VACCINES AND VACCINATION DURING AND POST COVID PANDEMIC

ADVANCES IN VACCINE DEVELOPMENT FOR CRIMEAN-CONGO HAEMORRHAGIC FEVER VIRUS.

Burt FJ[1, 2, 3] and Tipih T[1]

[1]Division of Virology, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa
[2]Division of Virology, National Health Laboratory Service, Universitas, Bloemfontein, South Africa.
[3] South African Research Chair (SARChI): Vector borne and zoonotic pathogens research

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History of the virus

A disease named Crimean haemorrhagic fever was first observed on the Crimean Peninsula in 1944.

Congo virus isolated in 1956 from a febrile child in the Belgian Congo (now DRC).

Attempts to isolate the virus were unsuccessful until they 1967 when suckling mice were inoculated.

The causative agent of Crimean hemorrhagic fever was isolated in 1967, and identical to Congo virus.

Hence the name Crimean-Congo haemorrhagic fever virus (CCHFV)

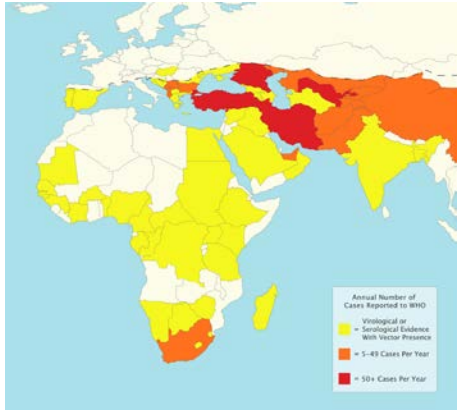
CCHFV is a tick-borne zoonosis distributed in Africa, Asia, eastern and south western Europe, Middle East and the Balkans.

The distribution of CCHFV correlates with that of ticks belonging to the genus Hyalomma.

The distribution of these ticks has expanded in recent years.

CCHFV is listed by the WHO as a priority pathogen for research due to the absence of an approved vaccine or specific anti-viral treatment.

The discovery of suitable animal models in recent years has enabled progress in vaccine development.



Pictures courtesy of Prof R Swanepoel, Map: WHO

The 2018 list of diseases to be prioritized under the WHO R&D Blueprint

Potential to cause a public health emergency and the absence of efficacious drugs and/or vaccines, hence a need for accelerated research and development for

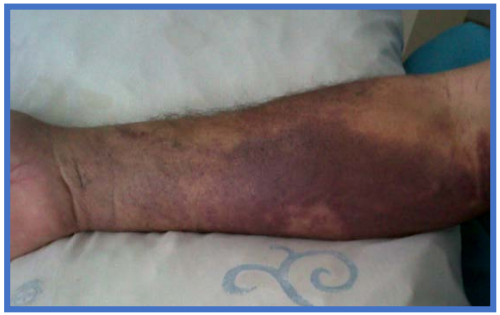
- Crimean-Congo Hemorrhagic Fever
- Ebola Viral Disease and Marburg Viral Disease
- Lassa Fever
- MERS and SARS
- Nipah and henipaviral diseases
- Rift Valley Fever
- Zika disease
- Disease X

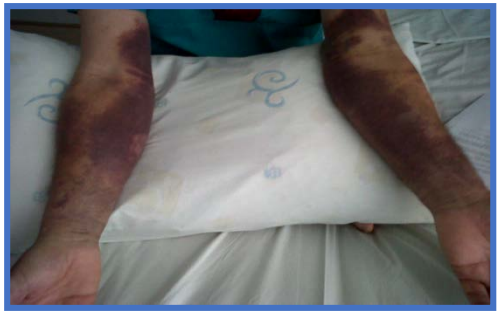
- The prioritization process has 3 components: a Delphi process to narrow down a list of potential priority diseases, a multicriteria decision analysis to rank the short list of diseases, and a final Delphi round to arrive at a final list of 10 diseases

- Si Mehand M, Millett P, Al-Shorbaji F, Roth C, Kieny MP, Murgue B. World Health Organization methodology to prioritize emerging infectious diseases in need of research and development. Emerg Infect Dis. 2018 Sep [*date cited*]. https://doi.org/10.3201/eid2409.171427

CCHF vaccine development

- Why do we need a vaccine, the disease, cycle in nature and recent emergence
- What is the current status of vaccine development
- What population to target, at risk of infection





Pictures: FJ Burt

Transmission:

Humans become infected by contact with infected blood or other tissues of livestock or human patients, or from a tick-bite.

