


CASE REPORT

First report of an imported case of haemorrhagic fever with renal syndrome in South Africa

N Moolla,^{1,2} PhD ; D Adler,³ MB BCh, FC Path (SA); L Blumberg,¹ MB BCh, MMed (Clin Micro); A Glass,^{3,4} MB BCh, FC Path (SA); A Grobbelaar,¹ MSc; C le Roux,¹ MSc; J Paweska,^{1,2,5} DVSc; J Weyer,^{1,2,6} PhD, MPH

¹ Centre for Emerging Zoonotic and Parasitic Diseases, National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg, South Africa

² Department of Medical Virology, Faculty of Health Sciences, University of Pretoria, Tshwane, South Africa

³ Department of Medicine, Sandton MediClinic, Johannesburg, South Africa

⁴ Lancet Laboratories, Johannesburg, South Africa

⁵ Department of Molecular Pathology, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

⁶ Department of Microbiology and Infectious Diseases, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Corresponding author: N Moolla (naazneem@nicd.ac.za)

Haemorrhagic fever with renal syndrome (HFRS) is caused by hantavirus infection. Hantaviruses are not endemic to South Africa, and we report the first detection of an imported case of HFRS in the country. The case involved a traveller from Croatia who presented to a Johannesburg hospital with an acute febrile illness with renal dysfunction. The patient reported visiting rurally located horse stables in Croatia before falling ill, and that a worker in the stables with similar illness was diagnosed with HFRS. Given the exposure history and clinical findings of the case, a clinical diagnosis of HFRS was made and confirmed by laboratory testing.

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Hantaviruses are negative, single-stranded RNA viruses harboured by small mammals (including bats, rodents, moles and shrews) and have wide geographical distribution across the Americas, Europe and Asia.^[1,2] In humans, hantavirus infection may cause two distinct forms of disease, known as haemorrhagic fever with renal syndrome (HFRS) or hantavirus cardiopulmonary syndrome (HPS).^[1] The latter is endemic to the Americas and is more severe than HFRS, with reported case fatality rates (CFRs) of 35 - 50%.^[2] Predominantly, Sin Nombre virus (SNV) is associated with a severe form of HPS, but it can be caused by infection with one of 25 currently identified hantaviral species.^[3] HFRS is endemic to several Asian and European countries, and is associated with CFRs of 1 - 15%.^[4] Dobrava virus (DOBV), Hantaan virus (HTNV), Seoul virus (SEOV) and Puumala virus (PUUV) are primarily associated with HFRS.^[4,5] Hantaviruses are transmitted from host rodent species to humans through aerosolised excreta.^[1] In the case of HFRS, clinical case presentation is characterised by the triad of fever, haemorrhage and acute kidney dysfunction.^[6] Infection presents in phases with distinctive indicators such as fever, hypotension, oliguria and diuresis.^[4] Prodromal HPS symptoms are typically those of a nonspecific febrile illness (fever, myalgia, dizziness, headaches and gastrointestinal symptoms) progressing to hypotension, shock and pulmonary oedema, signalling the onset of the cardiopulmonary phase of the disease, often requiring hospitalisation.^[7]

Although hantaviruses have a wide geographical distribution, local circulation of hantaviruses in reservoir animals has not yet been reported from South Africa (SA).^[8] We report the first laboratory-confirmed imported case of a hantavirus infection in this country.

Case presentation and management

In May 2021, a 37-year-old SA businessperson, living and working in Crikvenica, Primorje-Gorski Kotar County, Croatia, presented

with a 1-week history of an acute febrile illness and blurred vision. The patient had symptoms before travelling from Croatia to Johannesburg. When he was hospitalised in Johannesburg, pulmonary oedema, cardiomegaly and renal dysfunction were noted. In exploring possible exposures, the patient reported visiting horse stables located in a rural part of Crikvenica and that he enjoyed cycling in the countryside. He also reported that a worker at the stables in question was diagnosed with HFRS at the time of his visits to the facility.

At hospitalisation (approximately 5 - 7 days after onset of the illness), the patient's full blood count indicated a haemoglobin concentration below normal, starting at 13.3 g/dL on admission and dropping to 11.1 g/dL 2 days later. During the course of hospitalisation, blood results indicated a moderate thrombocytopenia (lowest at $64\,000 \times 10^9/L$), returning to normal 4 days later, a normal white cell count (with mild neutrophilia), and marginally raised liver enzyme levels (serum alanine transaminase reached a maximum of 124 IU/L and gamma-glutamyl transferase a maximum of 105 IU/L). Renal function tests included the following results: mildly lowered serum sodium (dropping from 137 mmol/L at admission to a low point of 127 mmol/L), low bicarbonate levels (18 - 20 mmol/L), raised serum urea levels (up to 15.9 mmol/L), and raised serum creatinine levels (up to 346 $\mu\text{mol/L}$). Other findings included raised C-reactive protein levels during the course of hospitalisation, in the range of 27.5 - 65.6 mg/L. The patient was hospitalised for a total of 10 days. Blood cultures and COVID-19 testing were repeatedly negative. Polymerase chain reaction (PCR) investigations for herpes simplex 1 and 2, human herpesvirus type 6 and varicella zoster, enterovirus, mumps, parechovirus, Epstein-Barr virus and cytomegaloviruses were negative.

