

***Adverse Events Following Yellow Fever Vaccine
Post-marketing surveillance in Brazil***

GLOBAL VACCINE RESEARCH FORUM

INITIATIVE FOR VACCINE RESEARCH

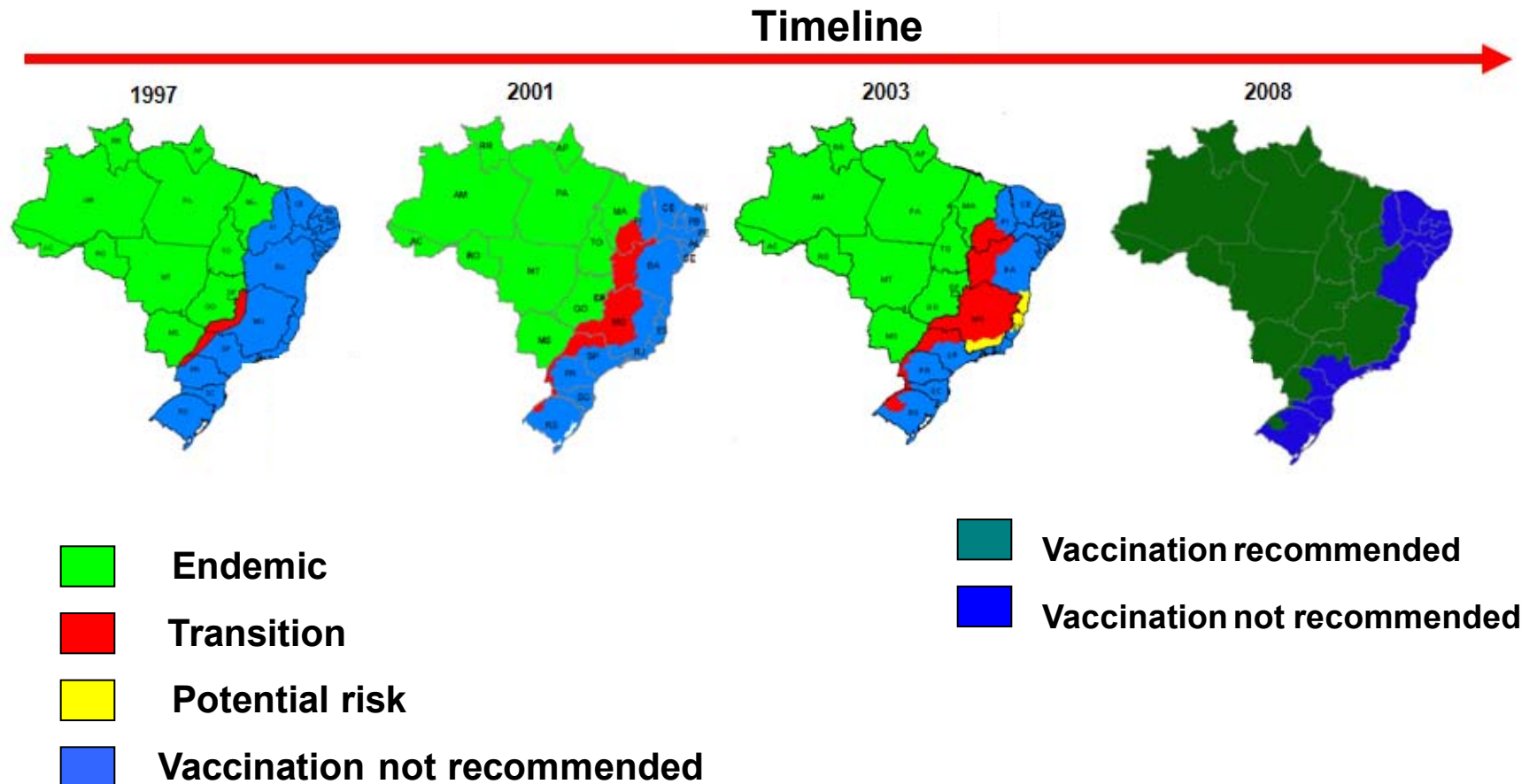
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EXPANSION OF AREAS WITH RECOMMENDATION FOR ROUTINE YELLOW FEVER VACCINATION



