

GACVS Meeting, 3-4 Dec 2003

**Yellow Fever: Global Vaccination
Control Strategies & Vaccine Safety
Overview**

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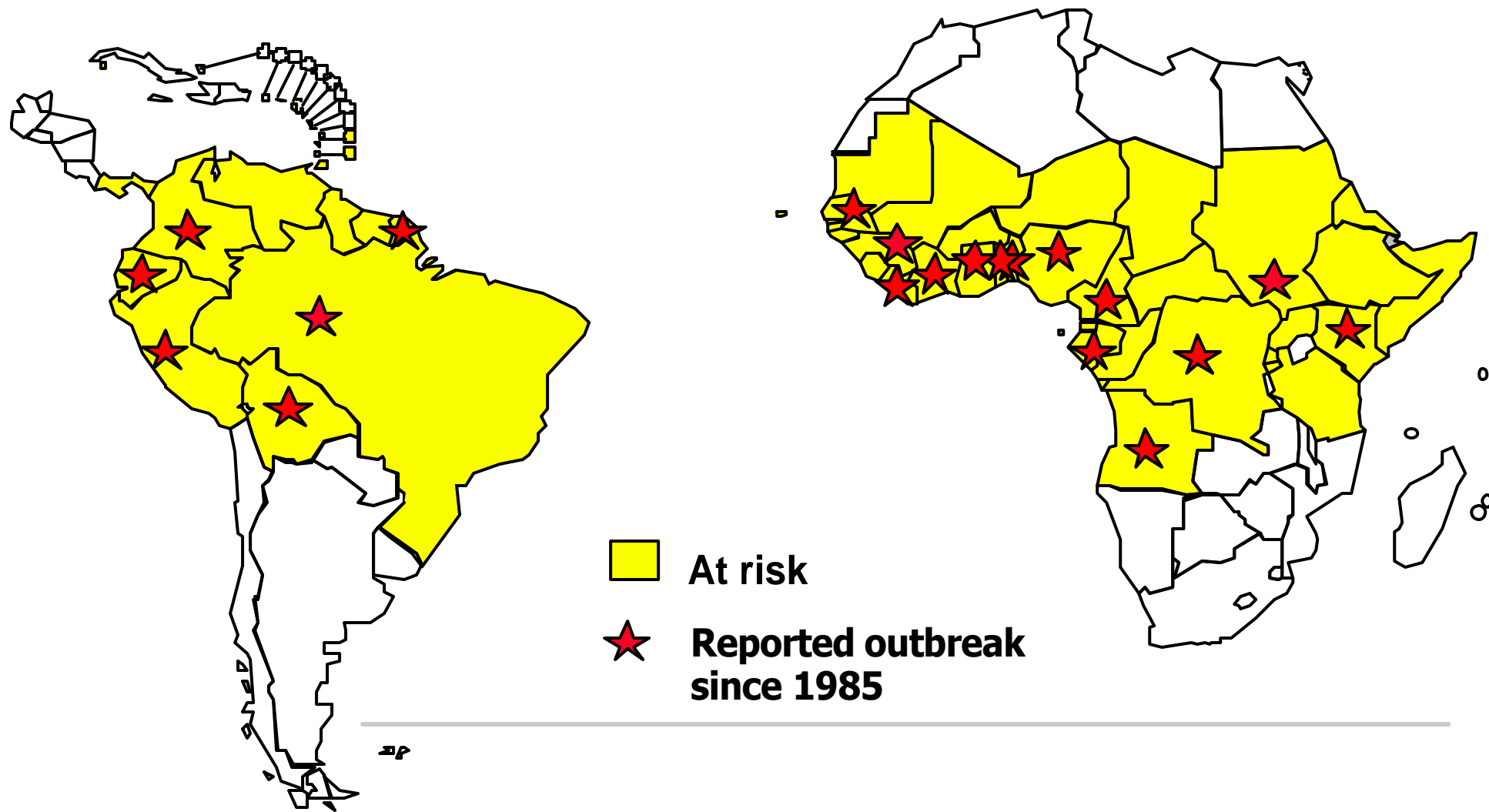
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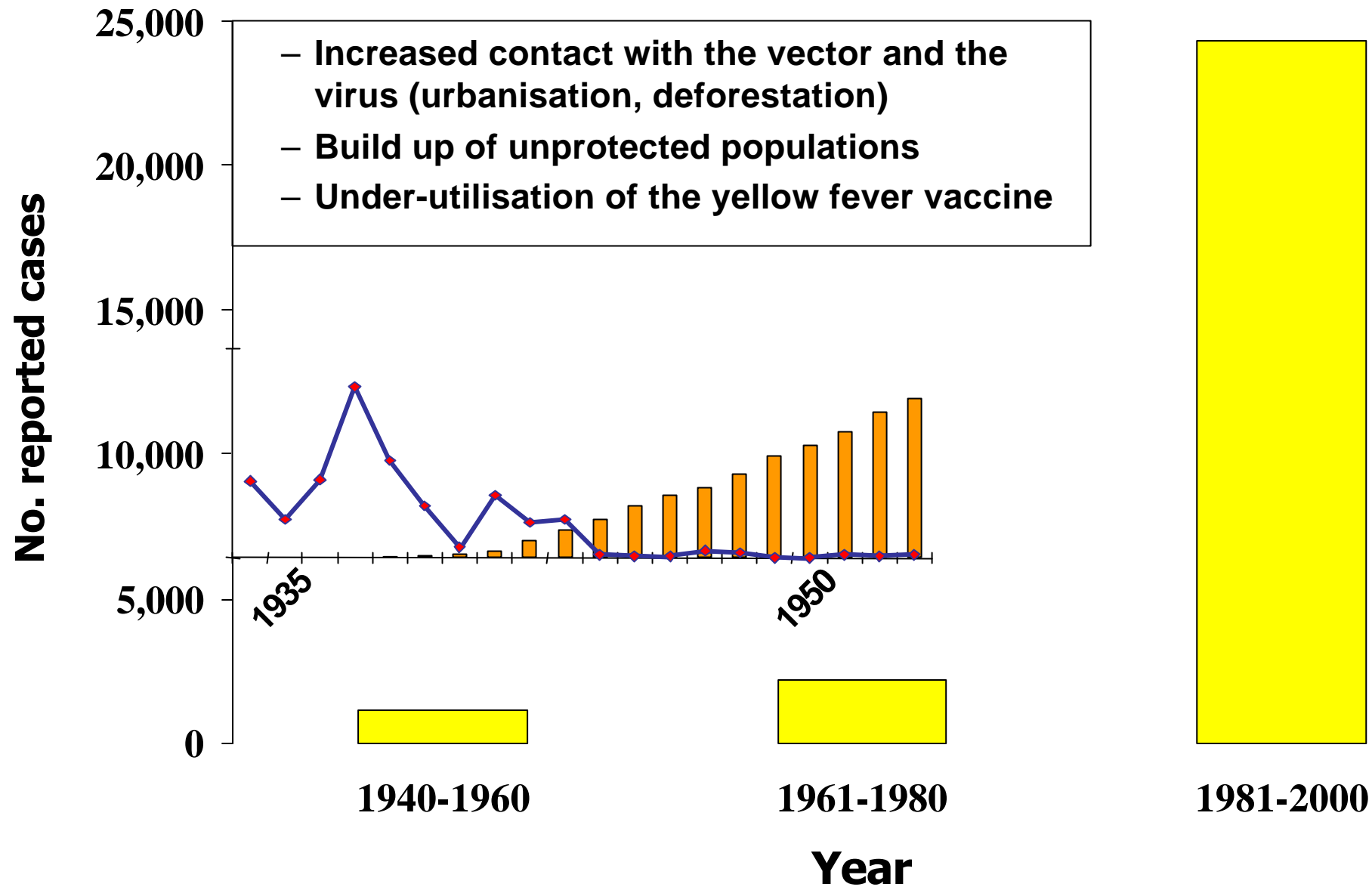
Countries at risk for yellow fever