Incubation period:

53 patients 1 to 3 days after tickbite

35 patients 5-6 days after contact with infected blood or tissues

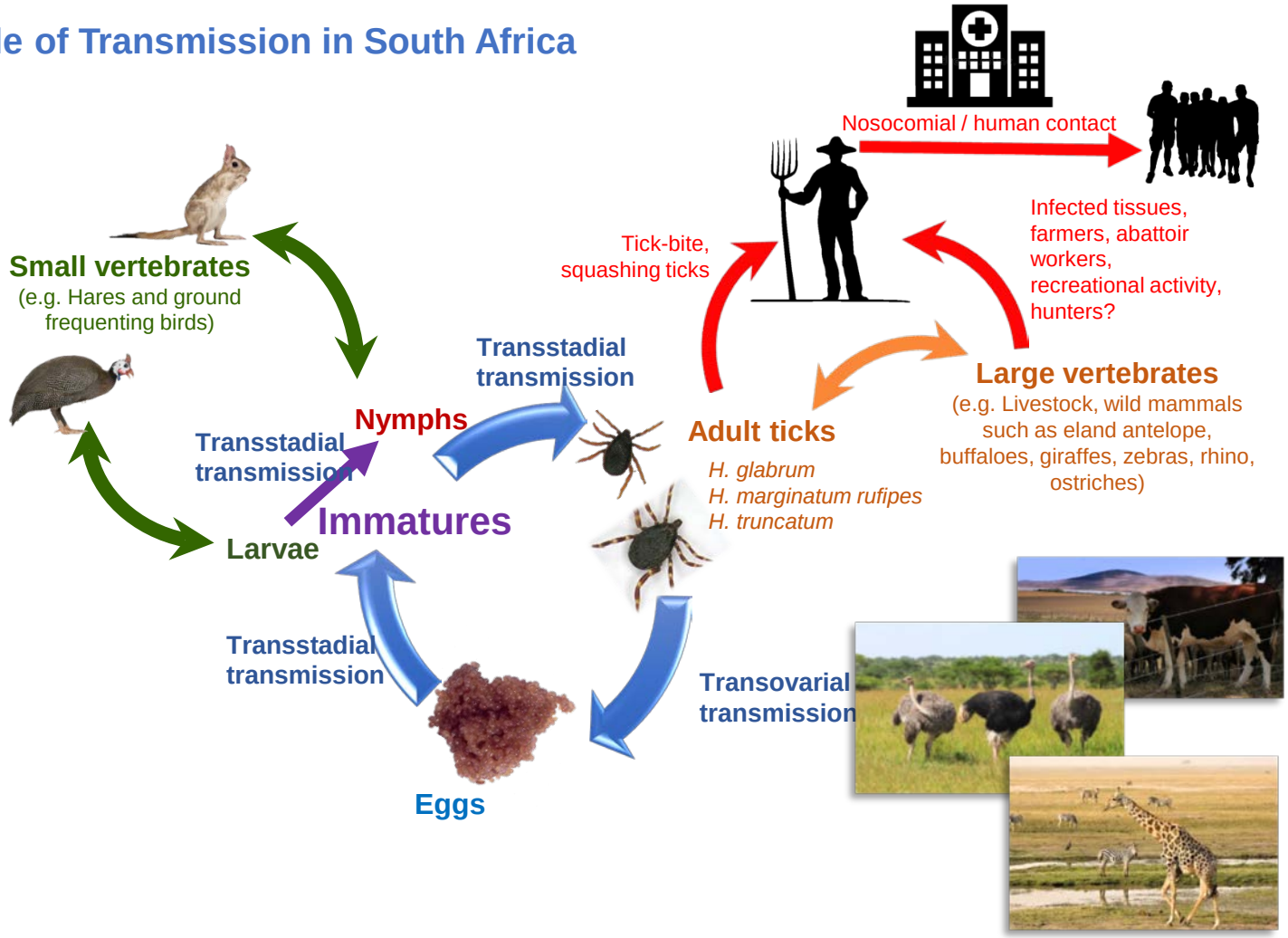
Clinical presentation:

Sudden onset with severe headache, fever, chills, nausea and general influenza-like symptoms, myalgia and petechial rash, frequently followed by a haemorrhagic state.

