



Review

Rickettsiae and rickettsial diseases in Croatia: Implications for travel medicine



Boris Dzelalija^{a,b}, Volga Punda-Polic^b, Alan Medic^c,
Marinko Dobec^{d,*}

^a Department of Infectious Diseases, Zadar General Hospital, Zadar, Croatia

^b School of Medicine, University of Split, Split, Croatia

^c Institute of Public Health, Zadar, Croatia

^d Medica, Medizinische Laboratorien Dr. F. Kaeppli, Wolfbachstrasse 17, CH-8024 Zurich, Switzerland

Received 28 March 2016; received in revised form 30 June 2016; accepted 30 June 2016

Available online 9 July 2016

KEYWORDS

Rickettsia;
Rickettsiosis;
Travellers;
Croatia

Summary *Aim:* To review the current state of knowledge concerning rickettsiae and rickettsioses in Croatia and to discuss their implications for travellers.

Methods: The PubMed database was searched from 1991 to 2015 by combining the words “rickettsia,” “rickettsiosis”, “travellers” and “Croatia”.

Results: Since 1969, Croatia appears to be free of epidemic typhus (ET) caused by *Rickettsia prowazekii* and the last case of Brill-Zinsser disease was recorded in 2008.

Mediterranean spotted fever (MSF) caused by *Rickettsia conorii* is the most frequent human rickettsial infection in Croatia, followed by murine typhus caused by *Rickettsia typhi*. Human cases of MSF and murine typhus have been predominantly observed along the eastern Adriatic coast from Zadar to Dubrovnik and between Zadar and Split, respectively.

Rickettsia akari, etiologic agent of rickettsialpox, was isolated from blood of a patient diagnosed with MSF in Zadar, but no cases of rickettsialpox were reported.

Several species of pathogenic (*Rickettsia slovaca*, *Rickettsia aeschlimannii*, *Rickettsia helvetica*, and *Rickettsia raoultii*) and species of undetermined pathogenicity (*Rickettsia hoogstraalii* sp. nov.) rickettsiae were identified in ticks collected in different ecological regions of Croatia.

A search of the literature revealed no evidence of rickettsial infection in travellers visiting Croatia. Three imported cases of *Rickettsia africae* were observed in travellers returning from South Africa.

Conclusion: Rickettsiae and rickettsial diseases continue to be present in Croatia. As they can be acquired while travelling, physicians should consider rickettsial infection in the differential diagnosis of patients returning from Croatia and presenting with febrile illness.

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* Corresponding author. Fax: +41 44 269 99 09.

E-mail address: dobec@medica.ch (M. Dobec).

1. Introduction

Rickettsiae are gram-negative, obligate intracellular bacteria belonging to the family *Rickettsiaceae*, order *Rickettsiales*. Members of the genus *Rickettsia* may be classified into spotted fever group (SFG) rickettsiae, typhus group (TG) rickettsiae, the *Rickettsia bellii* group, and the *Rickettsia canadensis* group [1,2]. The largest group comprises the spotted fever group rickettsiae (SFG) and consists of a multitude of pathogenic and non-pathogenic species, transmitted mainly by ticks [1,3–6]. Rickettsial infections are prevalent throughout the world and may cause serious diseases in humans [1–6]. Rickettsioses are increasingly being recognized among international travellers [7,8]. Besides that, rickettsiae are also recognized as potential threat for humans during the current refugee crisis in Europe [9].

Since 1988, more than 450 cases of travel-associated rickettsioses have been reported in the literature [10,11].

The diseases known as rickettsioses have been recorded throughout the littoral of Croatia, including Istria and Hrvatsko Primorje [12]. The Croatian coastal area between Zadar and Dubrovnik is an endemic area for *Rickettsia conorii* and *Rickettsia typhi* [13]; Fig. 1].

As shown in Table 1, over 13 million travellers visited Croatia in 2014. Out of them, more than 11 million people visited Adriatic Croatia and over 5 million spent vacation in Dalmatia, which is known to be endemic for rickettsiae [13,14]. The surface of this area is 12,951 km² and it is populated with 856,758 inhabitants [15,16].

