Risk Assessment Group

CONSULTATIVE SIGNAL ASSESSMENT
PRIMARY RISK ASSESSMENT
EVIDENCE BASED RISK ASSESSMENT
PUBLIC HEALTH EVENT ASSESSMENT

CONFIRMED CASE OF VHF ARGENTINA

Date of the signal	Date of the PHEA	Signal provider	Experts consultation	Method
11/01/2020	12/01/2020	SPF/FOD	**Permanent experts:** Dr Valeska Laisnez (AZG), Dr Romain Mahieu (COCOM-GGC), Dr Paul Pardon (FOD), Dr Carole Schirvel (AViQ), , Ms Laura Piraprez (OstBelgien) Dr Sophie Quoilin (Sciensano). **Specific experts :** Dr Michèle Gérard (St Pierre), Dr Erika Vlieghe (UZA), Dr Marjan Van Esbroeck (ITG), Ms Amaya Leunda (SBB-Sciensano), Ms Natalia Bustos Sierra (Sciensano), Dr Tinne Lernout (Sciensano)	eMail
Date of update	Closing date			

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Signal Indicator-based information	A 41 years old woman is hospitalised in Saint-Pierre, Brussels where she was admitted on 06/01 with an alteration of her general condition after having started flu-like symptoms on 28/12 in Argentina. Based on the clinical symptoms, the evolution and origin of the patient a diagnosis of viral haemorragic fever of Argentina was suspected and confirmed by PCR on Saturday 10/01.

RATIONALE FOR EVENT ASSESSMENT	
Nature of the risk (e.g.: microbiological, chemical, ….)	Junin virus (JUNV), Arenavirus, cause of viral haemorrhagic fever. Isolated for the first time in 1958, in Argentina. Endemic zone is limited to a 150.000 Km² zone, 5 million people, in Argentina including the province Santa Fe where the patient originates from.
Description of the risk	Health care personal in St Pierre and lab technicians in St Pierre, Hôpital Brugmann, UZ Leuven and ITG have been exposed while giving care to the patient or processing blood samples between 06/01 and 10/01 (between admission and suspicion diagnosis). Junin virus is a Biosafety Level 4 pathogen while adequate protective measures were not applied since VHF was not suspected from the start of hospitalisation. Viremia is the highest during the second phase of the illness when neurological symptoms start, which corresponds to the start of hospitalisation.
Reliability of the risk	Clinical evolution and origin of the patient. Confirmed by RT-PCR in NRC in Hamburg on 11/01/2020.

Hazard description	
Incubation period	Typically 7–14 days with extreme cases extending from 5 to 21 days. Secondary infection to very high-load inoculum (parenteral exposition) may result in the reduction of the incubation period to 2 days.
Clinical presentation - complications	Three phases: 1. Prodromal : 6–14-day with insidious onset with symptoms such as Flu-like symptoms: chills, malaise, anorexia, headache, myalgia centered particularly over the lower back, moderate hyperthermia (38 to 39°C) Gastrointestinal symptoms: nausea or vomiting, epigastric pain, constipation, or mild diarrhoea Retro-orbital pain, Photophobia, dizziness 2. Neurologic and haemorrhagic: 8–12 days following its onset, about 20–30% of patients, with symptoms as Confusion, convulsions, coma Bleeding from body orifices 3. Convalescence
Transmission	Small rodent spreading the virus through saliva and urine. Human infection with an Arenavirus is incidental to the natural cycle of the viruses and occurs when an individual comes into contact with the excretions or materials contaminated with the excretions of an infected rodent, such as ingestion of contaminated food, or by direct contact of abraded or broken skin with rodent excrements. Infection can also occur by inhalation of tiny particles soiled with rodent urine or saliva (aerosol transmission).
Contagiousness	Start with symptoms (phase 1 < phase 2). Person-to-person transmission of Arenavirus is associated with direct contact with the blood or other body fluids, containing virus particles, of infected individuals. Contact with objects contaminated with these materials, such as medical equipment, or aerosolisation is also associated with transmission. Person-to-person transmission is very rare probably due to the relatively low titre of circulating virus. Nosocomial transmission has been reported.
Case fatality ratio	15 up to 30% without treatment, 1% if treatment during first week.
Diagnosis	Virus isolation from blood and mucosal secretions can be done starting from the prodromal phase of the disease: -RT-PCR offers greater sensitivity for the low viremia encountered during the early period, which allows a faster response to infection

	-IgM and IgG ELISA, antigen detection ELISA and neutralisation tests are also frequently used to detect Junin virus. Not existing in Belgium but available in Hamburg.
Treatment	Immune plasma from convalescent patients (effective if started during first week) also Ribavirin seems to be efficient.
Epidemiological situation (in Argentina)	About 1000 cases by year but since start of vaccination policy in 2005, +/- 50 cases/year. Mainly between April and July. Those most commonly affected are male field workers who may come into contact with rodent excreta.