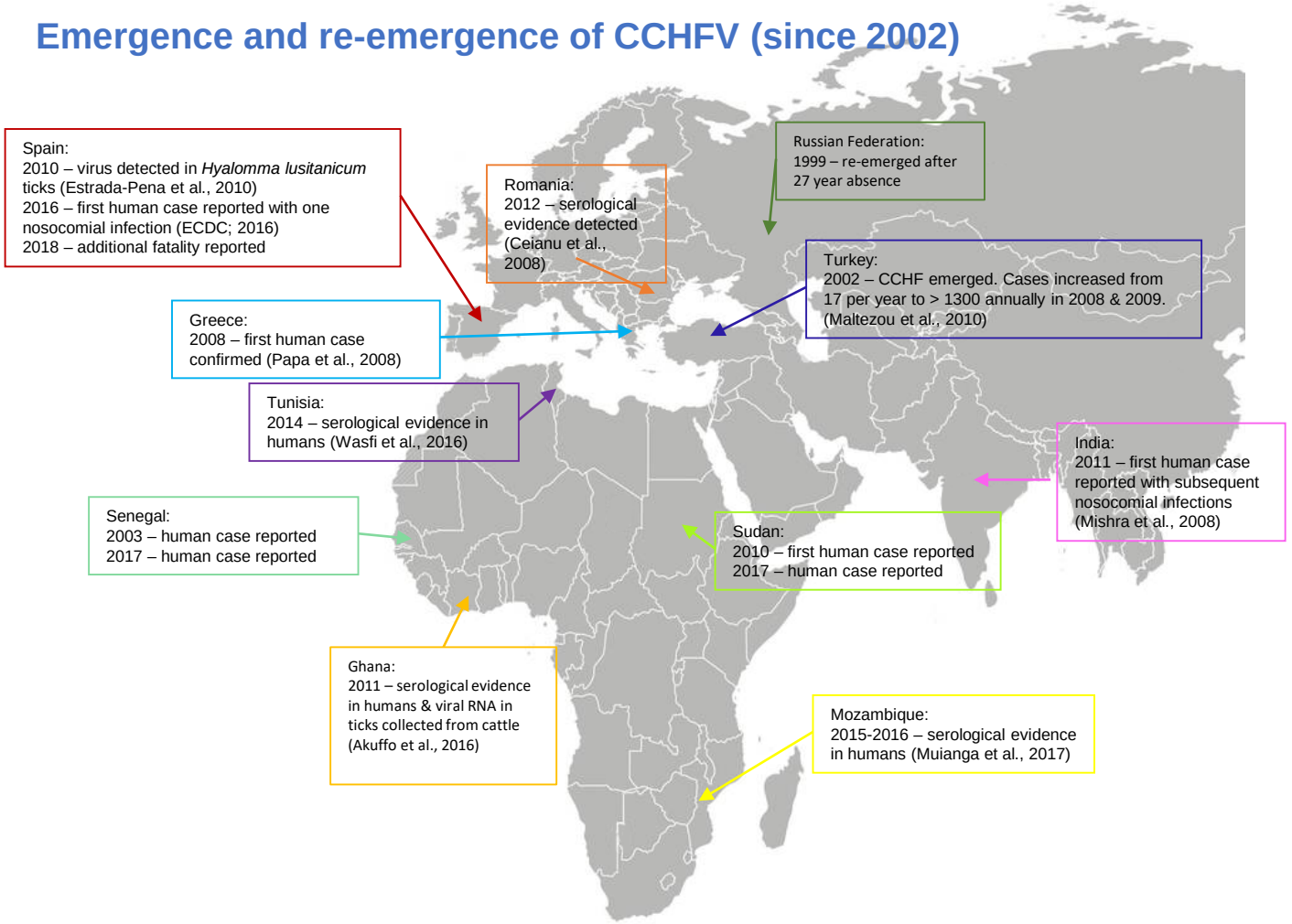
Fatality rate:

