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Review

Nosocomial infections caused by Crimean–Congo haemorrhagic fever virus

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SUMMARY

Crimean–Congo haemorrhagic fever (CCHF) is an acute febrile illness, often accompanied by haemorrhagic manifestations, with a high case fatality rate (CFR). The causative agent is CCHF virus (CCHFV), and is transmitted to humans mainly through tick bites or exposure to blood or tissues of viraemic patients or livestock. Human-to-human transmission usually occurs in hospital settings, and healthcare workers (HCWs) are mainly affected. A review on nosocomial CCHFV infections was performed to elucidate the routes and circumstances of CCHFV transmission in hospital settings.

From 1953 to 2016, 158 published cases of CCHFV nosocomial infection in 20 countries in Africa, Asia and Europe were found. Almost all cases were symptomatic (92.4%), with an overall CFR of 32.4%. The majority of cases occurred in hospital clinics (92.0%) and 10 cases (8.0%) occurred in laboratories. Most cases occurred among HCWs (86.1%), followed by visitors (12.7%) and hospitalized patients (1.3%). Nursing staff (44.9%) and doctors (32.3%) were the most affected HCWs, followed by laboratory staff (6.3%). The primary transmission route was percutaneous contact (34.3%). Cutaneous contact accounted for 22.2% of cases, followed by exposure to aerosols (proximity) (18.2%), indirect contact (17.2%) and exposure to patient environment (8.1%).

CCHFV can cause nosocomial infections with a high CFR. During the care and treatment of patients with CCHF, standard contact precautions, barrier precautions and airborne preventive measures should be applied. In order to improve patient safety and reduce healthcare-associated CCHFV exposure, there is a need for guidelines and education for HCWs to ensure that CCHF is appropriately included in differential diagnoses; this will enable early diagnosis and implementation of infection prevention measures.

Introduction

Crimean–Congo haemorrhagic fever (CCHF) is a severe, acute, febrile illness, often accompanied by haemorrhagic manifestations. The reported case fatality rate (CFR) ranges

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from 5% to 30% [1]. The causative agent is Crimean–Congo haemorrhagic fever virus (CCHFV) (Orthonairovirus genus, Nairoviridae family) which is spread in Africa, Asia, the Middle East and southeastern Europe, following the geographic distribution of the virus vector, *Hyalomma* spp. ticks [1–4]. More than 1000 CCHF cases are reported each year and both the incidence and geographic distribution have increased over the last decade [5]. The disease is considered as emerging, with Spain being the most recent country reporting emergence of CCHFV infections in humans [6–8].

The virus is transmitted to humans mainly through bites of infected ticks, but also through percutaneous or permucosal exposure to blood or tissues of viraemic patients or livestock. Human-to-human transmission of CCHFV usually occurs in hospital settings. Healthcare workers (HCWs), including doctors, nurses, laboratory staff, research scientists, emergency service staff and cleaning personnel, are at risk of occupational infection following accidental exposure to blood or body fluids contaminated with the virus. There are several reports of hospitalized patients acting as index cases resulting in nosocomial infections and outbreaks [9–11]. Thus, implementation of infection control measures, careful management of CCHF patients and prompt administration of prophylactic treatment to exposed persons is essential [12]. Ribavirin is recommended by the World Health Organization (WHO) as postexposure prophylaxis [13].

The aim of the present analysis is to review nosocomial CCHFV infections and outbreaks worldwide.

Methods

Information sources and search strategy

The online medical databases used to identify case reports and case series of nosocomial CCHFV infection were PubMed (MEDLINE), Web of Science and Cochrane Library. To ensure literature saturation, a hand search of the reference lists of relevant reviews and studies identified through the search was conducted. To increase the sensitivity and specificity of the search, 'free-text' terms and Medical Subject Heading (MeSH) terms were used, respectively. While using free-text terms, alternative spellings, synonyms and changes in terminology over time were taken into account. There was no language or publication date restriction. The final search was performed in October 2018.

