African Vaccine Manufacturing Initiative
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# Yellow Fever

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World Health Organization

# Outline

- Background – About Yellow Fever
- The Yellow Fever Initiative
- Outbreaks
- The YF Initiative
- Long term strategy



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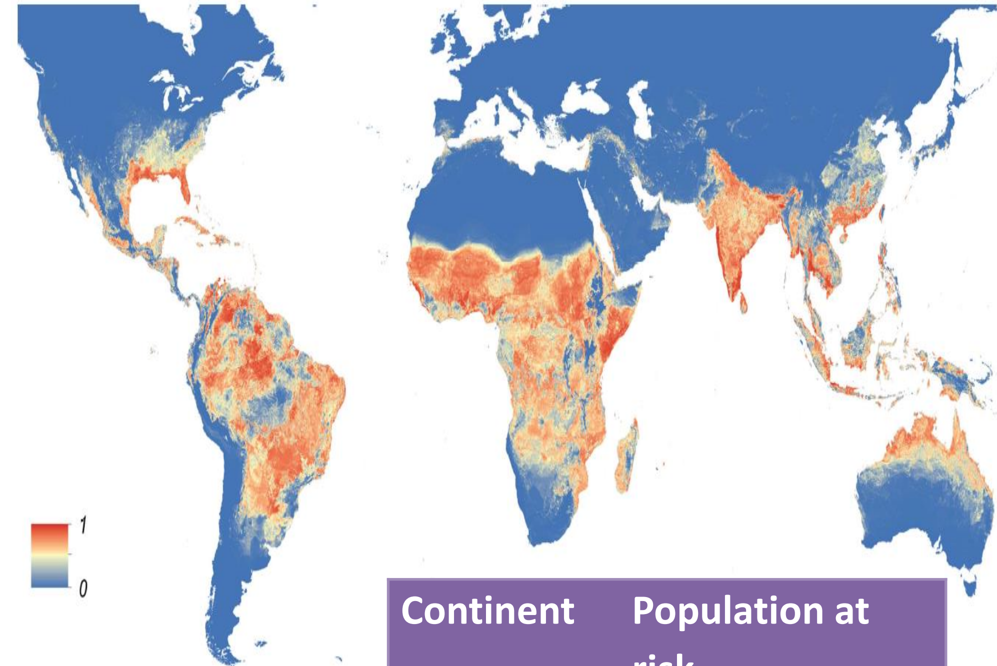
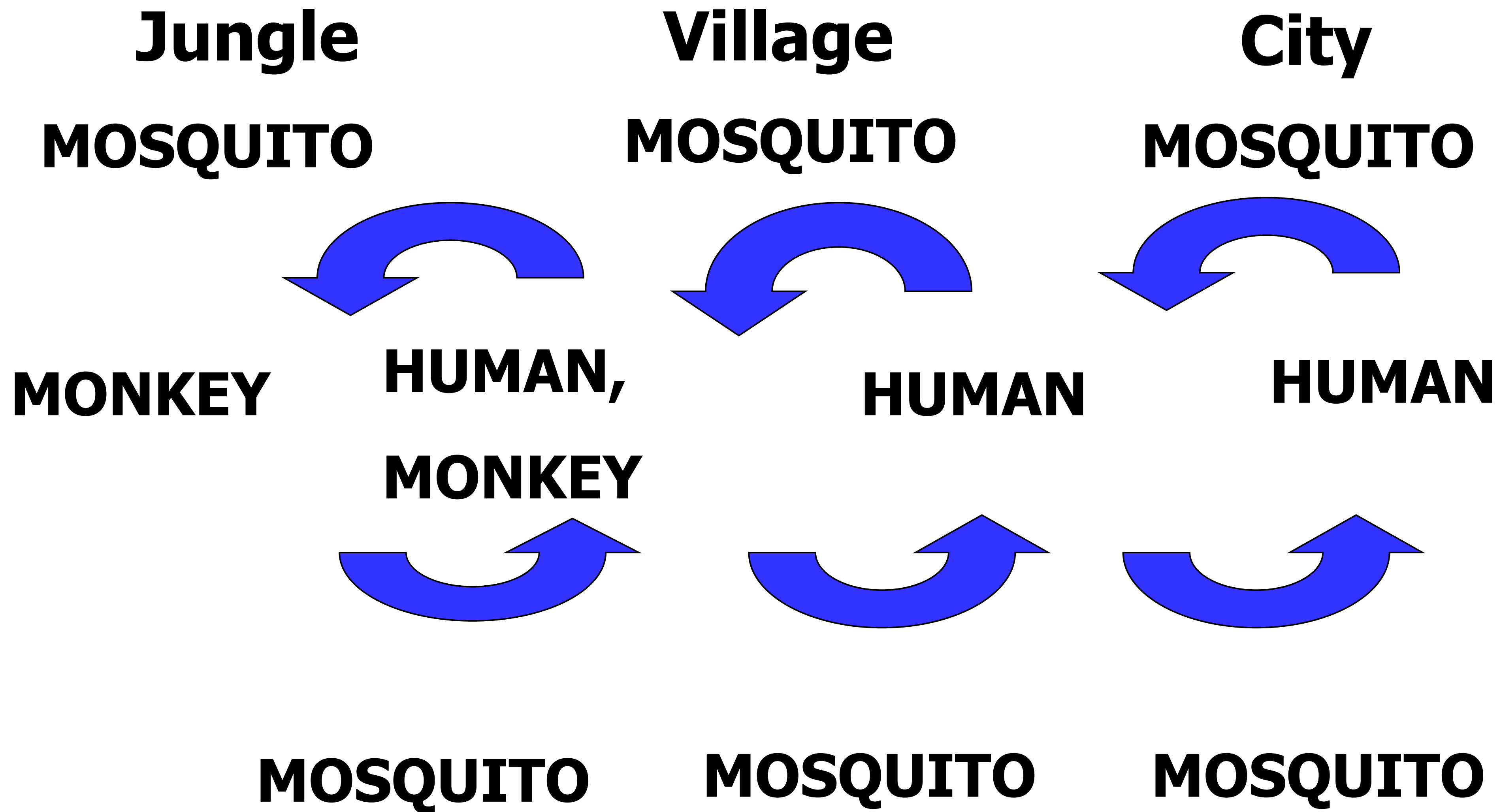
# About Yellow Fever