The disease has a 24% fatality rate in SA can cause nosocomial infections

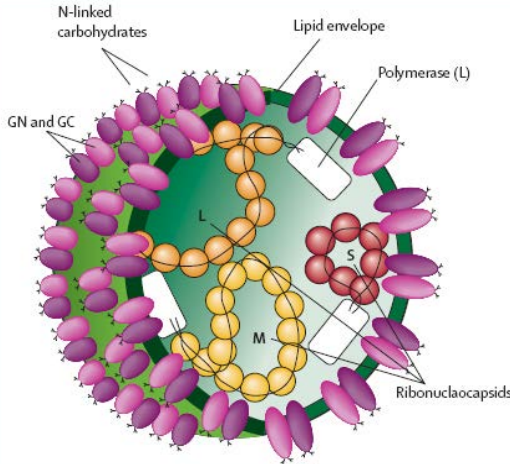
Cycle of Transmission in South Africa



Emergence and re-emergence of CCHFV (since 2002)



CCHF belongs to family *Nairoviridae*
Member of the genus *Orthonairovirus*
Enveloped, 3 segmented RNA virus



S encodes nucleoprotein: the most abundant and immunodominant protein- a target for diagnosis

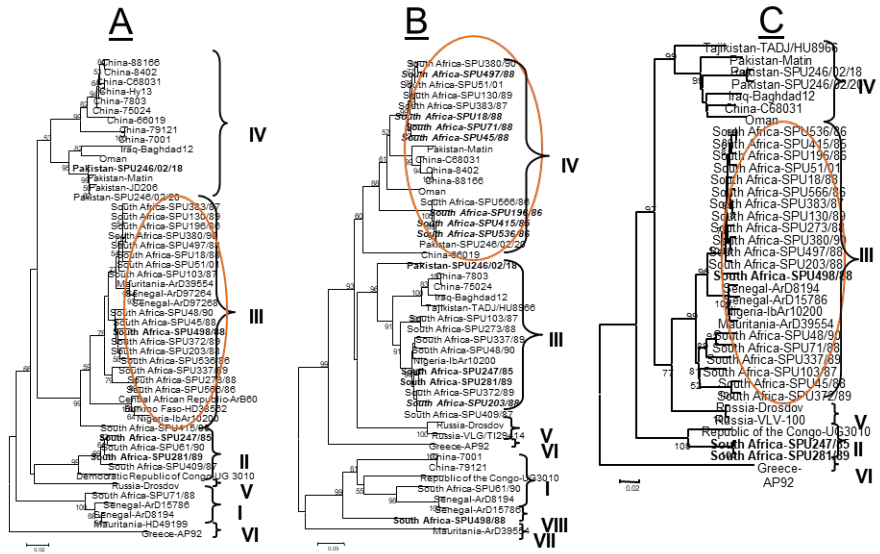
M encodes glycoprotein: possibly important for vaccine development

L large encodes the polymerase

A schematic representation of a *Bunyaviridae* virion. CCHF virus has a 3 segmented RNA genome (Ergönül, 2006).

The Genetic diversity of CCHFV

Determining the sequence of the different strains of CCHF virus in South Africa and globally



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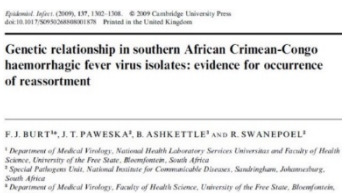
Protocols

A Simple-Probe® real-time PCR assay for genotyping reassorted and non-reassorted isolates of Crimean-Congo hemorrhagic fever virus in southern Africa

Kulsum Kondiah[a], Robert Swanepoel[b], Janusz T. Paweska[b], Felicity J. Burt[c,*]



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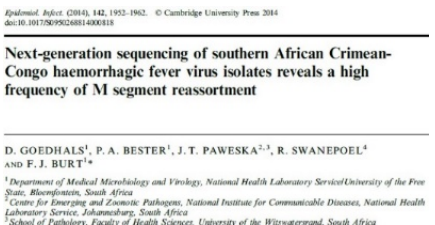
Genetic relationship in southern African Crimean-Congo haemorrhagic fever virus isolates: evidence for occurrence of reassortment

F. J. BURT[1]*, J. T. PAWESKA[2], B. ASHKETTLE[3] AND R. SWANEPOEL[3]

[1] *Department of Medical Virology, National Health Laboratory Services Universitas and Faculty of Health Science, University of the Free State, Bloemfontein, South Africa*

[2] *Special Pathogens Unit, National Institute for Communicable Diseases, Sandringham, Johannesburg, South Africa*