The formed search query for MEDLINE was: 'crimean congo' [All Fields] OR 'cchf' [All Fields] OR 'crimean haemorrhagic' [All Fields] OR 'crimean kongo' [All Fields] OR 'hemorrhagic fever virus, Crimean–congo' [MeSH Terms] OR 'hemorrhagic fever, crimean' [MeSH Terms], and 1422 records were retrieved. The search query was adapted to the syntax and subject headings of the other two databases. For Web of Science, it was: TOPIC: (crimean congo) OR TITLE: (crimean congo) OR CONFERENCE: (Crimean congo) OR TOPIC: (CCHF) OR TITLE: (CCHF) OR CONFERENCE: (CCHF) and 1368 records were retrieved. The search query for Cochrane Library was: 'crimean congo' (word variations have been searched) OR MeSH descriptor: [Hemorrhagic Fever, Crimean] explode all trees, and 13 results were retrieved.

Managing search results and study selection

All retrieved records were imported into EndNote Version X7 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA], where duplicate records were removed. The relevant studies were selected by screening titles and abstracts. Full-text documents were obtained from all relevant articles and from articles in which it was not possible to decide about their relevance based on their title and/or abstract.

Data extraction

The data extraction form was in Excel (Microsoft Corp., Redmond, WA, USA) format. Data extracted from the selected articles were: information on country of origin of the nosocomial cases, year of publication and occurrence, first author of publication, patient demographic data (including age, sex and occupation), mode of CCHFV transmission, clinical presentation and course of infection (including presence of haemorrhagic manifestations), postexposure treatment, diagnostic methods used (i.e. serology, molecular or clinical) and outcome of the disease.

To identify duplicate or overlapping cases, the criteria used were author names, location and setting, year and date of incidence, and specific details of patients' demographic data [14]. In the event of duplicate or overlapping cases, information from the related reports were combined. The data were extracted by two independent researchers.

Data analysis

Data were summarized using descriptive statistics. For qualitative variables, the summary measure used was frequency distribution, expressed as percentage of the total frequency (relative frequency, %). Statistical analysis of the qualitative variables was performed using Pearson's Chi-squared test, as no expected frequencies were <1, and no more than 20% of the expected frequencies were <5. All tests were two sided and the significance level was set at $P<0.05$. The analysis was undertaken using SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA).

Eligibility criteria

The study included case reports and case series of HCWs, patients and visitors who acquired CCHFV infection in healthcare facilities through a defined transmission route. HCWs included people working in hospitals, laboratories, research, emergency services or cleaning personnel. There was no restriction on sex, race, hospital setting or country. Seroprevalence studies and screening reports for tracing contacts were excluded.

Definitions and outcome of interest

The 'index case' was defined as the patient who was first noticed by the health authorities, and who made them aware of the infection. 'Secondary cases' were defined as cases with infection acquired after exposure to the index case, and

'tertiary cases' were defined as cases who acquired the infection from a secondary case.

All secondary and tertiary cases were categorized into three risk groups according to the reason for being present in the hospital. Group 1 included HCWs, Group 2 included hospitalized patients, and Group 3 included visitors. Cases of Group 1 (HCWs) were further divided into four subgroups: 1a, doctors; 1b, nursing staff; 1c, laboratory workers (virologists and technicians); and 1d, other hospital workers (i.e. office and cleaning personnel).

Based on the route of virus transmission, all secondary and tertiary cases were divided into five transmission groups. Group A consisted of cases with percutaneous exposure, including all persons who had accidental needlestick injuries, or those with skin lesions who came into direct contact with infected blood or tissues; Group B included cases with cutaneous exposure of intact skin to body fluids, such as blood, sweat, saliva, vomit and excreta; Group C included cases with indirect contact involving body fluids or physical contact with the patient using gloves; Group D consisted of cases who were in close proximity with the patient without physical contact (e.g. participation in aerosol-producing procedures or contact with contaminated material); and Group E included cases with exposure to the patient environment, including those who did not come into contact with a patient but entered a room in which a patient was hospitalized and came into contact with potentially contaminated surfaces, such as the bed, desk or medical equipment.

The primary outcomes of interest were CCHFV infection (asymptomatic or symptomatic) and mortality rate. The secondary outcome of interest was postexposure treatment with ribavirin, plasma, erythrocytes and/or platelet administration.

Results

Publication characteristics

In total, 1749 unique records were initially retrieved and screened for relevance by title, abstract or full-text availability. One hundred and forty articles were identified as potentially relevant and reviewed for eligibility. In total, 62 full-text articles reporting nosocomial sporadic infections or outbreaks caused by CCHFV were published. Four articles were excluded as they did not provide adequate information regarding patient occupations, exposure histories, clinical courses and outcomes. The excluded cases were from Afghanistan (one case in 2008) [15], Bulgaria (20 cases in 1953–1974) [16], Pakistan (10 cases in 1976 and one case in 2010) [17,18] and Russia (one case in 1961, two cases in 1966 and five cases in 1999) [19]. Finally, the study included 58 articles, reporting 158 cases of CCHFV nosocomial infection (Figure 1 and Table I).