Risk characterisation	
Description of the event	**Patient** Women, originated from Perez, Argentina (Province of Santa Fe) Lawyer, 41 years old Flight to Europe with a friend to participate to a training on environmental rights. **Travel** Flight to Madrid on 01/01/2020 and continued to Amsterdam where they arrived on 02/01. Stayed in a hotel in Amsterdam from 02/01 to 06/01. Took the bus on 06/01 to Brussels (Gare du midi) and went to an Airbnb in an Uber taxi. Then took an ambulance to CHU St-Pierre where she was admitted the same day in ICU CHU St-Pierre due to epileptic seizure. **Clinical evolution** Onset of symptoms: 28/12/2019 in Argentina with Flu like symptoms. 01/01 : Took the flight (moderate fever, inappetence, sore throat). 02/01 : Madrid, stayed in the airport transit area (not in good condition). Didn't vomit and no cough on both flights. 03/01 – 06/01: Stay in a hotel in Amsterdam and started vomiting, 2 x/day. 06/01: no vomiting in the bus, no use of the toilets, arrival in Brussels, she faint in the Airbnb and admitted at St Pierre for epileptic seizure. Blood samples disseminated in four different labs and processed without the necessary level 4 biosafety level. 28/12 to 06/01 = period probably corresponding to first phase when viremia is low. 06/01 to 11/01 (diagnosis) = period probably corresponding to second phase 'neurological – haemorragic' when viremia becomes higher. **Diagnosis** : Sample sent on 10/01 in the evening and diagnose by RT-PCR performed by NRC in Hamburg on 11/01. **Treatment** : by ribavirin. On 13/01, patient in ICU, intubated, stable but still in critical condition. **Exposition**: 1. During travel: flight Buenos Aires-Madrid, flight Madrid-Amsterdam, stay in Amsterdam, bus Amsterdam-Brussels, Uber, AirbnB. Few contacts because already not feeling very well. 2. Three close contacts : The friend travelling together with the patient and who continued her travel to France, Limoges to follow a course until 18/01. They were going to stay longer for tourism until 25/01, but she is now planning to return to Argentina from 18/01. The companion and mother of the patient who arrived in Brussels on 08/01 after having been informed of her hospitalisation. Last contact with the patient at the airport on 01/01. They are staying at a friend's house in Uccle/Brussels. 3. Health care personal: Ambulance staff for transport to St Pierre (06/01), emergency ward (06/01), hospitalisation unit, lab, …? Samples have been in sent in 4 different labs: St Pierre, Brugmann, ITG and UZ Leuven without mention of VHF risk as patient admitted with epilepsy.

	Close contacts have no symptoms as of 13/01. Two health care workers in St Pierre who took care of the patient have fever on Monday 13/01.

EVENT ASSESSMENT	
1 - Unusual or unexpected ?	**Unexpected** because limited exposed population (5 Argentinian provinces corresponding to 5 million people), rare since vaccine strategy, mainly between April and July and among men working in agriculture.
2 - Public health impact ?	Very low for the general population or travellers, limited to people exposed to the patient (aerosol) and blood.
3 - Risk for dissemination?	No risk for dissemination Person to person when contact with blood or by aerosol: mainly nosocomial risk
4 - Limitation of international movement of persons/goods	No
5 – Notification	Event to be notified to European Authorities and WHO.

