Emerging Infections in the Middle East with a focus on CCHF

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Conflict of Interest

Nill

Outline

- Introduction to Emerging Infectious Diseases in the Middle East
- Examples of Emerging Infectious Diseases in the Middle East
- Detailed Review of Crimean-Congo Hemorrhagic Fever (CCHF)
- Case Study: Oman’s Experience with CCHF

Re-Emerging Vaccine-Preventable Diseases in War-Affected Peoples of the Eastern Mediterranean Region-An Update

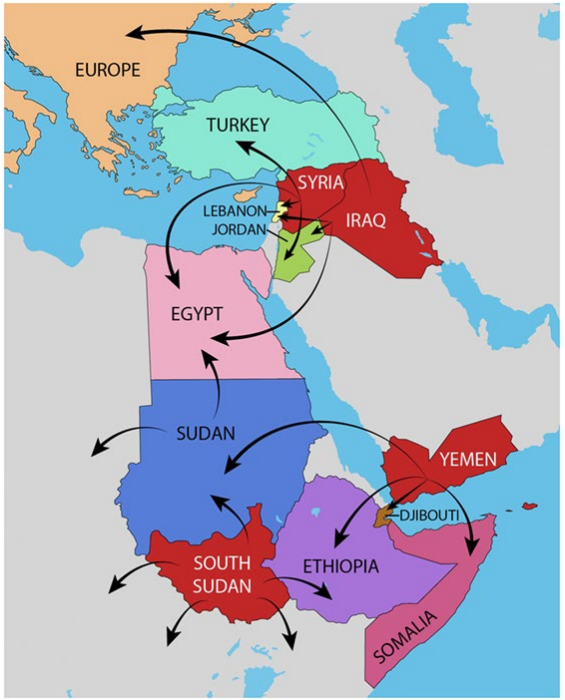


TABLE 1 | Summary of three major re-emerging vaccine-preventable diseases in the Eastern Mediterranean Region.

Human disease	Infectious agent	Mode of transmission	Symptoms	Treatment	Available vaccine	Re-emerging EMR countries
Poliomyelitis[a]	Polio virus	Fecal–oral	Asymptomatic, may affect the CNS and cause paralysis	Supportive	*Salk Vaccine*—IPV: inactivated polio vaccine *Sabin Vaccine*—OPV: oral polio vaccine	Syria, Iraq
Measles[b]	Measles virus	Direct contact with infectious droplet or by airborne spread	Maculopapular rash, fever, cough, coryza, conjunctivitis, koplik spots	Supportive	Either alone or as part of a combination (e.g., MMR, MMRV)	Iraq, South Sudan, Syria, Yemen
Cholera[c]	*Vibrio cholerae* bacteria	Fecal–oral through contaminated food and water	Profuse watery diarrhea ("rice-water" diarrhea), symptoms of dehydration	Rehydration therapy, antibiotics for severe illness	Two oral killed vaccines: Dukoral and Shanchol (Shantha Biotechnics-Sanofi Pasteur)	South Sudan, Yemen

Raslan R, et al. Front Public Health. 2017 Oct 25:5:283.

EID outbreaks in the EMR, Current situation analysis

- Outbreaks from emerging infectious diseases are frequently occurring in countries with complex humanitarian emergencies.
- Late detection of the outbreaks and subsequently delayed response are causing these outbreaks to flare up.
- Fragile health systems, insecurity and accessibility are major hindrance in containing these outbreaks at source.

Emerging Infectious Disease outbreaks in the EMR

Vector borne-diseases

- Dengue
- Chikungunya fever
- **Viral hemorrhagic fever**
  - Crimean-Congo hemorrhagic fever
  - Rift valley fever
  - Yellow fever
  - Al-Khurma HF

Emerging Zoonoses

- MERS CoV
- Influenza with new sub-type
  - Avian influenza A(H5N1)
  - Influenza H1N1

Water-borne diseases

- Cholera
- Hepatitis A & E

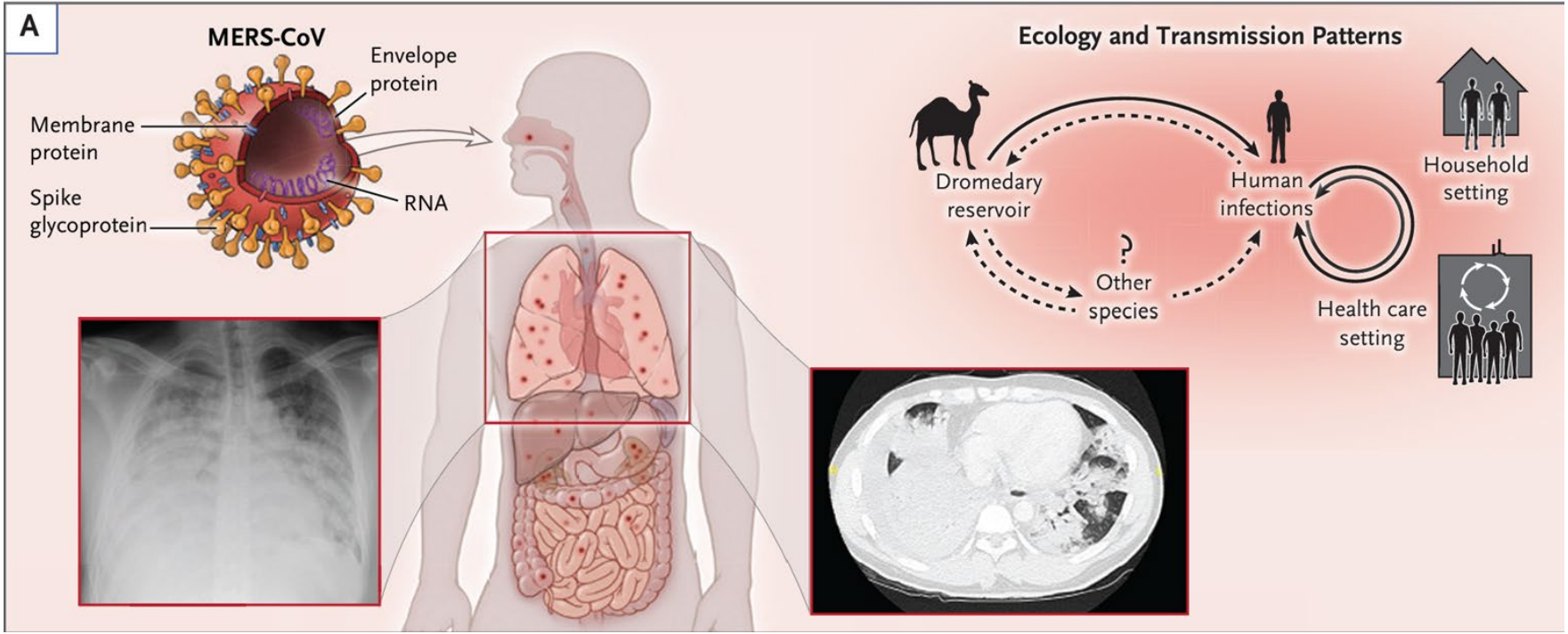
Meningococcal meningitis

Prioritizing Diseases for Research and Development in Emergency Contexts (WHO)

- COVID-19
- Crimean-Congo haemorrhagic fever
- Ebola virus disease and Marburg virus disease
- Lassa fever
- Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS)
- Nipah and henipaviral diseases
- Rift Valley fever
- Zika
- “Disease X”