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.



Resurgence of Yellow Fever in Africa



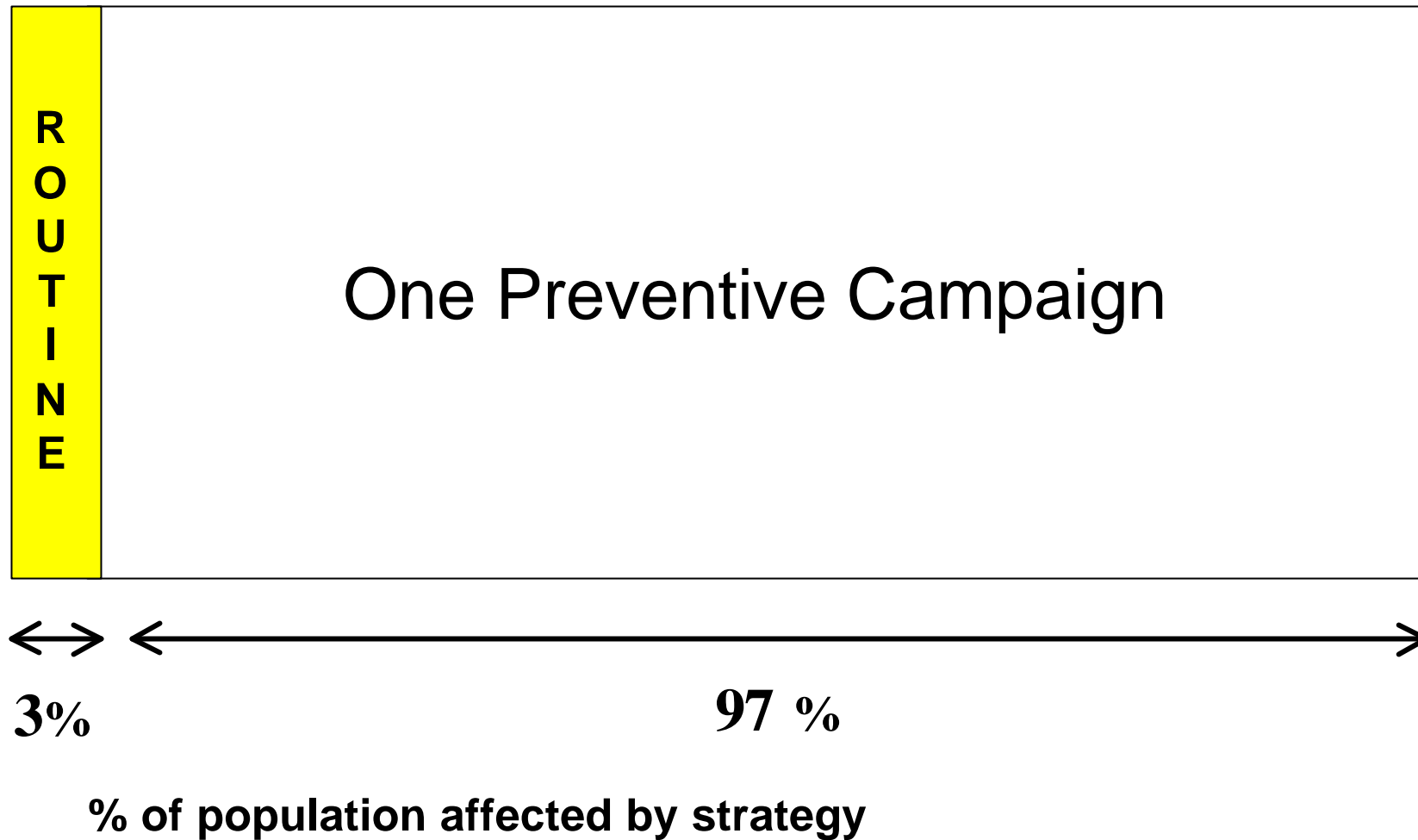
Strategy for Prevention and Control of YF