- Mosquito-borne viral hemorrhagic infection with a high case fatality rate.
- Clinical manifestations include hepatic dysfunction, renal failure, coagulopathy, and shock.
- Travelers to tropical regions of South America and sub-Saharan Africa where the disease is endemic are at risk for acquisition of infection and require immunization.
- First account of sickness diagnosed as YF occurred in 1648
- Causative agent: genus Flavivirus
- Vector: Aedes aegypti (mosquito)
- Nonhuman primates maintain disease
- 500,000 – 700,000 deaths each year from hepatitis-related liver cancer and cirrhosis




| Continent | Population at risk |
|---|---|
| **Africa** | 127,000,000 |
| **Americas** | 514,000,000 |
| **Asia** | 2,680,000,000 |
| **Europe** | 45,900,000 |
| **Oceania** | 22,600,000 |
| **Total** | 3,187,000,000 |

# Cycles of YF Transmission – Sylvatic & Domestic



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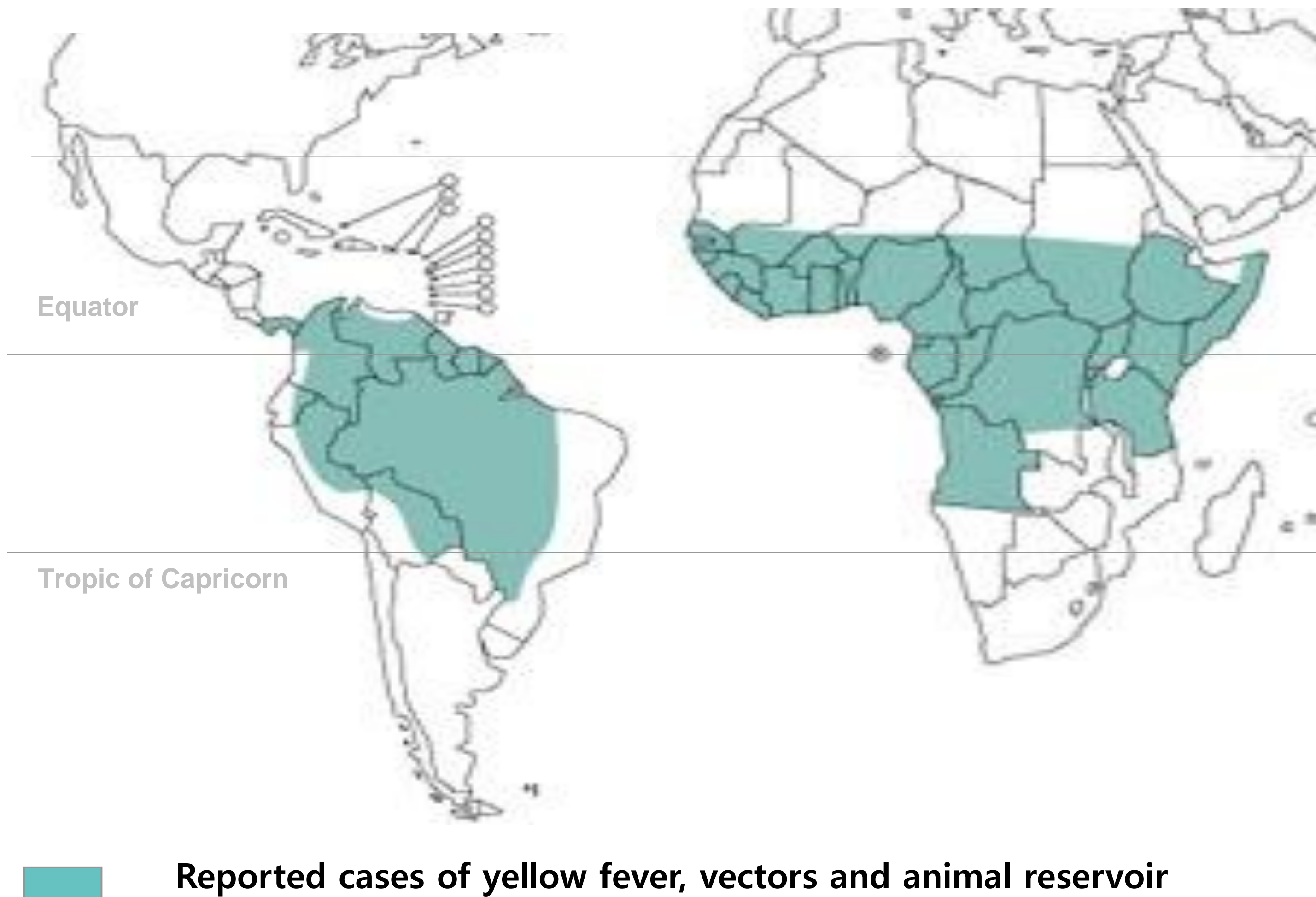
# Risk of yellow fever transmission in the world