The 158 reported cases occurred from 1964 to 2016 in 20 countries in Africa, Asia and Europe, and were either single cases or part of nosocomial outbreaks. The majority of cases

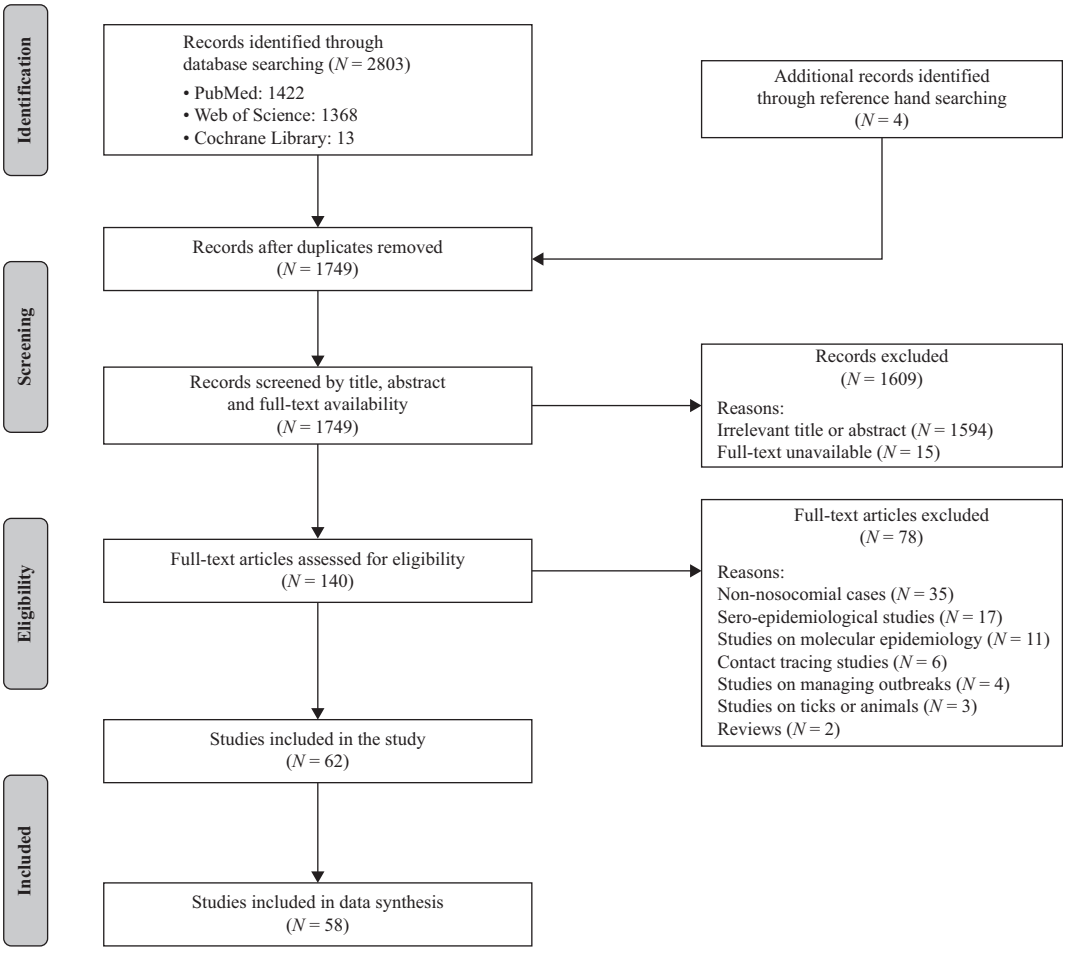

Figure 1. Flow diagram of study retrieval and selection.