1. Routine infant immunization
2. Mass Preventive campaign
3. Surveillance and epidemic response



YF Prevention Strategy

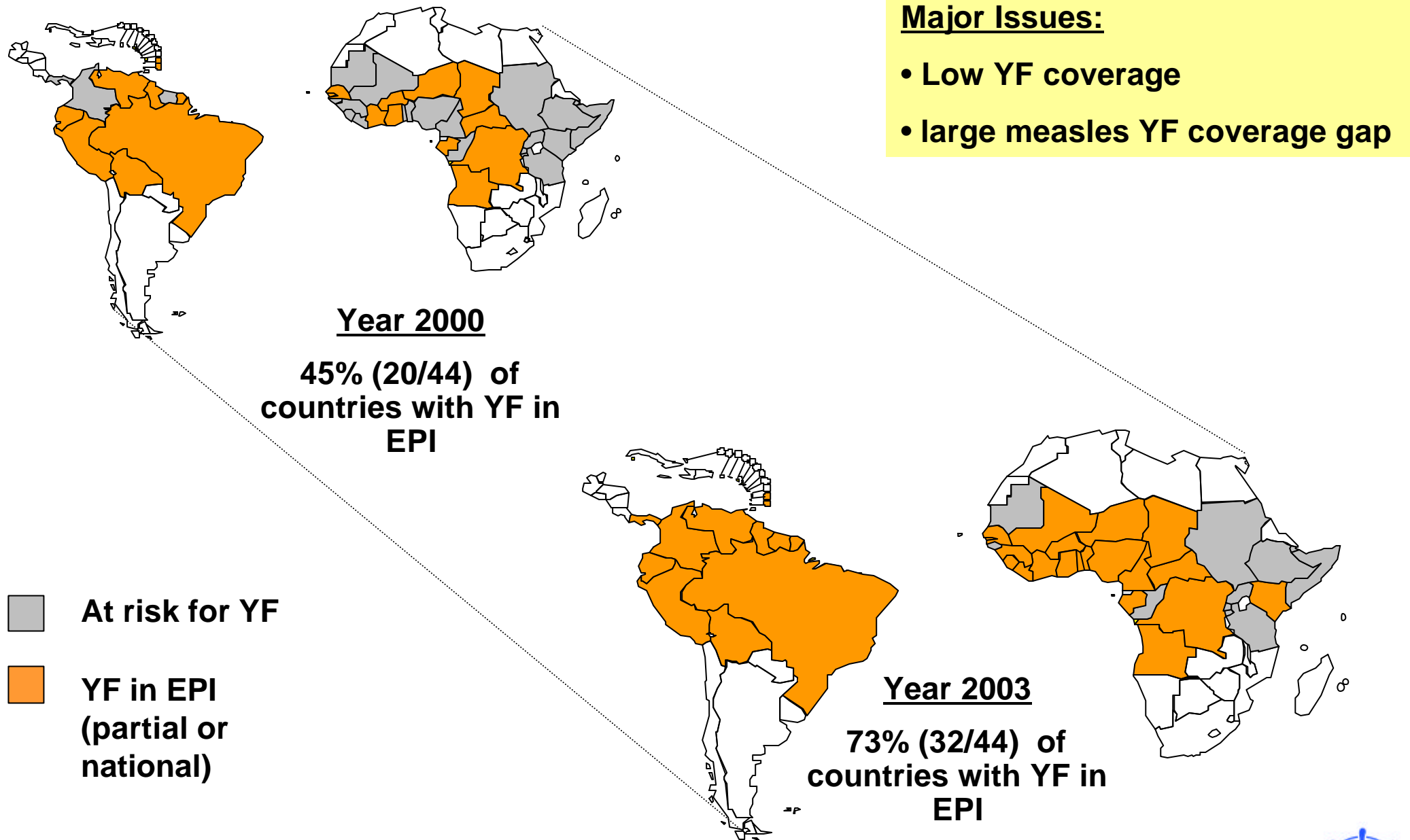
Increase Population Immunity through vaccination



