Considerations to integrate vaccine trials to the plague response: perspectives from Madagascar

Workshop « Efficacy trials of Plague Vaccines: endpoints, trial design and site selection »

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Plague in Madagascar
1898: introduction of the Plague in Madagascar (Toamasina)

- 1898: Toamasina epidemic
  - 24 November 1898: 1st case

- 1921: Antananarivo
  - Following the construction railways

- Spread in Madagascar

- Endemic to the present day
Plague in Madagascar
Endemic area with a plague season

• Endemic area
  • Rural areas of the Central highlands
  • Natural foci of plague
  • Altitude > 800 m

• Plague Season
  • October – April

• Bubonic form predominant
  • 2015: 326 cases 32% of pneumonic forms
  • 2016: 283 cases 12% of pneumonic forms

Source: Plague Unité – LCP, IPM
Plague epidemic in 2017

The beginning

- **Index case**: end of August
  - 31 year-old-man
  - Died from respiratory distress on August 28
  - Going from endemic area and travelling in a bush taxi
    - Ankazobe ⇒ Antananarivo ⇒ Moramanga

- **September 2, 3**
  - 2 passengers died (Toamasina, Antananarivo)
  - Two deceased in the same family around second passenger

- **September 11**: confirmation PP outbreak
  - 47 year old woman died in Antananarivo
  - Linked to Tamatave cluster

Source: IPM
Plague epidemic in 2017

Keys information

Epidemic plague in Madagascar

2414 cases
1902 Pneumonic  (78.8%)
22.7% confirmed or probable
322 Bubonic  (15.4%)
34.1% confirmed or probable

7318 contacts of plague cases
- Identification, treatment, follow-up
- Chemoprophylaxis national regimen: triméthoprim-sulfaméthoxazole
Plague epidemic in 2017

Keys information

• Response coordinated by MoH co-led by WHO
• Enhanced epidemiologic surveillance
• Laboratory confirmation
  • RDT, PCR-qPCR, culture, no serology
• Contact
  • identification, antibiotic administration and follow-up
• Case Management (isolation and treatment)
• Safe and dignified burials
• Social mobilization and community engagement
Elements of outbreak situation \( \leftrightarrow \) on vaccine trial
Different stages of a vaccine trial

• **Objective:** evaluate effectiveness of plague vaccine

• **Key points for vaccine trial protocol**
  - Public health authorities agreement
  - National ethic committee authorization
  - Recruitment and follow-up of volunteers
    - Vaccinated and non vaccinated
    - Explanation, consent
    - Vaccination
  - Diagnosis of plague cases to evaluate the vaccine
Elements of outbreak situation on vaccine trial

- **Point 1**
  - Public health authorities agreement
  - National ethic committee authorization

- **During epidemic**
  - Authorities little concerned by research activity
    - Priority given to controlling the epidemic

- **Difficulties to introduce news policies during epidemic**
  - Therapeutic treatment regimen
  - Secure burial protocol

- **Contact and convince authorities from the beginning of outbreak**
Elements of outbreak situation ⇔ on vaccine trial

• Point 2
  • Recruitment and follow-up

• Who will implement the trial?
  • Health care workers with a heavy workload
  • Health care system saturated
    • Medical care complicated because health service saturated
      • Means insufficient because not adapted to an epidemic situation

• Need to strengthen care teams
  • Teams in charge of the trial are familiar with the field conditions and Malagasy culture +++
Elements of outbreak situation ↔ on vaccine trial

• Point 2
  • Recruitment and follow-up

• Acceptability of concerned population
  • Suspicion of population +++
    • Violent reactions to rumors of vaccinations against the plague
    • People don’t want to be used as an experiment during an epidemic

• Duration of trial
  • Risk that end of the epidemic happens before the end of the trial
    • Need for clear timeline
    • Authorization, recruitment, vaccination schedule, follow-up...
Elements of outbreak situation ⇐ on vaccine trial

• Points 3
  • Diagnosis of plague cases to evaluate the vaccine

• Find the plague cases +++

• 2017 plague outbreak
  • Clinical management of patients in 9 to dedicated care centers

• Population: very important fear of plague
  • Reluctance to consult health care system
    • hide the disease ++
      • Don’t want to be hospitalized => reputation of HCS
      • Still shameful disease

  ⇒ impact on evaluation of the vaccine

• Very high antibio-prophylactic use in non contact subjects
  ⇒ Possible impact on clinical forms, diagnostic test results
Elements of outbreak situation on vaccine trial

• Point 3
  • Diagnosis of plague cases to evaluate the vaccine

• How to define a plague case?
  • Plague Biologic diagnosis during epidemic is essential
    • IPM: only laboratory
      • More than 100 samples / days (RDT, PCR or qPCR, culture)
      • Serology not possible
        • impossible to routinely collect samples of blood
        • not planned in the national strategy
    • Sensitivity and specificity <100%
  • Differential diagnosis: most often not done in HCS
  • Clinical suspicion ⇒ suspect case even if tests are negative
  • Need for a sensitive and specific biological diagnosis
Conclusion

Elements of outbreak situation ↔ on vaccine trial

• incidence
  • favors the demonstration of the efficacy of a vaccine (especially by increasing the power of study)

• But some epidemic-related conditions can make it complicated
  • Priority for the authorities
  • Acceptability of the population
  • Implementation difficult given the heavy workload of health workers.

• Uncontrolled consumption of antibiotics
• Sensitivity and specificity of diagnostic tests

• Race against time!