Virus Research xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Virus Research

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

Hantaviruses and cardiopulmonary syndrome in South America

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Hantavirus disease
Cardiopumonary syndrome
Emerging disease
South-American disease

ABSTRACT

Hantavirus (*Bunyaviridae*) cardiopulmonary syndrome (HCPS) is an emerging health problem in South America due to urban growth and to the expansion of agriculture and cattle-raising areas into ecosystems containing most of the species of *Sigmodontinae* rodents that act as hantavirus reservoirs. About 4000 HCPS cases have been reported in South America up to 2013, associated with the following hantaviruses: Andes, Anajatuba, Araraquara (ARQV), Paranoá, Bermejo, Castelo dos Sonhos, Juquitiba, Araucária, Laguna Negra, Lechiguanas, Maripa, Oran, Rio Mamore and Tunari. The transmission of hantavirus to man occurs by contact with or through aerosols of excreta and secretions of infected rodents. Person-to-person transmission of hantavirus has also been reported in Argentina and Chile. HCPS courses with a capillary leaking syndrome produced by the hantavirus infecting lung endothelial cells and mostly with a severe inflammatory process associated with a cytokine storm. HCPS starts as a dengue-like acute febrile illness but after about 3 days progresses to respiratory failure and cardiogenic shock, leading to a high fatality rate that reaches 50% for patients infected with ARQV.

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1. Introduction

Hantaviruses are important zoonotic pathogens related to rodents and other small mammals (shrews, moles and bats). When infecting man, hantaviruses can cause severe diseases with high case-fatality rates such as hemorrhagic fever with renal syndrome (HFRS) in Asia and Europe and hantavirus cardiopulmonary syndrome (HCPS) in the Americas. In both syndromes, capillary leakage of intravascular fluid into interstitial tissue leads to respiratory and renal failure and shock (Jonsson et al., 2010). However, a recent comparative analysis of HFRS and HCPS cases has revealed that syndromic names are mostly didactic and, in fact, patients from the Americas also have renal failure and patients from Europe and Asia have respiratory failure. Thus, the worldwide use of the term *Hantavirus disease* has been recently proposed (Clement et al., 2012; see also chapter X of this Special Issue).

The first case of an American hantavirus producing human disease, a cardiopulmonary syndrome caused by Sin Nombre virus (SNV), was reported in the United States Hughes et al. (1993). Dozens of hantavirus genotypes have been reported since then in the Americas associated with autochthonous rodent species of the subfamily *Neotominae*, *Sigmodontinae* and *Arvicolinae* (Jonsson et al., 2010). In South America, hantavirus reservoirs are *Sigmodontinae* American rodents that harbor the following viruses associated with human disease: Andes, Maciel, Oran, Lechiguanas, Laguna Negra and Bermejo in Argentina, Andes in Chile, Laguna Negra and Bermejo in Paraguay, Laguna Negra, Tunari and Bermejo in Bolivia, Maripa in French Guyana, Juquitiba, Andes and Lechiguanas in Uruguay, and Araraquara, Juquitiba/Araucária, Castelo dos Sonhos, Laguna Negra and Anajatuba in Brazil (Firth et al., 2012). A map of South America showing hantaviruses associated with disease and their rodent reservoirs is shown in Fig. 1.

Hantavirus disease is an emerging health problem in South America due to urban growth and the expansion of agriculture and cattle-raising areas into ecosystems containing most of the species of *Sigmodontinae* rodents that act as hantavirus reservoirs (Figueiredo et al., 2009b). The biodiversity of natural ecosystems of South America supports about 500 known species of *Sigmodontinae* (Mills, 2006; Mills et al., 2007; Fig. 2).

The transmission of hantavirus to man occurs mostly by contact with or through aerosols of excreta and secretions of infected rodents (Butler and Peters, 1994), although human-to-human transmission of hantavirus has been reported in Argentina and Chile (Martinez et al., 2005; Padula et al., 1998; Wells et al., 1997).