Source: Health Surveillance Secretary,
Ministry of Health

2009 – HSS - MoH



YFV recommended

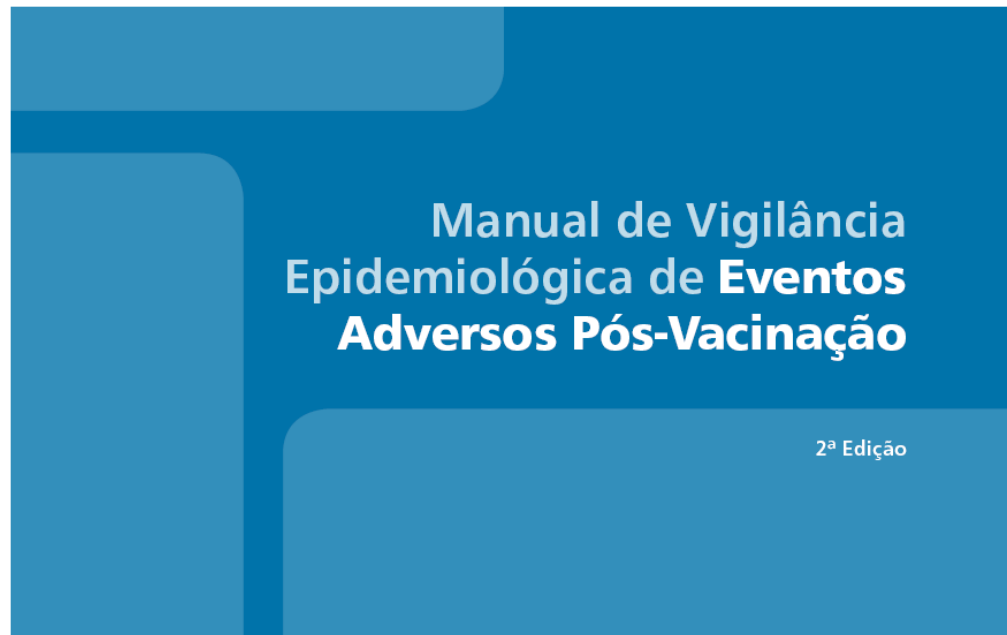


YFV not recommended

Surveillance of adverse events

- **The Brazilian Ministry of Health (MoH) National Immunizations Program has a National System for Surveillance of Adverse Events Following Immunization (AEFI) since 1998, when a Manual on AEFI was written and an electronic database was implemented. The source of information are the approximately 30,000 Health Stations all over the country**

***Manual for Surveillance of Adverse Events Following
Immunizations of the Brazilian National Immunizations Program,
MoH***



Includes form for notification, fluxogram, and protocol for investigation of YFV-associated viscerotropic disease

Ministry of Health Manual for Surveillance of AEFI, for intermediate level health workers

MINISTÉRIO DA SAÚDE



*Vigilância dos Eventos Adversos Pós-Vacinação:
cartilha para trabalhadores de sala de vacinação*

- **Detection and diagnosis at local level.**
- **State level consolidation of cases.**
- **Final diagnosis by central level, with experts participation.**

Sentinel hospitals

- **Sentinel hospitals for surveillance of ictero-hemorrhagic febrile syndrome are being implemented.**
- **Acute, febrile, ictero-hemorrhagic syndrome is a compulsory event for immediate notification.**
- **Differential diagnosis in Brazil: wild yellow fever, *YFV-associated viscerotropic disease (YFV-AVD)*, dengue, hantavirus, leptospirosis, meningococcal infection, malaria (*P. falciparum*), rickettsial infections, typhoid fever, Brazilian purpuric fever, other arboviral infections.**

- **The Customer Service of Bio-Manguinhos Market Relations Department, and reports from other countries, are also sources of information on AEFI. A Pharmacovigilance Unit has been established in Bio-Manguinhos/Fiocruz, connected to the MoH and the Brazilian Regulatory Agency.**