Public health impact	
Criteria	Description
Risk	Confirmed Argentina VHF, biosafety level 4 pathogen. Event was not managed as a potential biosafety level 4 pathogen during 4 days exposing health care workers. Rare pathogen, no/few specific procedure available.
Measures	Patient hospitalised in reference hospital for VHF. Hygienist CHU St Pierre managing the risk inside the hospital in coordination with health inspectorate. Stock shortage of ribavirin in Belgium, SPF/FOD public health contacted to help in finding ribavirin and organised import from Dusseldorf (10 vials - 2 gram ribavirin/amp). Also contact with the Netherlands to make favipiravir available for treatment. SPF/FOD public health took contact with WHO and NFP Argentina about the availability of the vaccine and the immunoglobulins. Health inspectors of Brussels managing the risk outside the hospital: three close contacts identified and followed by the health inspector. They will inform the health inspector each day about health condition.
Assessment	Rare pathogen and therefor few procedures available. Any procedure for Arenavirus (Eg.: Lassa virus) can be used. Risk extremely low for travellers in the same flight or bus because person to person transmission is rare and travellers had no contact with body fluids of the patient. Risk is high for health care workers if [1] (1) Penetration of skin by a contaminated sharp instrument (eg, needlestick injury), (2) Contamination of mucous membranes or broken skin with blood or bodily secretions (eg, blood splashing in the eyes or mouth), (3) Participation in emergency procedures (eg, resuscitation after cardiac arrest, intubation, or suctioning) without use of appropriate personal protective equipment, (4) Prolonged (ie, for hours) and continuous contact in an enclosed space without use of appropriate personal protective equipment (eg, a health care worker accompanying a patient during medical evacuation).

[1] As mentioned in procedure for Lassa fever

	In case of processing samples without incident, the risk for health care workers will be considered as low. In other situation (having been in the same room without contact with the patient or sample), the risk for health care workers will be considered as low. As long as the patients present no symptom, he/she is not contagious.
Additional measures	France, Netherlands, Spain and Argentina, EWRS and WHO have been informed about the confirmation of the diagnosis and the control measures taken. They will be informed about the evolution of the patient, the follow up of the close contacts, the measures taken for the exposed health care workers and their follow up. Information on the different public transport used by the patient is available. No contact tracing of travellers in the flights or in the bus is necessary: Junin and Lassa are both Arenavirus and according to RAGIDA recommendations passengers have to be traced back if exposure of body fluid has been reported what it was not the case (*Gilsdorf et al*). Contacts will be asked to report any symptoms during a period of 21 days. Beside the follow up of the three close contacts for 21 days, a list of all health care workers (HCW) exposed will be made and the risk evaluated case by case depending on the date of the exposure, type of exposure, protective measures used, event like needle stick injury, … They will be also followed for 21 days. The follow up of the exposed HCW will be done by the respective health regional services and communicated to the SPF/FOD. A procedure has to be defined for health care workers presenting symptoms. In such a case, differential diagnose will nevertheless first target the usual pathologies (e.g.: rapid test flu in case of fever/flu like symptoms, …). Following information received from Argentina: - evaluate if relevant to still vaccinate health care workers; - make available immunoglobulins. Do we have to give a prophylaxis to HCW? Availability of the ribavirin will be ensured. Samples will be processed with a biosafety level 3 while culture/virus identification can only be done in a level 4. Procedure Ebola can be used therefor. Revise assessment if change in the risk.
Long term discussion	Lessons learnt to limit the number of exposed health care workers in a globalisation perspective with billion people travelling.

TIMELINE

Month	Dec-19				Jan-20																
Day	28	29	30	31	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Place	Argentina				Left Argentina	Arrival in Madrid en then flight to Amsterdam				Arrival in Brussels Admitted St pierre											
Clinical status	Start flu like symptoms				Moderate fever, inappetence, sore throat.			Start vomiting		Worsening symptoms (fainted, confusion, epileptic seizure)				Intubation Sample to Hamburg Ribavirin Seizure, iatrogenic bleeding							
Week evolution	J1: prodromal phase						J7	From J8-12: Neurological-haemorrhagic phase						J14							J21

REFERENCES

Andreas Gilsdorf, Dilys Morgan and Katrin Leitmeyer. Guidance for contact tracing of cases of Lassa fever, Ebola or Marburg haemorrhagic fever on an airplane: results of a European expert Consultation. BMC Public Health 2012, 12:1014. http://www.biomedcentral.com/1471-2458/12/1014

D.A. Enria (*), A.M. Briggiler and M.R. Feuillade. An overview of the epidemiological, ecological and preventive hallmarks of Argentine haemorrhagic fever (Junin virus). Bull Inst. Pasteur 1998, 96, 103-114.

Ashley Grant, Alexey Seregin, Cheng Huang, Olga Kolokoltsova, Allan Brasier, Clarence Peters and Slobodan Paessler. Junín Virus Pathogenesis and Virus Replication. Viruses 2012, 4, 2317-2339.

