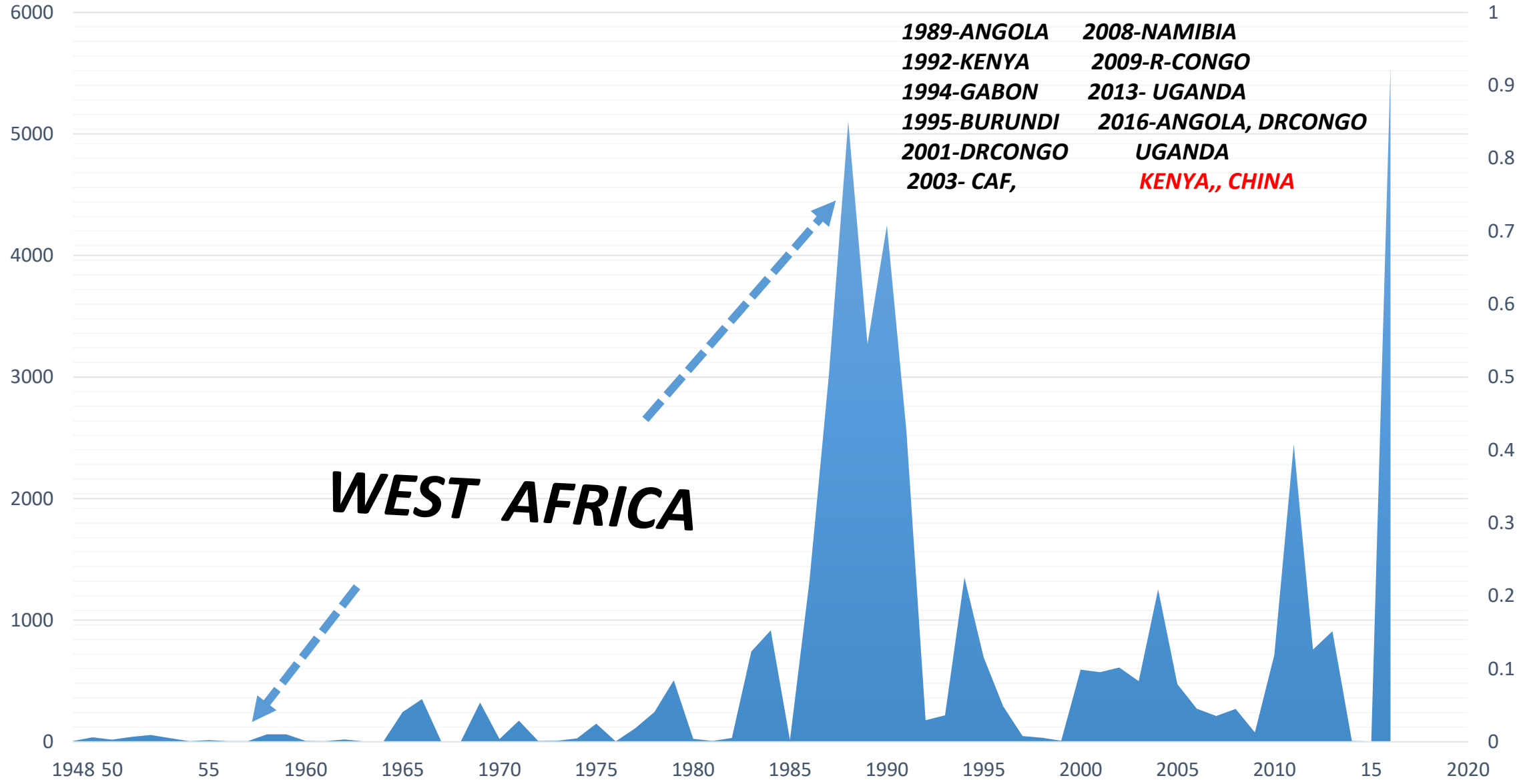
### **Current Yellow Fever outbreaks**

- **Impact of Yellow Fever outbreaks globally**

# ~ 70 years of reporting Yellow Fever to WHO

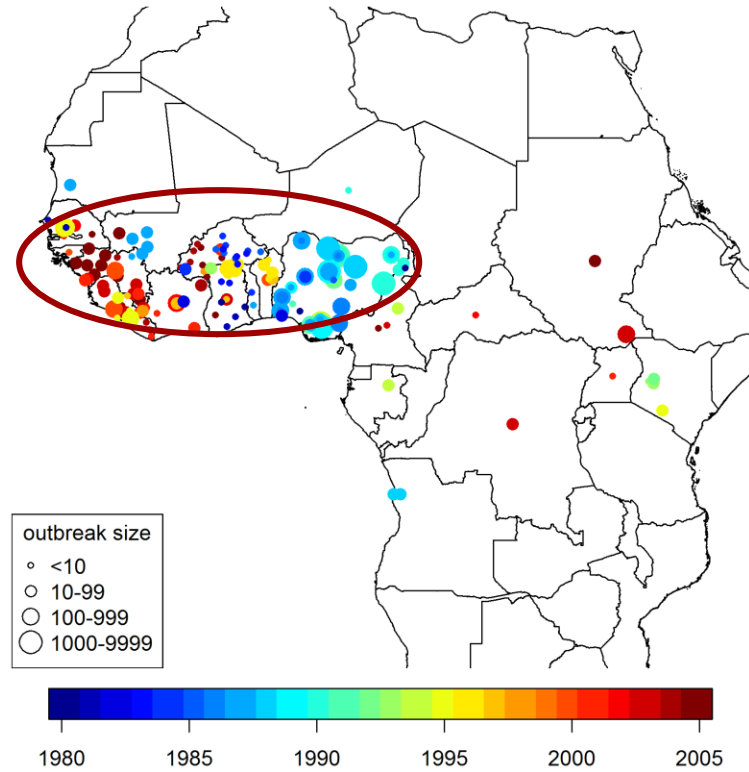


# THE RELENTLESS MARCH OF Yellow fever THROUGH AFRICA

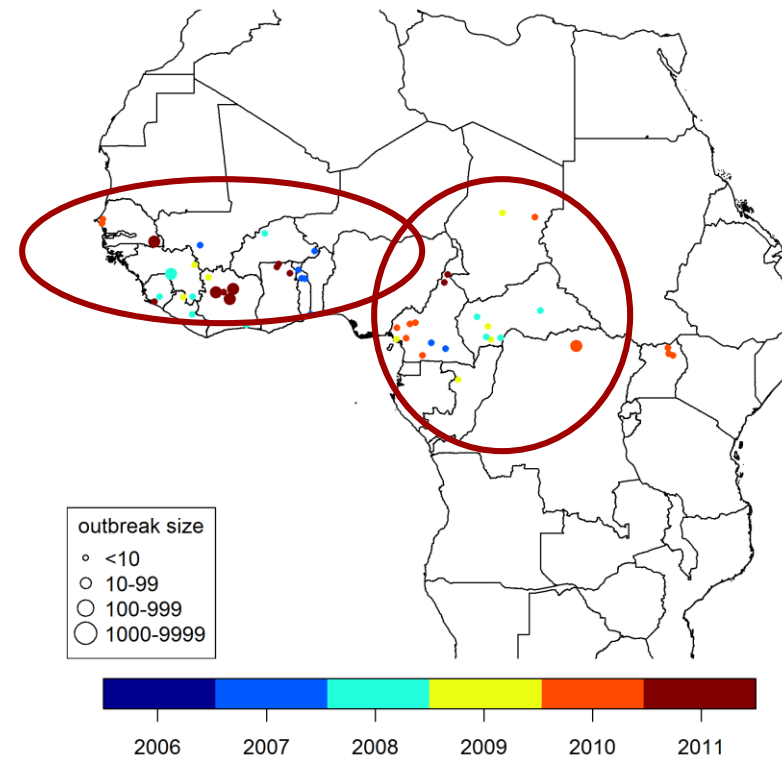