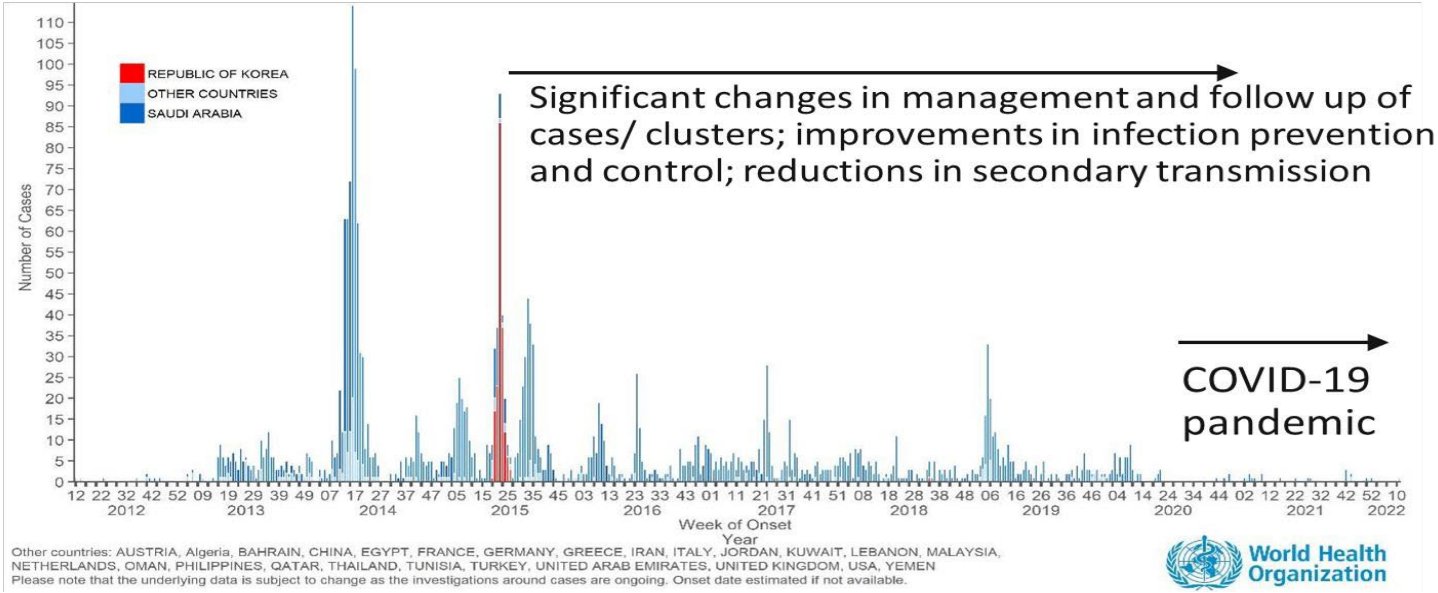
https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts

Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia



Zaki AM, et al.N Engl J Med. 2012 Nov 8;367(19):1814-20.; Arabi YM, et al. N Engl J Med. 2017 Feb 9;376(6):584-594

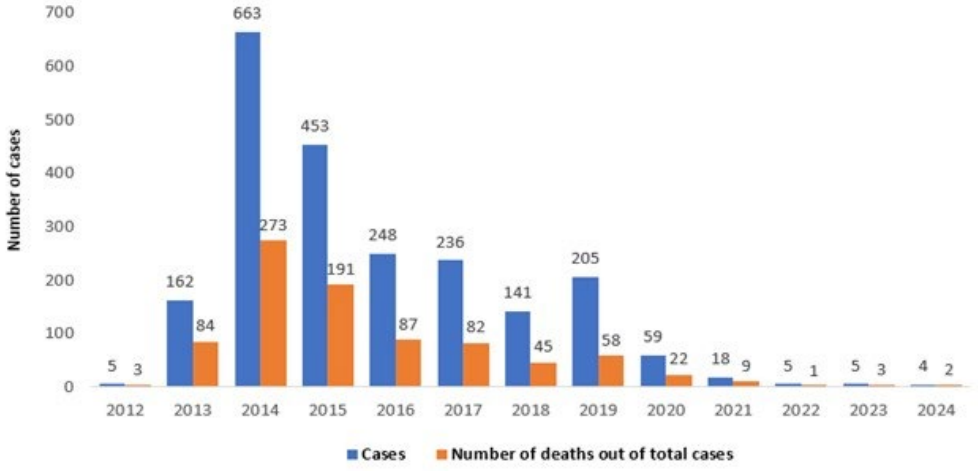
WHO MERS-CoV global epidemic curve



Since 2012, there have been approximately 2,600 confirmed human cases from 27 countries globally

Middle East respiratory syndrome coronavirus-Kingdom of Saudi Arabia, 08 May 2024

- 3 human cases, including one death,
- between 10 & 17 April 2024,
- All three cases were males, aged between 56 and 60 years
- The 3 cases are epidemiologically linked to exposures in a health-care facility in Riyadh,



https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON516

Cases of invasive meningococcal disease reported in travellers returning from the Kingdom of Saudi Arabia

As of 17 May 2024

- 12 cases have been reported, from France (4), UK (3), and USA (5).
- Cases reported performing Umrah in KSA.
- Belong to meningococcus serogroup W
- No history of meningococcal vaccination.

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

https://www.ecdc.europa.eu/en/news-events/cases-invasive-meningococcal-disease-reported-travellers-returning-kingdom-saudi-arabia

Congo/Crimean haemorrhagic fever in Dubai. An outbreak at the Rashid Hospital

- A hospital outbreak of haemorrhagic fever took place in Dubai in November, 1979.
- The index case died in the casualty department shortly after admission.
- There were five secondary cases among hospital staff, two of whom died.

Suleiman MN, et al.Lancet. 1980 Nov 1;2(8201):939-41

CCHF

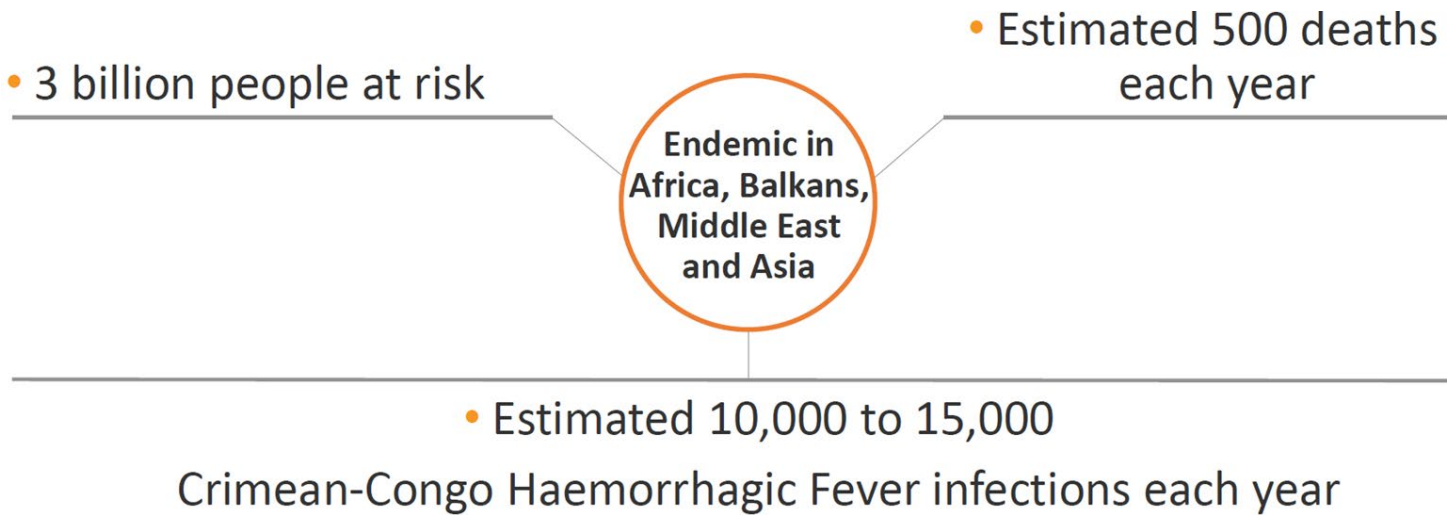
CCHF is viral illness that occurs in Africa, Asia, Eastern and Southern Europe, and Central Asia