Table I
Nosocomial cases of Crimean–Congo haemorrhagic fever included in the analysis by country and year of occurrence

Country (total number of cases)	Year of occurrence	Index case, outcome	Number of nosocomial cases			Reference
			Secondary cases (fatal)	Tertiary cases (fatal)	Total (fatal)	
Albania (1)	2001	1, ND	1 (0)		1 (0)	[20,21]
Bulgaria (2)	1999	Laboratory	1 (0)		1 (0)	[22]
	2008	1, fatal	1 (0)		1 (0)	[23,24]
Egypt (1)	1981	Laboratory	1 (1)		1 (1)	[22]
Germany[a] (2)	2009	1, fatal	2 (0)		2 (0)	[25]
India (12)	2011	1, fatal	3 (2)	4 (1)	7 (3)	[26–29]
	2012	1, fatal	1 (1)		1 (1)	[31]
	2015	1, fatal	4 (2)		4 (2)	[30]
Iran (15)	1999	1, ND	1 (1)		1 (1)	[34]
	1999	Laboratory	1 (1)		1 (1)	[34]
	1999	1, fatal	1 (0)	1 (1)	2 (1)	[33,34]
	2001	1, fatal	1 (0)		1 (0)	[33]
	2008	6, 1 fatal	1 (0)		1 (0)	[35]
	2009	1, fatal	1 (1)	4 (0)	5 (1)	[10]
	2011	1, fatal	1 (1)		1 (1)	[32]
	2012	1, fatal	3 (1)		3 (1)	[36,37]
Iraq (2)	1979	ND	2 (2)		2 (2)	[38]
Kazakhstan (8)	1964	1, ND	2 (0)		2 (0)	[40]
	2009	1, fatal	4 (2)		4 (2)	[39,41]
	2009	1, fatal	1 (1)		1 (1)	[39,41]
	2010	1, fatal	1 (ND)		1 (ND)	[41]
Kosovo (7)	2001	1, ND	4 (ND)	3 (ND)	7 (ND)	[42]
Mauritania (15)	2003	1, fatal	15 (6)		15 (6)	[11]
Pakistan (13)	1994	1, fatal	3 (0)		3 (0)	[43,46]
	2000	1, ND	1 (1)		1 (1)	[49]
	2000	1, ND	1 (0)		1 (0)	[49]
	2000	Laboratory	1 (1)		1 (1)	[48]
	2000	1, fatal	1 (1)		1 (1)	[48]
	2002	1, fatal	2 (1)		2 (1)	[44,45]
	2011	1, ND	2 (1)		2 (1)	[47]
	2016	1, fatal	2 (1)		2 (1)	[50]
Russia (11)	1968	Laboratory	1 (0)		1 (0)	[51]
	1970	Laboratory	1 (1)		1 (1)	[51]
	2005	1, fatal	1 (0)		1 (0)	[41]
	2011	1, fatal	8 (0)		8 (0)	[19,52]
Senegal (3)	1993	Laboratory	2 (0)		2 (0)	[22]
	1998	Laboratory	1 (0)		1 (0)	[22]
Serbia (1)	2001	1, fatal	1 (0)		1 (0)	[53]
South Africa (9)	1984	1, fatal	6 (1)	1 (0)	7 (1)	[54–58]
	1985	1, recovery	1 (1)		1 (1)	[55,56]
	2006	Laboratory	1 (1)		1 (1)	[22]
Spain (1)	2016	1, fatal	1 (0)		1 (0)	[6–8]
Sudan (6)	2008	1, fatal	4 (4)	1 (1)	5 (5)	[59]
	2010	1, recovery	1 (0)		1 (0)	[59,60]
Tajikistan (14)	1993	1, fatal	4 (0)		4 (0)	[61]
	2001	1, fatal	3 (1)	1 (0)	4 (1)	[61]
	2009	1, ND	6 (1)		6 (1)	[61]
Turkey (30)	2003	1, ND	1 (1)		1 (1)	[64]
	2005	1, recovery	1 (0)		1 (0)	[62]
	2005	1, fatal	3 (0)		3 (0)	[62]
	2006	1, recovery	1 (0)		1 (0)	[9]
	2006	1, fatal	1 (1)		1 (1)	[62]
	2007	1, recovery	1 (0)		1 (0)	[62]
	2008	1, fatal	3 (0)		3 (0)	[62]
	2008	1, recovery	1 (0)		1 (0)	[62]

Table I (*continued*)

