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Crimean-Congo haemorrhagic fever in travellers: A systematic review

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Summary *Background:* The recent Ebola epidemic has increased public awareness of the risk of travel associated viral haemorrhagic fever (VHF). International preparedness to manage imported cases Ebola virus infection was inadequate, highlighted by cases of nosocomial transmission. Crimean-Congo haemorrhagic fever (CCHF) is a re-emerging tick-borne VHF centred in the Eurasian region, affecting a large geographical area and with human-to-human transmission reported, especially in the healthcare setting.
Objectives: To systematically review the characteristics of travel associated Crimean-Congo haemorrhagic fever.
Methods: A systematic review of travel-associated cases of CCHF was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement protocol. PubMed, SCOPUS, Science Citation Index (SCI) and ProMED databases were searched for reports published between January 1960 and January 2016. Three independent reviewers selected and reviewed studies and extracted data.
Results: 21 cases of travel associated CCHF were identified, of which 12 died (3 outcome unknown) and 4 secondary (nosocomial) infections were reported. Risk occupations or activities for CCHF infection were reported in 8/12 cases when data were available. Travel from Asia to Asia occurred in 9 cases, Africa to Africa occurred in 5 cases, Africa to Europe in 3 cases, Asia to Europe in 2 cases and Europe to Europe in 2 cases.
Conclusion: CCHF related to travel is rare, is generally associated with at risk activities/occupation and is frequently fatal. Key to early diagnosis and prevention of nosocomial transmission is an

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understanding of CCHF risk factors and the geographical distribution of CCHF. International travel to CCHF endemic areas is increasing and clinicians and laboratory personnel managing returning travellers should maintain a high index of suspicion.

1. Introduction

Increasing numbers of people travel each year and developing regions now represent half of all travel destinations. More than half of travellers to developing regions become ill during their journey and up to 8% attend medical facilities during or after their travel [1,2]. Gastrointestinal illness, fever, and skin disorders remain the most common reasons for travellers seeking medical care [3,4].

The causes of febrile illness imported by travellers vary with their travel destination and occupational and recreational exposures. Vector borne diseases are common, particularly malaria and tick typhus in travellers returning from Africa and dengue and chikungunya from South Asia [5]. Within this group of patients it is important to consider the rare possibility of a viral haemorrhagic fever (VHF) [6,7]. These include a diverse group of viruses causing diseases ranging from asymptomatic infection to fatal syndromes and imported cases have significant public health implications. VHFs can be transmitted to humans by vectors such as mosquitoes and ticks or by contact with blood or other animal secretions. The majority also have potential for transmission from human to human.

The recent epidemic of Ebola virus disease (EVD) in West Africa has increased healthcare worker and public awareness of the risk of travel associated VHF. International preparedness to manage imported cases was inadequate, highlighted by onward transmission of EVD to healthcare workers in Europe and the USA [8,9].

Crimean-Congo haemorrhagic fever (CCHF) is a re-emerging tick-borne VHF causing outbreaks in the Eurasian region, especially in Turkey, Russia, Iran, Pakistan, and Afghanistan in the last 15 years. It affects a large geographical area and human-to-human transmission is reported, especially in the healthcare setting [10]. It is a life threatening disease characterized by fever and haemorrhage, often with non-specific prodromal symptoms such as fatigue, myalgia and headache [11]. It has a case fatality rate of 5—80% [12] and as there is no FDA approved antiviral treatment [13], supportive treatment is essential [14].

Despite regular seasonal CCHF outbreaks [15], travel associated CCHF is rarely reported including in large surveillance studies of ill returning travellers [3]. In this study, we aimed to systematically review the characteristics of travel associated Crimean-Congo haemorrhagic fever and to provide practical advice for healthcare professionals.

2. Materials and methods

2.1. Search strategy

We planned and reported this systematic review in accordance with guidelines for performing and reporting systematic reviews and meta-analyses (PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

2.1.1. Data sources and searches

We searched for English and foreign language studies published between January 1960 and January 2016 in the following databases: PubMed (including MEDLINE), Science Citation Index (SCI) and Scopus. Broad search terms of "Crimean-Congo hemorrhagic fever" or "Crimean-Congo haemorrhagic fever" were utilised. The same search terms were also used to search the ProMED Mail database (http://www.promedmail.org/). We also searched for additional relevant studies by reviewing references from the included publications.

2.1.2. Study selection and data extraction

Three reviewers (HL, RO & TF) independently screened the titles and abstracts of all studies identified by the search strategy for their eligibility. For inclusion, each study had to meet the following criteria [1]: report a laboratory confirmed case of Crimean-Congo haemorrhagic fever and [2]; be associated with international travel. Foreign nationals residing in CCHF endemic countries, who were diagnosed and treated there were excluded. When the title and abstract did not clearly indicate whether the inclusion criteria were met, a full-text copy was retained and reviewed. Full-text copies of the potentially relevant studies were retrieved and evaluated for inclusion as described previously by two reviewers (HL & TF), who then independently extracted data from each study meeting the inclusion criteria. A standard table was utilised to ensure consistency of data extracted from each article. For cases, data were extracted on date, country of origin and final destination, age and gender, reported risk factors, secondary transmission and clinical outcome.

3. Results

Our initial search identified 3950 records. After exclusion of duplicates, 2151 records were screened by title and abstract. Two hundred and sixty-five full-text articles/reports were retrieved and reviewed and cross-references yielded an additional 2 cases. The total number of travel-associated CCHF cases identified was 21 (Fig. 1).

We found two types of travel-related CCHF case: i) Those acquiring the disease during travel to CCHF endemic countries; ii) Residents in endemic countries acquiring the disease and then travelling and crossing borders to seek healthcare. The data on cases identified in these groups are summarized in Table 1 [16—28]. (Data on cases travelling from Afghanistan to Pakistan are reported separately in Table 2 due to limited detail reported on risk factors, outcome and method of laboratory confirmation) [29—36].