[3] *Department of Medical Virology, Faculty of Health Science, University of the Free State, Bloemfontein, South Africa*



Epidemiol. Infect. (2014), **142**, 1952–1962. © Cambridge University Press 2014

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Next-generation sequencing of southern African Crimean-Congo haemorrhagic fever virus isolates reveals a high frequency of M segment reassortment

D. GOEDHALS[1], P. A. BESTER[1], J. T. PAWESKA[2,3], R. SWANEPOEL[4] AND F. J. BURT[1]*

[1] *Department of Medical Microbiology and Virology, National Health Laboratory Service/University of the Free State, Bloemfontein, South Africa*

[2] *Centre for Emerging and Zoonotic Pathogens, National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg, South Africa*

[3] *School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, South Africa*

[4] *Zoonoses Research Unit, Department of Medical Virology, University of Pretoria, South Africa*

CCHF animal models

Humans and suckling mice are susceptible to infection

CCHFV vaccine development has been facilitated by the discovery of animal models that are permissive to infection, succumb to disease and share some similarity in disease pathology as described in human disease.

Experimental infection of knockout mice shows disease and pathological changes parallel to findings in humans

- lack of signaling to all types of IFN: STAT-1$^{-/-}$
- lack of type 1 IFN signaling: IFNAR$^{-/-}$
- temporarily suppressed type 1 IFN system IS

- humanized mouse model displayed different patterns of disease when inoculated with different strains

- Non human primate, *Cynomolgus macaque* inoculated with Hoti or Afg09-2020 develop clinical picture and clinical chemistries similar to human disease.
- Primates survived Afg09-2020 but developed disease ranging from mild to severe with Hoti

Vaccine type	CCHFV antigen[a]	Animal	Dose[b]	Antibody response	T cell response	Challenge[c]	Efficacy, % survival	Reference
Sub unit vaccines	Gc-e ectodomain (adjuvanted)	STAT1	2 dose	Yes[1]	NT	IbAr10200 strain	0%	Kortekas et al., 2015
	Gn ectodomain (adjuvanted)			Yes[1]	NT	IbAr10200 strain	0%	
	Gc- eΔ ectodomain (adjuvanted)			Yes[1]	NT	IbAr10200 strain	0%	

[1]Neutralizing antibodies *in vitro*, [2]Non-neutralizing antibodies *in vitro*, [3]Antibody ability to neutralize *in vitro* not assessed

[a]All vaccine candidates were based on IbAr10200 strain unless otherwise stated.

Kortekaas J, Vloet RP, McAuley AJ, et al. Crimean-Congo hemorrhagic fever virus subunit vaccines induce high levels of neutralizing antibodies but no protection in STAT1 knockout mice. Vector Borne Zoonotic Dis. 2015; 15(12):759-64.

Vaccine type	CCHFV antigen[a]	Animal	Dose[b]	Antibody response	T cell response	Challenge[c]	Efficacy, % survival	Reference
Transgenic Plants	Gn and Gc (Iranian strain)	BALB/c mice	Fed leaves	Yes[3]	NT	NT	NT	Ghiasi et al., 2011
		BALB/c mice	Fed roots	Yes[3]				
		BALB/c mice	Fed leaves injected 5 µg Gn/Gc	Yes[3]				
		BALB/c mice	Fed roots injected 5 µg Gn/Gc	Yes[3]				
		BALB/c mice	Bulgarian vaccine, injected four doses at 2 week intervals (s.c.)	Yes[3]				

Ghiasi SM, Salmanian AH, Chinikar S, et al. Mice orally immunized with a transgenic plant expressing the glycoprotein of Crimean-Congo hemorrhagic fever virus. Clin Vaccine Immunol. 2011; 18:2031–7.

