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HFRS and hantaviruses in the Balkans/South-East Europe

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ABSTRACT

Hemorrhagic fever with renal syndrome is endemic in the Balkans with epidemic outbreaks and sporadic cases that have been recorded yearly since the disease was first recognized. The incidence of Balkan HFRS is modest, with approximately one hundred cases reported in most years. Seroepidemiological investigations conducted in several Balkan countries revealed an overall seroprevalence of 6% in Bosnia and Herzegovina, 1.6% in Croatia, 4% in Greece and 1.7% in Slovenia, respectively. The complex ecology of the Balkan Peninsula supports the existence of diverse rodent and insectivore species which harbor several pathogenic and non-pathogenic hantaviruses. Among them only Dobrava (DOBV) and Puumala (PUUV) viruses are associated with disease in humans. Comprehensive clinical studies compared clinical signs and symptoms between patients infected with either virus. A spectrum of clinical picture of the disease ranges from mild illness typical of PUUV infections to a severe form with fulminant hemorrhagic fever and an overall mortality rate of 9.8% among DOBV infected patients. While severe DOBV cases are recognized from Slovenia in the North to Greece in the South, PUUV infections are more frequent in northern part of the area. Balkans represent an area with a potential need for hantavirus vaccines, but due to co-existence of DOBV and PUUV causing HFRS in the same region, a universal vaccine is required.

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1. Historical perspectives

Hemorrhagic fever with renal syndrome is endemic in the Balkan Peninsula, and may have existed there for decades. The first probable case of HFRS was reported in the former Yugoslavia in 1952 as a case of acute renal failure successfully treated by peritoneal dialysis (Simic, 1952). The patient was a soldier who was infected in the forest surrounding Fojnica in Bosnia and Herzegovina (B&H), where, in the later outbreaks, hundreds of HFRS cases have occurred. Then, in 1954, Radošević and Mohaček described four sporadic cases of HFRS in Croatia where one of the cases was infected during the season timberwork in the forest of Pohorje in Slovenia. At the time, the authors were already aware of the clinical resemblance of the disease to that occurring in Scandinavia; therefore they named it Nephropathia Epidemica (Radosevic and Mohacek, 1954). Afterwards, clinical cases of HFRS were also reported from Albania (Eltari et al., 1987), Bulgaria (Verbe and Gabev, 1963), Greece (Antoniadis et al., 1984) and Romania (Manasia et al., 1977).

Epidemic outbreaks as well as sporadic cases have been recorded yearly, since the disease was first recognized in South-East Europe. The first documented epidemic of HFRS occurred

in a military camp in the forest of Fruška Gora in Serbia in 1961 (Heneberg et al., 1964). A second epidemic in 1967, affecting more than 200 individuals with 5 fatalities, was centered in Bosnia and Herzegovina (Fojnica and Foča) and in Croatia (Plitvice Lakes) (Vesnjak-Hirjan et al., 1971). In summer of 1983 an outbreak of HFRS occurred in the state of Epirus, north-western Greece. A total of 8 patients were hospitalized during the outbreak; 3 were severely ill and 1 died (Siamopoulos et al., 1985). A total of 276 persons with symptoms clinically compatible with a diagnosis of HFRS were officially reported in 1986 from all republics and provinces of the former Yugoslavia with the highest incidence in Montenegro (Avšič-Županc et al., 1989; Gligic et al., 1989). A nation-wide epidemic of HFRS occurred in all six republics and two provinces of former Yugoslavia in 1989 when 226 HFRS cases were serologically confirmed. The severity of disease differed from region to region, with an overall fatality of 6.6% (Gligic et al., 1992). One of the largest outbreaks of HFRS took place in the Balkan region during the war in 1995 when clinical diagnosis was serologically confirmed in 128 patients, mainly soldiers, from the Tuzla region in B&H (Hukic et al., 1996) and in 85 patients, mostly soldiers (3 fatal), from several localities in Croatia (Kuzman et al., 1997; Markotić et al., 1996, 2002b). The next epidemic year that have affected Balkan countries was in 2002 with >500 clinically diagnosed patients mainly registered in Croatia, Slovenia and B&H (Heyman et al., 2009; Hukic et al., 2010; Koren et al., 2008; Kuzman et al., 2003). The same year an unusual outbreak of 11

