WHO consultation on RVF therapeutics and vaccine evaluation: Clinical disease

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Tasks

• Review what is known about the clinical manifestations of RVF disease
• Discuss complications of disease
• Considerations for
  • clinical trials
  • vaccine trials
Where do the data come from?

Case reports of laboratory acquisitions, field reports

1930's-40's

Mild, self-limiting

Ocular disease

Severe disease
Hemorrhagic fever
Meningoencephalitis

South African emergence
South Africa 1975
Sudan 1976
Egyptian emergence 1977

1950's

1970's

1990's

Madagascar
Mauritania/West Africa

2000’s

Saudi Arabia and Yemen 2000/1
Egypt 2003
Kenya, Somalia, Tanzania, Sudan 2006/7

2010’s

South Africa, 2010
Mauritania, 2012
Niger, 2016

1930's-40's: vaccine development

1960’s: vaccine development

1970’s: animal models human vaccine trials

1980’s: animal models human vaccine trials

Detailed clinical summaries

1990’s: animal models human vaccine trials

2000’s: animal models human vaccine trials
Spectrum of Rift Valley fever disease in humans

- Fever
- Headache
- Myalgia
- Malaise
- Arthralgia
- Nausea/vomiting

Abrupt onset
Tmax: 40°C

Fever
Retinitis, <2%
Hemorrhagic fever
Jaundice, Hepatitis <1%
Meningoencephalitis, <1%

Hemorrhagic fever:
Jaundice, Hepatitis <1%

2-6 days duration
<10% biphasic

3-6 day incubation

Day Post Symptom Onset:

7
14
21
28

Weakness and fatigue accompany convalescence up to 3 weeks

up to a 3% mortality rate (estimated from Egyptian outbreak)
Ocular disease

• 2-20% of identified cases in prior reports
• patients note a visual disturbance
• retinopathy
• exudative lesions
• can be bilateral
• permanent visual loss in up to 50% of cases

Al-Hazmi et al, CID 2003
Severe disease- hepatic often hemorrhagic

- 7-18% of identified cases in prior reports
- severe enough to require hospitalization
- jaundice, epistaxis, hematemesis, hematochezia, hematuria, petechiae, ecchymosis, purpura
- indirect hyperbilirubinemia, leucopenia, thrombocytopenia, anemia, prolonged bleeding time, elevated creatinine, elevated liver function tests
- pathology with severe liver necrosis, diffuse intraparenchymal hemorrhages
Meningoencephalitis

- 17-22% of identified cases in prior reports
- altered mental status, coma, nuchal rigidity, hyperreflexia
- can be accompanied by other features—hepatitis, renal failure, retinitis
- low level pleocytosis in CSF, normal glucose and protein
- many cases fatal, long term sequelae in survivors
- only one case report with CT/MRI data
Maternal to fetal transmission?

- Spontaneous abortions are a major feature of livestock disease
- Case reports demonstrate that maternal to fetal transmission can occur in humans
- Emerging data that RVFV infection during pregnancy is associated with miscarriage

Unanswered questions

• What underlying factors contribute to disease manifestation/severity?
  • Host genetics- Innate immunity?
  • Co-morbidities- malaria? schistosomiasis? HIV? hepatitis?
  • Virus genetics/evolution/reassortment?

• What role do the endothelium and coagulation pathways play in disease?
  • Case reports of thrombi-
    • fatal pulmonary embolism
    • coronary thrombus
    • retinal thrombus
  • Many mentions of vasculitis- CNS disease, retinal disease
What is the true burden of disease?

CDC RVFV Distribution map

Where the studies have been done:

https://www.cdc.gov/vhf/rvf/outbreaks/distribution-map.html

Clark et al. PLOS NTD, 2018
What is the true frequency of various disease manifestations?

• Ocular- 2 -20% of cases
• Hemorrhagic 7 -18% of cases
• Meningoencephalitis: 17-22% of cases
• Major reporting bias
  • data only available if patient sought medical attention and was diagnosed
What is the true CFR?

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<th>Deaths</th>
<th>CFR</th>
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<td>Niger</td>
<td>2016</td>
<td>105</td>
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</table>

https://www.who.int/news-room/fact-sheets/detail/rift-valley-fever
Considerations for clinical trials

• How to identify cases?
  • Healthcare infrastructure
  • Access to diagnostics
  • Lack of specificity of symptoms

• Rapidity of symptom onset and disease progression could make it logistically challenging to implement
  • Infectious virus in the blood up to 10 days post symptom onset

• Will treatment lead to increased risk of developing meningoencephalitis?
  • Ribavirin
  • Antibody therapies in animal models
  • Safety and use in pregnancy
Considerations for vaccine trials

• Single exposure is considered to lead to lifelong immunity
• Need to identify sero-negative individuals
  • Some endemic areas >50% seropositivity by adulthood
• Outbreak setting vs. high risk populations
  • Short incubation period makes reactive use logistically challenging
• Consideration of immune status if using live attenuated platform
• Use in pregnant women and children?
  • up to 20% of cases are 10-19 yo in some outbreaks