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http://dx.doi.org/10.1016/j.virusres.2014.01.015
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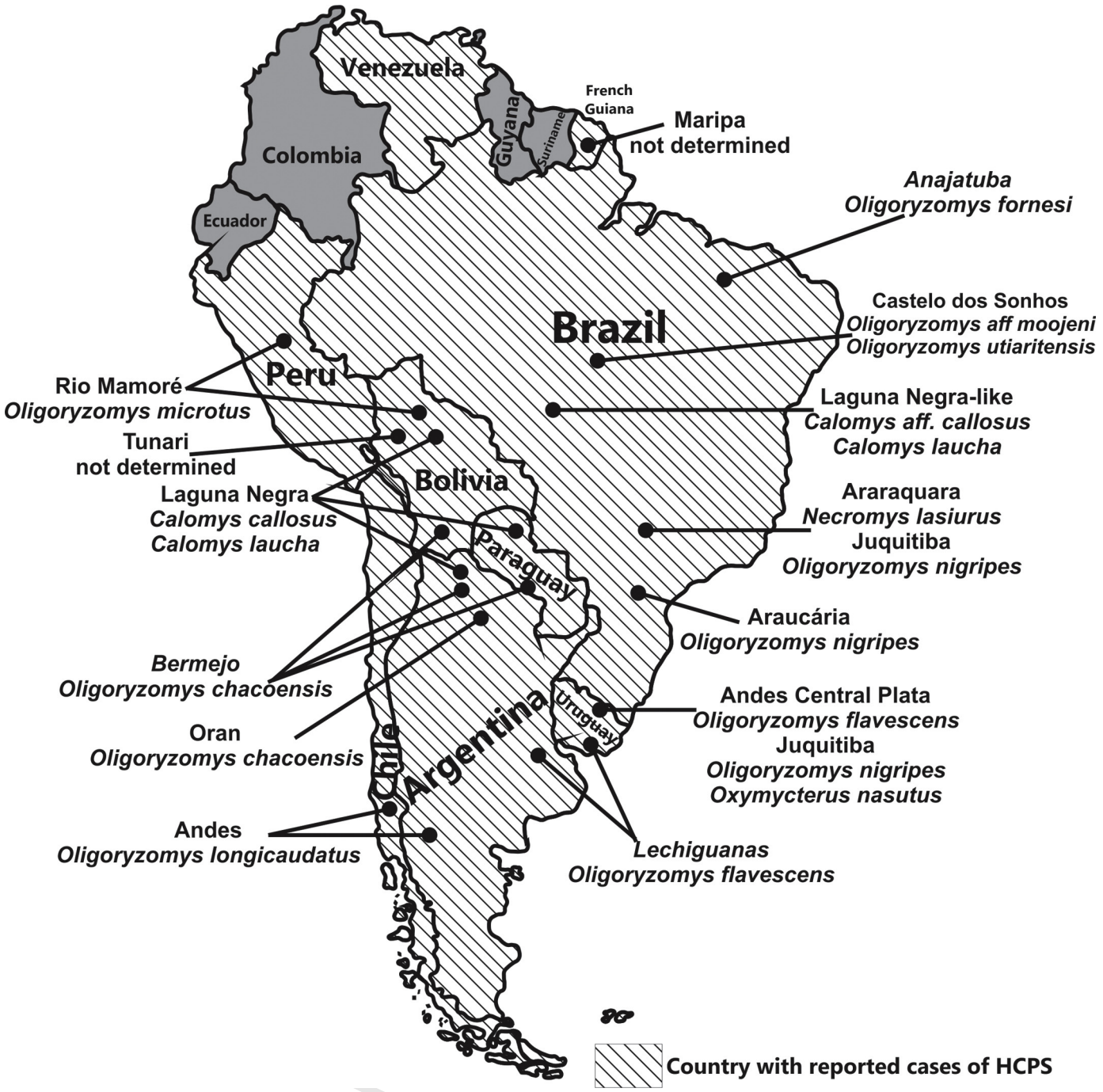

Fig. 1. Map of South America showing the distribution of Hantavirus that cause Cardiopulmonary Syndrome and their respected rodent-reservoirs. The viruses found are Andes virus (variant Bermejo, Oran, Lechiguanas, Andes Central Plata, Araucária, Araraquara, Juquitiba, Castelo dos Sonhos and Tunari), Rio Mamoré virus (variant Maripa and Anajatuba) and Laguna Negra virus (variant Laguna Negra-like).

2. The virus

Hantaviruses constitute a genus of the family *Bunyaviridae* that includes a large number of small mammal-borne viruses distributed worldwide. The hantavirus RNA genome, packed in particles 80 to 120 nm in size, comprises RNA of approximately 12,000 nucleotides divided into three negative-sense and single-stranded fragments (Schmaljohn and Dalrymple, 1983). These are named S (small), M (medium), and L (large) and encode the nucleoprotein (N), envelope glycoproteins (Gn and Gc), and the L protein or viral RNA (vRNA)-dependent RNA polymerase (RdRp, the largest viral protein, 250 to 280 kDa), respectively. The viral RNA segments are complexed with the N protein forming a circular molecule by base-paired inverted complementary sequences at the 3′ and 5 ‘ends of linear viral RNA (Schmaljohn and Nichol, 2007). The American hantavirus and the vole-borne Puumala and Tula virus branch of hantavirus, both contain an evolutionarily conserved NSs open reading frame (ORF) in an overlapping ORF in the S RNA segment (Jaaskelainen et al., 2007; Vera-Otarola et al., 2012; Virtanen et al., 2010).

The 3 RNA segments can reassort in case of double infection with hantavirus, resulting in virus mutants. Therefore, the viral RdRp can produce punctual nucleotide changes during RNA, translation also producing mutant hantaviruses (Razzauti et al.,

Please cite this article in press as: Figueiredo, L.T.M., et al., Hantaviruses and cardiopulmonary syndrome in South America. Virus Res. (2014), http://dx.doi.org/10.1016/j.virusres.2014.01.015

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