The principal reservoir and vector of CCHF are ticks of the genus Hyalomma

The incidence of CCHF has increased rapidly in WHO EMRO

The known distribution of CCHFV covers the greatest geographic range of any tick-borne virus

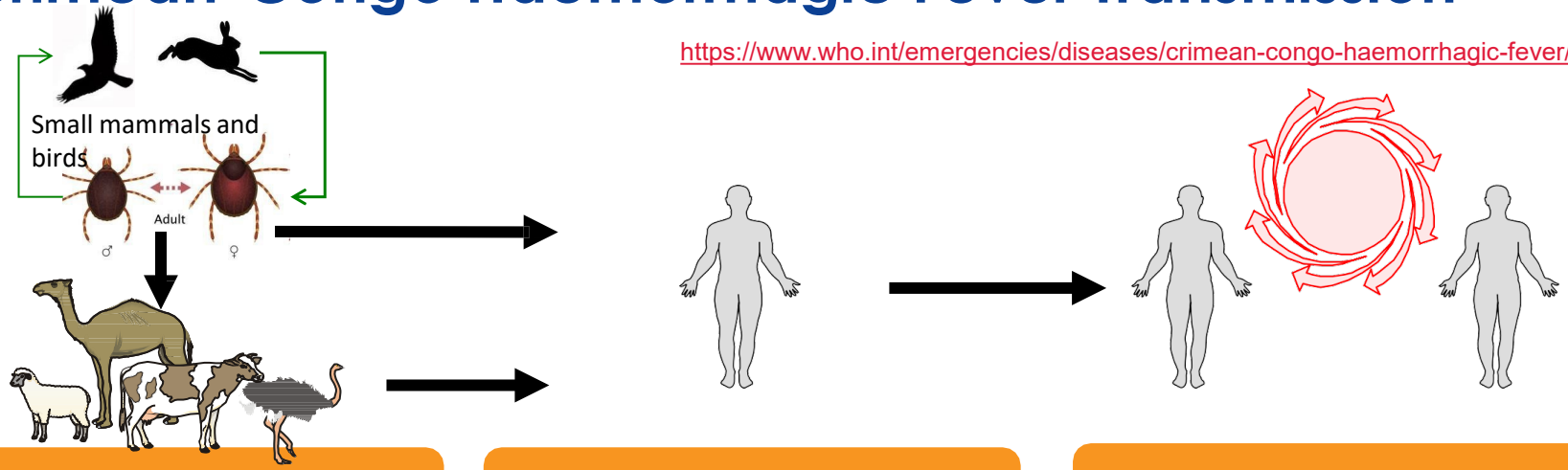
Burden of Crimean-Congo Haemorrhagic Fever



https://www.who.int/emergencies/diseases/crimean-congo-haemorrhagic-fever/en/

Crimean-Congo Haemorrhagic Fever Transmission

https://www.who.int/emergencies/diseases/crimean-congo-haemorrhagic-fever/en/



Reservoir *Hyalomma* ticks

- In nature, CCHF virus maintains itself in a cycle involving ticks and vertebrate.
- Most animals don't show symptoms.

Primary human infections

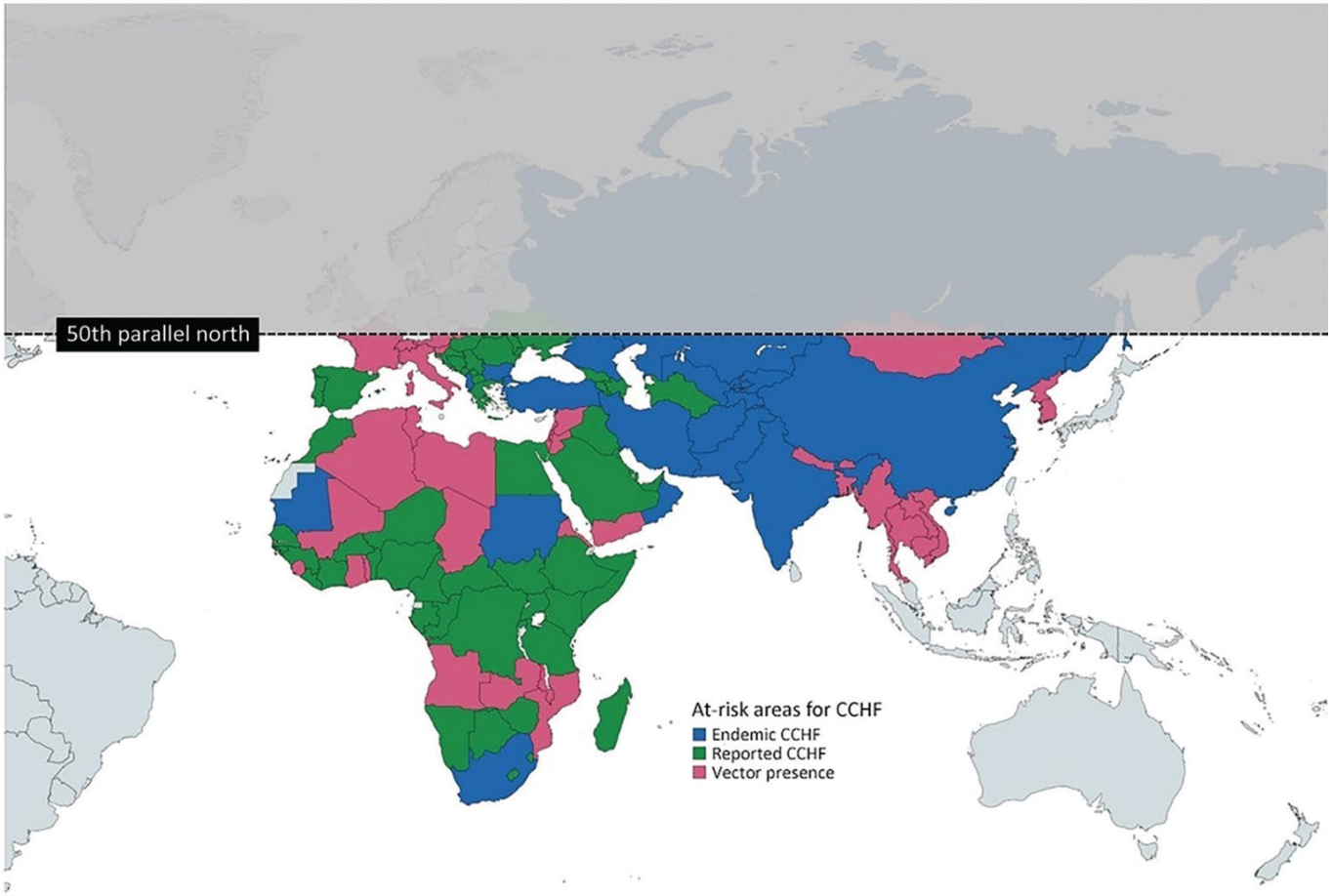
80 to 90 % of humans are infected through:

- tick bite or direct contact with blood of infected ticks;
- direct contact with blood/tissues of infected wild animals and livestock.

Secondary human infections

- Secondary H2H transmission occurs through direct contact with the blood, secretions, organs or other body fluids of infected persons.
- High transmission risk when providing direct patient care or handling dead bodies (funerals).

Geographic distribution of CCHF and Hyalomma spp. ticks.