Vaccine type	CCHFV antigen[a]	Animal	Dose[b]	Antibody response	T cell response	Challenge[c]	Efficacy, % survival	Reference
Virus-like replicon particles	GPC, L and NP (IbAr10200 L, NP and Oman-1998 GPC)	IFNAR$^{-/-}$	High dose	Yes[3]	NT	CCHFV-IbAr10200	100%	Scholte et al., 2019
		IFNAR$^{-/-}$	Low dose	Yes[3]	NT	CCHFV-IbAr10200	78%	
	GPC, L and NP (IbAr10200 L, NP and Oman-1998 GPC)	IFNAR$^{-/-}$	10^5 $TCID_{50}$ (s.c.)	Yes[3]	NT	CCHFV Oman-199723179	100%	Spengler et al., 2019
	GPC, L and NP (IbAr10200 L, NP and Oman-1998 GPC)	IFNAR$^{-/-}$	10^5 $TCID_{50}$ (s.c.)	Yes[3]	NT	Turkey-200406546	100%	
tc-VLP	Gn, Gc and NP	IFNAR$^{-/-}$	10^6 VLPs/mouse (i.p.) day 0, 28 and 49	Yes[1]	Yes	CCHFV strain IbAr 10200	40%	Hinkula et al., 2017

Scholte FEM, Spengler JR, Welch SR, et al. Single-dose replicon particle vaccine provides complete protection against Crimean-Congo hemorrhagic fever virus in mice. Emerg Microbes Infect. 2019; 8(1):575-578.

Spengler JR, Welch SR, Scholte FEM, et al. Heterologous protection against Crimean-Congo hemorrhagic fever in mice after a single dose of replicon particle vaccine. Antiviral Res. 2019; 170:104573.

Hinkula J, Devignot S, Åkerström S, et al. Immunization with DNA plasmids coding for Crimean-Congo hemorrhagic fever virus capsid and envelope proteins and/or virus-like particles induces protection and survival in challenged mice. J Virol. 2017; 91(10):e02076-16

Vaccine type	CCHFV antigen[a]	Animal	Dose[b]	Antibody response	T cell response	Challenge[c]	Efficacy, % survival	Reference
DNA	GPC	BALB/c	3 dose	Yes[1]	NT	NT	NT	Spik et al., 2006
		BALB/c	3 dose	Yes[1]	NT	NT	NT	
	Gn, Gc and NP (multiple plasmids)	IFNAR$^{-/-}$	3 dose	Yes[1]	Yes	CCHFV strain IbAr 10200	100%	Hinkula et al., 2017
	GPC	IFNAR$^{-/-}$	3 dose	Yes[1]	NT	CCHFV strain IbAr 10200	71%	Garrison et al., 2017
	GPC	IS C57BL/6	3 dose	Yes[1]	NT	CCHFV strain IbAr 10200	60%	
	NP (Ank-2 strain)	BALB/c and IFNAR$^{-/-}$	day 0 and day 14	Yes[2]	Yes	Ank-2 strain	75%	Farzani et al., 2019a and 2019b
	NP (Ank-2 strain)	BALB/c and IFNAR$^{-/-}$	pV-N13 (50 µg) (i.m.) day 0 and 14	Yes[2]	Yes	Ank-2 strain	100%	
	NP (Ank-2 strain)	BALB/c and IFNAR$^{-/-}$	pV-N13 (40 µg) + pCD24 (10 µg) (i.m.) day 0 and 14	Yes[2]	Yes	Ank-2 strain	100%	
Replicating RNA	Alphavirus based replicon RNA NP or GPC or both	C57BL6/J	1 dose	Yes	Yes	UG3010 heterologous challenge	Combination reqd for protection	Leventhal et al 2022

Vaccine type	CCHFV antigen[a]	Animal	Dose[b]	Antibody response	T cell response	Challenge[c]	Efficacy, % survival	Reference
Modified Vaccinia Ankara (MVA) vector	GPC	IFNα/βR$^{-/-}$	2 dose	Yes[3]	Yes	IbAr10200	100%	Buttigieg et al., 2014
	GPC	129Sv/Ev	2 dose	Yes[3]	Yes	Not challenged	N/A	
	NP	IFNα/βR$^{-/-}$	2 dose	Yes[3]	Yes	IbAr10200	0%	Dowall et al., 2016
	NP	129Sv/Ev	2 dose	Yes[3]	Yes	Not challenged	N/A	
	NP (3010 strain)	IFNα/βR$^{-/-}$	2 dose	Yes[3]	Yes	Not challenged	N/A	
	NP (3010 strain)	129Sv/Ev	2 dose	Yes[3]	Yes	Not challenged	N/A	
Recombinant Adenovirus type 5	NP	IFNα/βR$^{-/-}$	1 dose	NT	NT	IbAr 10200	33%	Zivcec et al., 2018
	NP	IFNα/βR$^{-/-}$	2 dose	Yes[3]	NT	IbAr 10200	78%	

