Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Development of vaccines against Crimean-Congo haemorrhagic fever virus

Stuart D. Dowall, Miles W. Carroll, Roger Hewson *

Public Health England, Porton Down, Salisbury, Wiltshire SP4 0JG, UK

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Crimean-Congo haemorrhagic fever
Vaccine
Review

ABSTRACT

Crimean-Congo haemorrhagic fever virus (CCHFV) is a deadly human pathogen of the utmost seriousness being highly lethal causing devastating disease symptoms that result in intense and prolonged suffering to those infected. During the past 40 years, this virus has repeatedly caused sporadic outbreaks responsible for relatively low numbers of human casualties, but with an alarming fatality rate of up to 80% in clinically infected patients. CCHFV is transmitted to humans by Hyalomma ticks and contact with the blood of viremic livestock, additionally cases of human-to-human transmission are not uncommon in nosocomial settings. The incidence of CCHF closely matches the geographical range of permissive ticks, which are widespread throughout Africa, Asia, the Middle East and Europe. As such, CCHFV is the most widespread tick-borne virus on earth. It is a concern that recent data shows the geographic distribution of Hyalomma ticks is expanding. Migratory birds are also disseminating Hyalomma ticks into more northerly parts of Europe thus potentially exposing naïve human populations to CCHFV. The virus has been imported into the UK on two occasions in the last five years with the first fatal case being confirmed in 2012. A licensed vaccine to CCHF is not available. In this review, we discuss the background and complications surrounding this limitation and examine the current status and recent advances in the development of vaccines against CCHFV.

1. Introduction

1.1. Background

Crimean-Congo haemorrhagic fever (CCHF) is a virulent human disease and the most wide spread tick-borne viral infection of man. It occurs over much of Asia, extending from the XinJiang region of China to the Middle East and Southern Russia, to focal endemic areas over much of Africa, parts of Eastern Europe and most recently the Iberian Peninsula [1,2]. There are currently no licensed vaccines or therapeutics to treat CCHF. The aetiological agent, CCHF virus (CCHFV), is a single-stranded, negative sense RNA virus classified within the *Nairovirus* genus of the family *Bunyaviridae*. It is maintained in an enzoonotic cycle involving tick-mediated transmission between several species of vertebrate including wild and domestic mammals (Fig. 1). While animals develop a transient viremia, they remain asymptomatic, and direct transmission to humans involved in the slaughter and butchering of such domestic animals is a common infection route. Human infections also occur through tick bite, tick crushing in the hand, or exposure to the blood or other body fluids of an infected CCHF patient [1–3]. CCHF was first brought to modern medical attention in 1945, when it was recognised as an acute febrile illness, accompanied by fever and severe bleeding in over 200 Soviet military personnel and local inhabitants supporting war devastated Crimea [4]. Originally termed Crimean Haemorrhagic Fever, its viral aetiology was identified in 1947 through experiments which included the inoculation of psychiatric patients and human "volunteers" with ultra-filtrates of patient serum and/or extracts of pooled ticks [4,5]. However, it was not until 1968 that the virus was first isolated [6], which resulted in the international recognition that 'Crimean haemorrhagic fever' virus was identical to the 'Congo' virus identified in Africa in 1958 [7]. Ultimately, these investigations led to the designation 'Crimean-Congo Haemorrhagic Fever virus', a political name conceived during the Cold War [8].

1.2. Emergence and growing threat

CCHF is an emerging virus whose incidence and geographic range has been increasing since its early identification. For example, since 2002, the disease has been reported with increasing

* Corresponding author.
E-mail address: roger.hewson@phe.gov.uk (R. Hewson).