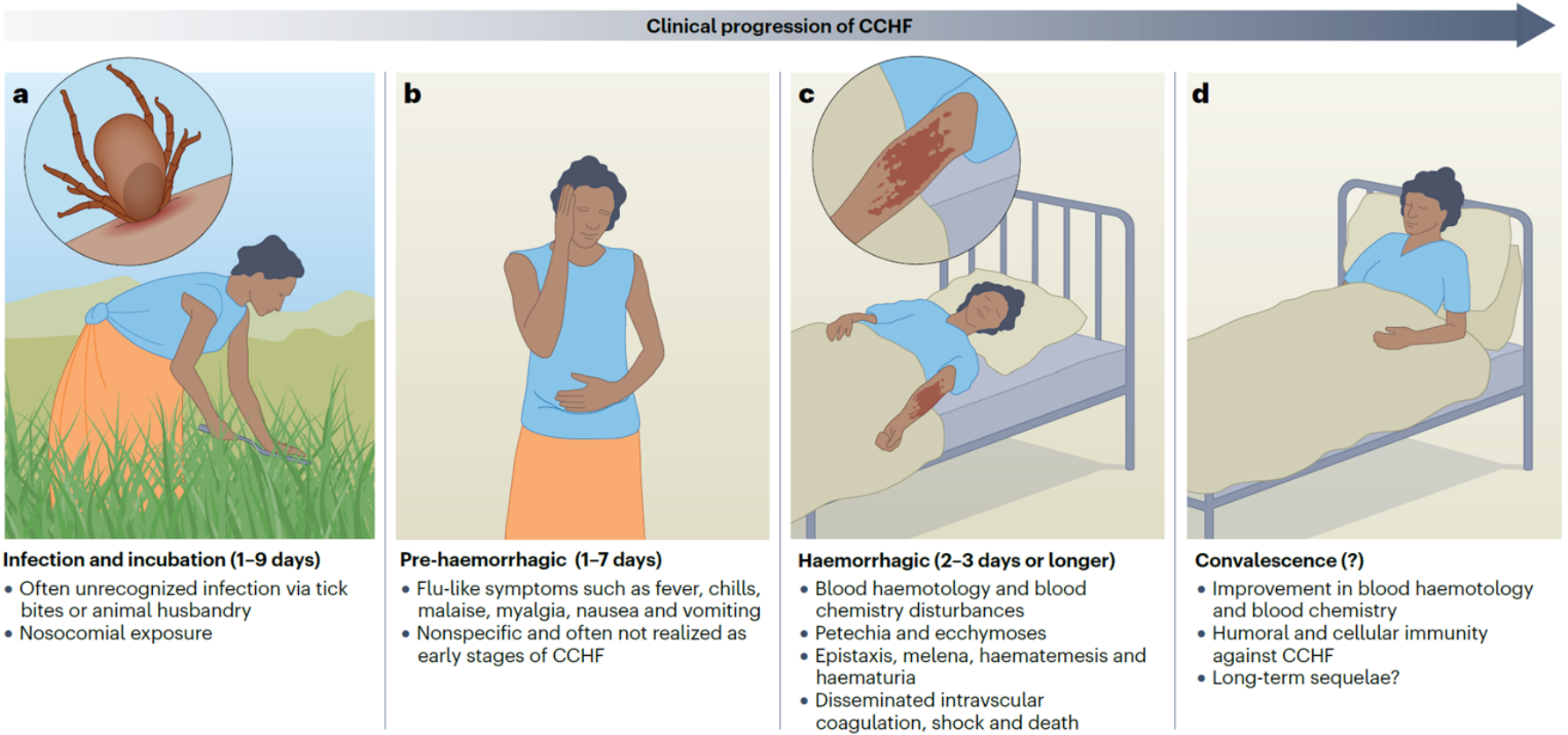
Frank MG, et al. Emerg Infect Dis. 2024 May;30(5):854-863

An Emerging Biothreat: Crimean-Congo Hemorrhagic Fever Virus in Southern and Western Asia

For the past 20 years,
since 1998,
11 countries reported their
first autochthonous
Crimean-Congo
hemorrhagic fever cases

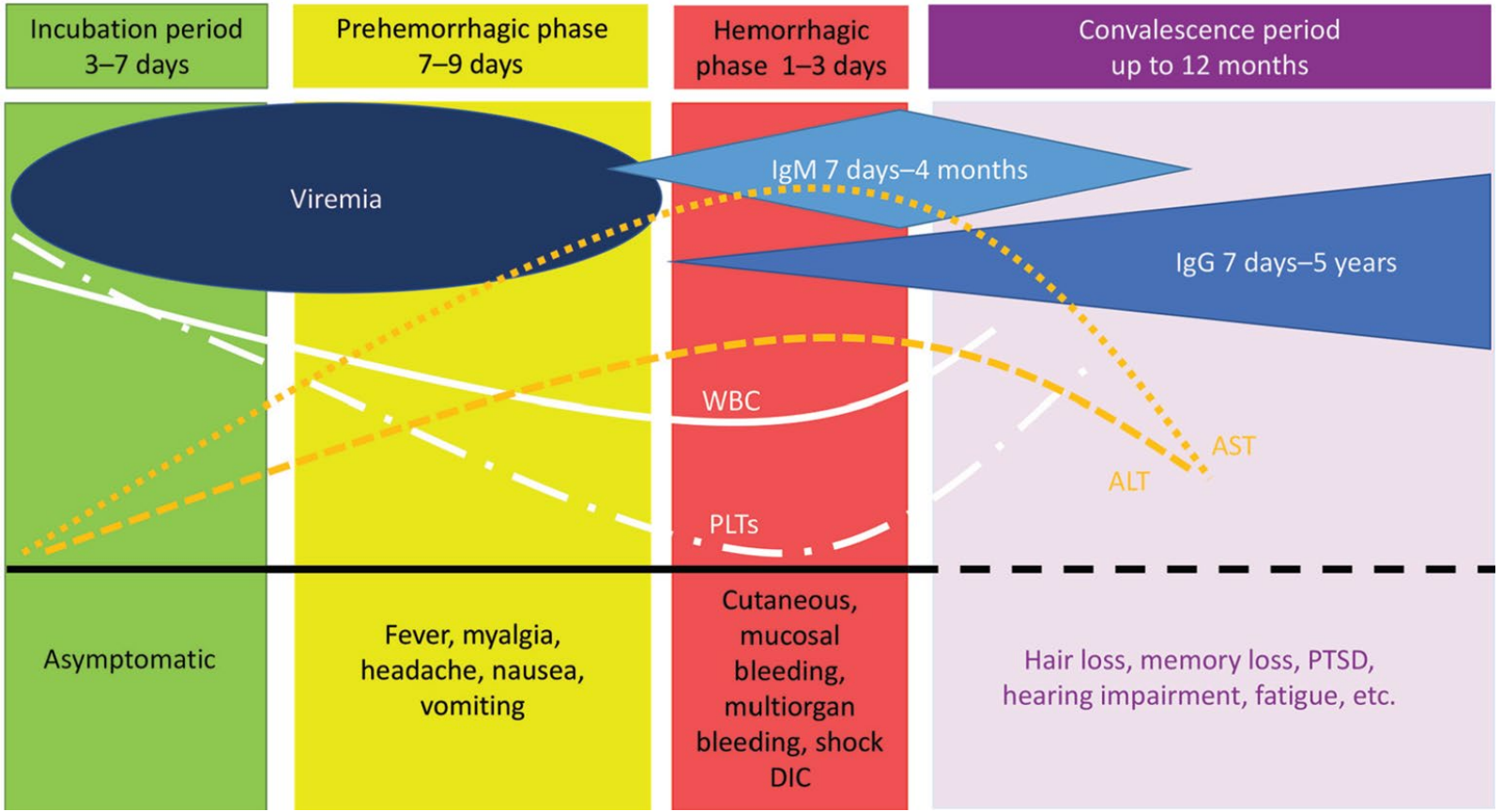
Year	Country
2016	Spain
2012	Egypt
2011	India
2009	Georgia
2008	Sudan
2008	Greece
2003	Senegal
2002	Turkey
2000	Kenya
1999	Iran
1998	Afghanistan

Blair PW, et al. Am J Trop Med Hyg. 2019 Jan;100(1):16-23.