Reported cases of yellow fever, vectors and animal reservoir

47 endemic countries: ❑
Africa (33)
South America (14)

~897 million people at risk ❑
>20% in urban areas (178 ❑ million)



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# Yellow Fever Initiative: A Simple & Effective Strategy

**Objective: Prevent yellow fever epidemics and secure vaccine supply**

- **Control outbreaks:**
  - Risk assessment and surveillance
  - Early detection of outbreaks
  - Rapid response
- **Build population immunity**
  - Protect children through routine immunization
  - Protect the community through mass preventive campaigns
- **Secure vaccine supply**
  - Maintain the emergency stockpile
  - Forecast vaccine requirements
  - Support emerging manufacturers
- **Monitor risk, quality, effectiveness and impact**
  - Ensure high vaccination coverage
  - Monitor vaccine quality and safety
  - Strengthen disease surveillance
  - Support operational research and innovation

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# Yellow Fever Burden (2013)

## ANNUAL ESTIMATION FOR AFRICA

Infections: 840,000 to 1.7 million

Cases: 84,000 to 170,000

Deaths: 29,000 to 60,000

Assumptions:
10% of infections will develop severe symptoms.
35% of severe cases will die



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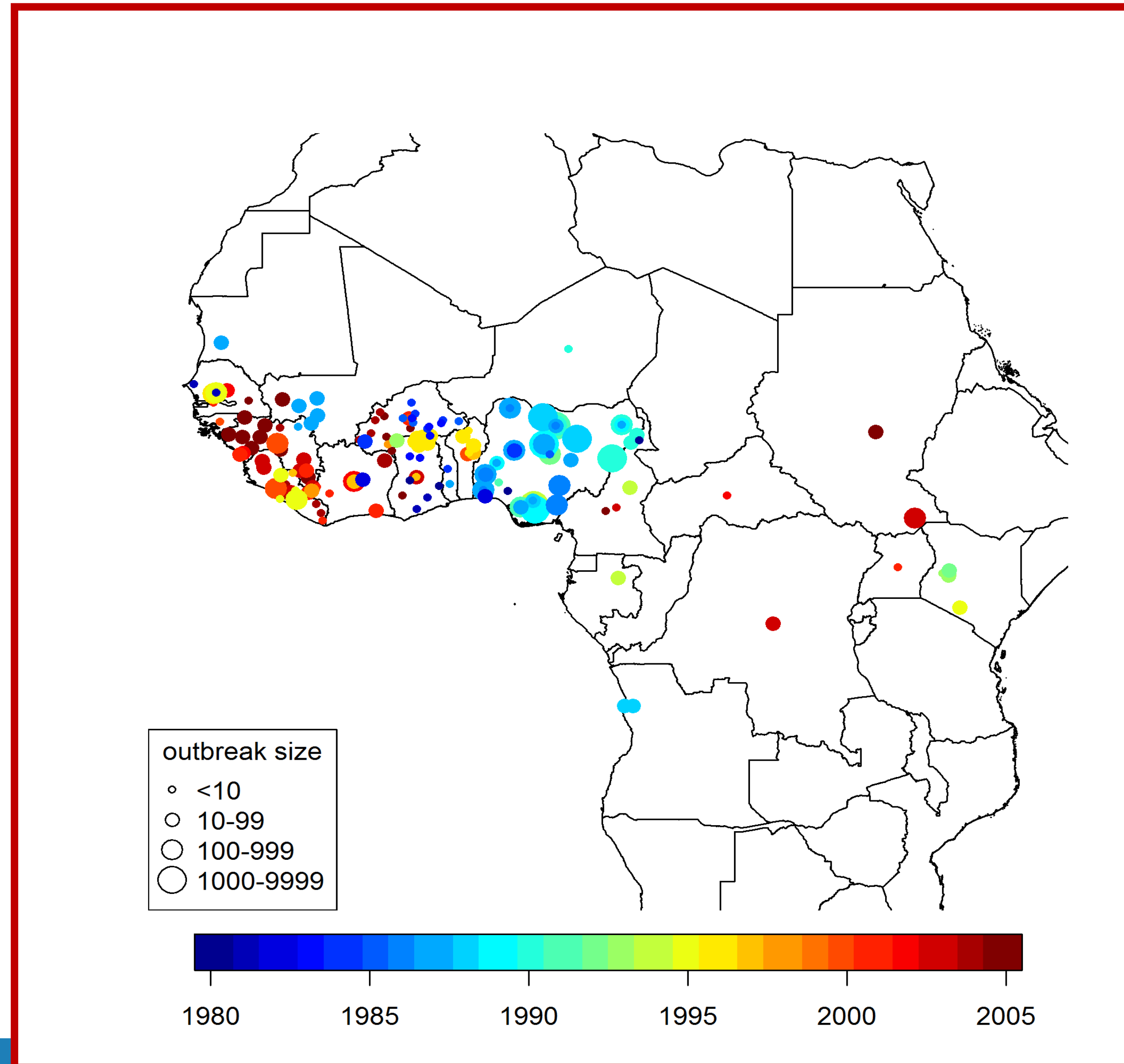
# YF outbreaks before 2006



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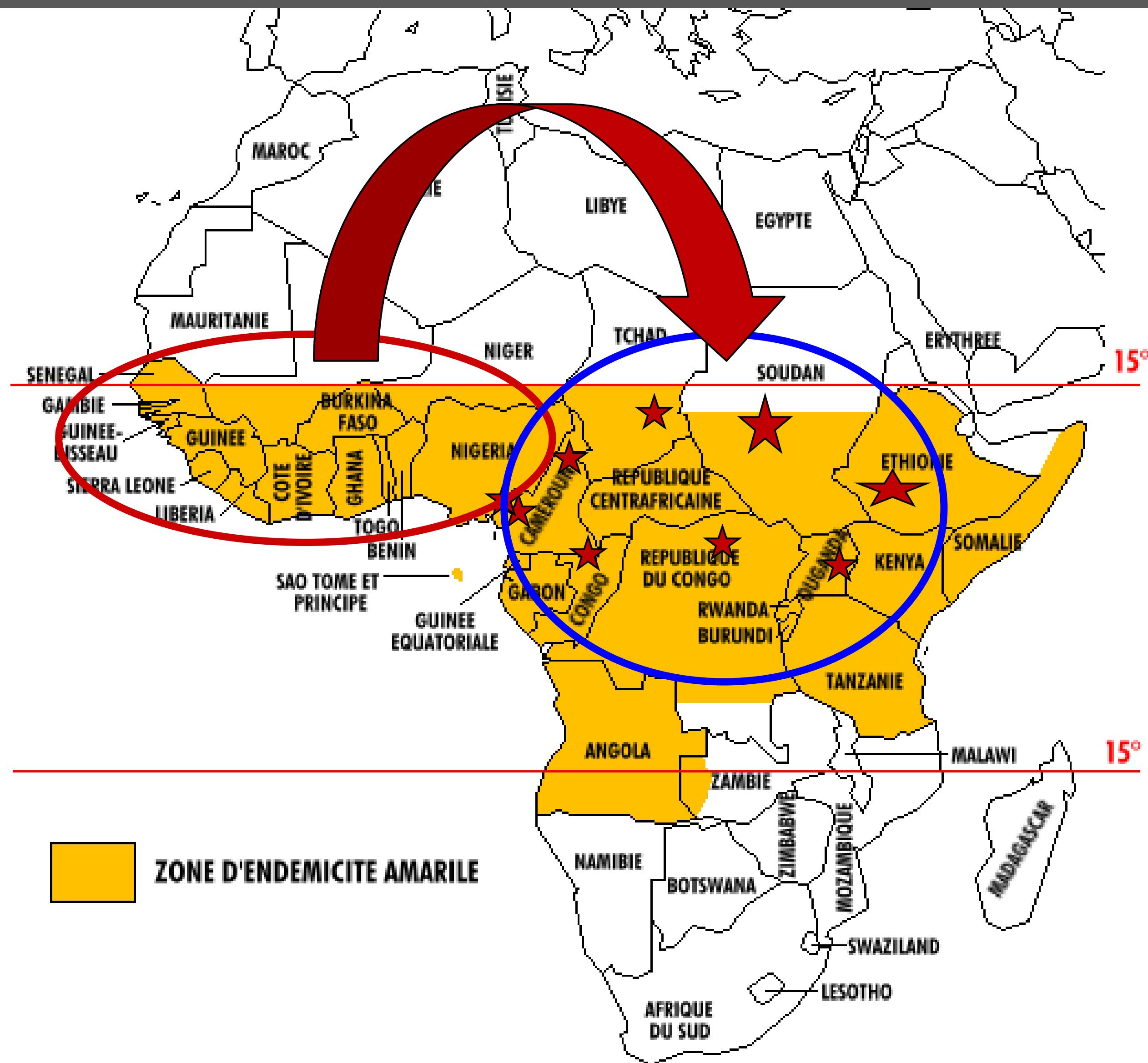
# From West to Central & East Africa