Note: routine coverage should be maintained above 80% for effectiveness of the strategy



1. Introduction into routine infant immunisation



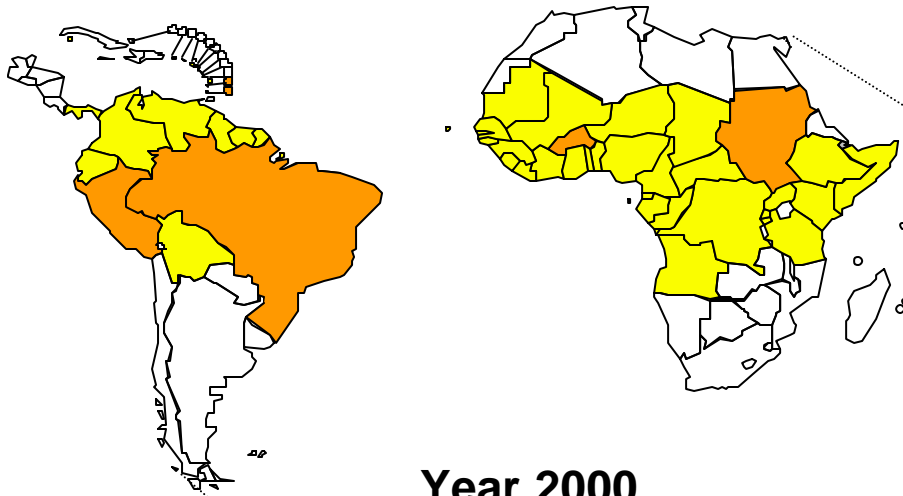
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2. Mass Preventive Campaigns

Major Issues:

- Limited resources for implementation
- 6 m doses available but op. costs not yet raised.