Given the history of possible exposure in a rural area of Croatia, Crimean-Congo haemorrhagic fever, Mediterranean spotted fever

and HFRS were considered in the differential diagnosis, with the latter considered most likely given the clinical presentation and possible exposure history. Blood samples were referred to the Centre for Emerging Zoonotic and Parasitic Diseases at the National Institute for Communicable Diseases (NICD) in Johannesburg for hantavirus investigation. The sample collected at roughly day 10 of illness tested positive for hantavirus IgG (1:100) and IgM (1:100) antibodies using a multiparametric indirect immunofluorescence assay that can detect HTNV, PUUV, SEOV, SNV, DOBV and Saaremaa virus (SAAV), in accordance with the manufacturer's instructions (Euroimmun AG, Germany). Cross-reactivity for DOBV and SEOV serotypes was noted, which is expected between the subtypes and does not allow for identification of the exact aetiological agent.^[9]

No detectable hantavirus RNA was found in this sample. In order to confirm the diagnosis of HFRS, a sample collected earlier during the course of illness (~4 days after disease onset) was sourced from a private pathology laboratory in SA and sent to the NICD for investigation. This sample tested positive by reverse transcription PCR (RT-PCR) for hantavirus RNA, using previously published protocols.^[10] A third blood sample collected during convalescence (~21 days after disease onset) also tested positive for hantavirus IgG (1:10 000) and IgM (1:100) using the same assay as before, and indicated increasing IgG titres (results not shown). This was in keeping with the expected humoral response for HFRS patients with IgM class antibodies detected simultaneously with the onset of clinical symptoms, peaking at days 7 - 11 after symptom onset and declining in the convalescent phase of the illness, while the levels of IgG antibodies may continue to rise.^[6] In order to confirm the aetiological agent of HFRS in this case, Sanger sequencing and sequencing analysis (results not shown) were conducted using the positive RT-PCR product obtained from the earliest blood sample. The results confirmed that PUUV was the causative agent of the illness.

The renal dysfunction and pulmonary oedema were managed conservatively, and the patient made a full recovery.

Patient consent

The reporting of this case study is provided for in the Human Research Ethics Committee of the University of the Witwatersrand (ref. no. M210752 and protocol title: Essential communicable disease surveillance and outbreak investigation activities of the National Institute for Communicable Diseases). This protocol allows for the waiving of patient consent in the reporting of infectious diseases of public health importance in SA.

Discussion

Globally the number of hantavirus infections is increasing in endemic regions, with significant escalations in case numbers in parts of Europe.^[11-16] The number of reports of cases imported to non-endemic areas and involving travellers is also increasing.^[11-13] Changes in rodent population density in endemic regions, together with climatological and ecological changes and human-driven alterations in landscape that favour interaction with rodents (such as changes in agricultural activities), are purportedly driving the emergence of hantaviruses.^[11]

Given the increasing risk of hantavirus infection, it is pertinent to consider it in the differential diagnosis of patients presenting with clinical disease that fits with symptoms of hantavirus infection and exposure histories that may indicate a risk of hantavirus exposure. In non-endemic areas, the latter include travel history to an endemic area, and also the activities that the patient may have engaged in, for example, the occupation, hobbies and travel-related activities. The typical incubation period for HFRS is 1 - 2 weeks following

exposure.^[1] Timely diagnosis of cases contributes to improved clinical outcomes and reduction of unnecessary investigations and treatment.^[14] There is currently no specific antiviral treatment for hantavirus infection, and management is empirical and supportive. Results of some studies show that ribavirin administration may be a beneficial treatment option for HFRS.^[2,4] In rare cases, sequelae involving the kidneys may be noted.^[6] The severity of the disease partly depends on the viral species involved in the infection.^[1] With HFRS, PUUV and SEOV infections tend to be milder (CFR <1%), while DOBV and HTNV are considered more severe (CFR 5 - 15%).^[4,6] Nosocomial transmission of hantaviruses is rare and has only been reported for Andes virus (a hantavirus associated with HPS), so healthcare providers are generally not at increased risk and standard precautions are advised.^[17]

Conclusion

This report presents the first case of HFRS detected in SA. To date, no cases of HPS have been confirmed in SA. Both HFRS and HPS are non-endemic in SA and are category I notifiable medical conditions. Clinicians should consider the risk of hantavirus infection in travellers returning from endemic areas with possible rodent exposure (or exposure to rodent excreta) and presenting with either severe respiratory illness or renal function impairment.