Made Artika, Chairin Nisa Ma'roef. Laboratory biosafety for handling emerging viruses. Asian Pacific Journal of Tropical Biomedicine. 2017 7(5): 483-491.

M. C. WEISSENBACHER, L. B. DE GUERRERO, & M. C. BOXACA. Experimental biology and pathogenesis of Junin virus infection in animals and man. BULL. WORLD HEALTH ORGAN., Vol. 52, 1975.

CELIA AITKEN AND DONALD J. JEFFRIES. Nosocomial Spread of Viral Disease. CLINICAL MICROBIOLOGY REVIEWS, July 2001, p. 528–546 Vol. 14, No. 3.

R.H .. Kenyon, K.T. McKee, Jr., P.M. Zack M.K. Ri.ppy, A.P. Vogel, C. York, J. Meegan, C. Crabbs, CJ. Peters. Aerosol Infection of Rhesus Macaques with Junin Virus. Intervirology 1992;33:23-31.

Dr. Ginés González García. PROGRAMA NACIONAL DE CONTROL DE LA FIEBRE HEMORRÁGICA ARGENTINA MINISTERIO DE SALUD. Cuarta Edición 2007.

Factsheet. Viral Hemorrhagic Fevers Caused by Arenaviruses. http://www.cfsph.iastate.edu/

Pathogen Safety Data Sheets: Infectious Substances – Junin virus. https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment/junin-virus.html

Ricardo M. Gomez, Carolina Jaquenod de Giusti, Maria M. Sanchez Vallduvi, Jesica Frik, Maria F. Ferrer, Mirta Schattner. Junín virus. A XXI century update. Microbes and Infection 13 (2011) 303e311.

Charrel RN1, de Lamballerie X. Arenaviruses other than Lassa virus. Antiviral Res. 2003 Jan;57(1-2):89-100.

McKee, K.T. Jr.; Huggins, J.W.; Trahan, C.J.; Mahlandt, B.G. Ribavirin prophylaxis and therapy for experimental argentine hemorrhagic fever. Antimicrob. Agents Ch.1988, 32, 1304-1309. Viruses 2012, 4 2339

Barry, M.; Russi, M.; Armstrong, L.; Geller, D.; Tesh, R.; Dembry, L.; Gonzalez, J.P.; Khan, A.S.; Peters, C.J. Brief report: Treatment of a laboratory-acquired sabia virus infection. New Engl. J. Med. 1995, 333, 294-296.

Daniel G. Bausch, Christiane M. Hadi, Sheik Humarr Khan, and Juan J. L. Lertora. Review of the Literature and Proposed Guidelines for the Use of Oral Ribavirin as Postexposure Prophylaxis for Lassa Fever. Clinical Infectious Diseases 2010; 51(12):1435–1441

KELLY T. McKEE, JR.,'* JOHN W. HUGGINS,2 CREIGHTON J. TRAHAN,' AND BILL G. MAHLANDT. Ribavirin Prophylaxis and Therapy for Experimental Argentine Hemorrhagic Fever. ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 1988, p. 1304-1309.

Delia A. Enria ∗, Ana M. Briggiler, Zaida Sanchez. Treatment of Argentine hemorrhagic fever. Antiviral Research 78 (2008) 132–139

Janice M. Rusnak. Experience with Ribavirin for Treatment and Postexposure Prophylaxis of Hemorrhagic Fever Viruses: Crimean Congo Hemorrhagic Fever, Lassa Fever, and Hantaviruses. Applied Biosafety Vol. 16, No. 2, 2011.

Brian B. Gowena, and Mike Bray. Progress in the experimental therapy of severe arenaviral infections. Future Microbiol. 2011 December ; 6(12): 1429–1441.

Brian B. Gowen, Jonna B. Westover, Eric J. Sefing, Arnaud J. Van Wettere, Kevin W. Bailey, Luci Wandersee, Takashi Komeno, and Yousuke Furuta. Enhanced protection against experimental Junin virus infection through the use of a modified favipiravir loading dose strategy. Antiviral Res. 2017 September ; 145: 131–135.

Michelle Mendenhall, Andrew Russell, Donald F. Smee, Jeffery O. Hall, Ramona Skirpstunas, Yousuke Furuta, Brian B. Gowen. Effective Oral Favipiravir (T-705) Therapy Initiated after the Onset of Clinical Disease in a Model of Arenavirus Hemorrhagic Fever. PLOS Neglected Tropical Diseases October 2011 | Volume 5 | Issue 10 | e1342