Phase 1 clinical trail MVA GP CCHF vaccine (Public Health England)
Small trial
Safety in 24 volunteers (well tolerated)
Assess humoral and cellular immunogenicity in 12 volunteers (well tolerated, 2 doses immunogenic)

Buttigieg KR, Dowall SD, Findlay-Wilson S, et al. A novel vaccine against Crimean-Congo Haemorrhagic Fever protects 100% of animals against lethal challenge in a mouse model. PloS One. 2014; 9:e91516.
Dowall SD, Buttigieg KR, Findlay-Wilson SJ, et al. A Crimean-Congo hemorrhagic fever (CCHF) viral vaccine expressing nucleoprotein is immunogenic but fails to confer protection against lethal disease. Hum Vaccines Immunother. 2016; 12:519–27.
Zivcec M, Safronetz D, Scott DP, et al. Nucleocapsid protein-based vaccine provides protection in mice against lethal Crimean-Congo hemorrhagic fever virus challenge. PLoS Negl Trop Dis. 2018; 12(7):e000662

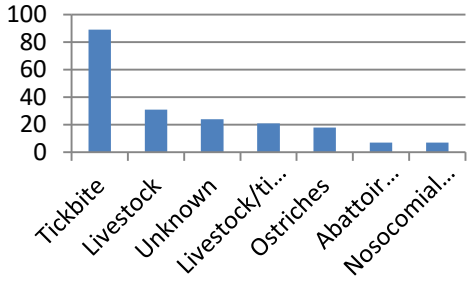
Vaccine type	CCHFV antigen[a]	Animal	Dose[b]	Antibody response	T cell response	Challenge[c]	Efficacy, % survival	Reference
Formalin Inactivated vaccine	Whole virus particle (Turkey-Kelkit06 strain)	IFNAR$^{-/-}$	3 dose 5 µg	Yes[1]	NT	Turkey-Kelkit06 strain	60%	Canakoglu et al., 2015
			3 dose 20 µg	Yes[1]	NT	Turkey-Kelkit06 strain	80%	
			3 dose 40 µg	Yes[1]	NT	Turkey-Kelkit06 strain	80%	105

Vaccine type	CCHFV antigen[a]	Animal	Dose[b]	Antibody response	T cell response	Challenge[c]	Efficacy, scheduled ethanase	Reference
DNA vaccine	GPC and NP (Hoti)	Cynomolgus macaque	3 doses (electroporation assisted IM)	Yes[3]	yes	1 x 10^5 TCID 50 Hoti (sc to cranial dorsum and IV)	Protection against viremia, high viral loads in tissues	Hawman et al., 2020

Summary

- Virus–like replicon particles expressing CCHF glycoproteins (GP), nucleoproteins (NP) and/or polymerase protein (L) conferred protection against challenge with survival rates varying from 40% to 100%.
- DNA based vaccines expressing GP precursor or NP provided 50% to 100% survival rates when challenged.
- Similarly, vectored vaccines have shown a range of survival rates up to 100% using GP however 0% using NP
- The presence of neutralising antibody did not necessarily correlate with protection suggesting that neutralising antibody is not the sole correlate of protection and protection likely requires both B and T cell responses.
- Protection in mice immunized with NP suggests a role for non-neutralising antibody.
- No established correlates of protection.
- In the absence of correlates of protection, the demonstration of vaccine clinical efficacy will be essential