# Outbreaks and suspected cases of YF in Africa

## Before 2006

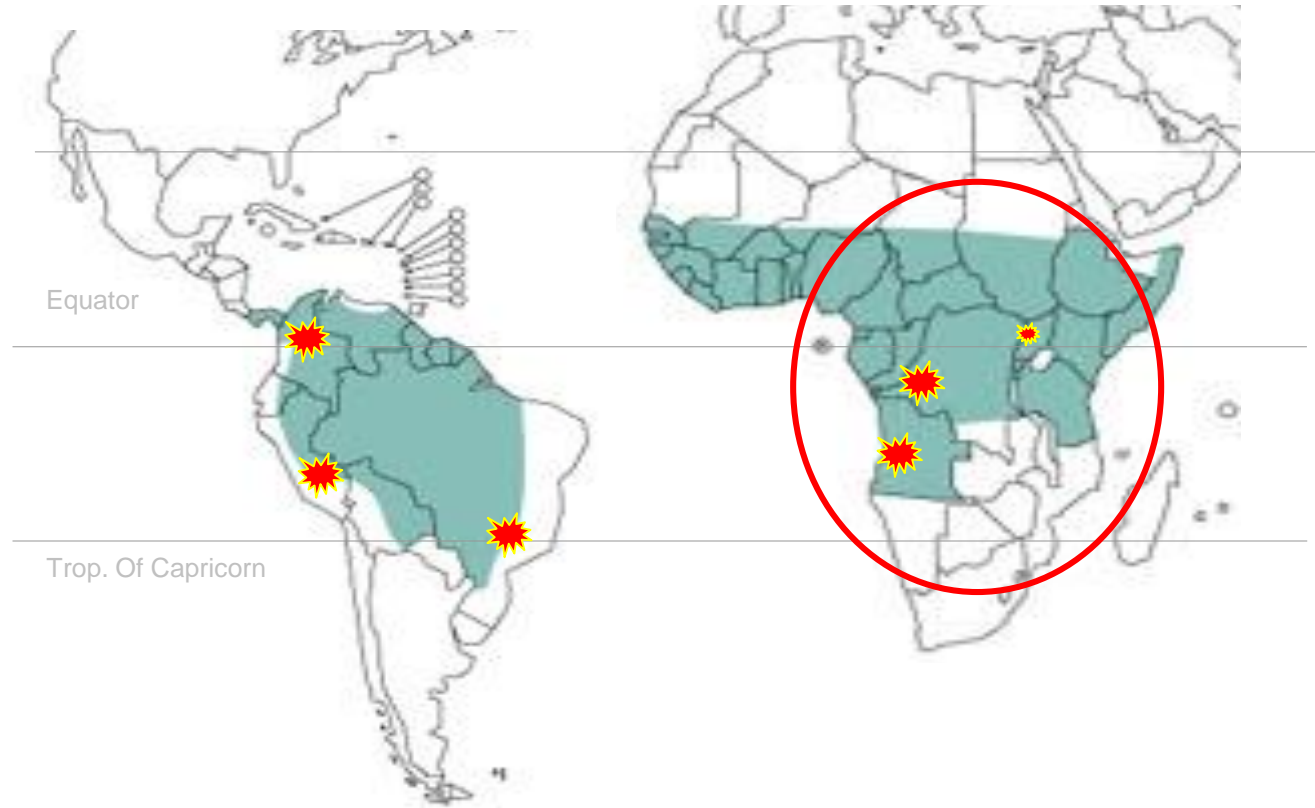


## After 2006



# YF outbreaks in 2016

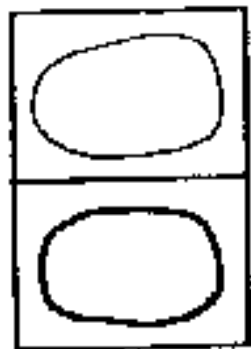
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 Countries reporting YF cases