Country (total number of cases)	Year of occurrence	Index case, outcome	Number of nosocomial cases			Reference
			Secondary cases (fatal)	Tertiary cases (fatal)	Total (fatal)	
	2008	1, recovery	1 (0)		1 (0)	[62]
	2002–2008	1, ND	2 (0)		2 (0)	[68]
	2011	1, fatal	1 (0)		1 (0)	[65]
	2008–2012	1, recovery	1 (0)		1 (0)	[63]
	2014	1, fatal	7 (0)	1 (1)	8 (1)	[66]
	2015	1, fatal	4 (0)		4 (0)	[69]
	2016	1, fatal	1 (1)		1 (1)	[67]
United Arab Emirates (5)	1979	1, fatal	5 (2)		5 (2)	[70]
Total (158)	1953–2016		142 (43)	16 (4)	158 (47)	

ND, not defined.
[a] The index case was imported from Afghanistan.

were from Asia (99/158, 62.7%), followed by Africa (34/158, 21.5%) and Europe (25/198, 15.8%). The reported nosocomial infections took place in Albania [20,21], Bulgaria [22–24], Egypt [22], Germany [25], India [26–31], Iran [10,32–37], Iraq [38], Kazakhstan [19,39–41], Kosovo [42], Mauritania [11], Pakistan [43–50], Russia [19,41,51,52], Senegal [22], Serbia [53], South Africa [22,54–58], Spain [68], Sudan [59,60], Tajikistan [61], Turkey [9,62–69] and United Arab Emirates [70] (Table I).

Patient characteristics

The median age of the 158 patients with nosocomial CCHFV infection was 29.0 years (range 15–55 years) and 52.6% were male. The majority of the reported cases (148, 92.0%) occurred in hospital clinics [hospital-acquired (HA)] and 10 cases (8.0%) occurred in laboratory settings [laboratory-acquired (LA)]. Among the 158 CCHF cases, 142 (89.9%) were secondary cases and 16 (10.1%) were tertiary cases.

All index case patients had severe disease with haemorrhagic manifestations, suggesting that the risk of virus transmission was high. Disease outcome was reported for 42 index cases, and 34 (80.9%) were fatal, suggesting that they had a high viral load.

Risk groups

Among the three risk groups (HCWs, hospitalized patients and visitors), the vast majority of nosocomial cases occurred among HCWs (Group 1) (136/158, 86.1%); 20 cases (12.7%) were reported in visitors (Group 3) and two cases (1.3%) occurred among hospitalized patients (Group 2) (Table II). The most affected subgroups among HCWs were nursing staff (71/158, 44.9%) and doctors (51/158, 32.3%), with fewer cases among laboratory workers (10/158, 6.3%) and other hospital workers (4/158, 2.5%).

Intensive care units (ICUs), emergency wards and infectious diseases departments were the wards with the highest reported percentages of CCHFV nosocomial infections (24.8%, 23.9% and 14.2%, respectively), followed by laboratories (8.8%) and gynaecology-maternity departments (8.8%). Other affected hospital settings were surgery, neonatal clinics, general wards, contagious isolation wards and morgues.

Table II
Number of nosocomial cases per risk group

Risk group	Subgroup	No of cases (%)	Fatal cases (%)
1. Healthcare workers	1a. Doctors	51 (32.3)	16 (34.0)
	1b. Nursing staff	71 (44.9)	22 (33.3)
	1c. Laboratory workers	10 (6.3)	5 (50.0)
	1d. Other hospital workers	4 (2.5)	0 (0)
Subtotal		136 (86.1)	43 (31.6)
2. Hospitalized patients		2 (1.3)	1 (50.0)
3. Visitors		20 (12.7)	3 (17.6)
Total		158 (100)	47 (32.4)

Transmission route groups

Detailed information regarding CCHFV transmission route was available for 99 cases. Percutaneous contact was the primary route of transmission (34.3%). The activities that resulted in percutaneous exposure were mouth-to-mouth resuscitation, needlestick injury, and contact of mucosal membranes or skin lesions with infected blood and bodily fluids. Among other routes of transmission, cutaneous contact accounted for 22.2% of cases, followed by exposure to aerosols (proximity) (18.2%), indirect contact (17.2%) and exposure to patient environment (8.1%) (Figure 2). The last group included eight cases in which the patients were infected when they entered the room of the index case and came into contact with contaminated environment, such as the bed, sink, desk or medical equipment.