Clinical progression of Crimean–Congo haemorrhagic fever.

Hawman DW, et al. Nat Rev Microbiol. 2023 Jul;21(7):463-477.



Classic Clinical Disease Course of CCHF

Frank MG, et al. Emerg Infect Dis. 2024 May;30(5):864-873.

Advantages and disadvantages of various diagnostic tests for CCHFV

Test selection	Timing	Advantages	Disadvantages
Viral detection†			
Viral culture‡	Early after symptom onset	Detects a wide diversity of CCHFV strains	Requires BSL-3 or BSL-4 laboratory, which are not readily available in endemic areas. Requires several days to yield a result.
NAAT, RT-PCR	≤10–12 days after symptom onset	If samples are inactivated, then NAAT can be run in BSL-2 or BSL-3 facilities. Several multiplex assays available, and some can quantify viral load.	Variable sensitivity depending on match between primers and infecting strain. Sensitivity and specificity can vary by geographic region. Better sensitivity (80%) when PCR combinations used, e.g., rRT-PCR and conventional PCR or rRT-PCR and nested PCR (*17*).
Viral antigen detection			
ELISA	≤5–9 days after symptom onset	Timely results. Viral inactivation can be performed. Requires less laboratory specialization.	Decreased sensitivity after CCHFV antibodies are detectable.
Immunohistochemistry	≤5–9 days after symptom onset	Can assist in retrospective diagnosis for fatal cases.	Requires biopsy or necropsy samples.

Frank MG, et al. Emerg Infect Dis. 2024 May;30(5):864-873.

CCHF Treatment

- Early aggressive intensive care support: monitor fluid, electrolyte balance, renal function, blood pressure, and oxygenation, and careful rehydration
- Support of coagulation system with blood component therapy.
- Antiviral drug ribavirin can be given early in course of the disease.

https://www.who.int/emergencies/diseases/crimean-congo-haemorrhagic-fever/en/

Treatments for Crimean–Congo haemorrhagic fever

Compound	Class	Target	Preclinical efficacy	Clinical efficacy	Comments
Ribavirin	Nucleoside analogue	RdRP	Controversial efficacy in rodent models	Controversial efficacy in patients	Poor efficacy; early treatment start needed; should be discontinued or used in combination therapy
Favipiravir	Nucleoside analogue	RdRP	Efficacy in rodent and NHP models	Limited data or benefit	Late treatment start effective in rodent models; clinical trials are needed
2′-Deoxy-2′-fluorocytidine	Nucleoside analogue	RdRP	Not done	No clinical data	More preclinical studies are needed
Molnupiravir	Nucleoside analogue	RdRP	No efficacy in rodent models	No clinical data	Unlikely to proceed
Plasma or antibodies from survivors	Neutralizing or non-neutralizing	Viral proteins	Not done	Limited data or benefit	More preclinical and/or clinical studies are needed
Monoclonal antibodies	Neutralizing or non-neutralizing	Viral proteins	Limited data in rodent models	No clinical data	More preclinical and/or clinical studies are needed
Corticosteroids	Anti-inflammatory	Host response	Not done	Limited data or benefit	More preclinical and/or clinical studies are needed

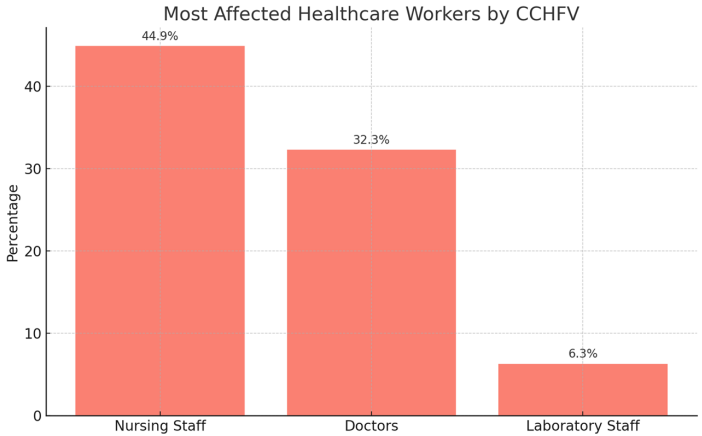
NHP, non-human primate; RdRP, RNA-dependent RNA polymerase.

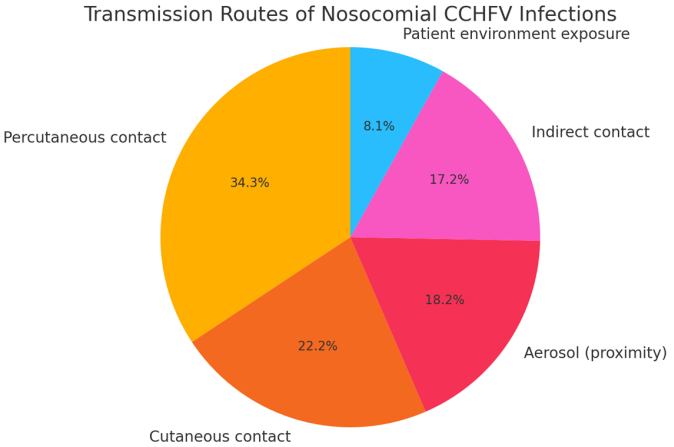
Hawman DW, et al. Nat Rev Microbiol. 2023 Jul;21(7):463-477.

Nosocomial infections caused by Crimean-Congo haemorrhagic fever virus

Tsergouli K, et al. J Hosp Infect. 2020 May;105(1):43-52.

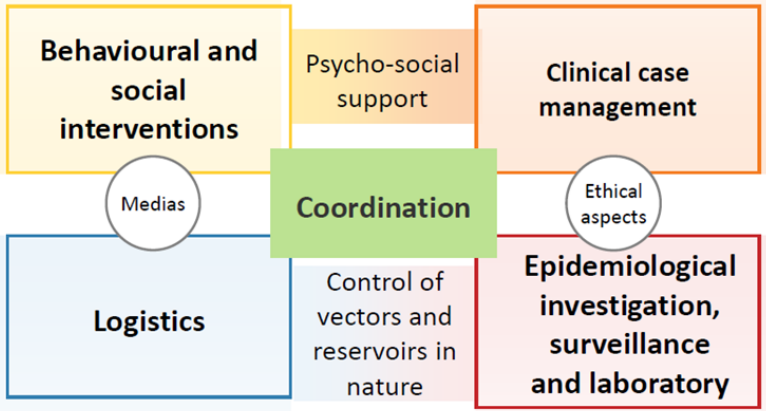
- From 1953 to 2016,
- 158 published cases of CCHFV nosocomial infection in 20 countries in Africa, Asia and Europe.
- Almost all cases were symptomatic (92.4%),
- an overall CFR of 32.4%.