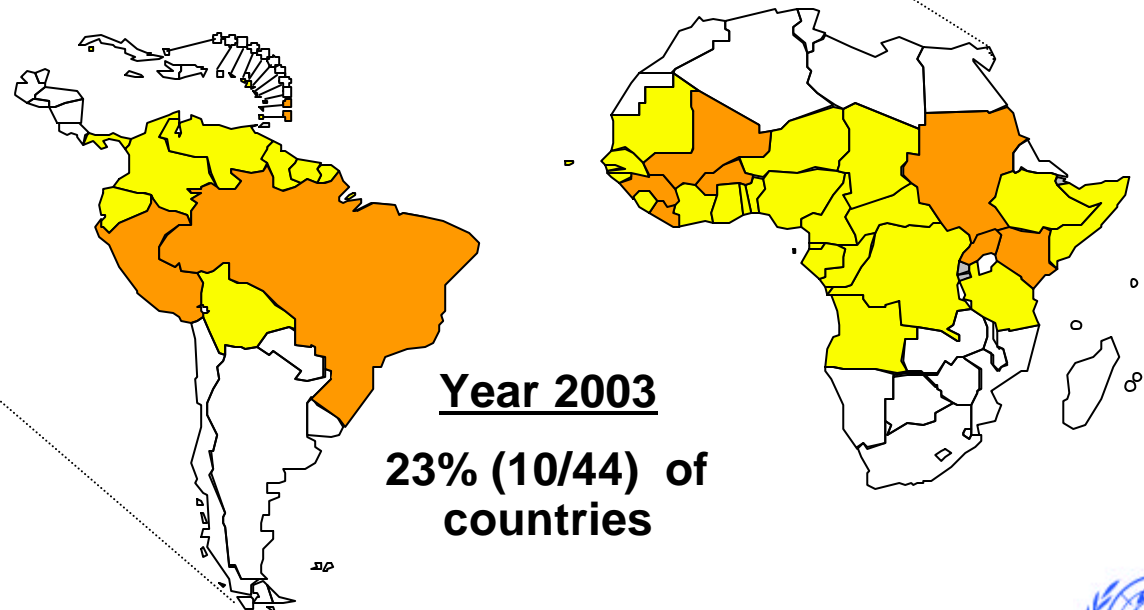


Year 2000

9% (4/44) of
countries

 At risk for YF
 Preventive
campaigns*

* based on reports to WHO, HQ



Year 2003

23% (10/44) of
countries

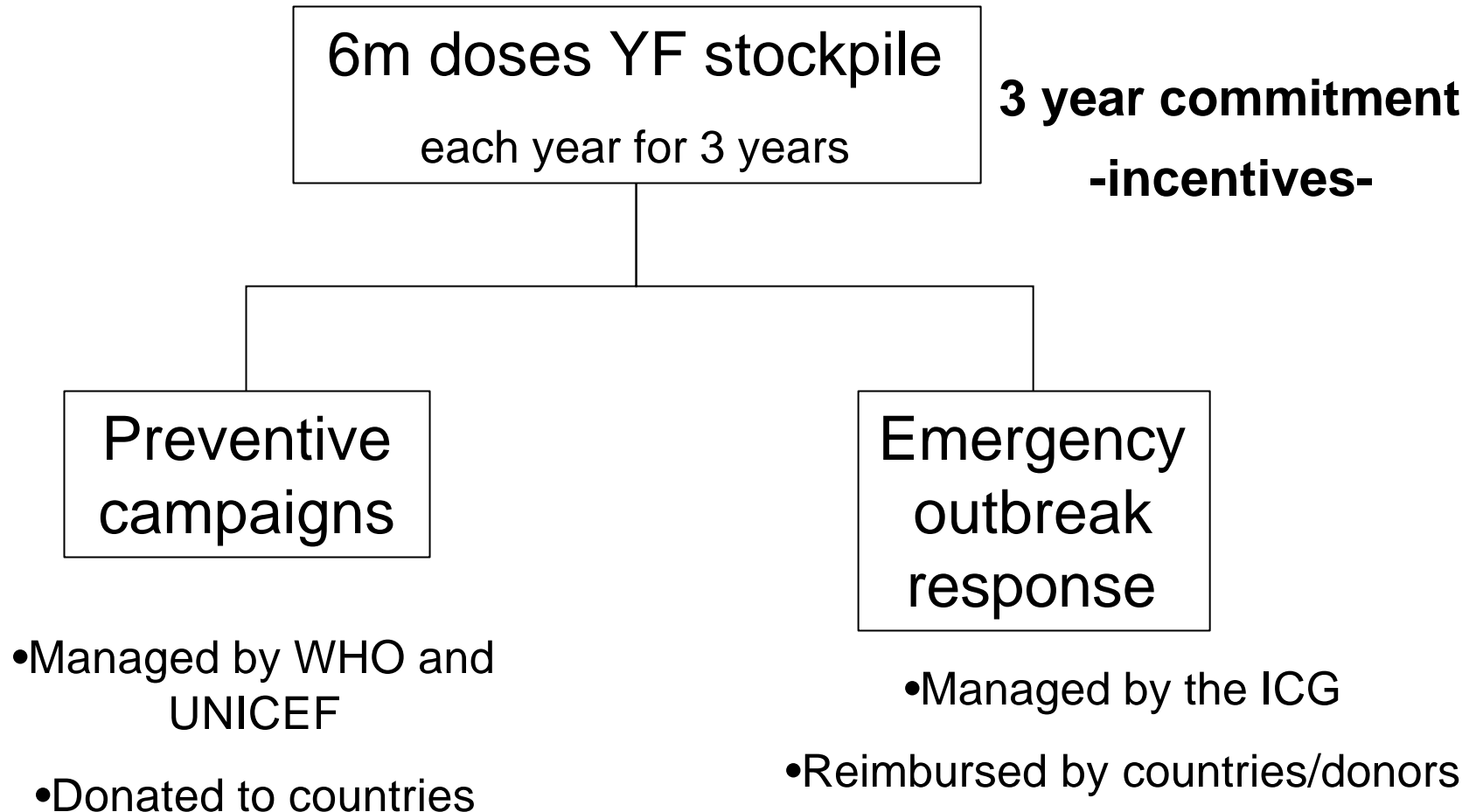
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GAVI Support