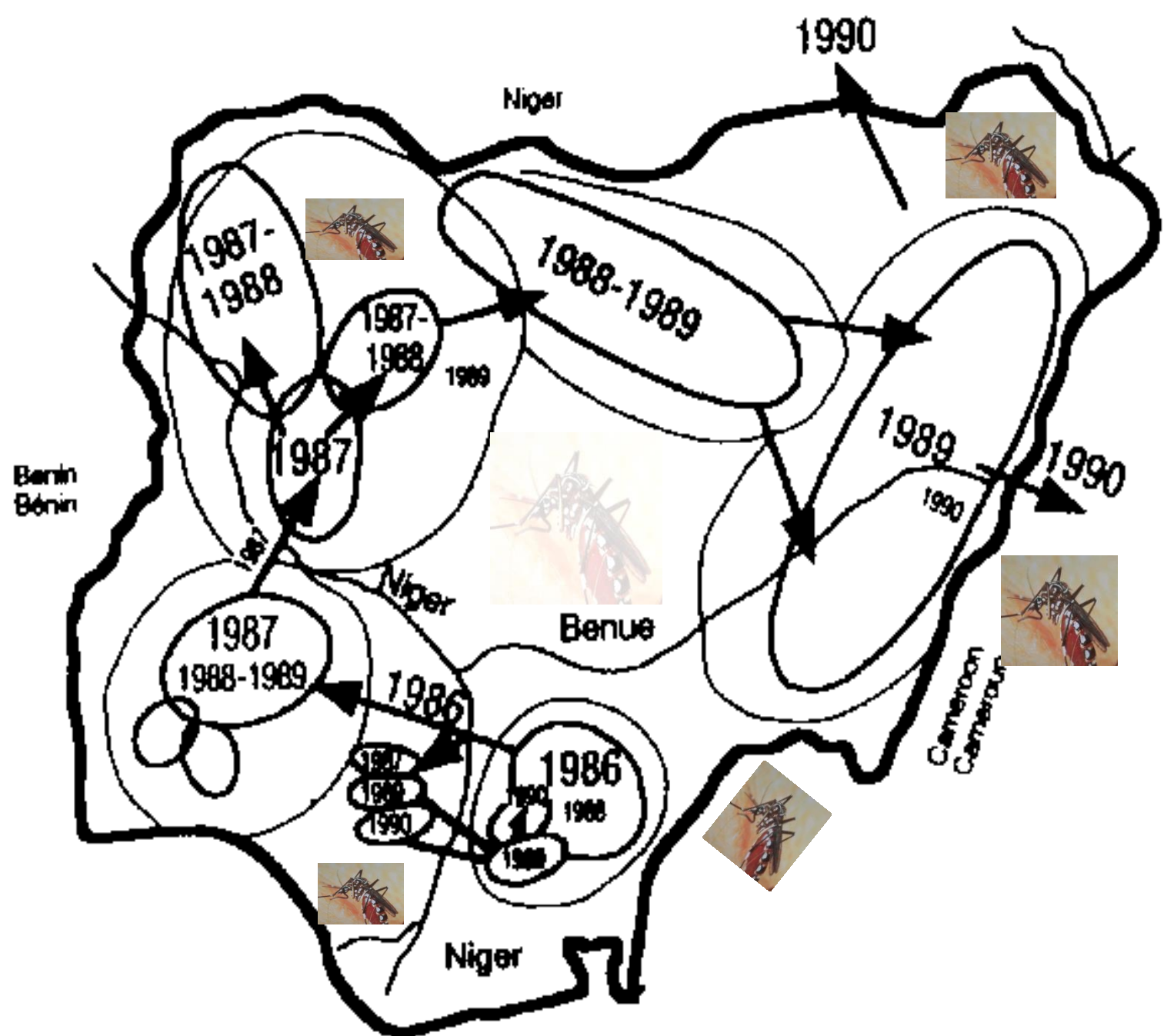


YF RUNNING CIRCLES ROUND  
NIGERIA, 1986-1990



Probable extent  
Etendue probable

Extent  
Etendue



AFRICAN

# concord

“There were shouts here and there... Death looked so cheap”

## NIGERIA'S YELLOW FEVER EPIDEMIC

BY [unreadable]  
PHOTOGRAPH BY [unreadable]  
ILLUSTRATION BY [unreadable]



# Mystery-disease kills 100 in Delta

By FRANCIS NIGUMAM

FROM THE TIME IT BEGAN, THE DISEASE KILLED EVERY DAY WITHIN THE LAST ONE MONTH.

LAGOS — The nominees for the National Republican Convention (NRC) candidates into the State House of Assembly have been fixed for this Friday, November 1, 1991. The party commission, by the chairman and deputy chairpersons in respect of local government nominees Oyetokunbo which had earlier been fixed for next Wednesday, November 6, 1991, will now take place.

### NRC fixes date for state assembly nomination

## YELLOW FEVER CLAIMS 100 LIVES IN IMO

From LIMUS ANYANWU, Owerri  
YELLOW fever outbreak claimed more than 100 lives in Imo State. The epidemic has been confirmed in the four local government areas of the state name-

Dr. Chigozie N. Ogbu, said that more than 45 deaths were recorded in the seven villages of Amimo community of Ikeduru Local Government Area between July

to condoning off the affected areas", he said. The commissioner confirmed that top officials of the Federal Ministry of Health had visited Imo State and that blood samples

NO. 6601

FRIDAY, APRIL 24, 1987

PRICE 50K

# YELLOW FEVER AGAIN

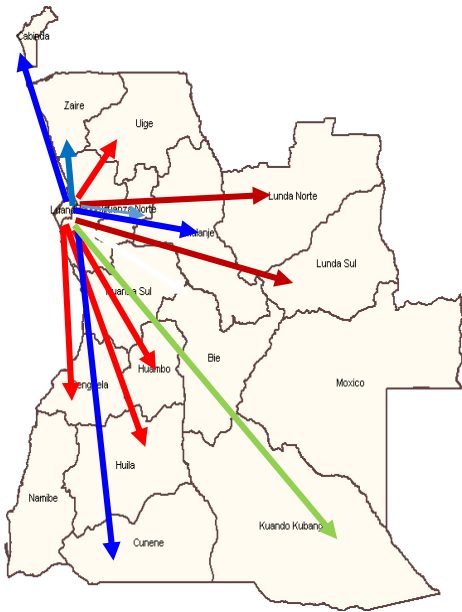
## 80 die in new outbreak

### ₦1.33m received for rice, cement

Immediately the money was paid into his account, Chief Anywolo said, he proceeded to Europe to negotiate with a foreign partner for arrangements on how the goods would be imported into the country. Unfortunately, he added, his bank account had been frozen by the Special Investigation Panel (SIP) before he returned from the trip to Europe.

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# SPREAD OF YELLOW FEVER CASES FROM ANGOLA



