Acute febrile illness: when to suspect a zebra instead of a horse

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Disclosures

- None

Case Presentation

DOI=1 45 yo male presents with fever 38.3 associated with chills, malaise, headache, myalgia and large-joint arthralgia. Tx with Tylenol

DOI=3 normothermic but with fatigue, malaise, nausea, vomiting, anorexia, oliguria

DOI=5 mid-epigastric discomfort, jaundice

DOI=7 presents to hospital in his country of origin

Admit Exam

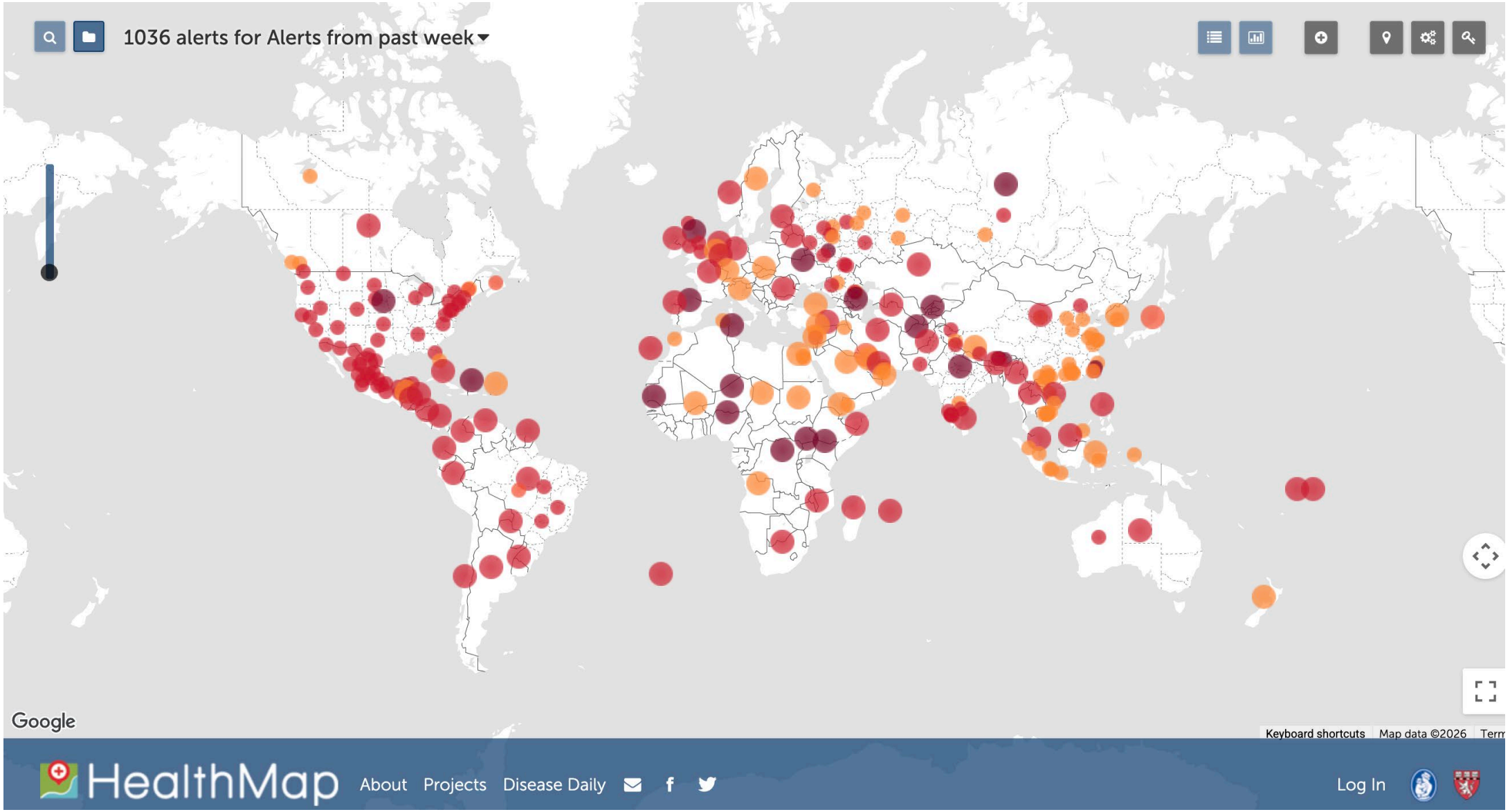
- 37C HR 90 RR 20 BP 120/70
- PE: Awake alert and fully oriented, significant for scleral icterus, no HSM, no joint tenderness or swelling, no rash or bleeding

PMH: No significant PMH
FH: Non-contributory

Social history

- Worked as a forklift worker in Luanda, Angola for 2 years prior to presentation
- Lived in rural district of Luanda
- Frequent mosquito bites
- No contact with with livestock
- No sick contacts
- No travel outside of the area