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HFRS cases appeared among former injecting drug users in the drug-treatable community Susret, Ivanovac, northeast of Croatia (Medved et al., 2002). In the following years of 2005 and 2008 an increased hantavirus activity was noticed again in Slovenia, Croatia and B&H (Heyman et al., 2011; Kraigher et al., 2012). The largest epidemic of HFRS so far occurred in 2012 in Slovenia and Croatia, with 188 and 184 laboratory confirmed cases, respectively.

2. Ecology

The ecology of hantaviruses in the Balkan Peninsula is complex, given the existence of diverse rodent species, which reflects the geographic location of the Balkan States at the meeting points of Europe, Asia, and North Africa. By the detection of viral antigen, antibody, RNA amplification or virus isolation the presence of several pathogenic and non-pathogenic hantaviruses has been demonstrated in the region. They are associated with four rodent genera: *Apodemus*, *Myodes*, *Microtus*, and *Rattus*; and also with insectivore carriers. The most prominent hantavirus carrier in the Balkans is the yellow necked mouse, *A. flavicollis*, host of Dobrava virus (DOBV), which is generally widespread throughout the region. These rodents prefer mature deciduous forests with areas where sufficient plant diversity ensures an adequate food supply each year (Kryštufek, 1991; Vukičević-Radić et al., 2006). Following a number of severe HFRS cases in the south-eastern part of Slovenia, DOBV was isolated in 1988, from the lungs of the yellow necked mouse captured in Dobrava village. In 1992, it was fully characterized and recognized as a unique hantavirus species (Avšič-Županc et al., 1992). Subsequently, the presence of DOBV in hosts and humans was reported from several countries in South-East Europe: Albania, B&H, Bulgaria, Croatia, Greece, Romania, Serbia and Montenegro (reviewed in Heyman et al., 2009). Another *Apodemus* host, *A. agrarius* or striped field mouse, is commonly found in grassy fields, cultivated areas and woodlands of the Balkans (Kryštufek, 1991; Vukičević-Radić et al., 2006) and it is a reservoir host for Saaremaa virus (SAAV) (Plyusnin et al., 1997, 1999). Recently it was suggested to classify SAAV from outside Saaremaa island as Kurkino genetic lineage of DOBV. DOBV-Kurkino is responsible for a milder form of HFRS in Central Europe (Klempa et al., 2013), but in the Balkan region the virus was demonstrated only in rodents from Slovenia and Croatia (Avšič-Županc et al., 2000; Plyusnina et al., 2011). In south Balkan countries, like Greece, Romania, Albania, Macedonia, Serbia and Montenegro, almost all HFRS cases are caused by DOBV, but to the north, more Puumala virus (PUUV) infections are observed. For example in Slovenia and Croatia approximately 70% of HFRS cases are caused by PUUV. The major carrier of PUUV is *Myodes glareolus* or bank vole, which inhabits mostly wet coniferous and mixed forests to leafed forests, river banks and marshy areas in the Balkans (Kryštufek, 1991). In concordance with numerous HFRS cases caused by PUUV in Slovenia, Croatia and B&H high antibody prevalence in bank voles was reported (Avšič-Županc et al., 2007; Hukic et al., 2003; Tadin et al., 2012). The prevalence of hantavirus antibodies and antigens was detected on average in 16% of *A. flavicollis*, 8.1% *A. agrarius* and 16% of *M. glareolus*, but a significant difference was observed between epidemic and non-epidemic years. While during the non-epidemic years the prevalence of hantaviruses in hosts in endemic areas of HFRS in the former Yugoslavia was on average 9.2%, the prevalence of infection was on average 19.7% and 23% for the epidemic years 1986 and 1989, respectively (Avšič-Županc et al., 1990, 1993; Avšič-Županc and Poljak, 1994; Gligic et al., 1992; Lukač et al., 1990). Despite some evidence of possible human infection with TULV in Central Europe (Vapalahti et al., 1996), currently no clinical case due to TULV infection has been reported in the