General strategy to control CCHF outbreaks

- Conduct social and cultural assessments
- Engage with key influencers: women and /or youth associations, traditional healers, local authorities, religious & opinion leaders
- Formal and informal communication
- Address community concerns



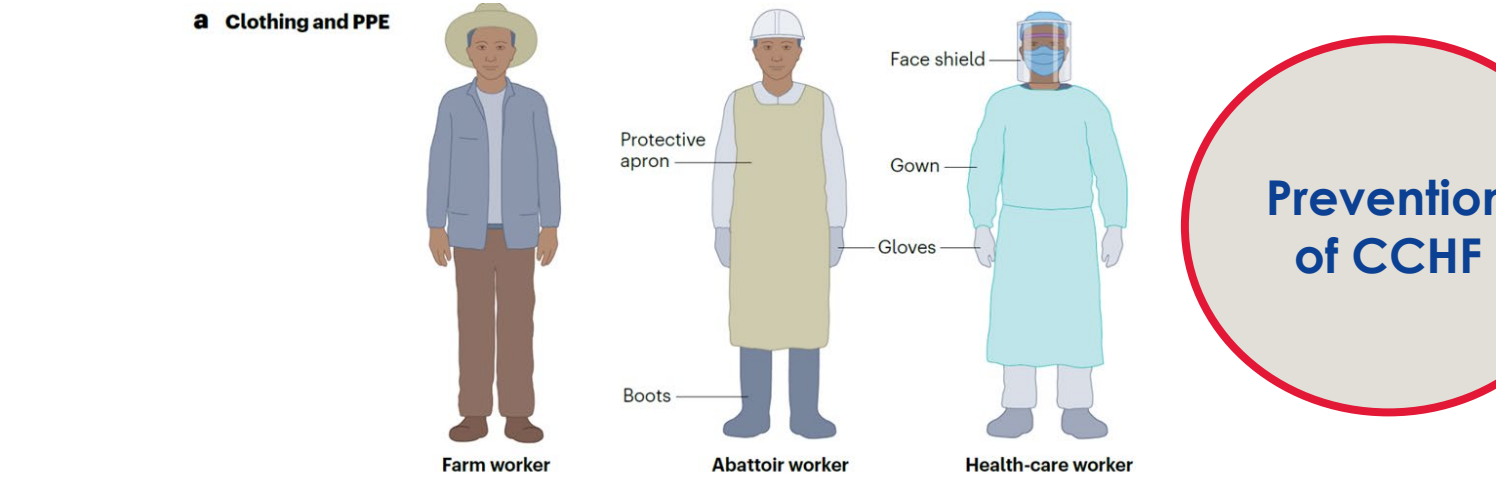
- Triage in/out
- Barrier nursing
- Infection control
- Organize funerals
- Clinical trials
- Ethics committee

- Security, police
- Lodging, food
- Social and epidemiological mobile teams
- Finances, salaries
- Transport vehicles

- Active case-finding
- Follow-up of contacts
- Specimens
- Laboratory testing
- Database analysis
- Search for the source

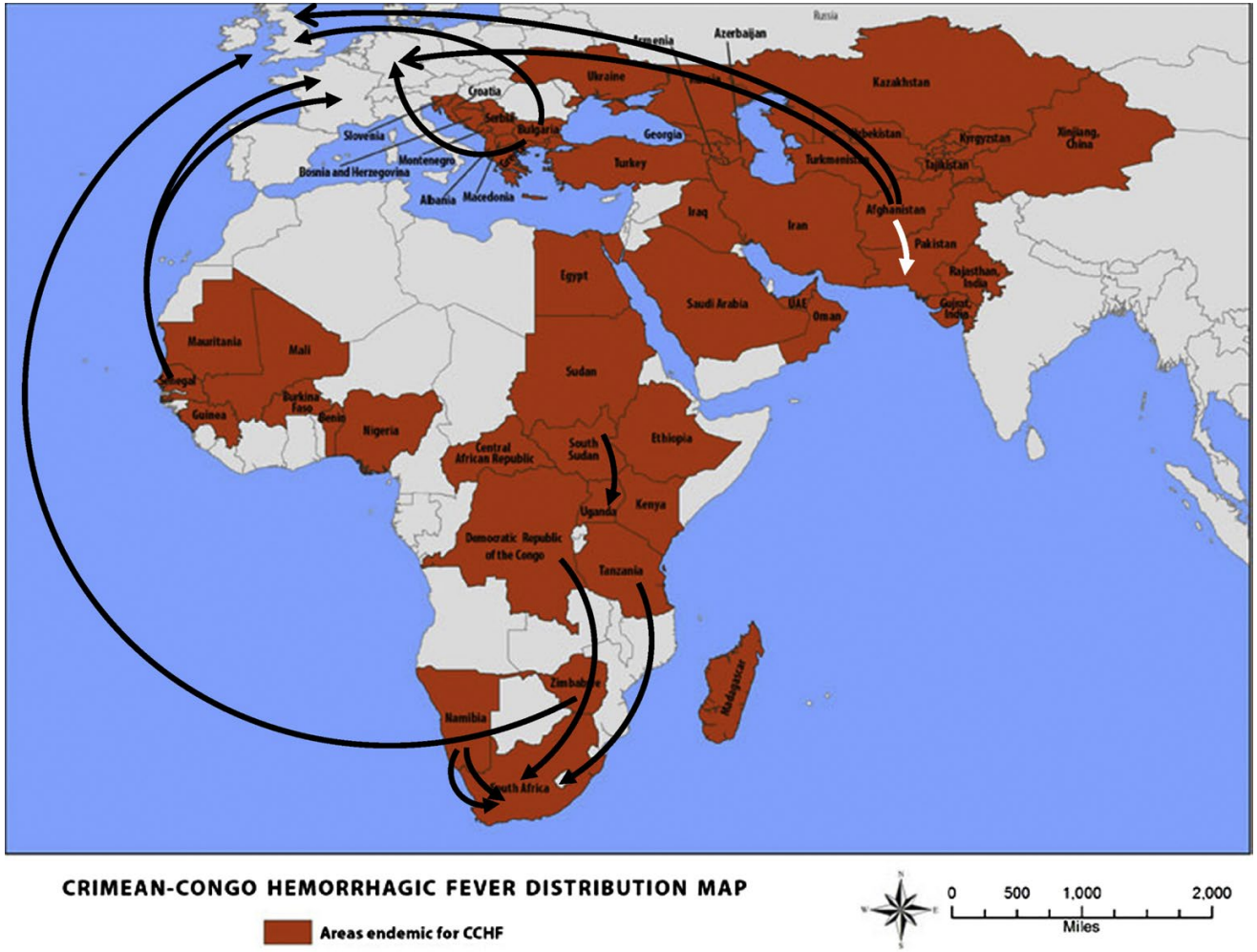
https://www.who.int/emergencies/diseases/crimean-congo-haemorrhagic-fever/en/

Prevention of CCHF



Hawman DW, et al. Nat Rev Microbiol. 2023 Jul;21(7):463-477.

Crimean-Congo haemorrhagic fever in travellers: A systematic review



Leblebicioglu H, et al. Travel Med Infect Dis. 2016 Mar-Apr;14(2):73-80.

Towards an understanding of the migration of Crimean-Congo hemorrhagic fever virus