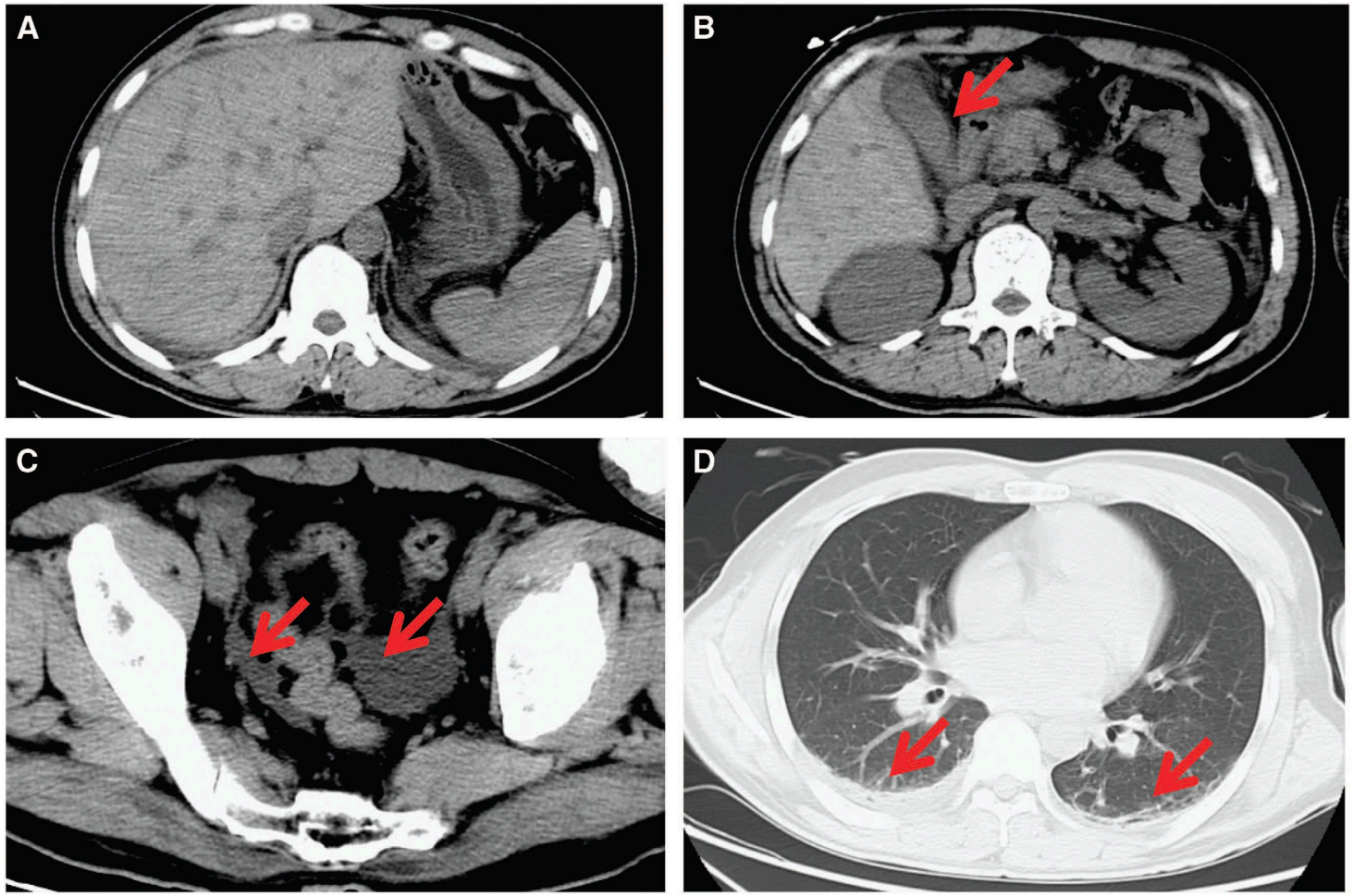
https://www.healthmap.org/en/index.php



Laboratory values at hospital presentation

- Creatinine: 1000 umol/L = 11.31 mg/dL
- BUN: 35 mmol/L
- T bili: 83.8 umol/L = 4.9 mg/dL
- ALT 5910 IU/L
- AST 7570 IU/L
- LDH: 1880 U/L
- CK: 6680 U/L
- WBC 6.8
- Plts 100

Radiology



Normal liver, spleen (A)
Gallbladder wall thickening (B)
Free fluid in plevis (C)
Trace pleural effusion (D)

What is on your differential?

Open evidence differential

- Ischemic hepatitis (shock liver) with acute tubular necrosis (ATN)
- Sepsis-associated multiorgan dysfunction syndrome (MODS)
- Rhabdomyolysis with secondary hepatic and renal injury
- Acetaminophen (paracetamol) toxicity
- Fulminant viral hepatitis
- HLH
- Acute Budd-Chiari syndrome
- Drug- or toxin-induced liver injury (non-APAP)

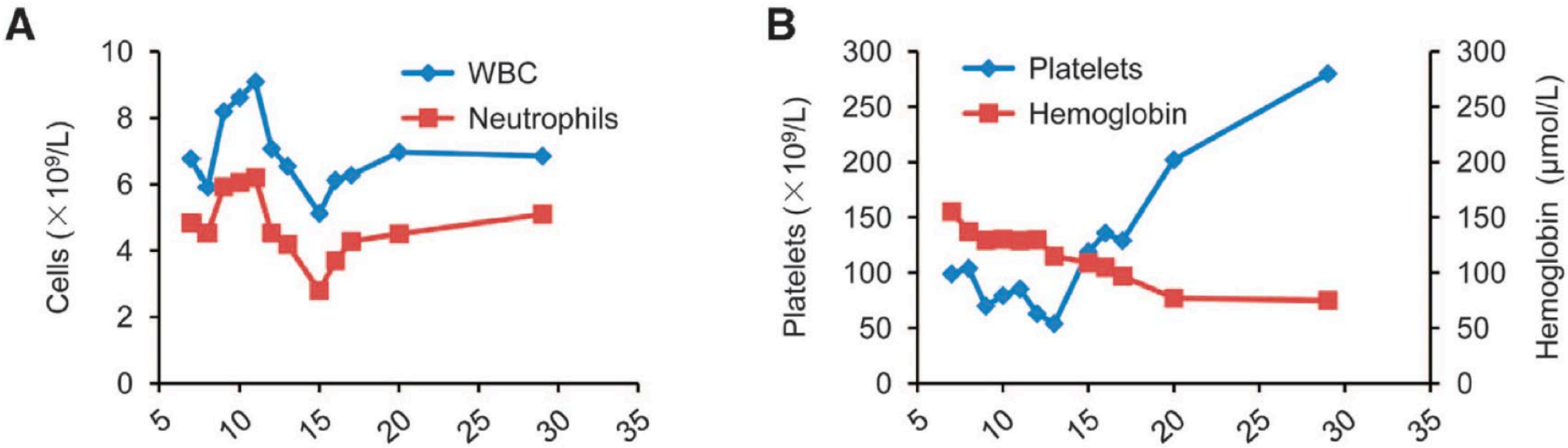
Open evidence differential if you mention Angola travel