The purpose of this article is to review the current state of knowledge on rickettsiae and rickettsioses and the frequency of rickettsial diseases among travellers to/from Croatia.

2. Methods

The sources of data used for this review were the PubMed database, published abstracts and articles reporting original data on rickettsiae and rickettsioses in Croatia, as well as data from the National Institute of Public Health mandatory infectious disease reports [17]. We searched the PubMed database from 1991 to 2015 by combining the words “rickettsia,” “rickettsiosis”, “travellers” and “Croatia”. Other data were obtained from the National and University Library in Zagreb, Croatia. The articles reporting original data on rickettsia and rickettsioses in Croatia were selected for further evaluation.

3. Results

A total of 36 references were revealed in the PubMed database. Of those, 18 publications, concerning infections of human and reservoirs, were selected for the current review.

In Croatia, rickettsioses are notifiable diseases, and the diagnosis of rickettsioses usually depends on clinical–epidemiological evidence supported by serologic confirmation. For diagnostic purposes, prior to 1988, complement fixation test was used. After 1988, the indirect immunofluorescence antibody assay (IFA) has been performed to determine the titres of IgM and IgG antibodies in

patients’ sera. In the 1990s, a few seroepidemiological studies were conducted with the aim to collect data related to the presence of rickettsiae as well as to determine their importance for public health in Croatia. As ticks are the most important vectors and reservoirs of SFGR, including human rickettsial pathogens, molecular methods were used to investigate, identify and characterize SFG rickettsiae in ticks collected in ecologically different areas of Croatia.

4. Typhus group (TG) rickettsiae

4.1. Epidemic typhus and Brill-Zinsser disease

During World War II (WW II), outbreaks of louse-borne epidemic typhus (ET) due to *Rickettsia prowazekii* transmitted by body louse (*Pediculus humanus corporis*) were common on the territory of former Yugoslavia, especially in mountainous areas of Bosnia and Herzegovina [18]. Epidemic typhus had great impact on the public health in the region. Between 1945 and 1969, a total of 2794 human cases of ET were officially reported in Croatia [17]. Improvement of socioeconomic conditions after WW II influenced a marked decrease of ET. In the decade after WWII, from 1945 to 1954, 2750 cases were recorded with an annual incidence between 7 and 2169. Most of the cases occurred sporadically. According to official notifications, the last case of ET was reported in 1969 [12,17,19].

According to data from the Croatian Institute of Public Health a total of 174 cases of Brill-Zinsser disease, recrudescence form of louse-borne epidemic typhus, were recorded in Croatia from 1957 to 2013. In the period from 1995 to 2013, only 3 cases were reported and the last case was recorded in 2008. Most of the patients gave a history of epidemic typhus during the period from 1941 to 1953, and more than half of them originated from Bosnia and Herzegovina. The mean age of these patients was 55.4 years (range 37–81) [12,19].

4.2. Murine or endemic typhus

Murine or endemic typhus is an infectious disease caused by *R. typhi*. In Croatia the disease was recognized on the island of Solta in 1942, where nine proven cases of murine typhus were recorded [12,13]. Since then, sporadic cases have been observed nearly every year. Between 1992 and 2003, 12 cases of murine typhus were reported [12]. These cases originated and occurred on the Croatian littoral and islands between Zadar and Split. Rats (which are the main host of *R. typhi*) are abundant in these littoral areas. Climatic and ecological conditions are also favourable for maintaining rat fleas (*Xenopsylla cheopis*) which may act both as reservoirs and as vectors of *R. typhi*. In the Zadar- and Split-Dalmatia County, murine typhus cases were distributed in practically all age groups, and cases occurred during the entire year [12,13,20]. The signs and symptoms of patients included fever (100%), headache (75.0%), rash (70.8%), malaise (53.2%), and arthralgia/myalgia (43.6%). Rash was distributed over the trunk and limbs, sparing the face, palms and soles [13]. Asymptomatic infections with *R. typhi* are more common than clinical disease [3,4]. Seroepidemiologic studies have shown the Zadar area to be highly endemic for *R. typhi* [20]. Antibody prevalence in

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