Target groups for vaccination

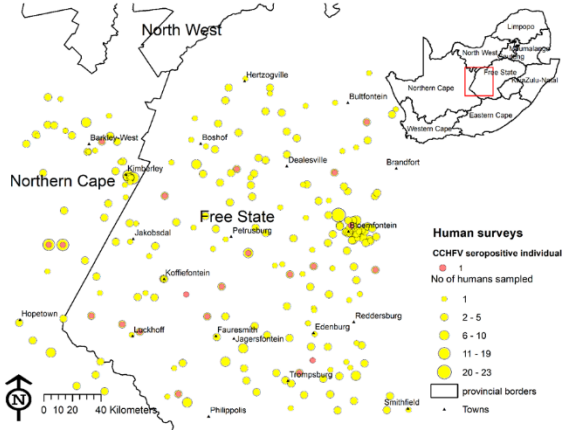


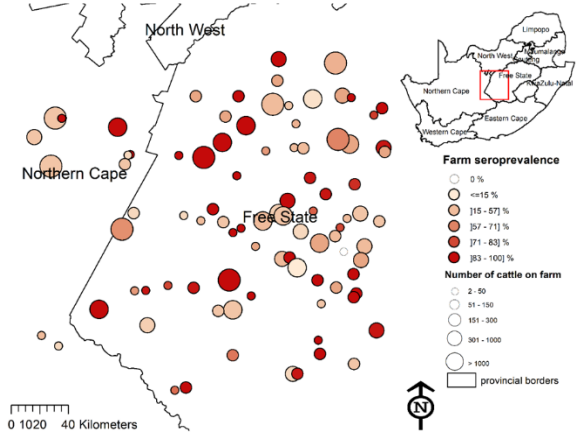
- 45.2% Tick bite or squashing ticks.
- 26.4% Contact with fresh blood or other tissues of livestock and/or ticks.
- 12.2% No direct evidence of contact but patients lived in or visited a rural area unknown, rural resident or visitor
- 9% Ostriches (abattoir)
- 3.6% abattoir workers, butcher
- 3.6% Nosocomial infections arose from contact with blood or fomites of known CCHF patients.

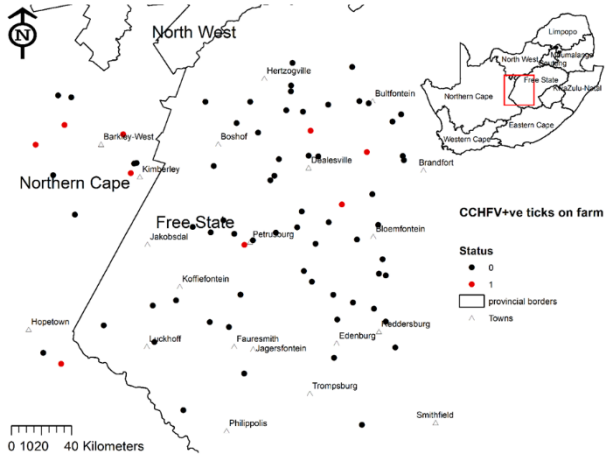
The sporadic nature of outbreaks suggests targeted vaccination to be more appropriate response
Specific risk groups have been identified

Farm workers handling domestic livestock
Abattoir workers and animal slaughterers
Rural residents at risk of exposure to tick-bite
Recreational activity providing opportunity for exposure eg hunting, outdoor activities
Large animal veterinarians

Healthcare workers at risk from nosocomial infections







RESEARCH ARTICLE

Risk factors associated with exposure to Crimean-Congo haemorrhagic fever virus in animal workers and cattle, and molecular detection in ticks, South Africa

Veerle Msimang[1,2]*, Jacqueline Weyer[2,3], Chantel le Roux[2], Alan Kemp[2], Felicity J. Burt[4,5], Stefano Tempia[6], Antoinette Grobbelaar[2], Naazneen Moolla[2], Melinda K. Rostal[7], Whitney Bagge[7], Claudia Cordel[8], William B. Karesh[7], Janusz T. Paweska[2,3], Peter N. Thompson[1]

PLOS Neglected Tropical Diseases | https://doi.org/10.1371/journal.pntd.0009384 May 28, 2021

Our findings support previous evidence of widespread high CCHFV seroprevalence in cattle and show significant occupational exposure amongst farm and wildlife workers.

Our seroprevalence estimate suggests that CCHFV infections are five times more frequent than the 215 confirmed CCHF cases diagnosed in South Africa in the last four decades (1981-2019).

With many cases undiagnosed, the potential seriousness of CCHF in people, and the lack of an effective vaccine or treatment, there is a need to improve public health awareness, prevention and disease control.

Conclusion

- The recent expansion of CCHFV endemic areas is a public health concern and this threat will continue with climate change and expansion of vector populations into new regions.
- Vaccine development, traditionally hampered by lack of a suitable animal model, has progressed in recent years due to availability of animal models.
- Knowledge gaps with regards to immune correlates of protection
- Further understanding of the immune correlates of protection will contribute towards development of an efficacious vaccine for a virus with potential to cause significant human disease.