Balkan Peninsula. However, TULV RNA was amplified from tissue samples of *M. arvalis*, *M. agrestis* and *M. subterraneus* (re-classified from *Pitymys subterraneus*) in Slovenia, Croatia and Serbia (Korva et al., 2009; Scharninghausen et al., 2002; Song et al., 2002). Moreover, as early as in 1989 there were reports of hantaviral antigens discovered in tissues of Eurasian common shrews (*Sorex araneus*), alpine shrews (*Sorex alpinus*), Eurasian water shrews (*Neomys fodiens*) and common moles (*Talpa europea*) in areas of the former Yugoslavia (Gligic et al., 1992). Later, in 2013 Seewis virus RNA was amplified from tissues of *S. araneus* captured in Slovenia (Resman et al., 2013).

3. Epidemiology

HFRS cases in the Balkan Peninsula are reported yearly, either as sporadic cases or major outbreaks influenced by the abundance of reservoir rodent populations (Table 1). The incidence of the disease is modest, with approximately 100 cases per year (Heyman et al., 2009), but, due to DOBV infection, the mortality can be high (on average 12%) (Avšič-Županc et al., 1999). Also, apparent seasonal distribution, with most cases occurring in the summer months is observed. Occupation is a dominant risk factor, with animal trappers, forestry workers, farmers and military personnel at highest risk (Heyman et al., 2009).

3.1. Albania and Macedonia

In Albania, the first serologically confirmed HFRS case dates to 1987, when a 27-year old man presented with acute renal failure and shock (Eltari et al., 1987). Also, in a HFRS epidemic, which occurred in Yugoslavia in 1986, 4 out of 6 Albanian patients had antibodies against hantaviruses (Gligic et al., 1989). In a study performed between 2003 and 2006, 11.7% of the patients with clinical suspicion of CCHF were actually confirmed as HFRS cases, which suggest that there are more unrecognized, severe HFRS cases in Albania (Papa et al., 2008).

The first report of a HFRS case in the Republic of Macedonia dates to 1987. In a 3-year period, from 1987 to 1990, at least 10 DOBV cases were diagnosed, with a 10% mortality rate (Polenakovic et al., 1995).

3.2. Bosnia and Herzegovina

B&H has been recognized as a highly endemic region in the Balkans for over 50 years. In addition to PUUV and DOBV, also a Seoul virus was also identified as a potential cause of HFRS in B&H (Clement et al., 1994; Lundkvist et al., 1997; Markotić et al., 1995). Infections caused by PUUV are more frequent (49.6%) than infections caused by DOBV (26.1%) during both epidemic and non-epidemic periods (Hukic et al., 2011). Since the first documented HFRS outbreak in 1967 more than 732 cases have been reported (Heyman et al., 2011). Most HFRS cases have been observed as large outbreaks, with significant number of patients and mortality varying from 4.86% in 1989 up to 7.3% in 1995 (Gligic et al., 1992; Markotić et al., 1996). The seroprevalence in the general population in B&H is 7.4% in the endemic region and 2.4% in the non-endemic region (Hukic et al., 2010). Former soldiers, as an occupational risk group, have significantly higher seroprevalence (16.1%) compared to the general population (6.2%) in the same area. In a comparison of the seroprevalence of PUUV and DOBV among healthy individual in endemic regions it was noted that antibodies against PUUV are present in almost 6% of population, while DOBV seroprevalence is only 1.5%. The difference is probably due to the fact that DOBV causes a more severe form of HFRS and consequently less cases remains undetected (Hukic et al., 2010).

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