A: Vaccine for Routine EPI

B: Stockpile



3. Surveillance: Detection and Reporting of YF

Target : 80% of districts report at least 1 suspect case of YF per year

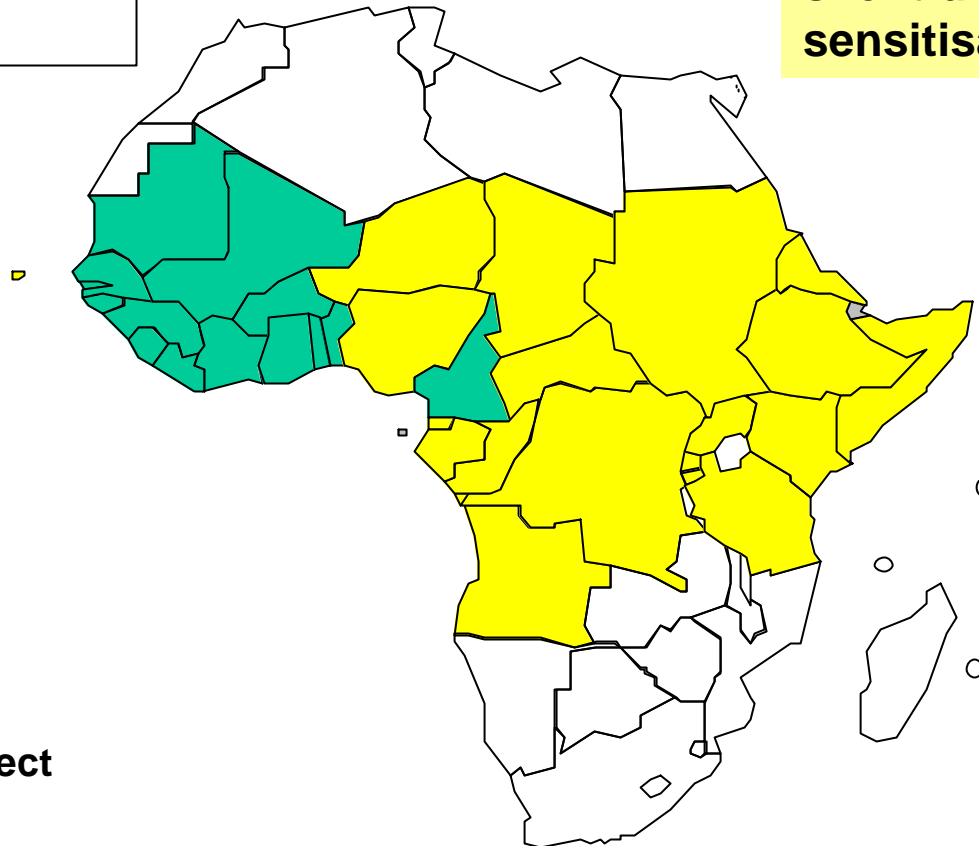
2003 Status:

West Block - 19%

Central Block: - 2%

Major Issues:

- **Difficult differential diagnosis**
- **Need to expand surveillance to silent districts & improve clinician sensitisation**



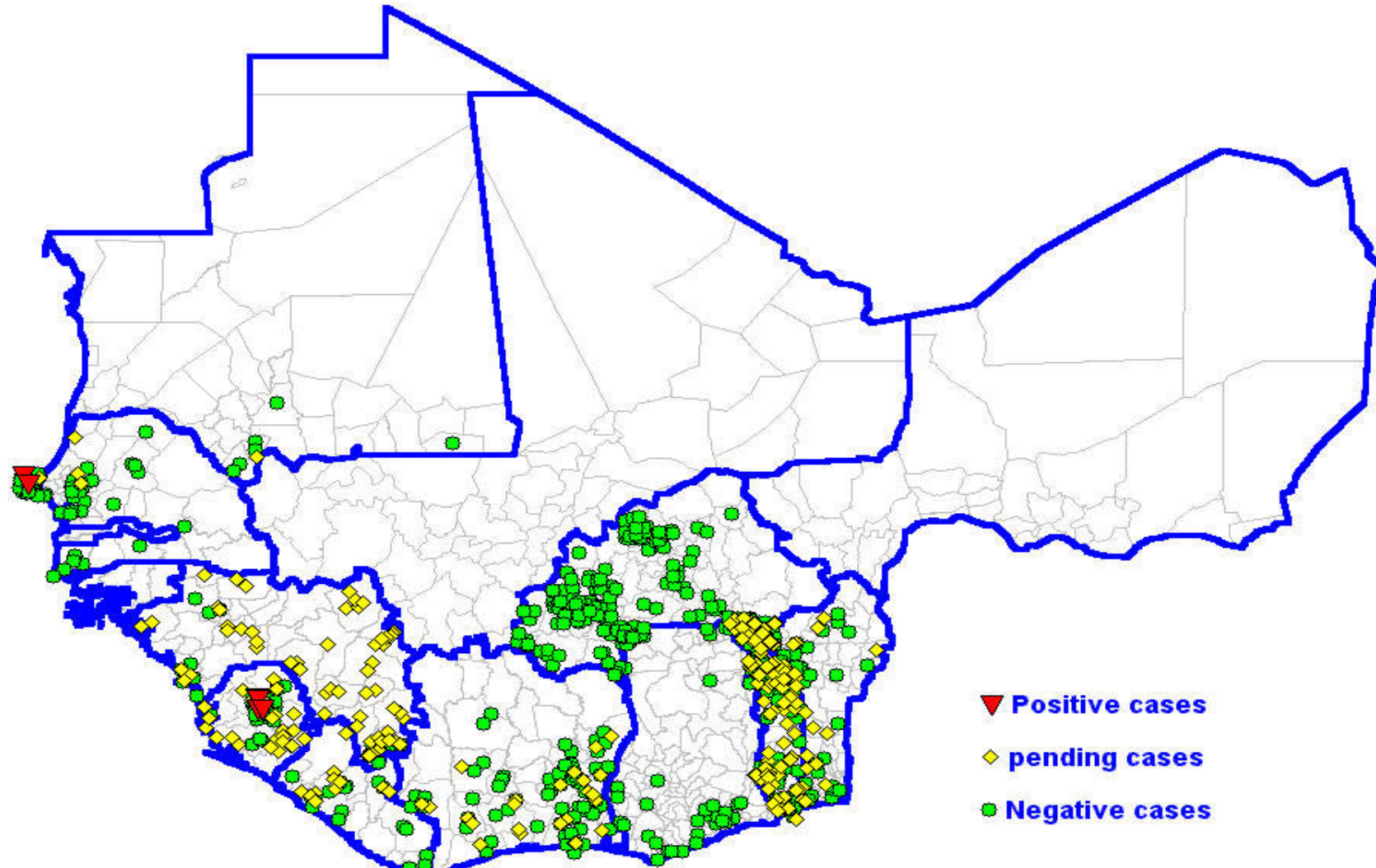
 **At risk for YF**

 **Reporting suspect YF cases**

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Yellow Fever Surveillance in African West Block: January - Sept 2003