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# AFRICA: Area with Increase of YF virus circulation

## Yellow Fever Vaccination Recommendations in Africa, 2010

Mauritania
Nouakchott
Senegal
Dakar
Gambia
Guinea-Bissau
Guinea
Conakry
Freetown
Sierra Leone
Liberia
Mali
Bamako
Burkina Faso
Niger
Niamey
Côte d'Ivoire
Yamoussoukro
Ghana
Accra
Togo
Benin
Porto Novo
Nigeria
Abuja
Chad
Ndjamena
Cameroon
Equatorial Guinea
Equatorial Guinea
Sao Tome
Sao Tome and Principe
Gabon
Congo
Central African Republic
Bangui
Democratic Republic of the Congo
Kinshasa
Brazzaville
Luanda
Angola
Sudan
Khartoum
Eritrea
San'a
Yemen
Djibouti
Djibouti
Somalia
Ethiopia
Mogadishu
Uganda
Kenya
Nairobi
Rwanda
Burundi
United Republic of Tanzania
Dar es Salaam
Seychelles
Comoros
Mayotte
Mozambique
Lilongwe
Zambia
Lusaka
Harare
Zimbabwe
Malawi
Antananarivo
Madagascar
Botswana
Namibia
0 235 470 940 Kilometers

- Vaccination generally not recommended*
- Vaccination recommended
- Vaccination not recommended

*Yellow Fever (YF) vaccination is generally not recommended in areas where there is low potential for YF virus exposure. However, vaccination might be considered for a small subset of travelers to these areas who are at increased risk for exposure to YF virus because of prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites. Consideration for vaccination of any traveler must take into account the traveler's risk of being infected with YF virus, country entry requirements, and individual risk factors for serious vaccine-associated adverse events (e.g. age, immune status).