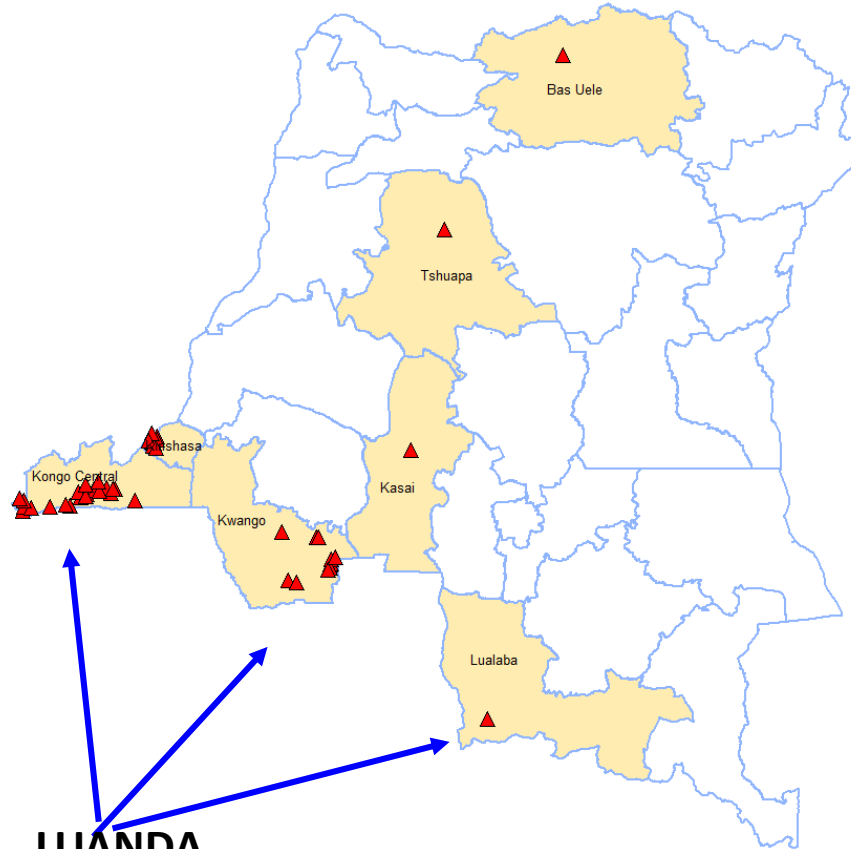
## NATIONAL

As of Sep.29 2016

- 4188 suspected cases /373 deaths in 16 of 18 provinces

- 17M people vaccinated in ANG & DRC

- 7M vaccinated with fraction dose of YF vaccine



LUANDA

## INTERNATIONAL

DRCongo- as of 5 Oct 2016

- 2870 suspected cases in 26 provinces
- 2473 samples lab tested, 76 confirmed/16 deaths
- Of 57 confirmed cases, 13 autochthonous
- Also cases exported to Mauritania (1) & Kenya (2)



## INTER-CONTINENTAL

China 11

# Yellow Fever Importation to Europe & America

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Year	<u>Imported</u>		<u>Case</u>		
	From	To	Age/Sex	Vacc. Status	Outcome
1979	Senegal	France	42/M	Not vaccinated	Died
1979	Senegal	France	25/M	Not vaccinated	Died
1988	West Africa*	Spain	37/F	Vaccinated**	Died
1996	Brazil	USA	42/M	Not vaccinated	Died
1996	Brazil	Switzerland	53/M	Not vaccinated	Died

**There have been 7 additional YF importation to Europe from Ivory Coast (1999), Gambia (2002), plus 5 additional cases from US to Europe..latest being March 2017 from Suriname to the Netherlands**

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\*, travelled through several countries: Niger, Mali, Burkina Faso & Mauritania

\*\* , Had history of vaccination 5 years prior to travel, but probably received Hep B, and not YF vaccine

# YELLOW FEVER IMPORTATION, 1979-2002



Year	From	To
1979	Senegal	France
1988	W. Africa	Spain
1996	Brazil	USA
1996	Brazil	Switzerland
1999	CIV	Germany
1999	Venezuela	USA
2000	Suriname	Netherlands
2001	Gambia	Belgium
2002	Brazil	USA

# **YELLOW FEVER & PUBLIC HEALTH**

**Africa contributes more than 90% of global yellow fever morbidity and mortality.**

**In 2013, YF burden in Africa estimated as 130,000 (range 51,000–380,000) and 78,000 (range 19,000–180,000) deaths**

## **YF**

- disrupts existing health care delivery services,**
- overstretch scarce internal resources,**
- fatigues donor assistance and**
- results in gross wastage of vaccines.**

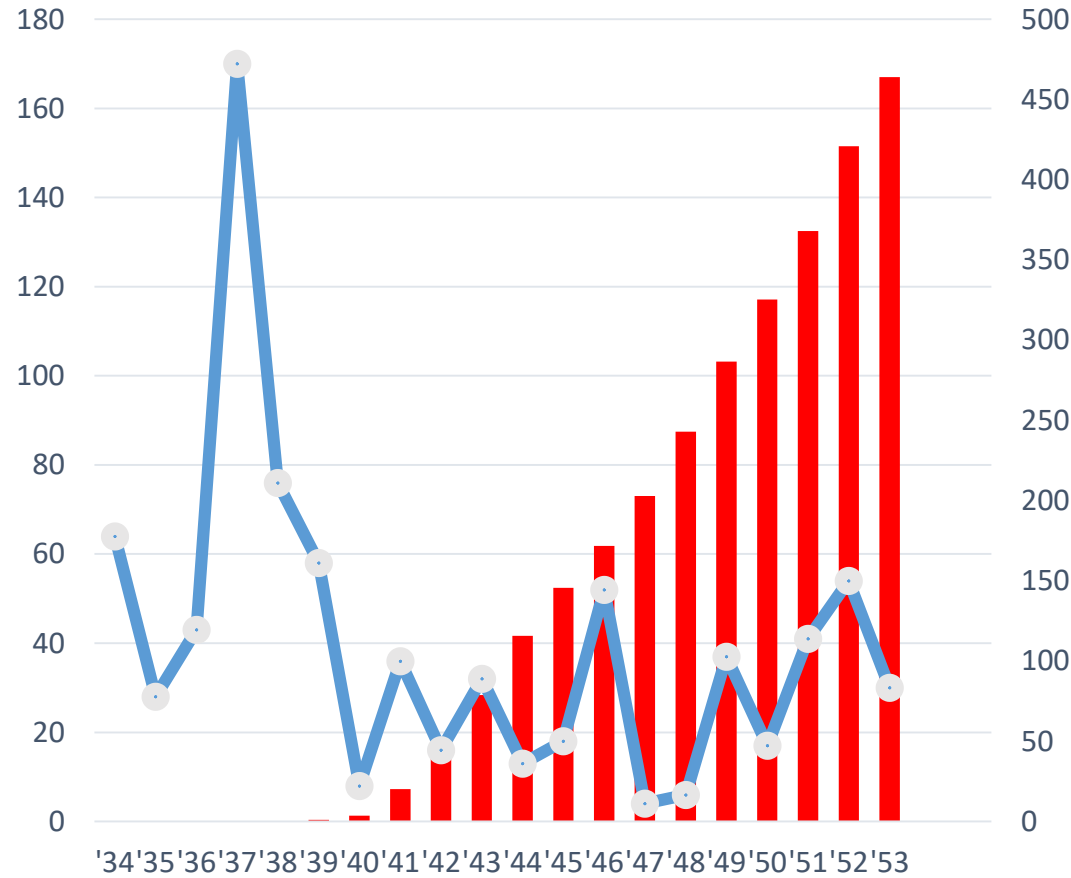
# **YELLOW FEVER & PUBLIC HEALTH**

*Resurgence of yellow fever in Africa because of*  
*collapse of health care delivery systems;*  
*lack of appreciation of the full burden/impact of YF*  
*low political commitment by governments*  
*poor disease surveillance; and*  
*uncoordinated outbreak response and control measures,*