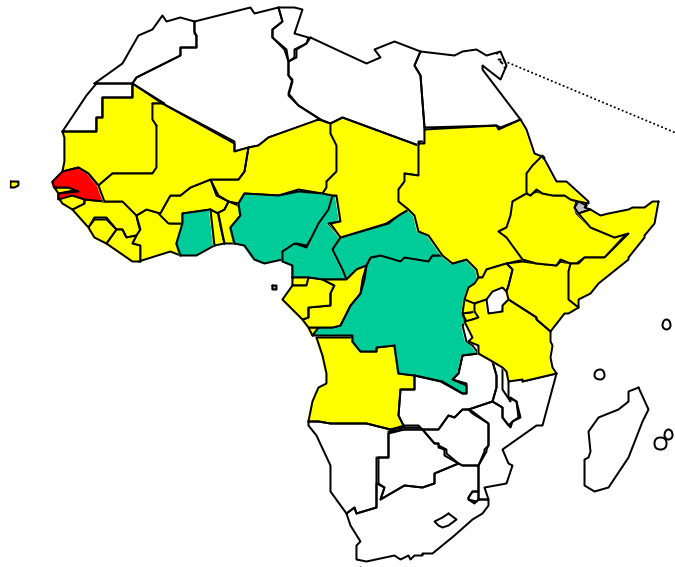
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3. Surveillance: African YF Laboratory Network

Year 2000

loose network with 5 labs

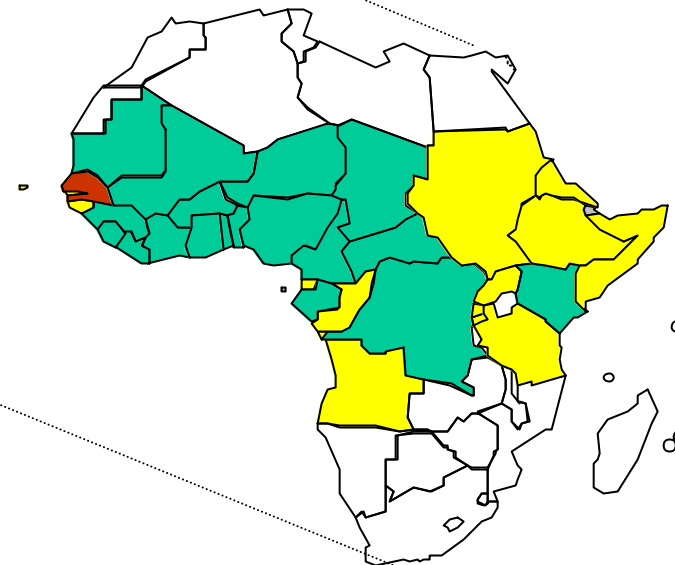





Major Issues:

- Not all trained labs are functioning.
- Need for on site training

Year 2003

20 National labs + 1 reference lab



-  At risk for YF
-  National Lab
-  Reference Lab

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Live attenuated YF vaccine

- **Single 17D strain** with 2 sub-strains; 17DD (Brazil), 17D-204 (all other manufacturers)

Major suppliers for global market	Aventis Pasteur (France) Biomanguinhos (Brazil) Institute Pasteur (Senegal)
Travel market	Aventis Pasteur (US) – US market + travel Evans Vaccines (UK)
Local consumption	Central Research Institute (India) Instituto Nacional de Salud (Colombia) Inst. of Polio and Viral Encephalitides (Russia)
Future production?	Berna (Switzerland) - vaccine technology acquired from Robert Koch Inst.



WHO Policy: Indications and contraindications

- **Indicated** for persons 9 months or older living in at-risk areas
 - Highest priority to those most likely to be exposed
- Immigrants from non-endemic to at-risk regions
- Travellers, at least 10 days before arrival
- **Contraindicated** in:
 - children less than 6 month
 - persons with severe allergy
- **Not recommended** (except during epidemics when risk of transmission is high) for:
 - 6-8 month olds
 - Pregnant women



WHO Policy: Indications and contraindications

Vaccination in HIV+ve individuals

- Vaccination of symptomatic HIV+ve individuals, and severely immunocompromised persons, not recommended.
- **YF Position Paper (Oct 2003):** For international travellers, where laboratory and other resources are available, YF vaccination may be offered to asymptomatic HIV-infected persons with CD4+ counts above 200 cells/mm³ who require vaccination for unavoidable travel.



