Recent Yellow Fever Epidemics in Brazil: Evolving Challenges

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Outline

1. Yellow fever in Brazil
   a) Historical remarks
   b) Control efforts in the early 20th century
   c) Recent epidemiology and strategies
      a) Decision to restrict vaccination areas

2. Recent (current) outbreak
   a) Expansion of geographical area
   b) Challenges for clinical management
   c) Therapeutic strategies

3. Vaccine shortage and fractional-dose vaccination
   1. Current knowledge
   2. Outstanding issues
Yellow Fever in Brazil

• First outbreak in Recife, 1685 followed by Salvador
  – 150 “silence”
• Endemic in most urban settings – alternating epidemics.
• Rio de Janeiro was endemic in the 1800-1900s
  – Economic and diplomatic damage
Initial Control Efforts
Initial Control Efforts
Recent (pre-2016) epidemiology and control
Recommended areas for vaccination

1998

Fonte: MS/FNS

Articles

Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases


Summary

Background The yellow fever vaccine is regarded as one of the safest attenuated virus vaccines, with few side effects or adverse events. We report the occurrence of two fatal cases of hemorrhagic fever associated with yellow fever 17DD subunit vaccine in Brazil.

Methods We obtained epidemiological, serological, virological, pathological, immunohistochemical, and molecular biological data on the two cases to determine the cause of the illnesses.

Findings The first case, in a five-year-old white girl, was characterised by sudden onset of fever accompanied by headache and vomiting. The patient was treated with antipyretic agents and supportive care. The second case involved a 28-year-old man who presented with fever, headache, and gastrointestinal symptoms. Both patients died within the first 24 hours of admission.

Interpretation These serious, and hitherto unknown, complications of yellow fever vaccination are extremely rare but the safety of yellow fever 17DD vaccine needs to be reviewed. Host factors, probably idiosyncratic reactions, might have led to an unexpected outcome.

Lancet 2001; 358: 92-97
See Commentary page 84
Critical aspects of yellow fever control in Brazil

1. Recommendations for vaccination only after cases and deaths have been recorded in such areas should be avoided; 2. The risk of urban transmission of the disease needs to be reduced, given the immense dispersion of *Ae. aegypti* and *Ae. albopictus* and the recent episode that occurred in Paraguay; 3. The worldwide scarcity of vaccine that could be used for urgent vaccination of populations in large urban centers if a disease outbreak occurred, either transmitted by *Ae. aegypti*, or resulting from a wild cycle on the periphery of these centers; 4. The difficulty in achieving timely vaccination (ten days before traveling) among tourists and migrants to areas with virus circulation; 5. Occurrences of serious adverse events associated with the vaccine have mainly been registered at the time of implementing vaccination in situations when thousands of people make demands on vaccination units within a short space of time and contraindications are often not respected; 6. The risk of adverse events is often greater among people receiving the vaccine for the first time than among revaccinated individuals, and this is the situation of the vast majority of people living in areas that are not considered endemic. Initially, the vaccine should be included in the child immunization calendar throughout the country and should be applied to people living in and visitors to areas that are characterized as receptive to transmission of the wild cycle of the disease, even if these areas have been silent for many years.
Current scenario
Recommended areas for vaccination
Current scenario

2016-2017

2017-2018

Fonte: CGDT/DEVIT/SVS/MS. Dados preliminares e sujeitos à revisão. A data de ocorrência não estava registrada em 38 das notificações.
Recent Outbreak

- 2016: 779 confirmed cases
  - 262 deaths (33.6% lethality)
- 2016: 7,518 suspected cases
  - 1376 confirmed
  - Lethality: 35.1%
Age and gender distribution

Fonte: CGDT/DEVIT/SVS/MS. *Dados preliminares e sujeitos à revisão.

FIGURA 5 • Distribuição por sexo e faixa etária dos casos confirmados de febre amarela notificados à SVS/MS, período de monitoramento 2017/2018 (Jul/17 a jun/18), Brasil, até a SE 19°.
Challenges in management

• Severity of cases in ICUs
• Tentative strategies
  – Liver transplant
  – Sofosbuvir
  – Plasmapheresis
Liver transplantation for fulminant hepatitis due to yellow fever

Alice Tung Wan Song, Edson Abdala, Rodrigo Bronze de Martino, Luis Marcelo Sá Malfli; Ryan Yukimatsu Tanigawa, Guilherme Marques Andrade, Liliana Ducatti, ... See all authors.