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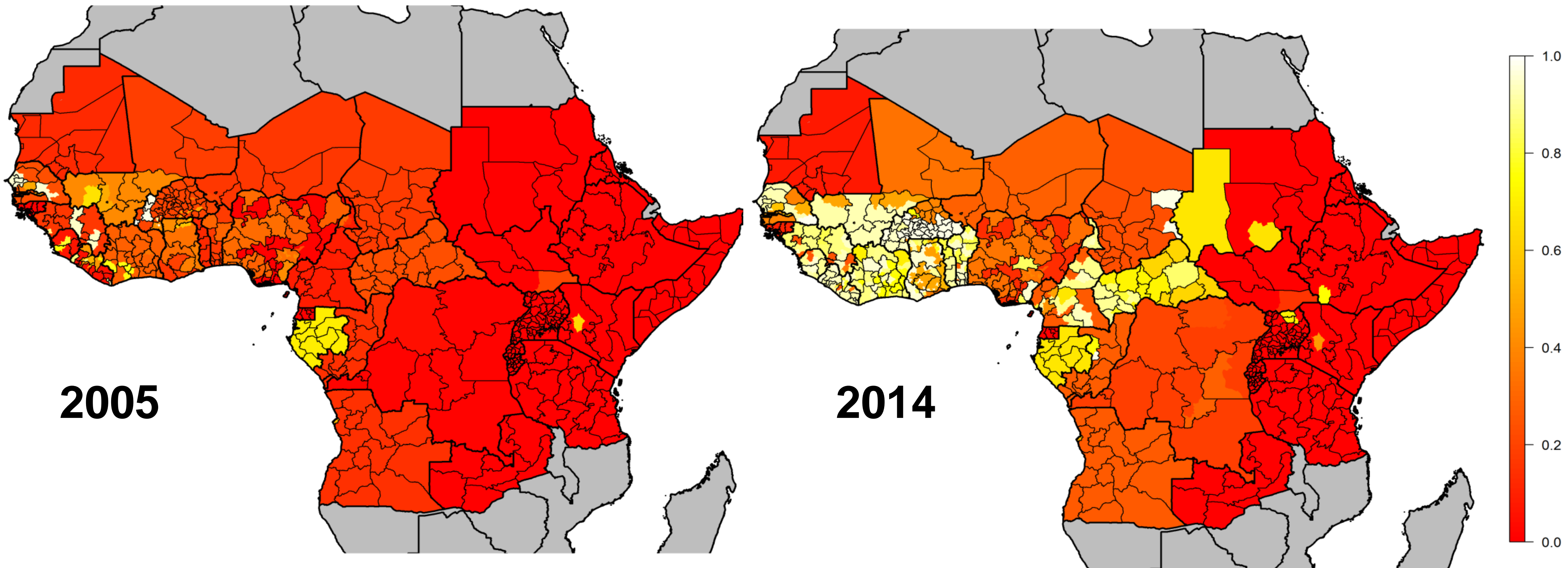
# YF vaccination coverage estimates
## (mass campaigns and routine EPI)




**Source: Imperial College, London**



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# First mass campaign FNV 1934-1953

## (not followed by routine EPI)

**YF vaccination and FNV 1934-1953**

N° people vaccinated: 0, 5000000, 10000000, 15000000, 20000000, 25000000, 30000000, 35000000, 40000000, 45000000, 50000000

N° of YF cases: 0, 20, 40, 60, 80, 100, 120, 140, 160, 180

1939 1940 1941 1942 1943 1944 1945 1946 1947 1948 1949 1950 1951 1952 1953

Years

Number of yellow fever vaccinations by scarification

Total cases notified for Africa

# Routine EPI is an important pillar for YF control

1. 11 out of 34 countries have not yet introduced routine EPI

9 countries belong to low endemic countries (group C)
2 countries (Uganda and Sudan) are on the process of introduction
Coverage – Regional coverage <70%

2. National Joint Reporting Form (JRF) for coverage

3. Not very reliable indicator for assessing what occurs in different ecological zones

4. YF Warning system/Tool developed
Districts with low coverage identified and systems put in place to improve



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# YF endemic countries included YFV in EPI (2014)

Angola (1999) .1

Benin (2002) .2

Burkina Faso (1987) .3

Cameroon (2004) .4

CAR (2000) .5

Chad (1985) .6

Congo (2004) .7

Cote d'Ivoire (1987) .8

DRC (2004) .9

Gabon (2003) .10

Gambia (1979) .11

Ghana (1992) .12

Guinea (2002) .13

Kenya (1992).14

Liberia (2001).15

Mali (1992).16

Niger (2000).17

Nigeria (1992).18

Sao Tome and Principe (2003).19

Senegal (1987).20

Sierra Leone (2002).21

Togo (1992).22

Guinea Bissau (2008).23

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# Why assessment of EPI vaccine coverage?

**A rapid assessment can alert if the threshold of vaccine coverage < 80% is close.**
***This can be done with a scoring system***

**When a district shows low coverage, there is an alert and the district could:**
**Perform a deep analysis of last years of EPI vaccine coverage**✓
**Identify the possible causes of low YF vaccine coverage**✓
**Fix the causes for low coverage (programmatic issues)**✓
**Benefit of catch-up campaigns when necessary**✓

**Frequently the causes of low coverage could be the same for other antigens of routine EPI.**

# Methodology

*Scoring*:

Score according to main indicators:

- Lowest scoring could be proposed for catch-up campaigns
- Middle scoring would be candidates for monitoring
- Highest scoring would be considered as good coverage

Software for scoring:

- User-friendly
- Access to national EPI programme via Internet

EPI routine immunization is important for long-term YF control



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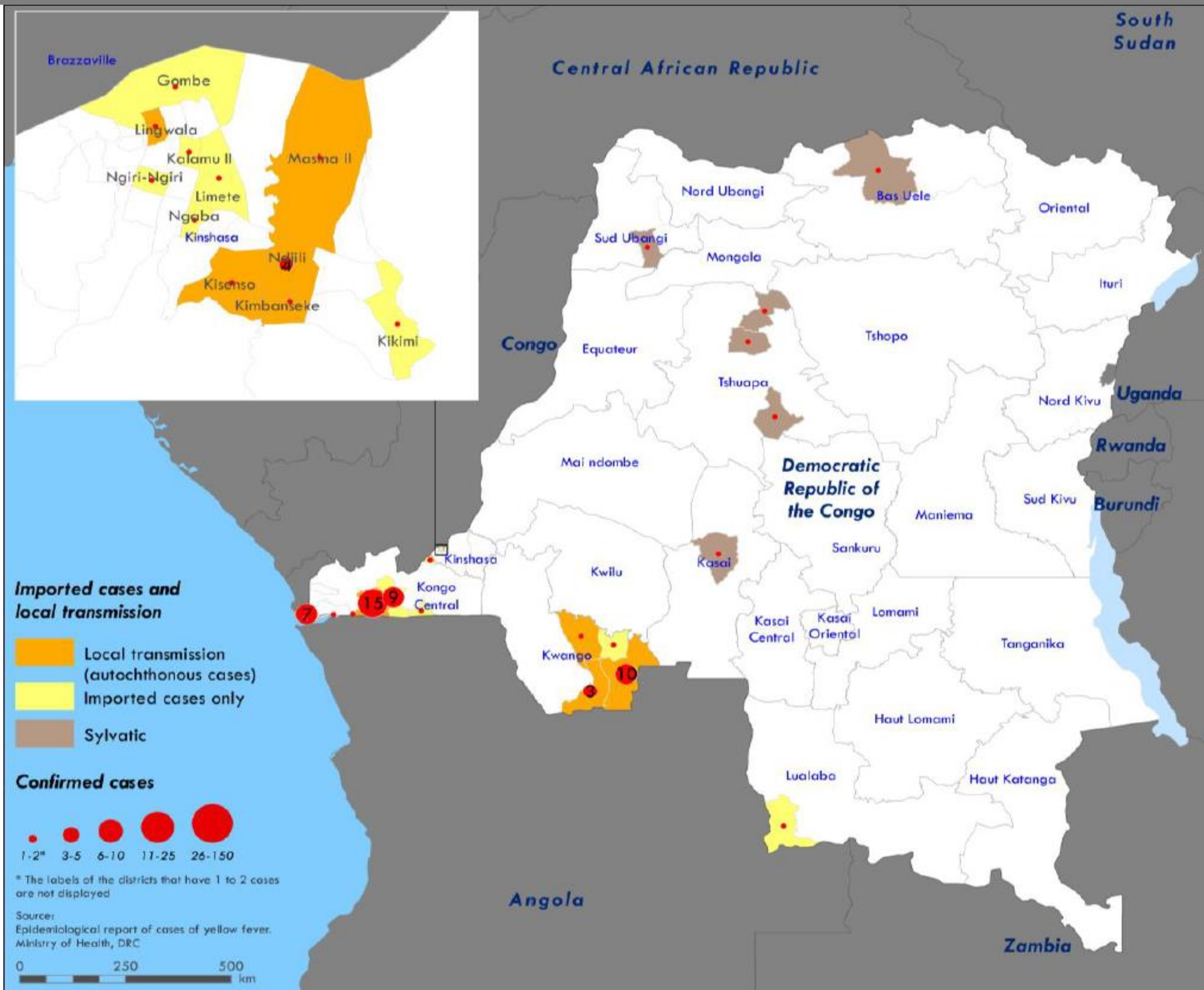
# OUTBREAKS

- Angola (first case reported in Dec 2015) unique due to **urban nature**
- DRC reported cases in connection with Angola in March 2016, outbreak officially declared on 23 April 2016
  - **Local transmission in DRC** confirmed in May 2016 in zones bordering Angola (13 confirmed cases to date are autochthonous)

| Cumulative data up to 12 October | ANGOLA | DRC |
|---|---|---|
| Total **cases reported** to central | 4,220 | **2,916** |
| Total samples tested | 3,666 | **2,800** |
| Total **confirmed cases** | 884 | **77*** |
| Total **reported deaths** | 373 | **120** |
| Total **deaths among confirmed cases** | 121 | **16** |