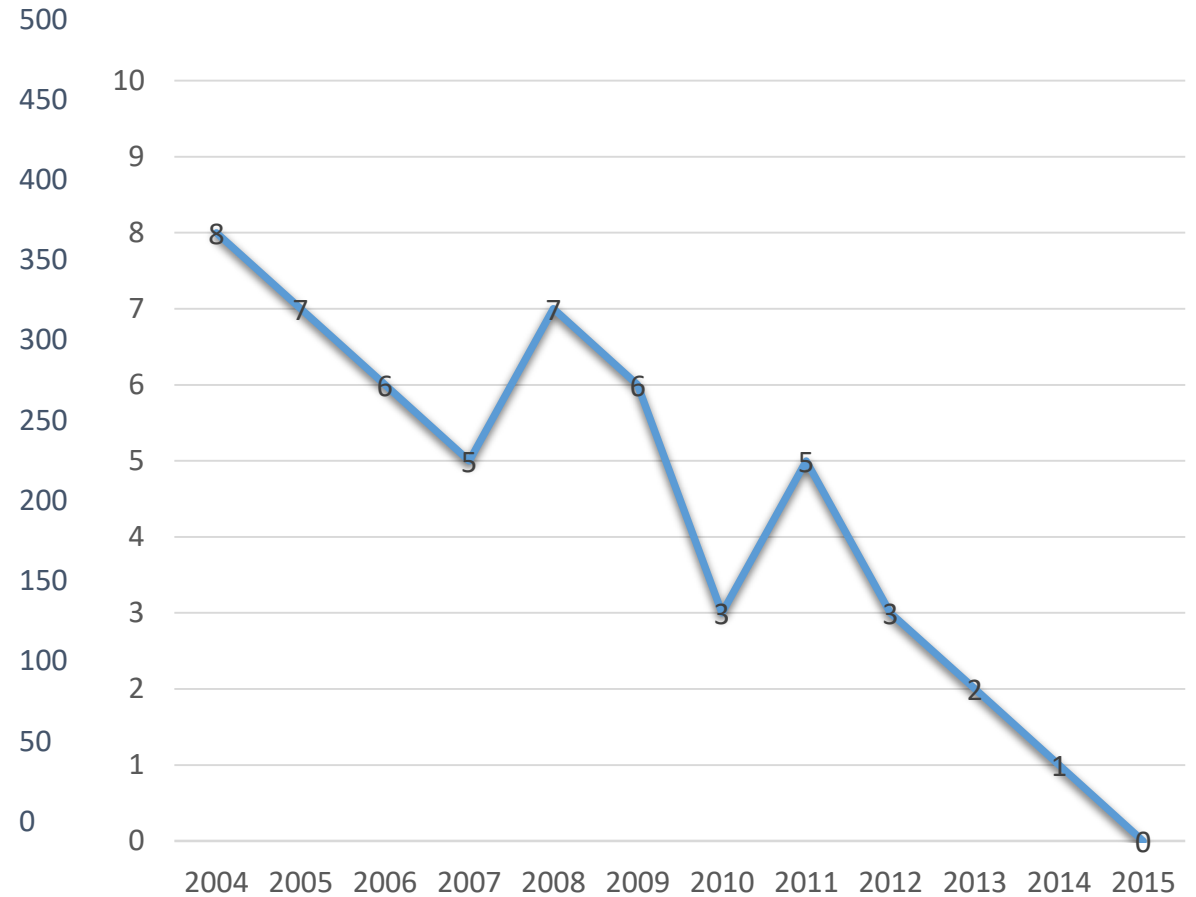
# Yellow Fever Control in West Africa

MASS YF CAMPAIGNS WITH FNV: 1934- 1953

WHO-UNICEF-GAVI INITIATIVE 2004-2015

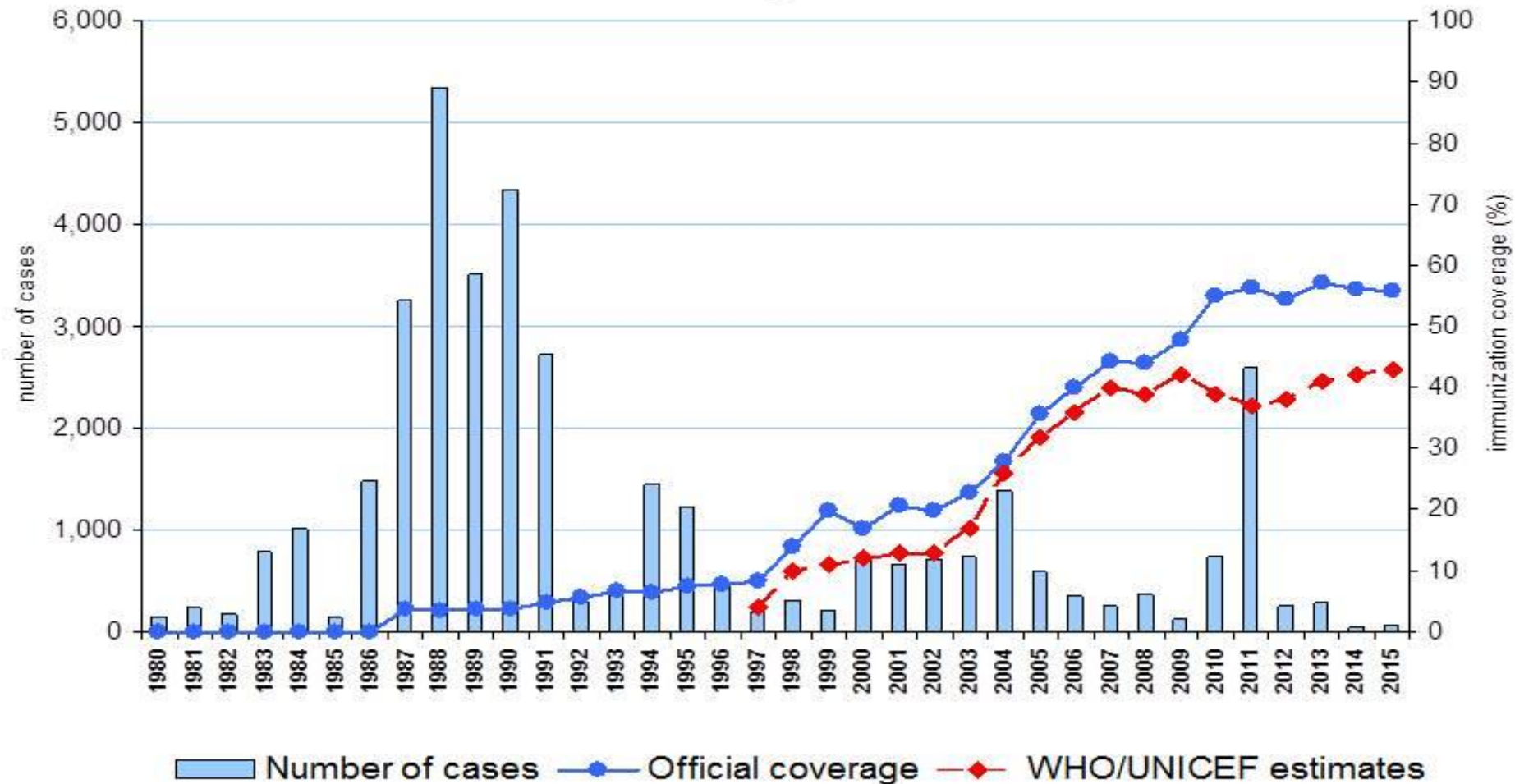


■ Cumulative number of vaccinations



— Number, reported outbreaks

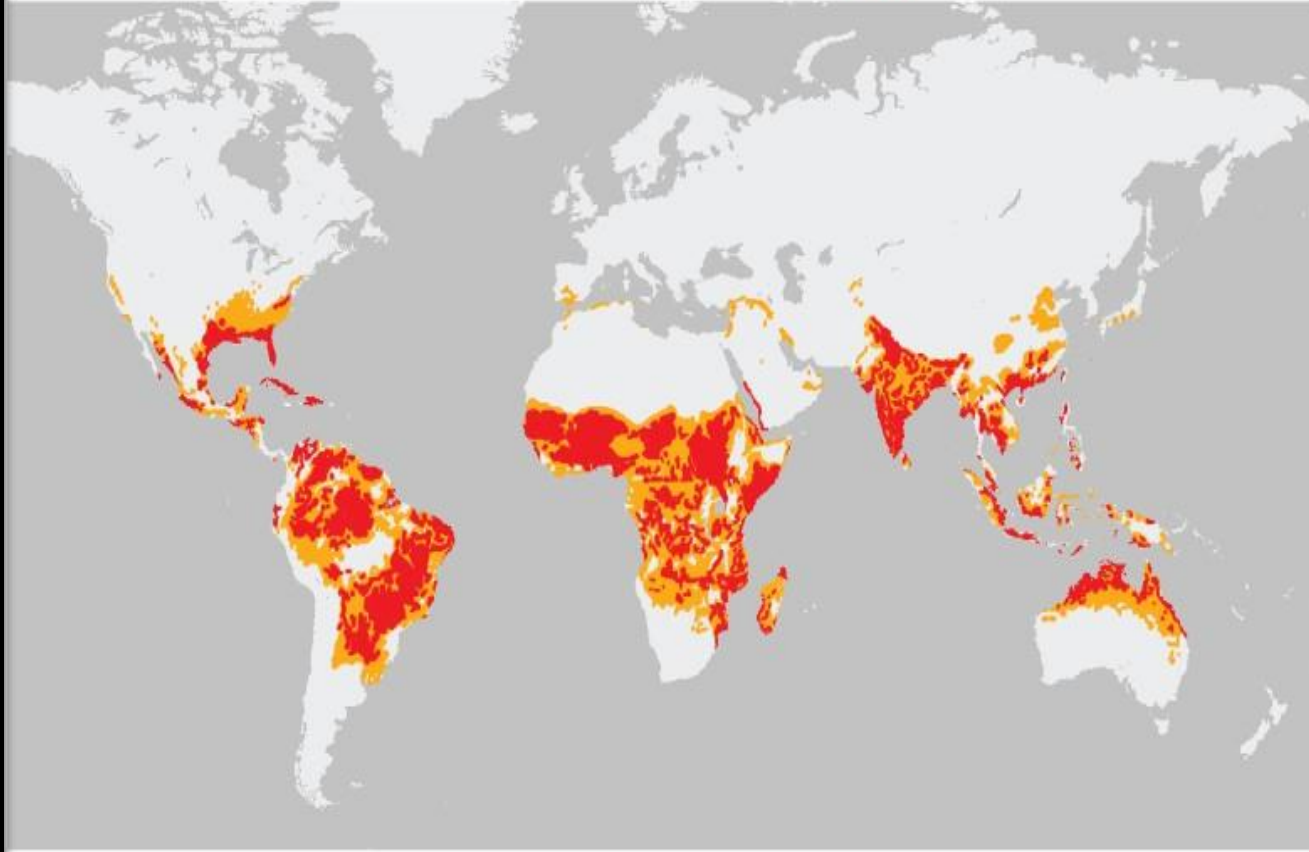
## Yellow fever global annual reported cases and YFV coverage, 1980-2015



# What is the risk of urban epidemics of yellow fever today?

## Prime locations

Many areas (**orange**) worldwide already have the right conditions for the yellow fever mosquito, which is currently found in the **red** regions



SOURCE: KRAEMER ET AL

## Risk Factors

- ***Ae. aegypti* & *Ae. albopictus* have global distribution**
- **YF at risk susceptible population exceeds 2.5 billion people**
- **Vector control unable to prevent epidemic DEN, CHIK & ZIKA**
- **EYE strategy to the rescue**

**WHAT IF  
YELLOW FEVER  
GETS INTO  
ASIA?**

Killing the Next Bin Laden / Steve Bannon's Russia Connection

**Newsweek**

ONE MILLION  
DEAD

**WHAT YELLOW FEVER  
IN ASIA CAN CAUSE**

Eliminating  
Yellow Fever  
Epidemics  
(EYE)



## ***WHY EYE?***

### **Previous Strategy**

- **Angola nor DRC not categorized as high-risk countries, so did not conduct PMVCs.**
- **The capital cities, Luanda and Kinshasa Outbreaks particularly affected**
- **Non immunized expatriate workers infected and exporting**
- **YF to countries outside endemic zone**
- **Millions of vaccine doses used, depleting stockpile**

## **EYE Goal:**

**To eliminate the risk of YF epidemics globally by 2026**

**Protect at-risk populations**

**Prevent international spread**

**Rapidly contain outbreaks**

### **Strategic Objective 1: Protect at-risk populations**

- |   |   |
|---|---|
| <b>Where risk is high, vaccinate everyone</b>                                 | <ul style="list-style-type: none"><li>• 475 mio vaccine doses for national preventive mass vaccination campaigns in 13 countries</li></ul>                            |
| <b>Vaccinate every child; find and vaccinate everyone who has been missed</b> | <ul style="list-style-type: none"><li>• 55 mio vaccine doses annually for routine immunisation in 26 countries</li><li>• Catch-up campaigns where indicated</li></ul> |
| <b>Strengthen surveillance and build laboratory capacity</b>                  | <ul style="list-style-type: none"><li>• Cost and work plan to be defined</li></ul>  |
| <b>Monitor immunity</b>   | <ul style="list-style-type: none"><li>• Cost and work plan to be defined</li></ul>  |