- Malaria
- Yellow fever
- Viral hemorrhagic fever (Marburg, Ebola, CCHF)
- Leptospirosis
- Dengue
- Rickettsiosis

Differential diagnosis

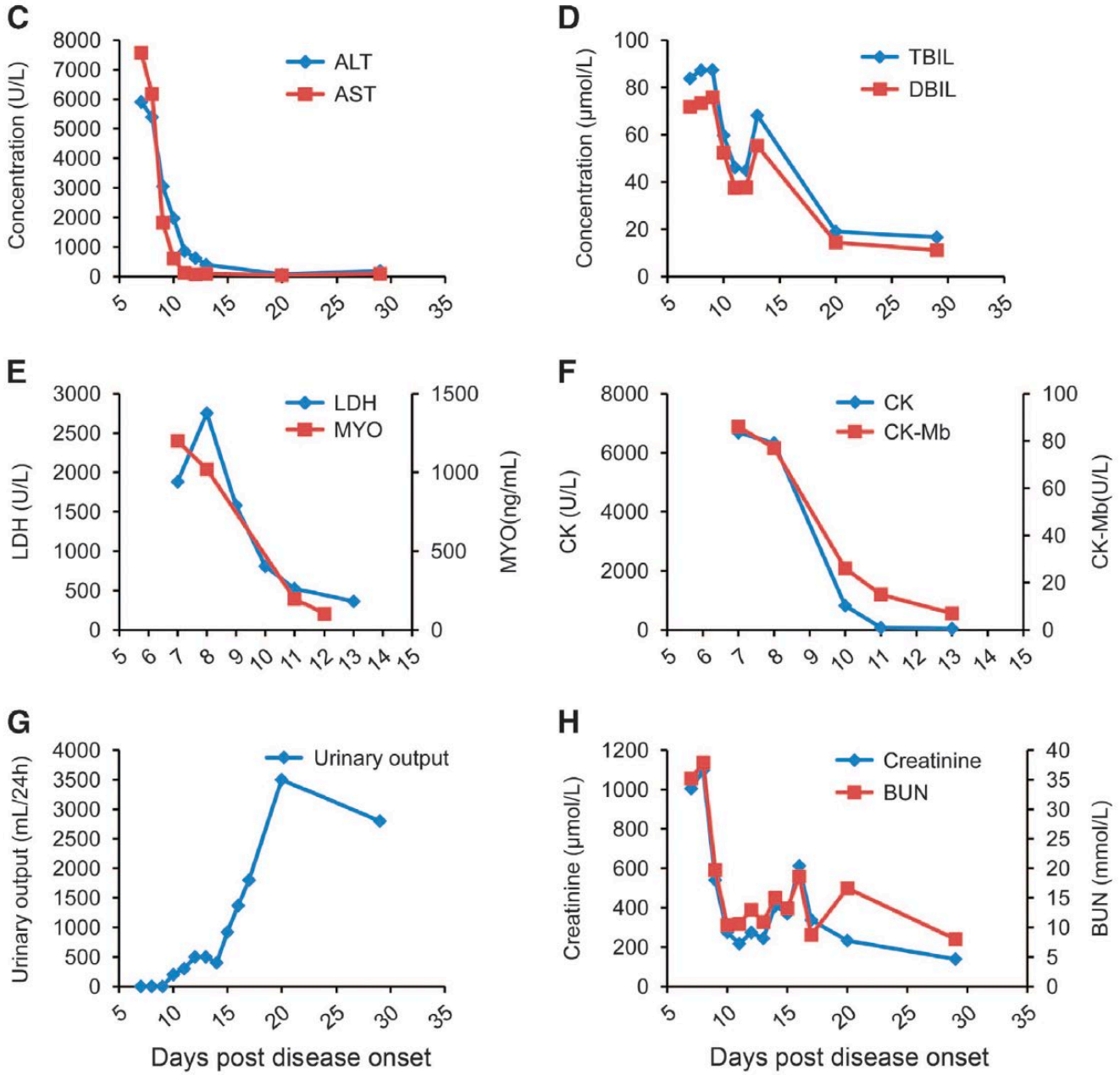
- Arthropod-borne illness:
  - Malaria
  - Dengue
  - Yellow fever
  - African tick bite fever
  - Typhus
  - Chikungunya
- Foodborne illness:
  - Typhoid fever
  - Hepatitis A/E
- Sexually transmitted illness:
  - Hepatitis B/C
- Other viruses
  - Adenovirus
  - Viral hemorrhagic fever
- Malignancy
- Autoimmunity
- Toxin/Drug exposure
- Sepsis