http://dx.doi.org/10.1016/j.vaccine.2017.05.031
0264-410X/

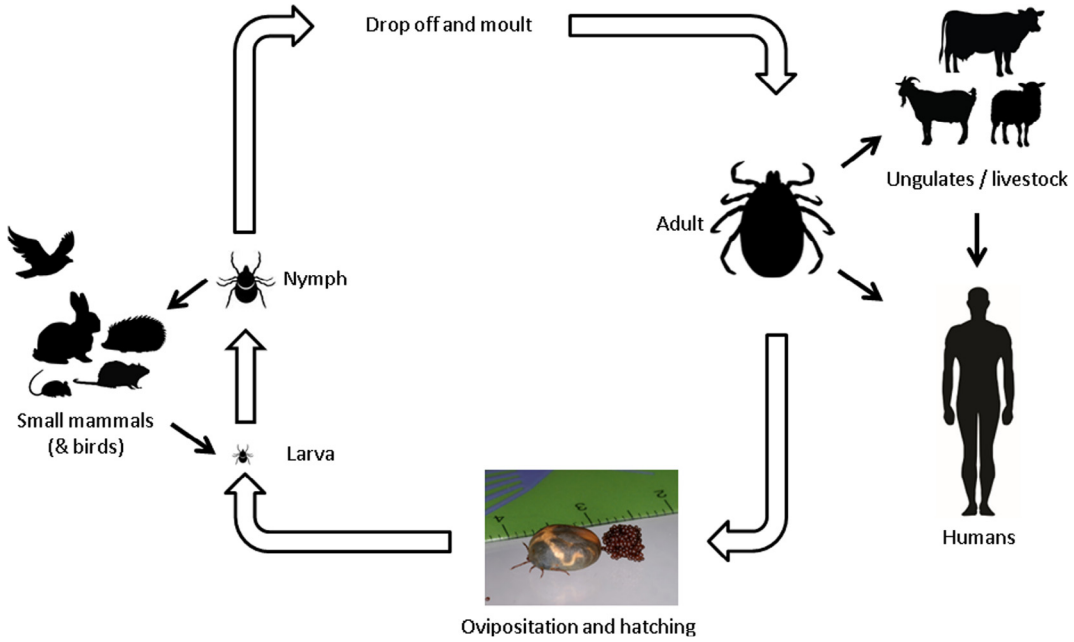

Fig. 1. Zoonotic cycle of Hyalomma tick species, the main vector for CCHFV (modified from [11]).

frequency in Turkey, Iran, India, Greece, the Republic of Georgia and Kosovo. In 2016 it emerged in Spain as two autochthonous cases, including one fatality as the result of a tick bite of the index case, in the province of Ávila, a location ~300 km from Cáceres where CCHFV was identified in ticks collected in 2010. Modelling of climate change has demonstrated that a rise in temperature and a decrease in rainfall in the Mediterranean region could result in a sharp rise in the distribution of suitable habitats for *Hyalomma* ticks [9], thus increasing the pool of human populations at risk. Reported cases of CCHF have risen during 2000–2009 (Table 1); it is expected that this trend will continue [10], although specific reports have taken several years to be published and an accurate assessment is not currently possible. It is widely accepted, however, that CCHF cases are under reported. Most endemic countries have poor healthcare systems where diagnosis is not straightforward and often non-existent. Additionally, infection is common in remote rural areas and mild symptoms of the disease are not diagnosed and so not reported.

CCHFV is notorious for causing nosocomial outbreaks, often resulting in severe disease with high mortality rates [12–15]. Human-to-human transmission via direct contact with contaminated blood and other tissues during surgical procedures, carried out in the absence of a correct diagnosis, is the principle source of infection [16]. Secondary human-to-human transmission in a care setting is frequently associated with exposure to infected blood, however cutaneous contact to non-sanguineous body fluids (e.g., saliva, sweat, vomitus, urine, and faeces) seems not to be linked to human-to-human transmission [17]. Standard barrier nursing methods are sufficient to prevent the transmission of CCHF virus in such circumstances [17,18]. However, when the risk of infection is generally of less concern, gloves, aprons, goggles etc., are not commonly used. This is a key factor in the zoonotic transmission of CCHFV from viremic animals during slaughter and butchering. Zoonotic transmission as a result of the slaughter and butchering of domestic animals increases during preparations for Eid-al-Adha, an annual religious festival celebrated by Muslims, during which many animals, including goats, sheep, cows, and camels are slaughtered [19,20]. As the timing of this festival follows the Islamic lunar calendar, it moves approximately 10 days earlier each year. Significantly in the next 10–20 years Eid-al-Adha

Table 1
Cases of CCHFV reported in the medical literature from different regions.

Year	Region (published CCHF cases/annum)[a]			
	Africa[b]	Asia[c]	Europe[d]	Middle East[e]
Pre-2000[f]	1.1 (since 1956)	13.5 (since 1965)	53.3 (since 1944)	4.9 (since 1979)
2000	1	48	94	20
2001	0	15	107	66
2002	0	12	186	111
2003	0	9	245	57
2004	38	13	364	26
2005	0	3	423	18
2006	0	10	651	50
2007	0	12	951	66
2008	8	14	1333	150
2009	2	21	1312	1

[a] CCHF cases reported in the medical literature and reported by Bente et al. [11].
[b] Cases since 2000 in Africa from Mauritania, Kenya and Sudan.
[c] Cases since 2000 in Asia from Kazakhstan, Tajikistan, Pakistan and India.
[d] Cases since 2000 in Europe from Bulgaria, Kosovo, Russia, Albania, Turkey and Greece.
[e] Cases since 2000 in the Middle East from Iran and Afghanistan.
[f] Cases per annum averaged from first year figure is available (in brackets) to year 2000.