Teaching points

- Hantaviruses are zoonotic rodent-borne infections widely distributed in the Americas and Eurasia.
- Hantavirus infection is associated with two distinct clinical syndromes, namely haemorrhagic fever with renal syndrome and hantavirus cardiopulmonary syndrome.
- Hantavirus infections are not considered endemic in SA, but may be a risk in travellers returning from endemic areas who have had exposure to rodents.

Declaration. None.

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Conflicts of interest. None.

1. Hart CA, Bennett M. Hantavirus infections: Epidemiology and pathogenesis. *Microbes Infect* 1999;1(14):1229-1237. [https://doi.org/10.1016/s1286-4579\(99\)00238-5](https://doi.org/10.1016/s1286-4579(99)00238-5)
2. Kruger DH, Figueiredo LT, Song JW, et al. Hantaviruses – globally emerging pathogens. *J Clin Virol* 2015;64:128-136. <https://doi.org/10.1016/j.jcv.2014.08.033>
3. Mattar S, Guzmán C, Figueiredo LT. Diagnosis of hantavirus infection in humans. *Exp Rev Anti Infect Ther* 2015;13(8):939-946. <https://doi.org/10.1586/14787210.2015.1047825>
4. Romero MG, Anjum F. Hemorrhagic fever renal syndrome. 8 December 2021. In: StatPearls [Internet]. Treasure Island, Fla.: StatPearls Publishing, 2022.
5. Vilibic-Cavlek T, Furic A, Barbic L, et al. Clinical and virological characteristics of hantavirus infections in a 2014 Croatian outbreak. *J Infect Dev Ctries* 2017;11(1):73-80. <https://doi.org/10.3855/jidc.7987>
6. Jiang H, Du H, Wang LM, et al. Hemorrhagic fever with renal syndrome: Pathogenesis and clinical picture. *Front Cell Infect Microbiol* 2016;6:1. <https://doi.org/10.3389/fcimb.2016.00001>
7. Macneil A, Nichol ST, Spiropoulou CF. Hantavirus pulmonary syndrome. *Virus Res* 2011;162(1-2):138-147. <https://doi.org/10.1016/j.virusres.2011.09.017>
8. Witkowski PT, Klempa B, Ithete NL, et al. Hantaviruses in Africa. *Virus Res* 2014;187:34-42. <https://doi.org/10.1016/j.virusres.2013.12.039>
9. Lundkvist A, Hukic M, Hörling J, Gilljam M, Nichol S, Niklasson B. Puumala and Dobrava viruses cause hemorrhagic fever with renal syndrome in Bosnia-Herzegovina: Evidence of highly cross-neutralizing antibody responses in early patient sera. *J Med Virol* 1997;53(1):51-59. [https://doi.org/10.1002/\(SICI\)1096-9071\(199709\)53:1<51::AID-JMV9>3.0.CO;2-P](https://doi.org/10.1002/(SICI)1096-9071(199709)53:1<51::AID-JMV9>3.0.CO;2-P)
10. Klempa B, Fichet-Calvet E, Lecompte E, et al. Hantavirus in African wood mouse, Guinea. *Emerg Infect Dis* 2006;12(5):838-840. <https://doi.org/10.3201/eid1205.051487>
11. Watson DC, Sargianou M, Papa A, Chra P, Starakis I, Panos G. Epidemiology of hantavirus infections in humans: A comprehensive, global overview. *Crit Rev Microbiol* 2014;40(3):261-272. <https://doi.org/10.3109/1040841X.2013.783555>

12. Puca E, Qato M, Pipero P, Akshija I, Kote M, Kraja D. Two cases of imported hemorrhagic fever with renal syndrome and systematic review of literature. *Travel Med Infect Dis* 2019;28:86-90. <https://doi.org/10.1016/j.tmaid.2018.07.010>
13. Jonsson CB, Figueiredo LT, Vapalahti O. A global perspective on hantavirus ecology, epidemiology, and disease. *Clin Microbiol Rev* 2010;23(2):412-441. <https://doi.org/10.1128/CMR.00062-09>
14. Brorstad A, Oscarsson KB, Ahlm C. Early diagnosis of hantavirus infection by family doctors can reduce inappropriate antibiotic use and hospitalisation. *Scand J Prim Health Care* 2010;28(3):179-184. <https://doi.org/10.3109/02813432.2010.506058>
15. European Centre for Diseases Prevention and Control. Hantavirus infection – Annual Epidemiological Report for 2018. 30 April 2020. <https://www.ecdc.europa.eu/en/publications-data/hantavirus-infection-annual-epidemiological-report-2018> (accessed 4 May 2022).
16. European Centre for Diseases Prevention and Control. Hantavirus infection – Annual Epidemiological Report for 2019. 22 April 2021. <https://www.ecdc.europa.eu/en/publications-data/hantavirus-infection-annual-epidemiological-report-2019> (accessed 4 May 2022).
17. Weinstein RA, Weber DJ, Rutala WA. Risks and prevention of nosocomial transmission of rare zoonotic diseases. *Clin Infect Dis* 2001;32(3):446-456. <https://doi.org/10.1086/318509>

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