CBCD Data



Liu et al, Emerg Microbe Infect 2017

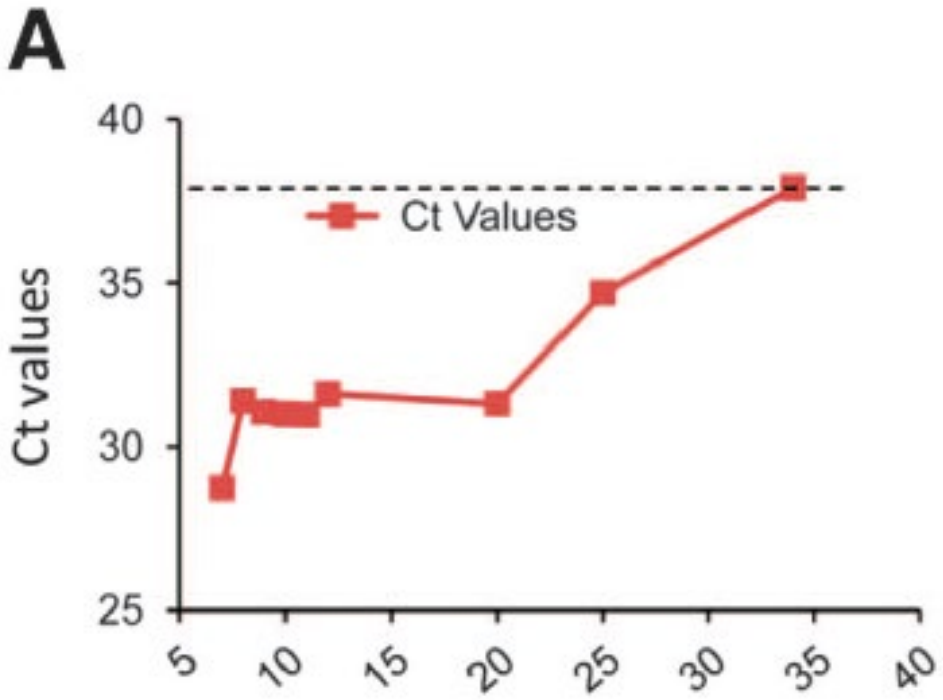
CHEM Data



Liu et al, Emerg Microbe Infect 2017

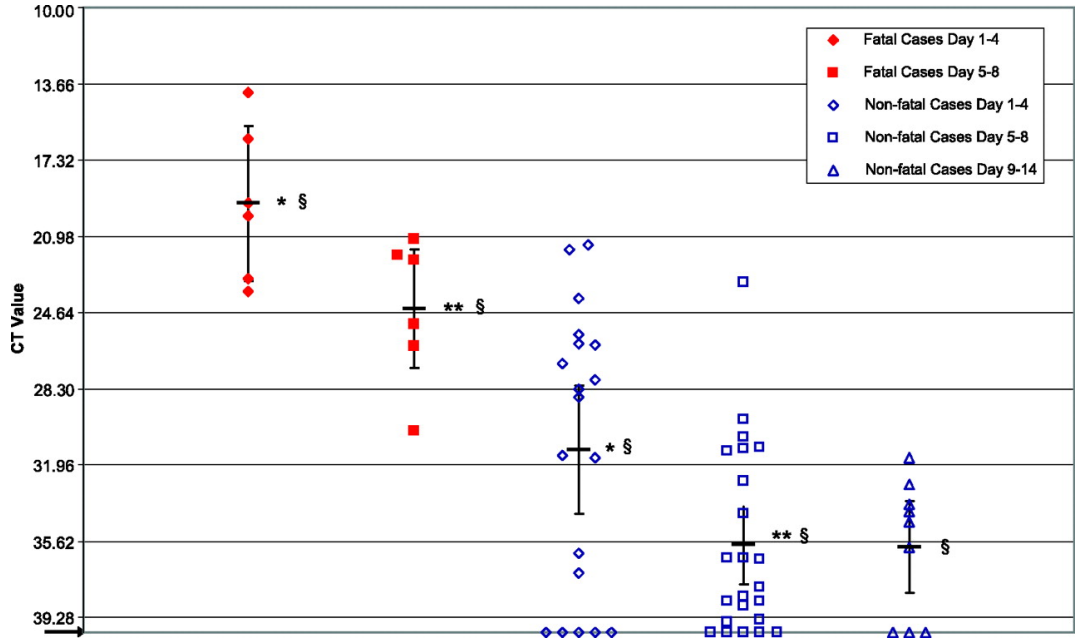
Rift Valley fever virus: viral load in blood