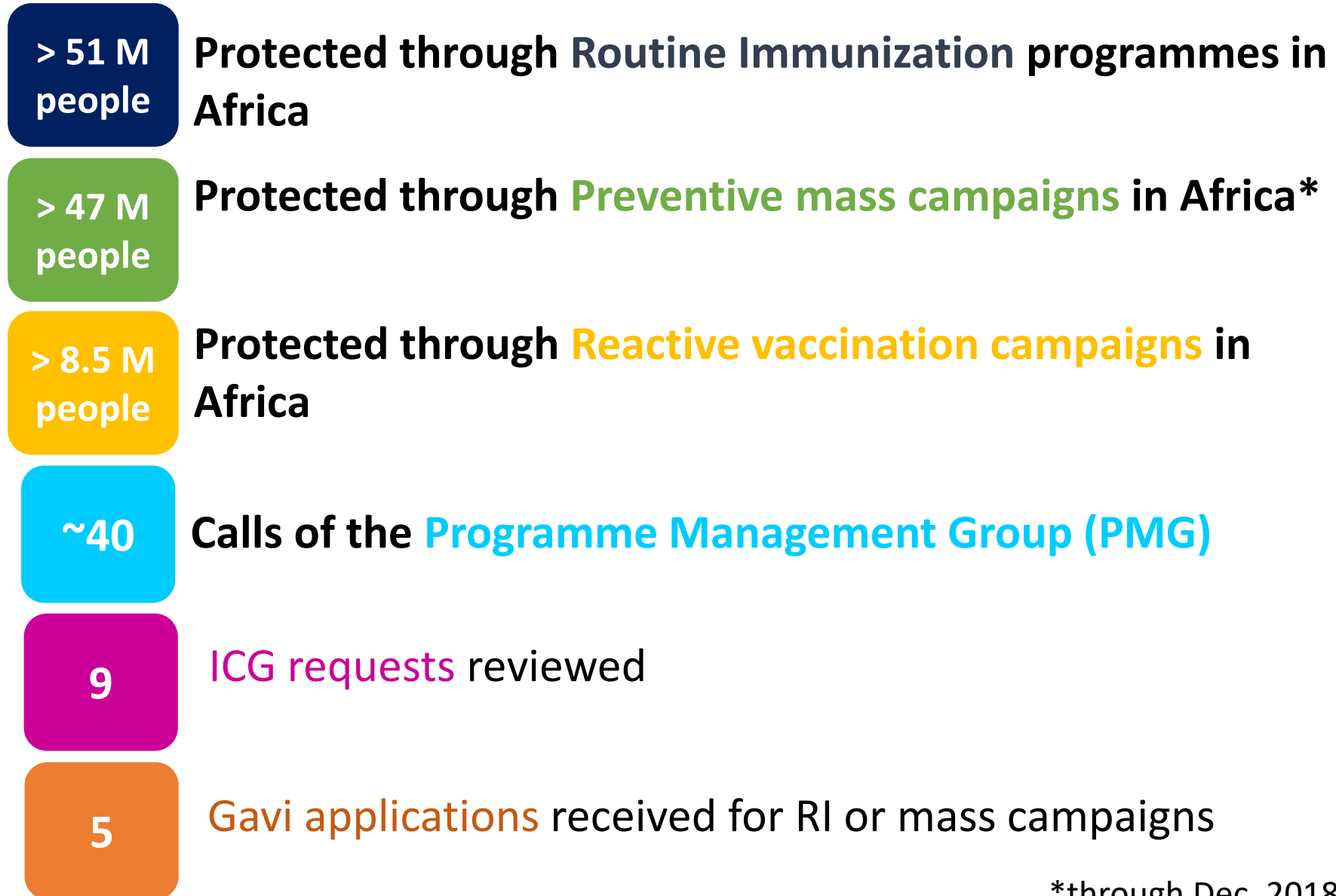
### **Strategic Objective 2: Prevent international spread**

- |   |  |
|---|--|
| <b>Protect high-risk workers</b>                  | <ul style="list-style-type: none"><li>• Cost and work plan to be defined</li></ul> |
| <b>Apply the International Health Regulations</b> | <ul style="list-style-type: none"><li>• Cost and work plan to be defined</li></ul> |
| <b>Build resilient urban centres</b>              | <ul style="list-style-type: none"><li>• Cost and work plan to be defined</li></ul> |

### **Strategic Objective 3: Contain outbreaks rapidly**

- |   |  |
|---|--|
| <b>Ensure emergency stockpile vaccines always readily available</b> | <ul style="list-style-type: none"><li>• maintain 6 mio vaccine doses for emergency stockpile</li></ul> |
| <b>Prepare for rapid response</b>                                   | <ul style="list-style-type: none"><li>• Cost and work plan to be defined</li></ul>                     |

# EYE in numbers since inception



\*through Dec, 2018

# Key milestones

By end of 2017



- EYE governance body is fully operational
- The implementation plan including indicators and deliverable is ready
- At-risk countries are engaged in the EYE strategy implementation

By end of 2018



- 3 African reference laboratories are fully functional with confirmation

By end of 2020



- All African high-risk countries have introduced the YF vaccine into routine immunization
- Campaigns have been completed or are well underway in 3 EYE priority countries (including Nigeria)
- 6 African sub regional reference laboratories are fully functional and an EQA/QC is fully functional for both serology and molecular diagnostic procedures