First published: 15 September 2018 | https://doi.org/10.1002/hep.30273
Challenges for management

1. Lack of point-of-care diagnostics
   1. Possible differential diagnosis

2. Low evidence of adjunctive and/or specific therapeutics
   1. Liver transplant: HCFMUSP: 7 performed (3 alive)
   2. Sofosbuvir – *in vitro* response
       1. Unclear role in patients
   3. Plasmapheresis

Figure 4

http://dx.doi.org/10.1101/266361
Vaccine shortage and strategies

1. Biomanguinhos – biggest manufacturer
   1. 9 million doses per month
   2. Estimated need: 26.9 million unvaccinated individuals
Reverse vaccine Revolution?
Fractional dose

1. Rapid expanding area for YF transmission
2. Poor vaccine coverage
3. Decision to promote mass campaign with fractional (1/5) dose
4. Current estimated coverage: 55.5%
   1. Registration is a problem:

Vaccine doses
Total pop.
FEBRE AMARELA: COBERTURA VACINAL
Municípios
2008 à 2018

- >= 90%
- > 75% e < 90%
- > 50 e < 75%
- < 50%

Cidades:
- Itaboraí
- São Gonçalo
- Barra do Piraí
- Seropédica
- Queimados
- Mesquita
- Belford Roxo
- Duque de Caxias
- São João de Meriti

Regiões:
- NORTE
- NOROESTE
- SERRANA
- MÉDIO PARAÍBA
- METROPOLITANA I
- METROPOLITANA II
- BAIXADA LITORÂNEA
FEBRE AMARELA: COBERTURA VACINAL
2008 à 2018

Nordeste: 79,23%
Serrana: 91,38%
Médio Paraíba: 75,02%
Metropolitana I: 55,79%
Metropolitana II: 58,81%
Baixada Litorânea: 78,85%
Centro Sul: 99,98%
Norte: 92,13%

Itaboraí
São Gonçalo
Itaboraí
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Seropédica
Queimados
Belford Roxo
Duque de Caxias
Mesquita
São João de Meriti
BAÍA DA ILHA GRANDE
METROPOLITANA I
METROPOLITANA II
BAIXADA LITORÂNEA
CENTRO SUL
NORTE
17DD yellow fever vaccine
A double blind, randomized clinical trial of immunogenicity and safety on a dose-response study

Reinaldo M. Martins,1,2 Maria de Lourdes S. Maia,1 Roberto Henrique G. Farias,1 Luiz Antonio B. Camacho,1 Marcos S. Freire,1 Ricardo Galler,1 Anna Maya Yoshiha Yamamura,1 Luiz Fernando C. Almeida,1 Sheila Maria B. Lima,1 Rta Maria R. Nogueira,1 Gloria Regina S. Sá,2 Darcy A. Hokama,2 Ricardo de Carvalho,1 Ricardo Aguiar V. Freire,3 Edson Pereira Filho,4 Maria da Luz Fernandes Leal1 and Akira Homma1

Duration of post-vaccination immunity to yellow fever in volunteers eight years after a dose-response study

Reinaldo de Menezes Martins1,2, Maria de Lourdes S. Maia2, Sheila Maria Barbosa de Lima1, Tatiana Guimarães de Noronha2, Janaina Reis Xavier1, Luiz Antonio Bastos Camacho1, Elizabeth Maciel de Albuquerque1, Roberto Henrique Guedes Farias1, Thaliha da Matta de Castro1, Akira Homma1, Collaborative Group for Studies on Duration of Immunity from Yellow Fever Vaccine

Camara-Azevedo et al. BMC Infectious Diseases 2014; 14:351
http://www.biomedcentral.com/1471-2334/14/351

RESEARCH ARTICLE
Open Access

Subdoses of 17DD yellow fever vaccine elicit equivalent virological/immunological kinetics timeline
Fractional dose

1. Option due to shortage of vaccine
2. Recommended by WHO in outbreak situations
3. Successfully applied in DRC and Angola
4. Protection of doses > 1000 UI seen similar to current dose
5. Duration of protection (PRNT assays) for at least 9 years.
ELIMINATING YELLOW FEVER

UPDATED STRATEGY FOR THE ELIMINATION OF YELLOW FEVER EPIDEMICS (EYE)

BACKGROUND
- Increased urbanization
- Remote populations in high-risk areas
- Rising global mobility challenges containment

RISK FORECASTING
- Yellow fever virus in EPI as a global threat
- Vaccine for yellow fever in EPI strategy

134 M PEOPLE PROTECTED

TODAY
- Key focus on Africa but also impact in South America

VECTORS
- Controlling mosquitoes will take volume approaches
- Other controls needed in strategies

World Health Organization

Yellow Fever partners meeting for the development of the updated strategy for the Elimination of Yellow fever Epidemics (EYE), September 12 2016

Sam Bradd
Challenges

• Can we predict and anticipate epidemics?
  – Role and how to perform epizootic surveillance
• How to best manage clinical cases
• Do we need new products and vaccination strategies?
  YES!
Ali, na beira do rio Pará, deixaram largado um povoado inteiro: casas, sobradinho, capela; três vendinhas, o chalé e o cemitério; e a rua, sozinha e comprida, que agora nem mais é uma estrada, de tanto que o mato a entupiu. Ao redor, bons pastos, boa gente, terra boa para o arroz. E o lugar esteve nos mapas, muito antes da malária chegar. E ela veio de longe ... Cada ano avançava um punhado de léguas, mais perto, mais perto, pertinho, fazendo medo no povo, porque era sezão da brava – da "tremedeira que não desamontava" – matando muita gente. – Talvez que até aqui ela não chegue... ... Então, houve gente tremendo, com os primeiros acessos da sezão. – Talvez que para o ano ela não volte, vá s'embora... Ficou. Quem foi s'embora foram os moradores: os primeiros para o cemitério, os outros por aí afora, por este mundo de Deus.

Sagarana,

Guimarães Rosa