*M vs L segment assays



Day post disease onset

Liu et al, Emerg Microbe Infect 2017



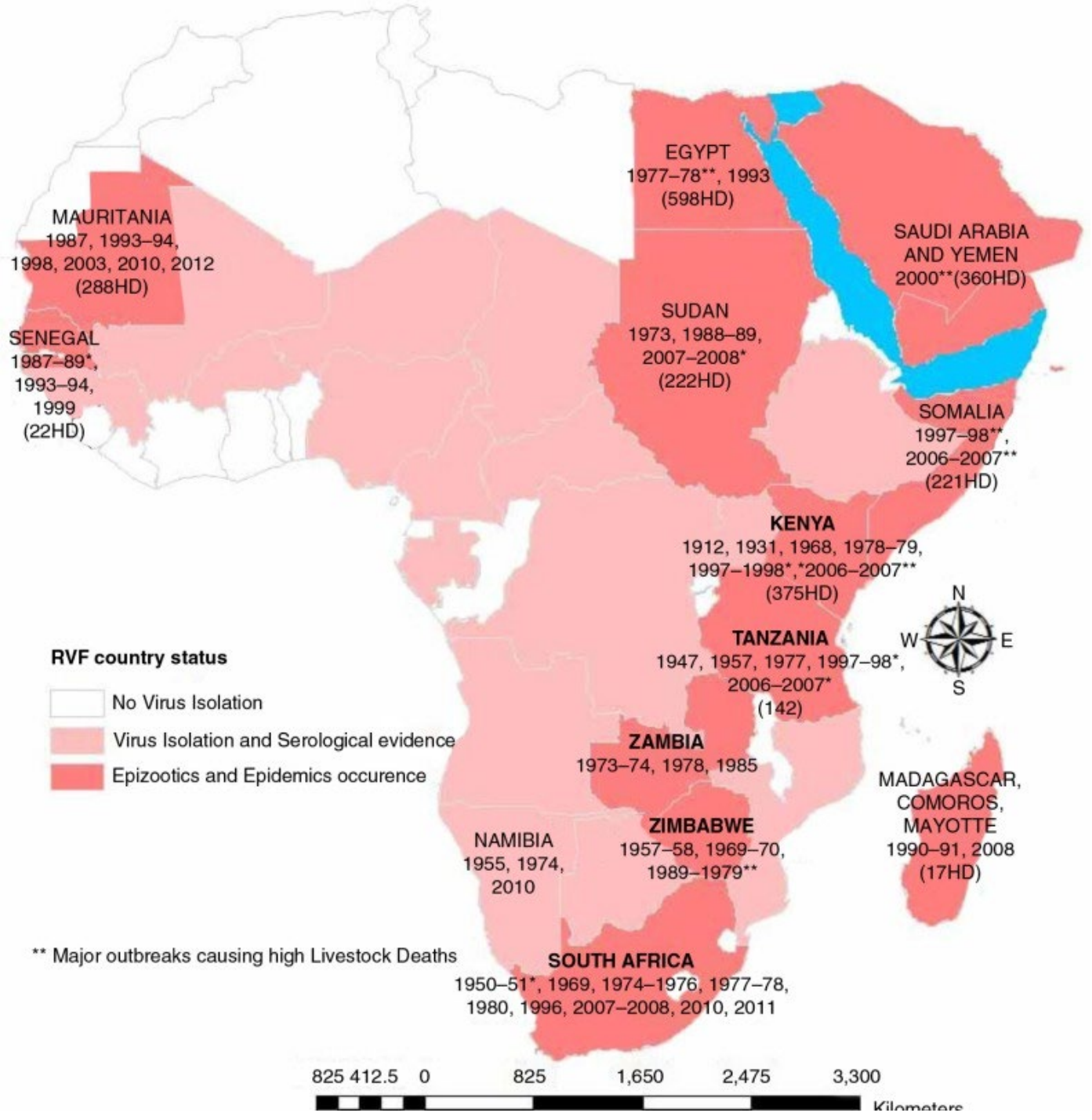
Bird et al, J. Clin Micro 2007

Clinical course

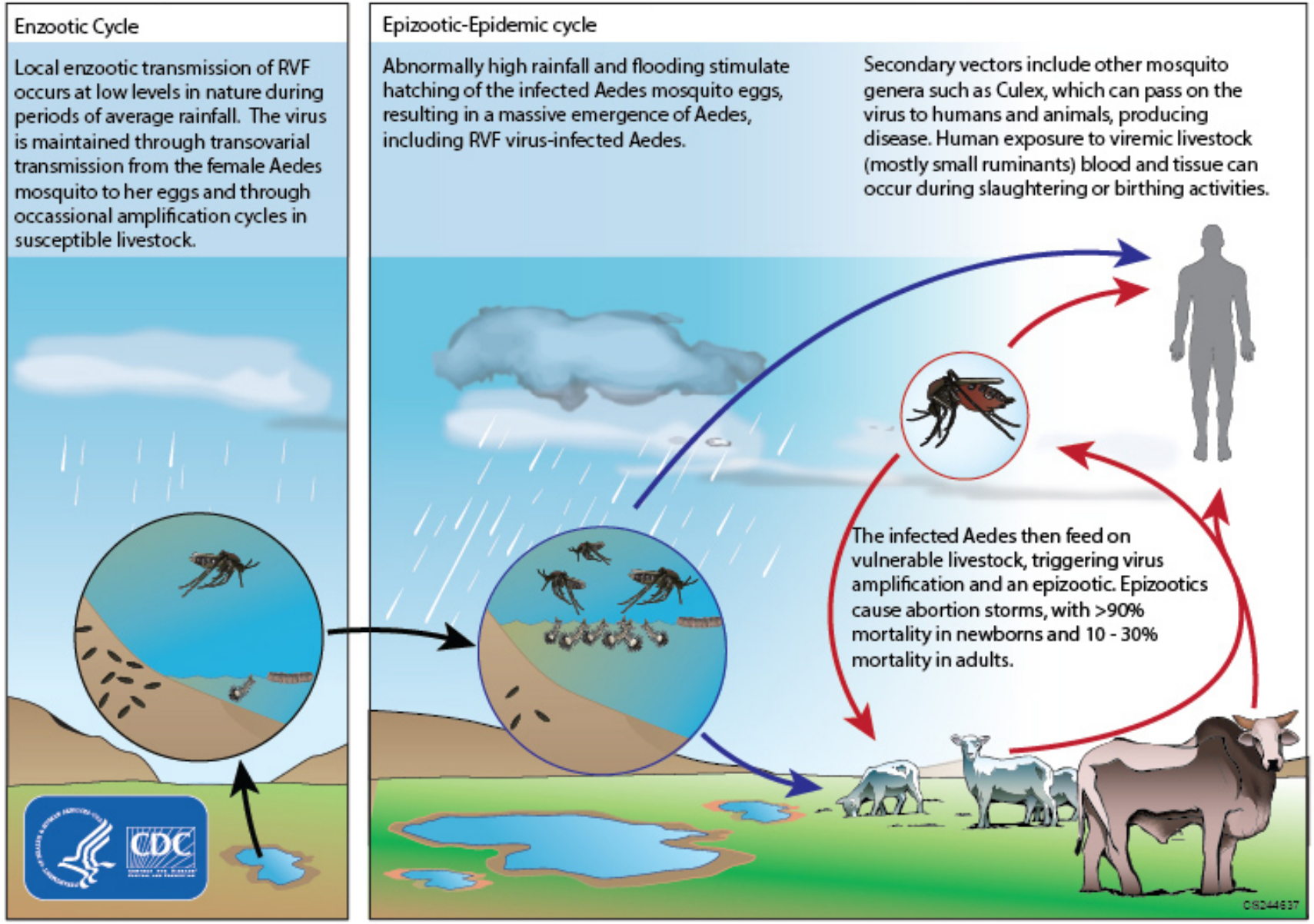
- Treated with HD and renal function improved, oliguria resolved
- Several weeks later presents again with fever, confusion and blurred vision
- Exam 39.2 HR 120 RR 22 BP 110/70
  - PE only significant for splenomegaly, ataxia, bilateral retinal hemorrhages, unable to count fingers
- Labs
  - WBC 5.1, Plts 373, Hgb 10
  - CSF: 323 WBC 58% lymphocytes, 38% PMNs glucose 70 mg/dL protein 455 mg/dL
- Hospital day 5 increased agitation/confusion-->unresponsive
- EEG: nonconvulsive status epilepticus
- MRI: Bilateral fronto-parietal high signal intensity in T2-weighted images and RT posterior thalamic hyperintensity. Multiple bilateral asymmetric cortical hyperintense areas c/w ischemic or inflammatory processes on axial diffusion MRI images.
- Discharged awake, blind, with quadriparesis and incontinence on anticonvulsants.