# Key elements reiterated – 1

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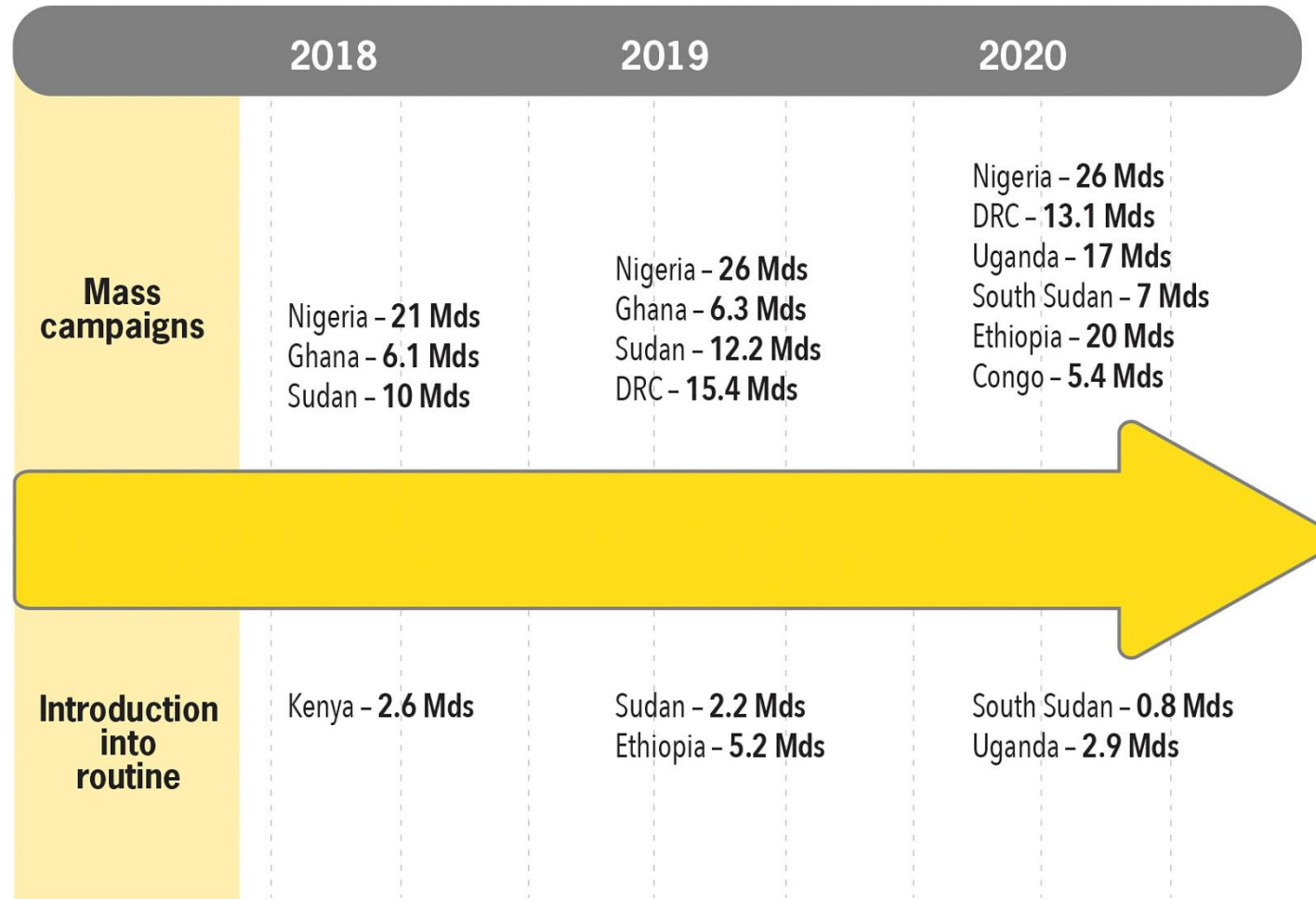
- **Increased risk of YF with unpredictable outbreaks**
  - Protect population at the source , increase urban readiness, direct protection of cities (e.g., Brazil, Pointe Noire in Congo).
- **YF-MCV1 gap in coverage is closing, however challenges remain with routine immunization**
  - Solutions are non YF-specific - the newly formed immunization operational working group will provide guidance
  - In some highest risk West Africa countries where mass campaigns were conducted still have sub-optimal vaccine coverages – putting under-protected populations at risk for outbreaks
- **Significant steps to increase lab capacity and network**
  - 2 additional regional reference laboratories (Centre Pasteur Cameroon and UVRI ) to complement IP Dakar, which serves as global reference laboratory and WHO- CC
  - Proposal being developed to request Gavi support

# Key elements reiterated - 2

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- Latest data on fractional YF vaccination (fYF) and co-administration of YF vaccines will be reviewed by experts
  - but no policy recommendation is expected soon
- The increased supply and confidence in production are very positive
  - but supply remains what limits the extent of mass campaigns
- Have a global outlook for risk and prioritization, including Africa and the Americas
  - Addressed by risk prioritization analysis and modelling working group
- Match supply presentation and demand
  - Addressed by demand and supply working group
- Questions related to strengthening laboratory capacity and network were discussed on a dedicated day (14 September)

# Main timelines for mass campaigns and routine immunization introduction, 2018-2020



\* Doses are expressed as millions of doses (Mds) and indicate estimated country demand for yellow fever vaccine, and may increase. For Routine requirements, doses indicated are total per year to reach all eligible children at full coverage (100%). Implementation is graduated; year 1 anticipated to be 50%, increasing to 80% in year 2, and 100% in year 3,

# Emerging issues and updates

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## ➤ Fractional vaccination (fYF):

- progress noted; data will be reviewed by experts' group in due time; no change of policy expected soon;
- YF should remain limited to emergency use in case of vaccine shortage

## ➤ Co-administration:

- Routine immunization: No interference with measles ; YF-MR/MMR: potential impact , but no policy recommendation yet (SAGE) ; decoupling is detrimental for coverage
- Mass campaigns: advantages and disadvantages ; no policy recommendation; up to the countries to decide, case by case basis, context-dependent: e.g., national campaigns stretching resources vs smaller scale campaigns where closer monitoring is possible

# Vaccine Supply

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- **Outlook for vaccine supply is improving, 130 million doses were available in 2018**
- **Manufacturers illustrating clear commitment, increased confidence in stable supply**
- **Anticipated there will be 140-170million doses per year as of 2019**
- **Demand for Africa likely to be met over time, accounting for programmatic constraints**
- **Unmet demand in PAHO from past years has lead to accumulation of 100 million susceptible**
- **Important to have credible demand & rationalize the allocation with global outlook**
- **Manufacturers' request for more frequent updates will be addressed through dedicated quarterly PMG calls**

# Day 2 – Session 4: Country Updates

- **Senegal and Columbia**
  - Two examples of endemic countries with successful elimination YF epidemics
  - Senegal commended as model of success, enabled by strong political engagement in African region
    - Combined vaccination approach
    - Strong community based & integrated surveillance, including for other arbovirus
    - Stressed importance of appropriate investigation capacity
- **Nigeria and DRC**
  - Committed to implementation of PMVC as well as strengthening surveillance and RI. Would like to expedite plan for implementing PMVCs
  - Highlighted that planning and capacity must happen at state level to enable success
  - RI strengthening remains a key issue and is being addressed by NERICC (Nigeria)
  - Both faced by challenges, but leveraging existing resources from polio and measles program
- **Sudan**
  - Planning for final phases of PMVC implementation is well underway
  - RI introduction in 2020 raises question of catch-up campaigns



**We must NOT close the eye to those NATIONAL competing interests against EYE success**



**We must open the EYE to ensuring NATIONAL OWNERSHIP of the EYE**

**We must see GOOD GOVERNANCE in affected YF countries**

**We must see ACCOUNTABILITY In the operation of the EYE and in its IMPLEMENTATION**

# Distinguished and Eminent Ladies & Gentlemen



**My sincere appreciation to YOU all**

# **DO NOT DISTURB: MOSQUITO FEEDING**