*including 7 cases of sylvatic YF not associated with the outbreak

# Distribution of confirmed yellow fever cases in DRC as of 12 October 2016



# Mass vaccination campaign response, DRC

Target pop: **2 m**
Doses sent: **2.2 m**
Coverage (admin): **98-114%**

Target pop: **975,681**
Doses sent: **1.1 m**
Coverage (admin): **70-114%**

Target pop:
**10,515,589**
Doses available:
**5.8 m**

Kongo Central
Kwango
Kwilu
Kasai
Lualaba

Reactive vaccination campaign May 2016: 9ZS Kongo Central + 2 ZS Kinshasa

Reactive vaccination campaign 20-29 July 3 ZS in Kwango and 1 ZS Kisenso

Preventive vaccination campaign 17 August – 5 September in 15 ZS along Angola border + 32 ZS in Kinshasa

Confirmed cases, vaccination not planned

# Preventive campaign using fractional dose Kinshasa, 17 – 26 August

- **Target area:** 32 health zones in Kinshasa
- **Target population: 7,586,400**
- **Vaccine doses available for Kinshasa:** 2,500,000
- **In order to ensure rapid vaccination of entire target population in Kinshasa, a fractional dose strategy was considered:**
  - **Fractional dose:** 1/5th (0.1 ml) of full dose administered subcutaneously (SC) using BCG syringe and needle
  - Everyone over the age of 2 years would receive a fractional dose ("**minimal dose**")

- Children 9-23 months and pregnant women received a **full dose**



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# Immune evaluation of fractional dose

## INRB/US CDC study

- **Primary Objective:** Assess the immunologic response to a fractional dose of YF vaccine **28 days** after vaccination by age group
- **Secondary objectives:**
  - Determine if **pre-existing flavivirus antibodies** influence the immunologic response
  - Assess whether the fractional dose vaccination results in sustained immunologic response at **12 months** post vaccination.
- **4 age strata:** 2-5 years, 6-12 years, 13-49 years, 50+ years
- Results expected late 2016 / early 2017

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# Gavi support until now

- Routine EPI vaccination introduced in EPI in 1979 in Burkina Faso and Gambia,
- Now in use in, 24 high risk Member States
- Support YV introduction for routine
- Stockpile support since 2003 (6 million doses)
- 58 million USD Gavi **Investment case** in 2006
  - continue the YF vaccine stockpile
  - support risk assessments
  - reactive and preventive campaigns in 12 countries
- Gavi endorsed **Vaccine Investment Strategy** in Dec. 2013
  - Based on WHO strategic framework 2012-2020
  - Continuation of preventive campaigns- incl. risk assessment
    - “B” countries and finalization of “A” countries
  - Usual Gavi application process
  - Campaigns started in Nigeria and Sudan

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### "A" Countries

**Countries reporting multiple YF outbreaks (≥2) in the previous 30 years**

- Benin
- Burkina Faso
- Cameroon
- Central African Republic
- Cote d'Ivoire
- **Ghana
- Guinea
- Liberia
- Mali
- Nigeria
- Senegal
- Sierra Leone
- Togo

### "B" Countries

**Countries reporting at least one YF event in the previous 50 years**

- **Angola
- Chad
- **Congo
- DR Congo
- Ethiopia
- Guinea Bissau
- Kenya
- Mauritania
- Niger
- South Sudan
- Sudan
- Uganda

### "C" Countries

**No reported outbreaks within last 50 years**

- Burundi
- **Equatorial Guinea
- Eritrea
- **Gabon
- Gambia
- Rwanda
- Sao Tome Principe
- Somalia
- Tanzania

**** non Gavi countries**

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# Goal of the YF-LTS document

- Gavi funding decision and decision on a new Gavi engagement strategy, December 2016
- Need to align with
  - African Regional Committee
  - SAGE
  - Partners
- WHO roadmap for yellow fever control
  - all countries including non Gavi ones

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# Need for revised strategy

- More aggressive in terms of vaccine introductions
  – Angola lesson: routine is not enough!
- Fit to long term supply projections
- Considering new factors
  – Risk of urban outbreak
    - Population density, movements
  – Extension to areas currently not considered at risk
  – Change in virus circulation?

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# Scope of the revised long term strategy

- Funding for Africa, but
  - Latin America to be included as much as possible to get a comprehensive vision
  - Assess the potential movement of the disease to other areas (e.g., Asia)
- Long term = 10 years?
- To cover all aspects of yellow fever control
  - Potential areas for other vector borne disease to be considered

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# Conclusion

- Major public Health Issue
- Future Outbreaks anticipated
- Strategy dependent on use of large numbers of does of vaccines in campaigns
- Routine use of vaccines scale-up
- Shortages of vaccines/unavailability/insifficient
- Potential for local production?

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# Thank you