Rift Valley fever virus

- Rift valley fever was first reported in 1930's in Kenya during a sheep epizootic
- Numerous epizootics and epidemics since that time
- Seroprevalence studies vary
  - in some endemic areas over 50% of adults are seropositive
- Areas of Turkey now reporting seropositive animals and humans



Rift Valley Fever (RVF) virus ecology



Anopheles

Aedes

Culex

Oddly, NOT person to person transmitted!

Original clinical description

576 . 809 . 429 + 616 . 95 + 619 . 31

ENZOOTIC HEPATITIS OR RIFT VALLEY FEVER.

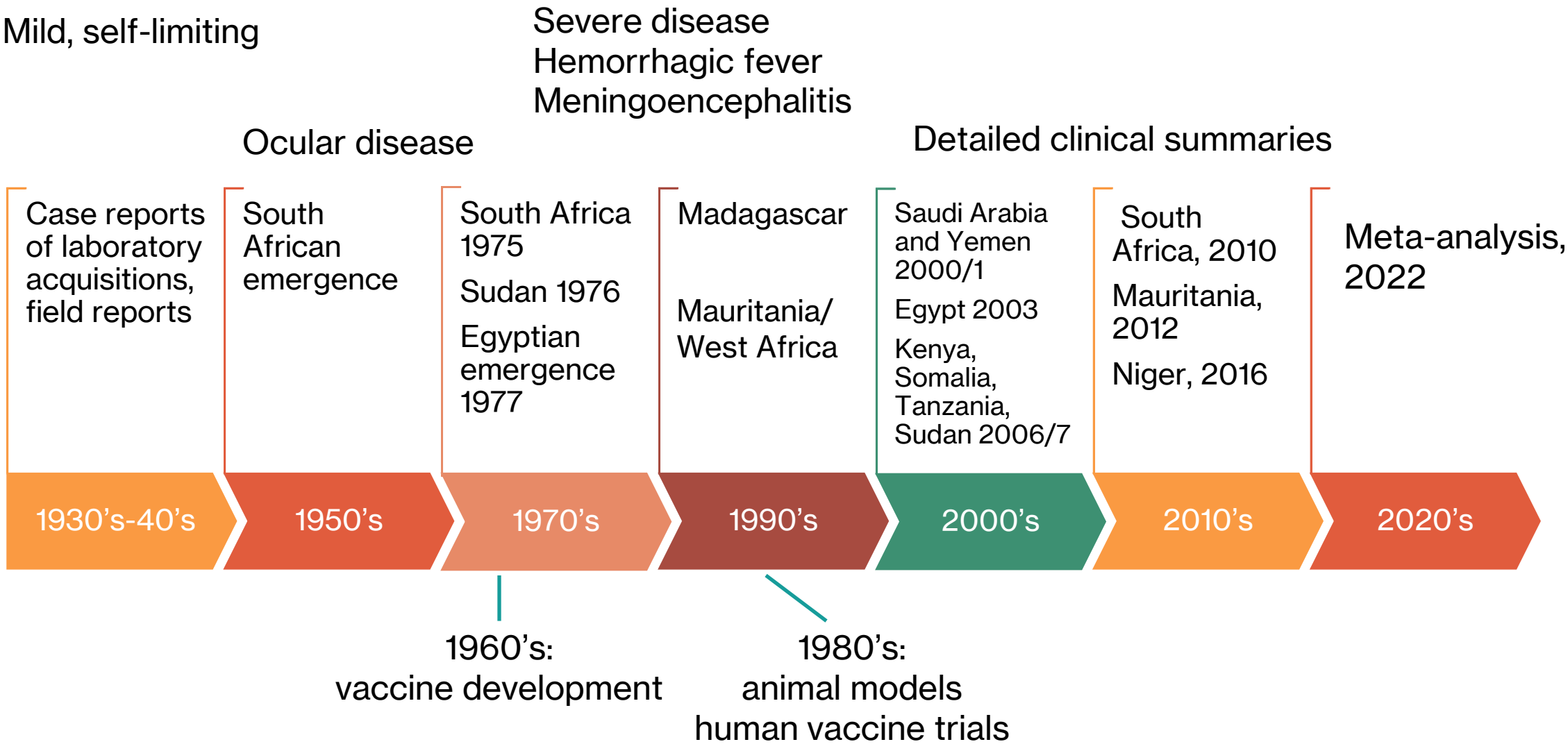
AN UNDESCRIBED VIRUS DISEASE OF SHEEP CATTLE AND MAN FROM EAST AFRICA.

R. DAUBNEY and J. R. HUDSON, Division of Veterinary Research, Kenya Colony.

With an account of an experimental inoculation of man by P. C. GARNHAM, *Medical Department.*

- All four Europeans working on the project had an acute febrile illness
  - Brief malaise
  - fever 12-36 hours
  - rigors for 3-6 hours
  - headache, back and joint pain gone by day 4
- All animal herders also had fever and pain for 4 days

Where do the data come from?