Common mild/moderate adverse events

- Historically considered to have a good safety profile
- No placebo controlled trials
- 12 clinical trials 1953 to 2002
 - Variable rates of mild/moderate AEFI depending on sample size and follow up methods
 - Any AEFI (headache, fever, malaise, local reactions etc.) from 0% to 42% of vaccinees
 - Headache, fever and local reactions most common
- Clinical trial of YF-Vax and Arilvax (n = 1400) reported 71.9% and 65.3% with at least 1 AE
- Hypersensitivity reactions; estimated 1 per million
 - mainly in persons with known egg sensitivity

Source: T Monath, Vaccines 2003



Rare and severe AEFI

- **Viscerotropic disease**
 - YF-like illness following vaccination
 - 18 (19?) confirmed or probable cases and 11 deaths (61%) reported since 2001 (onset from 1996 to date)
 - Risk not fully quantified
 - 1 per ~10 million doses (Brazil)
 - 1 per 200,000-300,000 doses (1 per 40,000 - 50,000 doses >60 y (US))
 - differences in surveillance systems and age of vaccinees
- **Neurotropic disease**
 - Since 1945, 26 cases of encephalitis
 - 16 cases < 7 months (13 <4 m pre 1960, no age restriction)
 - 2 reported fatalities; 3-yr old + 53 yr old with unrecognised HIV and CD4 count 108 mm³
 - Risk
 - Highest in infants for encephalitis: 0.5 to 4 per 1000 in infants < 4 months



WHO master seed and AEFIs

- 2.75 million doses of vaccine produced by RKI have been used over last 40 years (2.5 million in Germany)
- No episodes of viscerotropic disease reported (passive surveillance)
- Further studies needed - Working Group proposed to review quality and safety issues
 - Use of seed material (manufacturers)
- Agreement reached for seed material to be transferred to NIBSC



Special issues

Safety in HIV +ve and immunocompromised individuals

- Little available data on HIV
 - 18 HIV positive and 57 HIV negative (Abidjan; Sibailly et al, 1997)
 - Seroconversion 17% in HIV+ and 72 in HIV-
 - No reports on AEFI
 - 44 HIV positive (Paris)
 - 87% seroconversion with good tolerance
- Theoretical risk of neuroinvasion and encephalitis
 - 17D contraindicated in immunosuppressed states (incl. high dose corticosteroids)
 - Low-dose corticosteroid treatment and intra-articular c/steroid injections not a contraindication
 - Asymptomatic HIV infection a contraindication in UK



Special issues

AEFI surveillance in mass campaigns

- 2001-2002: Passive and active surveillance in Cote d'Ivoire (2.6 million vaccinated), **Guinea (1.6 million)**, Senegal (~4.4 million)
- Low sensitivity + problems with logistics
- Significant problem of bacterial contamination

Guinea:

- 284 AEFIs reported; 28 hospitalised including 12 in “programmatic cluster”



Guinea: Incidence of AEFI among vaccinees with known HIV status

- Cohort study
- All persons consulting for HIV antibody testing in the Donka hospital
- between October 21 and December 12 2002
- standard questionnaire
 - demographics, YF vaccination status
 - questions to their health status during the four weeks
- informed consent
- national ethics committee approval



Results

- 149 participants
 - Reasons for testing
 - 27 voluntary testing (18%)
 - 118 consultations for an health event (79%)
 - 4 non specified reason (3%)
 - HIV+: 39%
 - reporting sickness: 21% (no serious health event)
 - vaccinated 77%
- sickness among HIV positive: RR 1.7 (CI 0.9-3.1)
- HIV positive and vaccinated: RR 1.1 (CI 0.9-1.3)
- Risk of developing AEFI among vaccinated:
 - RR 1.6 (CI 0.8-3.1) for HIV positive
 - independent of sex and age



Conclusions

- Persons testing positive for HIV did not show a higher risk to develop minor adverse events after vaccination than HIV negative persons.
- Larger, prospective studies are needed to confirm these findings and to identify the risk for rare and serious events.
- **Limitations**
 - AEFI definition and classification retrospective & challenging
 - Selection bias



Main issues in evaluating safety of YF intervention strategies

- Risk of **severe AEFI**
 - YFV-associated viscerotropic disease (multiple organ failure)
 - Neurotropic disease (post-vaccination encephalitis)
- **Campaign safety** incl. programmatic errors
- Vaccine **safety in HIV+ve individuals** (other immunocompromised)
- Vaccine **effectiveness in HIV+ve individuals** (other immunocompromised)



Ongoing/Proposed activities

- What is the true risk of severe AEFI?
 - YFV-associated viscerotropic disease
 - Monitoring of cases (CDC active surveillance + case reviews, planned studies)
 - Enhanced surveillance of YFV-AVD in campaign settings planned
- In HIV+ve individuals (other immunocompromised),
 - Population based surveillance/studies
 - Special studies in HIV+ve cohorts (CDC/WHO protocol)
- how safe is YF vaccine use?
- how effective is YF vaccine?