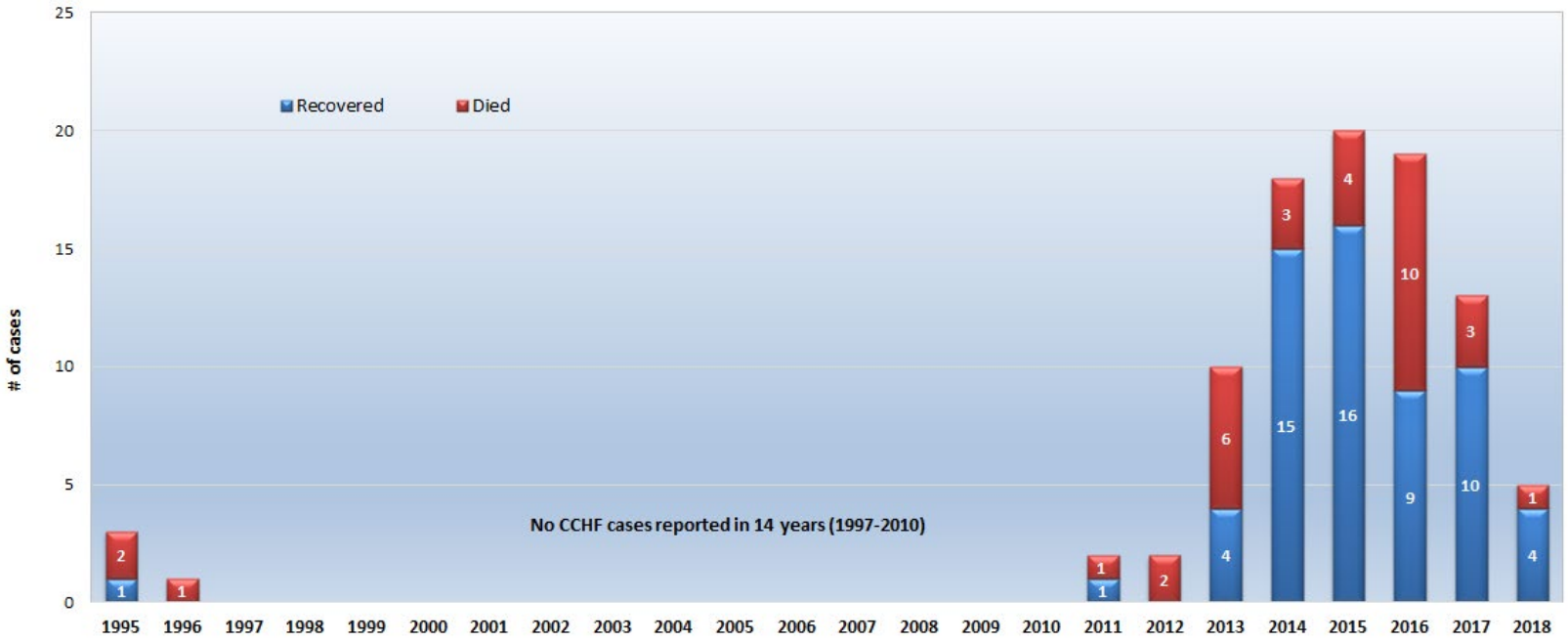
Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Genotype 6	Genotype 7
Iran	Iran	South Africa	Iran	South Africa	Greece	Iran
Pakistan	China	Namibia	Turkey	Namibia	Turkey	South Africa
UAE	Uzbekistan	UAE	Greece	DRC		Senegal
Madagascar	Kazakhstan	Senegal	Russia	Uganda		Mauritania
Oman	Tajikistan	Mauritania	Bulgaria			
Iraq		Nigeria	Kosovo			
		Burkina Faso	Albania			
		CAR				

Geographical distribution of CCHFV genotypes

CAR, Central African Republic; DRC, Democratic Republic of the Congo; UAE, United Arab Emirates.

Mild M, et al. J Gen Virol. 2010 Jan;91(Pt 1):199-207.

CCHF Oman 1995-2018



Al-Abri S, et al. PLoS Negl Trop Dis. 2019 Apr 25;13(4):e0007100.

Crimean-congo haemorrhagic fever: a seroepidemiological and tick survey in the Sultanate of Oman

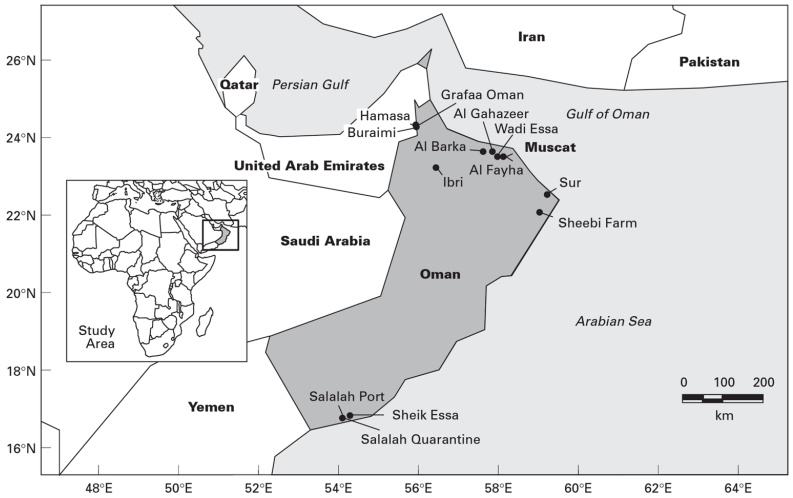


Table 2 Job category of non-Omani individuals ($n = 241$) by CCHF antibody status (top) and prevalence ratios of job category contrasts for antibody-positive individuals (bottom) – Oman, March 1996

Job category*†	Antibody positive (%)	Humans tested (Columnar %)
(I)	47 (44.3)	106 (44.0)
(II)	21 (20.2)	104 (43.2)
(III)	5 (16.1)	31 (12.8)
Total (%)	73 (30.3)	241 (100)

Job category†	Prevalence ratio	95% Confidence interval (lower, upper)
(I) *vs.* (III)	2.75	(1.20, 6.31)
(I) *vs.* (II)	2.20	(1.42, 3.40)
(II) *vs.* (III)	1.25	(0.51, 3.05)

*χ^2 (2) = 17.88; $P = 0.0001$. †Job category I, butcher; job category II, slaughterhouse worker, tanner, khooli (animal handler), farmer, or seller; and job category III, veterinarian, veterinary technician, clerk, cook, administrator, or other.

Williams RJ, et al. Trop Med Int Health. 2000 Feb;5(2):99-106.

Crimean-congo haemorrhagic fever: a seroepidemiological and tick survey in the Sultanate of Oman

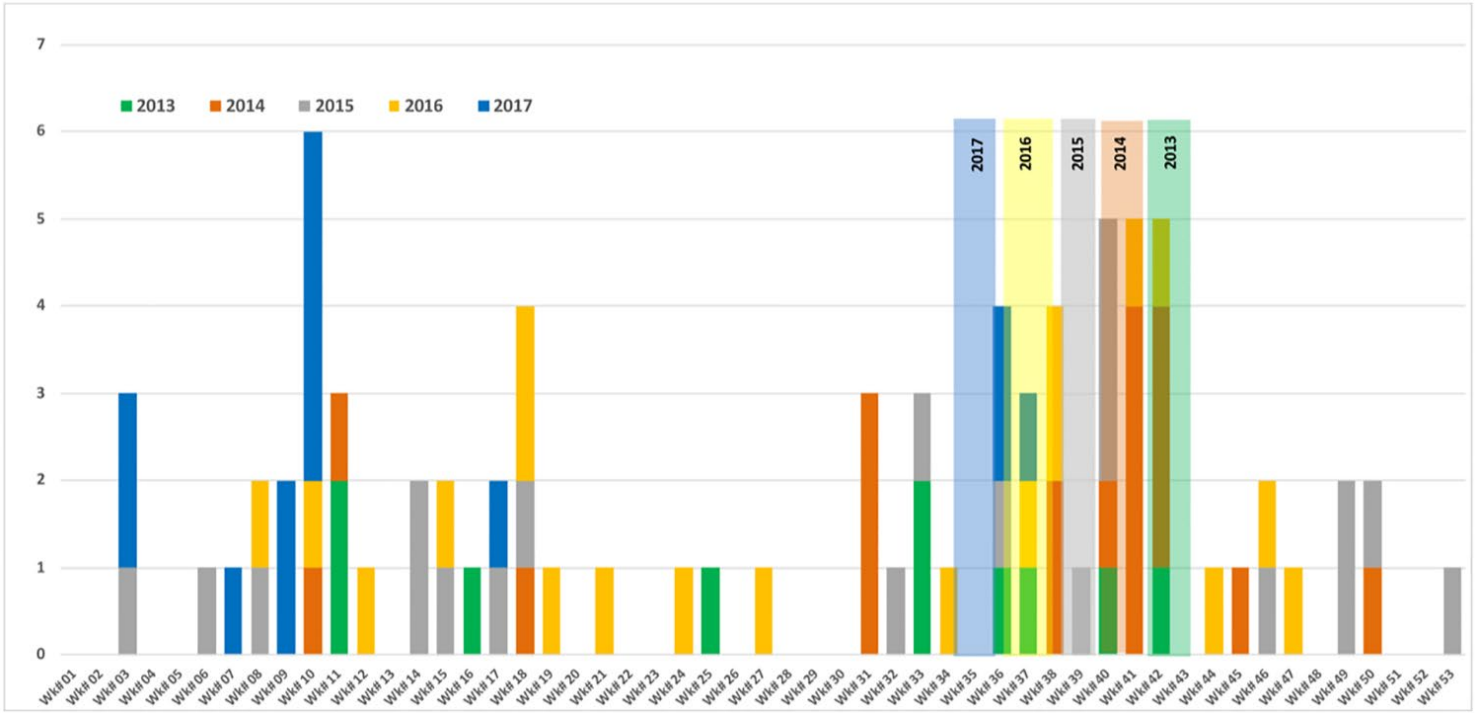
Table I Antigen-capture ELISA results for CCHF virus in tick pools from domestic livestock, number of antibody-positive animals, and number of animals with ticks – Oman, March 1996