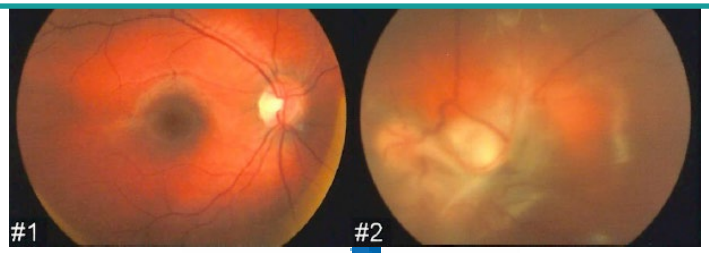


Spectrum of Rift Valley fever disease in humans

Abrupt onset
Tmax: 40C

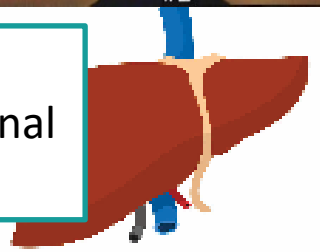
>80%
Fever
Headache
Myalgia
Malaise
Arthralgia
Nausea/vomiting

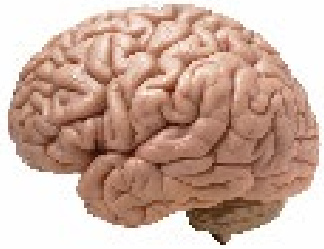
Retinitis, <2%



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

Hemorrhagic fever
Jaundice, Hepatitis, Renal insufficiency <1%





Meningoencephalitis, <1%

2-6 days duration
<10% biphasic

Weakness and fatigue accompany convalescence up to 3 weeks

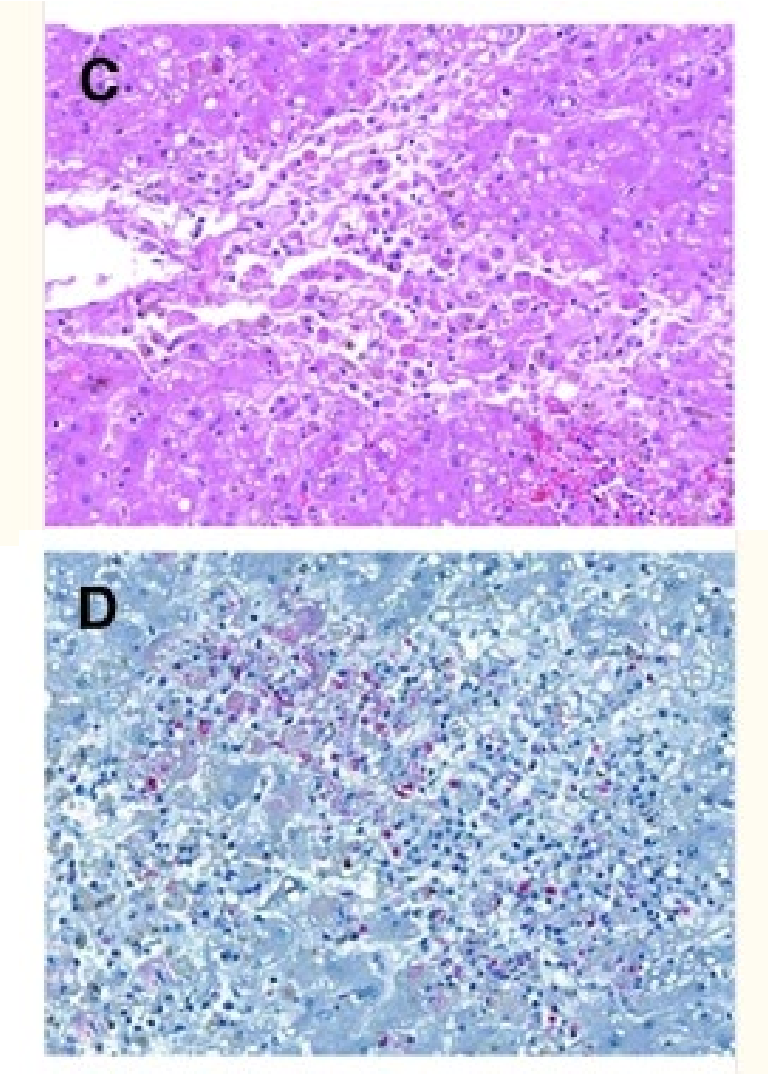
3-6 day incubation

7 14 21 28

Day Post Symptom Onset

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



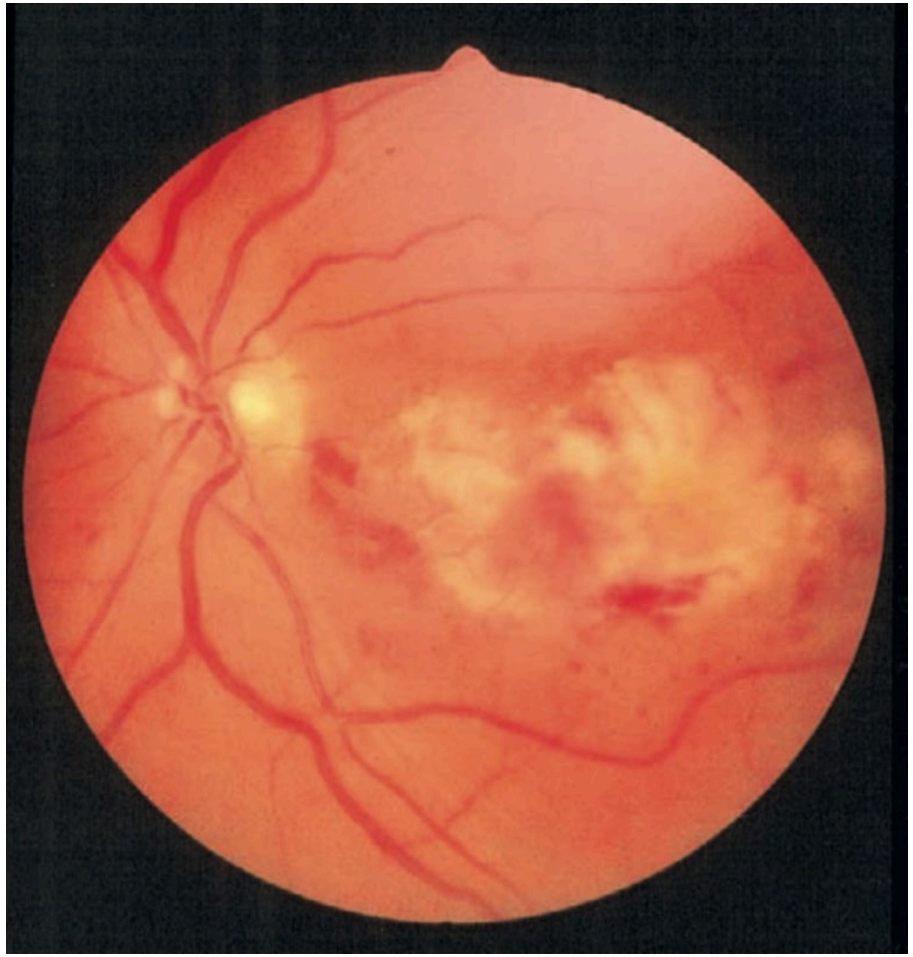
Shieh et al ASTMH J 2010

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 case reports with CT/MRI data (just descriptive, no images)

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

Madani et al CID 2003

Complication or laboratory value (no. of patients with available data)	No. (%) of patients with complication		No. (%) of patients without complication		OR (95% CI)	*P*
	Total	Died	Total	Died		
Bleeding manifestations (494)	35	23 (65.7)	459	39 (8.5)	20.6 (8.9–48.4)	<.0001
CNS manifestations (475)	81	43 (53.1)	394	29 (7.4)	14.2 (7.7–26.7)	<.0001
Jaundice (530)	96	44 (45.8)	434	28 (6.5)	12.5 (6.7–25)	<.0001
Creatinine level of >200 μmol/L (396)	88	49 (55.7)	308	16 (5.2)	25 (11.1–50)	<.0001
AST level of >500 U/L (528)	216	58 (26.9)	312	16 (5.1)	6.7 (3.6–12.5)	<.0001
ALT level of >500 U/L (518)	222	63 (28.4)	296	11 (3.7)	10.0 (5.0–20.0)	<.0001
Platelet count of <100 $\times$ 10^9 platelets/L (450)	173	54 (31.2)	277	10 (3.6)	12.2 (5.7–26.5)	<.0001
Hemoglobin concentration of <80 g/L (457)	69	24 (34.8)	388	42 (10.8)	4.4 (2.3–8.3)	<.0001
LDH level of >500 U/L (384)	231	57 (24.7)	153	4 (2.6)	12.2 (4.1–41.0)	<.0001
CK level of >400 U/L (311)	85	25 (29.4)	226	30 (13.3)	2.7 (1.4–5.2)	0.001
Leukocyte count of <3 $\times$ 10^9 leukocytes/L (479)	190	4 (2.1)	289	63 (21.8)	0.08 (0.02–0.23)	<.0001