All LA infections occurred among technicians, except one virologist. CCHFV transmission occurred during handling of infected specimens, such as blood samples, infected mice or viral cultures through percutaneous contact (needlestick injury, abrasions on hands without using gloves, and mouth-pipetting) or through aerosols (centrifuging of viral culture and preparation of sucrose acetone antigen). The main characteristics of LA cases are summarized in Table III. All these cases were symptomatic, and 60% presented haemorrhagic manifestations.

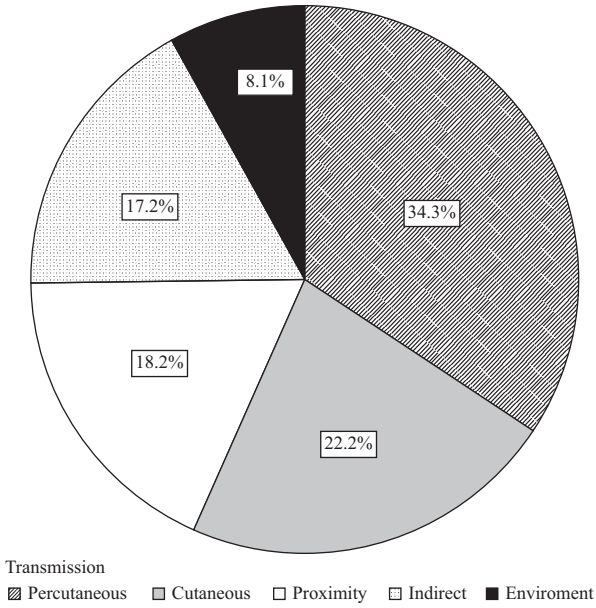

Figure 2. Pie chart of the transmission groups of nosocomial cases of Crimean–Congo haemorrhagic fever.

Diagnostic methods

The methods used for laboratory diagnosis of CCHF nosocomial cases were reported for 148 cases. For 57 (38.5%) cases, the diagnosis was based on serological methods (enzyme-linked immunosorbent assay). Reverse transcriptase polymerase chain reaction was used for 35 (22.2%) cases, the virus was isolated in five (3.4%) cases, and more than one diagnostic method was used for 40 (27.0%) cases. In 11 (7.4%) cases, the diagnosis was based solely on exposure history combined with clinical diagnosis or necropsy findings.

Clinical course and outcome of nosocomial cases

The majority of nosocomial CCHF cases were symptomatic (146/158, 92.4%). Haemorrhagic manifestations were present in 76.5% of symptomatic cases.

Disease outcome was reported in 148 of 158 cases and 48 cases were fatal. The overall CFR of nosocomial CCHF cases was 32.4%, and there was no difference in CFR between secondary and tertiary cases (32.6% and 30.8%, respectively, $P>0.05$), nor between HA and LA cases (31.2% and 50%, respectively, $P>0.05$).

Treatment

The treatment followed was described for 76 cases, no information was available for 78 cases, and no treatment was followed for four cases. Treatments included transfusion of blood and/or blood products (e.g. platelets, fresh frozen plasma), general supportive measures (including antibiotics, corticosteroids, paracetamol, non-steroidal anti-inflammatory drugs, insulin, diuretics), immunoglobulins, ribavirin and interferon. Alone or in combination, treatments were administered as follows: ribavirin in 53 (69.7%) cases, transfusion of blood and/or blood products in 45 (59.2%) cases, general supportive measures in 30 (39.5%) cases, immunoglobulin in 16 (21.1%) cases, and interferon in six (7.9%) cases. In the vast majority of cases, there was a lack of information regarding the time of administration (days after exposure and/or symptom onset), as well as the duration of treatment and dosages used. Thus, conclusions on the efficacy of the treatment options used may not be reached without the danger of systematic error.

Two of the four untreated cases survived. One non-fatal case was a technician who had a needlestick injury during a CCHFV passage procedure and was vaccinated immediately with the Bulgarian CCHFV vaccine; she presented benign febrile illness [22]. The second non-fatal case was a doctor who was infected with the virus during phlebotomy, and although she became

Table III
Characteristics of laboratory-acquired nosocomial cases of Crimean–Congo haemorrhagic fever (CCHF)