	Australian sheep		Imported animals*		Indigenous animals	
Number of antibody-positive animals/number tested	10/50	20%	58/123	47%	23/207	11%
Number of animals with ticks/number examined	45/92†	49%	42/123	34%	27/207	13%
Number of antigen-positive tick pools/number of tick pools	18/90	20%	1/50	2%	None	
Locations	Muscat,	Salalah,	Sur	Somalia‡		

*Category excludes Australian sheep. †There were 92 Australian sheep examined. Serum was collected from 50 of these 29 sheep had ticks that were collected for antigen-capture assay. An additional 42 sheep were examined for ticks only (no serum collected); of these animals, 16 were infested with ticks and only representative tick specimens were collected for antigen-capture assay. ‡Animals were sampled at the Salalah port

Williams RJ, et al. Trop Med Int Health. 2000 Feb;5(2):99-106.

Clinical and molecular epidemiology of Crimean-Congo hemorrhagic fever in Oman

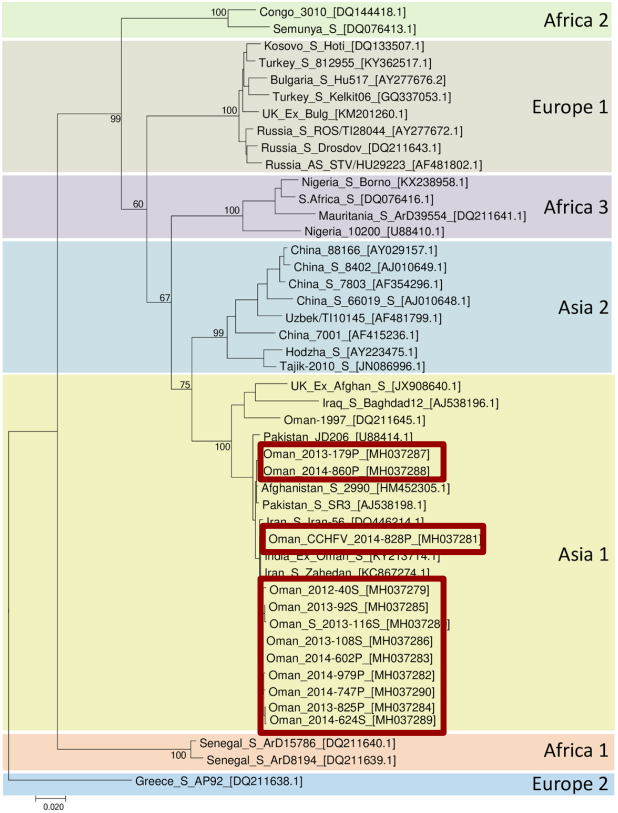


Al-Abri S, et al. PLoS Negl Trop Dis. 2019 Apr 25;13(4):e0007100.

Clinical and molecular epidemiology of Crimean-Congo hemorrhagic fever in Oman

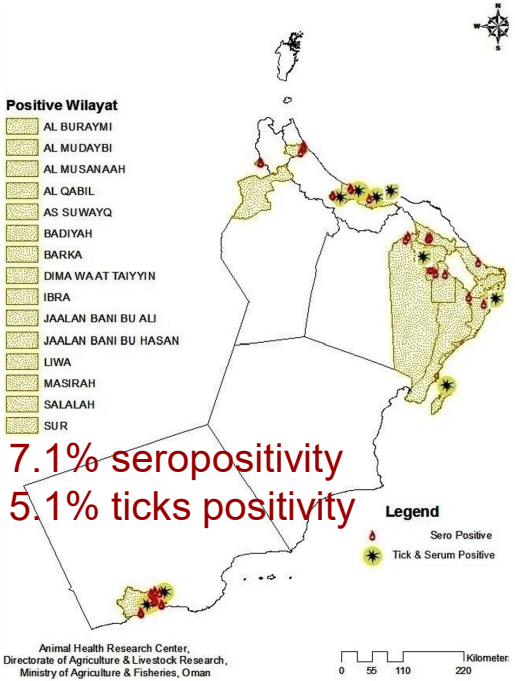
Exposure risk	#	(%)
Participation in slaughter	38	(43.2)
Animal trader, handler (milking)	25	(28.4)
Butcher (occupation)	9	(10.2)
Tick bite	1	(1.1)
Slaughter and tick bite	1	(1.1)
Unknown	14	(15.9)
Total	88	(100)

Al-Abri S, et al. PLoS Negl Trop Dis. 2019 Apr 25;13(4):e0007100.

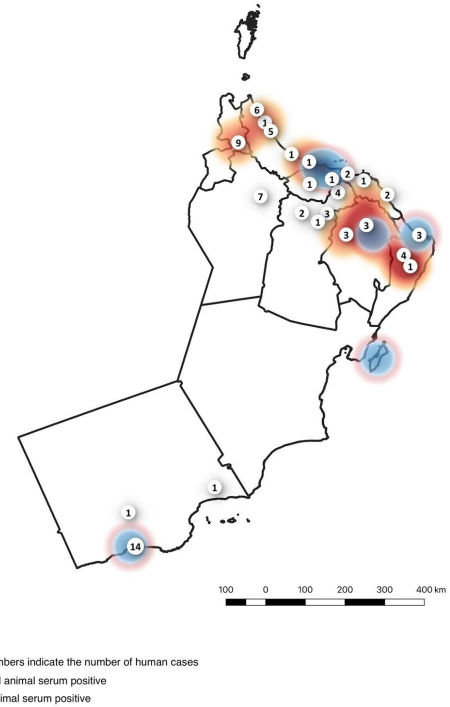


Clinical and molecular epidemiology of Crimean-Congo hemorrhagic fever in Oman

Wilayats and farms where ticks from animals or serum were found positive for CCHFV in Oman (2013 & 2014).



Map of Oman with number of CCHF cases, superimposed on results of previous animal serosurveys for CCHFV antibodies and tick surveys for CCHFV



Body MH, et al. J. Vet. Med. Anim. Health. Vol. 8(6), pp. 44-49, June 2016; Al-Abri S, et al. PLoS Negl Trop Dis. 2019 Apr 25;13(4):e0007100.

Conclusion

- Continuous political instability and war in EMR countries have created optimal conditions for the re-emergence of infections
- CCHF virus causes severe viral haemorrhagic fever outbreaks; with a case fatality rate of up to 40%.
- There is no effective treatment or vaccine available for either people or animals.