	Rift Valley fever virus positive (n=28)	Rift Valley fever virus negative (n=102)	p value
Age (years; mean [range, SD])	27·8 (17–37, 5·0)	26·8 (17–40, 5·7)	0·382
Pregnancy outcome			
Normal pregnancy	12 (43%)	87 (85%)	<0·0001
Miscarriage	15 (54%)	12 (12%)	<0·0001
Preterm delivery	1 (3%)	3 (3%)	0·422
Clinical symptoms			
Malaise	19 (68%)	33 (32%)	0·001
Diarrhoea	8 (29%)	38 (37%)	0·395
Rash	10 (36%)	30 (29%)	0·522
Bleeding	11 (39%)	10 (10%)	<0·0001
Haemorrhagic disease*	17 (61%)	31 (30%)	0·003
Laboratory findings			
Total white blood cell count ($\times 10^9$/L)	7·0 (3·5)	7·6 (4·0)	0·469
Platelet count ($\times 10^9$/L)	161 (89)	211 (126)	0·050
Haemoglobin concentration (%)	9·1 (1·8)	10·0 (1·7)	0·024
Haematocrit (%)	30·2 (5·1)	32·1 (5·3)	0·091

Data are mean (SD) or n (%), unless otherwise stated. *Defined as having any bleeding symptoms or moderate-to-severe thrombocytopenia ($<100 \times 10^9$ platelets per L).

***Table 3:* Association between Rift Valley fever virus positivity and pregnancy outcome, clinical symptoms, and laboratory findings**

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

Baudin et al Lancet Global Health, 2016

When to think outside of the box

HISTORY HISTORY HISTORY

- Travel/exposure history
  - Where have they been? Timeline of travel is critical
  - What activities have they been engaged in while there? Ask about work and recreation!
  - What insect exposures have they had?
  - What animal exposures have they had?
  - What food exposures have they had? Any raw dairy, raw meats, unpasteurized cheese? Exotic food (brain, raw fish/shellfish)
  - What sexual exposures have they had?

References

- https://pubmed.ncbi.nlm.nih.gov/28096531/
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- https://academic.oup.com/cid/article-abstract/36/3/245/351435?redirectedFrom=fulltext
- https://pmc.ncbi.nlm.nih.gov/articles/PMC2913495/
- https://pubmed.ncbi.nlm.nih.gov/14523773/
- https://pmc.ncbi.nlm.nih.gov/articles/PMC8986116/
- CDC EOC: 770-488-7100 (of course also discussing with your local public health dept)