- **YFV-associated viscerotropic disease (YFV-AVD) is a dissemination of vaccine virus, a serious disease of high lethality.**
- **YFV-associated neurological disease (YFV-AND) includes benign aseptic meningitis, encephalitis, and autoimmune central (ADEM) or peripheral (GBS) disease.**
- **Hypersensitivity events are < 2 hours, > 2 hours, and anaphylactic shock.**
- **Cases are classified as confirmed, probable, suspect, discarded or inconclusive, according to CDC/WHO criteria.**

- **A Brazilian Group of Experts developed a protocol for investigation of viscerotropic disease since 2004.**
- **WHO, 2008-2009: protocol for Screening and Investigation of Yellow Fever Serious Adverse Events Following Vaccination.**
- **Adequate and timely collection, transport and delivery of samples is essential.**
- **A kit for samples collection including a flowchart with detailed information on collection, storage and transport may help.**

Reference laboratories

- **Evandro Chagas Institute/Fiocruz**
- **Bio-Manguinhos – Fiocruz**
- **Adolfo Lutz Institute**
- **René Rachou Institute, Fiocruz**
- **State Public Health Laboratories**



- **Mild adverse events occur in about 5% of vaccinees (data from clinical studies).**
- **Serious adverse events (hypersensitivity, viscerotropic, neurological) are rare (data from passive surveillance).**

Severe adverse events after YFV in Brazil 2000-2009*

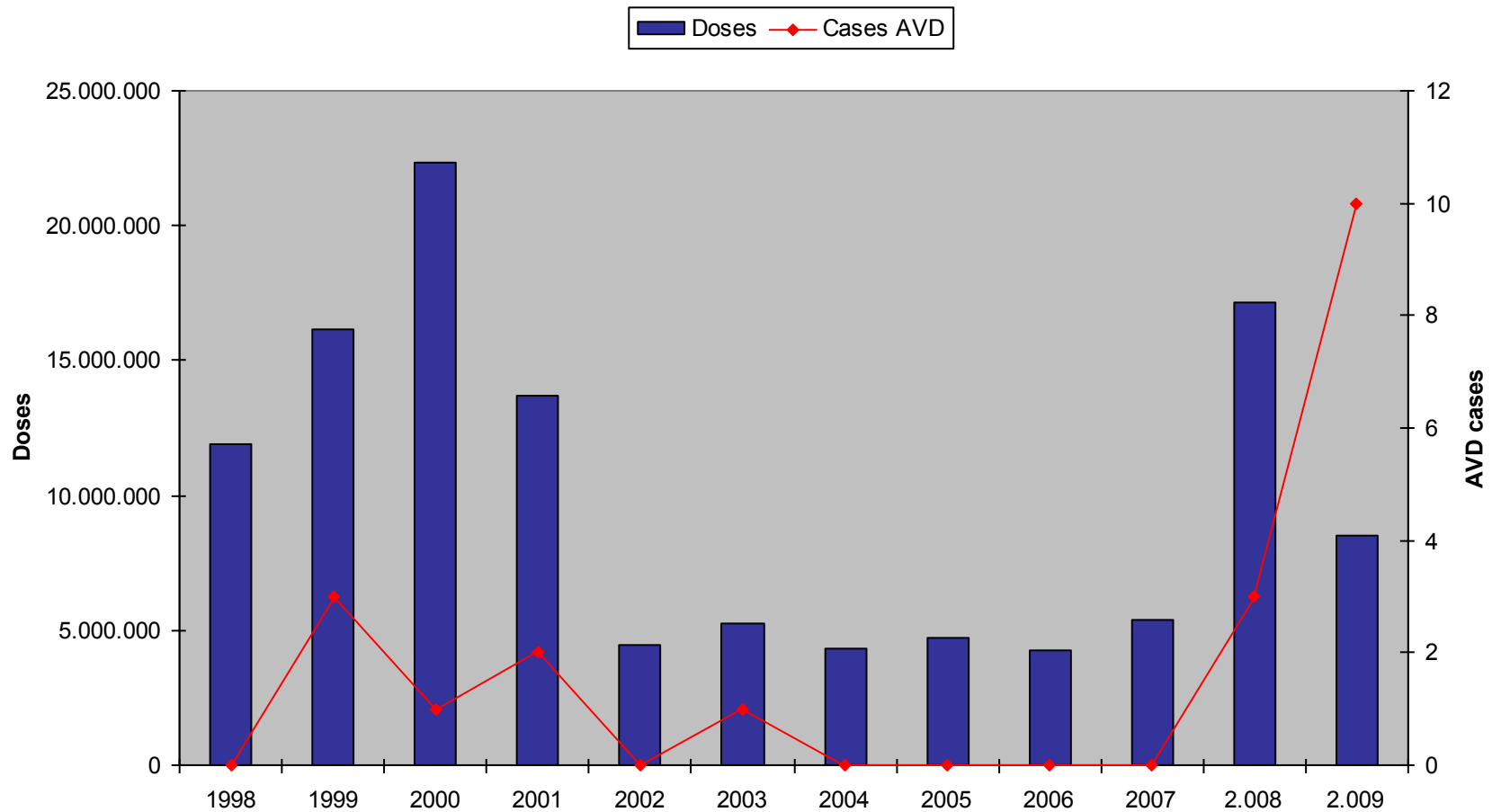
- **Hypersensitivity events (total) has been detected at a frequency of 0.9/100,000 doses, of which anaphylactic shock in 0.023/100,000 doses.**
- **YFV-AND (total) has been detected at a frequency of 0.084/100,000 doses.**
- **YFV-AVD has been detected at a frequency of 0.022/100,000 doses.**