Country	Year	Occupation	Transmission route	Fatal	Reference
Russia	1968	Technician	Centrifuging and preparation of plasma for infecting mice	No	[51]
Russia	1970	Technician	A flask with highly active virus-containing material was broken in a centrifuge rotor. Probable transmission through aerosols	Yes	[51]
Egypt	1981	Virologist	Mouth-pipetting a culture of a CCHFV isolate brought from Iraq	Yes	[22]
Senegal	1993	Technician	Exposed to aerosols while preparing sucrose acetone antigen from infected suckling mouse brain since not all equipment was located in a laminar flow cabinet or in BSL-3 laboratory	No	[22]
Senegal	1993	Technician	Handle of cages with infected mice on an open bench without wearing mask	No	[22]
Senegal	1998	Technician	Needlestick injury	No	[22]
Bulgaria	1999	Technician	Abrasion on the hand with a needle during CCHFV passage procedure in the brain of a baby mouse	No	[22]
Iran	1999	Technician	Direct contact with blood-contaminated specimen	Yes	[34]
Pakistan	2000	Technician	ND	Yes	[48]
South Africa	2006	Technician	Sorting and repacking various specimens into a refrigerator in which CCHF patient samples were stored. No record of any specific exposure	Yes	[22,55]

CCHFV, Crimean–Congo haemorrhagic fever virus; ND, not defined.

symptomatic, she refused therapy and hospitalization [68]. One of the fatal untreated cases was a pregnant woman who was infected during hospitalization in a room and bed previously occupied by a patient with CCHF. She was misdiagnosed with HELLP (haemolysis, elevated liver enzyme levels and low platelet levels) syndrome, and therefore not treated for CCHV [10]. The second fatal case was a nurse who gave mouth-to-mouth resuscitation to a patient with CCHF. Six days later, he presented to the hospital with fever, rigors and diarrhoea; he was treated empirically with antimalarials, and died 2 days later due to extensive haemorrhagic manifestations [70].

Discussion

CCHF is a re-emerging tick-borne viral haemorrhagic fever with potential for person-to-person transmission. Therefore, nosocomial transmission is not unusual, and cases have been reported in healthcare settings of endemic and epidemic countries [62,66,71]. A few nosocomial cases have also been reported in non-endemic countries [8,25,72—75]. The most recent example was in 2016 in Spain, when a secondary nosocomial infection was observed in the nurse who was taking care of a fatal index case while he was hospitalized in an ICU [8]. Nosocomial CCHF cases in non-endemic countries may also occur following imported cases, as happened during the hospitalization of a US soldier in Germany; the patient acquired CCHFV while working in field operations in Afghanistan [25]. In areas where CCHF has not been detected previously, the management of CCHF cases presents infection control challenges, as the risk of CCHFV nosocomial transmission is prominent due to lack of experience or inadequate protective measures implemented when caring for a patient [19]. The diagnosis of the disease is also usually delayed due to lack of awareness.

This review shows that approximately 200 cases of nosocomial CCHFV infection were reported in more than 20 endemic and non-endemic countries in Africa, central and western Asia, the Middle East and Europe. The number is estimated to be higher as only a few cases, and those of special interest, are published. Furthermore, mild or subclinical infections may be unnoticed, undiagnosed and thus unreported [76].

It was shown that CCHFV nosocomial infections occur mainly in clinics during hospitalization of index patients (HA infections 92%), and are less frequent in diagnostic and research laboratories (LA infections, 8%) where the accidents occur because of biosafety breeches during handling of the virus or patient samples.

All index cases were reported as having a severe form of the disease with clinically apparent haemorrhagic manifestations, and the vast majority of them (80.9%) had a fatal outcome suggesting that they had a high viral load. Person-to-person and nosocomial transmission tend to occur during the early stages of the disease, before CCHF is recognized; during that phase, the patient is highly viraemic. Therefore, awareness and prompt diagnosis of the disease is of utmost importance for both the patient and for public health [70,77,78]. It is also important to recognize that there is long-lasting high viraemia in some cases; nosocomial cases may then occur during later stages of the disease and after diagnosis [22,79].

The majority (86.1%) of CCHFV nosocomial transmissions were reported among HCWs who were taking care of index patients, and there were far fewer cases among persons who visited patients. Among HCWs, the most affected groups were nurses and doctors caring for CCHF patients with abundant haemorrhagic manifestations. The most dangerous procedures for acquiring CCHFV are interventions for gastrointestinal bleeding and emergency operations [80]. In general, HCWs are the second most exposed occupational group to CCHFV, after farmers in endemic areas who are at high risk of tick bites [1]. Seroprevalence studies in endemic regions showed that the percentage of HCWs with antibodies against CCHFV ranges from 0 to 3.87% [81—85].