These frequencies are low and probably underestimates risks.

*** 90,018,338 YFV doses administered**

Sources: Ministry of Health and Bio-Manguinhos/Fiocruz

YFV doses and YFV-AVD cases in Brazil



Sources: Ministry of Health and Bio-Manguinhos/Fiocruz

Recent YFV-AVD reports in campaigns, 2009

- **São Paulo state, 3 confirmed and 2 probable AVD cases per 1,600,000 YFV doses administered, ~1/300,000 doses (0.3/100,000 doses).**
- **Rio Grande do Sul state, 2 confirmed and 2 probable AVD cases, 3,600,000 doses administered, ~1/900,000 doses (0.11/100,000 doses).**

Sources: Ministry of Health and Bio-Manguinhos/Fiocruz

YFV-AND in Rio Grande do Sul campaign, 2009*

- **Aseptic meningitis: 35 confirmed cases, ~1/103,000 doses**
Guillain-Barré Syndrome: 2 probable cases, ~1/1,800,000 doses.
- **2 cases of encephalitis acquired through breast milk, confirmed**
- **1 case of demyelinating disease + optic neuritis, confirmed.**
- **Total neurological events: 40, ~ 1/90,000 doses, ~1.1/100,000 doses, most of them with good recovery and without sequella.**

*** ~ 3,600,000 doses administered**

Sources: Ministry of Health and Bio-Manguinhos/Fiocruz

Adverse events are more frequent after 1st doses 2000-2008

Dose	Doses Administered	Adverse events	Frequency /100,000 doses
1st dose	66,568,377	1358	2.04
Other doses	14,958,933	157	1.05
Total	81,527,310	1515	1.86

Sources: MoH - NIP, and Bio-Manguibhos/Fiocruz

- **YFV-AVD has not been reported in association with immunodeficiency diseases, although these are a contraindication for vaccination.**
- **Of 26 YFV-AVD cases reported with 17-DD vaccine, 12 (46%) had some kind of possible immunological disturbance in them or in close relatives, not true immunodeficiencies. These disturbances point to autoimmune diseases.**

- **Three YFV-AVD cases occurred in patients with SLE, and 2 cases in sisters who had an aunt with SLE. There is 1 other case of YFV-AVD after YFV from other producer in a patient with SLE**

Studies for improvement of yellow fever immunization in Bio-Manguinhos/Fiocruz

- **Immunological studies in individuals who received YFV with and without severe adverse events.**
- **A dose-response study is underway, to know if lower doses can be equally immunogenic and perhaps safer.**
- **An intradermal study, with even smaller dose, to be administered in a needle-free device (in a partnership with PATH), is being planned.**
- **Improvement on purification of vaccine with protamine sulphate.**
- **DNA recombinant technology.**

- **Even as it is now, yellow fever vaccine is a good vaccine and the most effective tool for the control of yellow fever, a extremely serious disease with a very high letality.**

Thank you !