Patient-to-patient nosocomial transmission of CCHFV was rarely reported, with only two published case reports [9,10]. In one case, the patient was co-hospitalized in the same room as the index case. The two patients shared the same toilet, suggesting that the virus might be transmitted from one patient to another via blood and/or other body fluids (although airborne transmission was not ruled out) [9]. The second case of patient-to-patient nosocomial CCHFV transmission was a pregnant woman who occupied a room that had previously been occupied by an index case without prior disinfection [10].

Dissemination of CCHFV in nosocomial settings is generally postulated to result from percutaneous or direct mucosal or skin contact with body fluids or droplets of severely ill patients. There is no direct evidence of aerosol CCHFV transmission [22]. Percutaneous exposure poses the highest risk of transmission, and the mortality rates of nosocomial infections are higher in such instances of CCHF and other viral haemorrhagic fevers [2,86]. HCWs should be trained and educated on safety measures, including the use of personal protective equipment (PPE), when handling sharp items and performing invasive procedures [87].

The second most frequently documented route of transmission was cutaneous exposure through contact of intact skin with infected blood and other body fluids. The risk of cutaneous transmission through unnoticed skin abrasions necessitates cautious handling of blood and blood products. In many cases, authors noted improper use, or even lack of use, of PPE before implementation of barrier precautions when patients were isolated [20,32,42,49,59,62,63,68]. In resource-poor countries, the emphasis on cost containment by reducing the use of items such as gloves, masks, gowns and even hand soaps and disinfectants favours nosocomial spread of the virus and the emergence of nosocomial cases among HCWs [88]. Moreover, poor compliance with, or ignorance of, the required precautions contributes further to nosocomial transmission [83,89,90].

Nosocomial CCHFV infections have been reported in individuals who were in proximity with the index case without having direct or even indirect contact [19,62], suggesting that airborne spread may occur. Despite the lack of direct evidence for airborne spread, HCWs performing aerosol-generating medical procedures should take appropriate precautions, being particularly careful with patients likely to be highly viraemic [10,19,25,35,62,63].

All LA nosocomial CCHF cases resulted from breaches of biosafety practice, such as mouth-pipetting, handling samples without gloves or biosafety cabinets, and exposure to droplets during centrifugation.

The number of tertiary cases was considerably lower than the number of secondary cases (16 tertiary vs 142 secondary). In many nosocomial outbreaks, there were no tertiary cases [17,46,53,57,70]. The virulence of the virus seems to be

diminished after passage, so infections from secondary cases are not usual [70].

The overall CFR of nosocomial CCHF cases was 32.4%, with no significant difference between secondary and tertiary cases (32.6% and 30.8%, respectively). The highest rates (up to 66%) have been reported during epidemics [71,82,91]. The CFR was higher in LA cases (50% vs 31.2% for HA cases). This may be because LA infections are associated with higher viral loads; a threshold of 10^8 viral genomes per mL of blood has been related to cases with a fatal outcome [79,92,93].

Ribavirin has been shown to have in-vitro activity against CCHFV and to reduce the mean time-to-death rates in infected suckling mice [94,95]. Ribavirin was first used for CCHF treatment and prophylaxis during a nosocomial outbreak in 1985 in the Republic of South Africa [58]. Use of ribavirin in CCHFV infections remains controversial as there are no placebo-controlled trials evaluating oral or intravenous use; it would be ethically difficult to perform such trials. However, several case reports and retrospective studies suggest that ribavirin is effective for CCHFV infections if administered promptly after symptom onset [12,96—98].

In conclusion, this review is constrained by the fact that many nosocomial cases of CCHF are not published. Another limitation is that the mode of transmission was not clearly established in some published cases; publications also often lacked information on treatment and outcomes of cases. However, this study does highlight the risk of spread of CCHFV in the nosocomial setting, especially to HCWs, but also to other hospitalized patients and visitors. Barrier precautions and airborne preventive measures should be employed in addition to standard precautions, especially for patients with severe disease (who are likely to have higher viral loads). Guidelines for, and education of, HCWs are required to ensure inclusion of CCHF in differential diagnoses, so that rapid testing is implemented.

Conflict of interest statement
None declared.

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