



## RAPID RISK ASSESSMENT

# Lassa fever in Nigeria, Benin, Togo, Germany and USA

23 March 2016

### Main conclusions and options for response

The two imported cases of Lassa fever recently reported from Togo indicate a geographical spread of the disease to areas where it had not been recognised previously. Delays in the identification of viral haemorrhagic fevers pose a risk to healthcare facilities. Therefore, Lassa fever should be considered for any patient presenting with suggestive symptoms originating from West African countries (from Guinea to Nigeria) particularly during the dry season (November to May), a period of increased transmission, and even if a differential diagnosis such as malaria, dengue or yellow fever is laboratory-confirmed.

Case ascertainment should involve asking about consumption of foods and drinks contaminated by rodent urine or droppings and exposure to *Mastomys* rodents or to patients presenting with haemorrhagic fever.

#### Prevention of nosocomial transmission

Patients suspected of viral haemorrhagic fever should be placed in ad-hoc isolation and cared for using appropriate personal protective equipment (PPE). Once diagnosis is confirmed, the patient should be transported to a specialised treatment centre, the competent public health authority should be notified immediately and contact tracing should be systematically initiated.

In nosocomial settings with adequate barrier nursing and prevention and control measures, the secondary attack rate for Lassa fever is extremely low.

#### Laboratory

Testing of samples for Lassa virus should be performed under BSL-4 laboratories. Sufficient capacity exists in the EU for testing purposes, however given the wide genetic diversity of circulating Lassa viruses, laboratory protocols for RT-PCR detection should be revised periodically.

#### Post exposure prophylaxis

Intravenously administered ribavirin is the treatment for confirmed cases of infection with Lassa virus. Risk/benefit considerations need to be drawn carefully on a case-by-case basis. In particular, this applies to cases presenting relative contraindications for the use of ribavirin.

There is currently no evidence supporting the use of ribavirin as a post-exposure prophylaxis (PEP). Oral administration of ribavirin is currently only recommended as a precautionary measure for PEP in the event of 'high-risk exposure' to Lassa virus following a risk-benefit analysis.

#### Advice to travellers

Travellers to West Africa should be informed of the risk of exposure to Lassa fever virus, particularly in areas currently experiencing outbreaks. The risk is higher in rural areas, where living conditions are basic.

Erratum, 30 March 2016.

Following feedback from the German authorities, the following amendments were made.

On page 3, the phrase 'However, samples tested negative for PCR on 19 March 2016.' was replaced with 'However, samples were later found to have been false-positive in serology (IgM). Neither patient was ever PCR positive.'

On page 4, the following clause was added: ', as well as people handling or preparing the body of a person infected by Lassa fever (i.e. undertakers).'

Christina Frank was added to the list of consulted experts.

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Travellers should avoid consumption of foods and drink contaminated by rodent droppings, exposure to rodents or to patients presenting with haemorrhagic fever.

Those travelling to these regions to provide care should be aware of the risk of exposure and should apply appropriate personal protective measures.

## Source and date of request

ECDC internal decision, 17 March 2016.

## Public health issue

This document assesses the risk of Lassa fever infection in Europe in relation to the ongoing outbreak of Lassa fever in Nigeria, Benin and Togo, following the notification of one case being medically evacuated from Togo to Germany and the infection of a secondary contact, and another case being medically evacuated to the United States.

## Consulted experts

Internal experts consulted (in alphabetical order): Cornelius Bartels, Denis Coulombier, Laura Espinosa, Laurence Marrama, Emmanuel Robesyn, Bertrand Sudre, Hervé Zeller.

External experts consulted: Christina Frank (Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin) and Timo Wolf (University Hospital, Frankfurt).

The external experts have submitted declaration of interest statements pertaining to this risk assessment.

## Disease background information

Lassa fever is an acute viral haemorrhagic illness caused by the arenavirus, Lassa virus, which is endemic in West Africa. The disease can be severe and death occurs in around 15–20% of severe hospitalised cases. The pathogen was identified in 1969 when three American nurses became infected in Lassa, Nigeria [1]. The disease is caused by an enveloped bi-segmented negative strand RNA virus (risk group class 4) from the *Arenaviridae* family. The reservoir of Lassa virus is a multimammate rat, a peridomestic rodent widely distributed across sub-Saharan Africa.

The incubation period is usually around 10 days, with a range of between one to three weeks [2]. About 80% of those who become infected with Lassa virus have mild or no symptoms and one in five infections results in severe disease [2]. In 20% of symptomatic cases, the clinical course results in a severe disease with multi-organ impairment. When symptomatic, the onset of symptoms is non-specific, with a general weakness, muscle aches and fever. Various symptoms are reported during this first phase such as nausea, vomiting, sore throat, pharyngitis, dry cough, chest and abdominal pain. In severe form, the symptoms increase in intensity over a period of days and are characterised by haemorrhaging (e.g. mucosal, intestinal and pulmonary), facial oedema, respiratory distress, central nervous system symptoms and shock [3]. Proteinuria may be noted. Death occurs in around 15–20% of severe hospitalised cases. Lassa fever in pregnancy is particularly severe, with spontaneous abortion and a high death rate during the third trimester.

The disease is endemic in the countries of the Mano river basin (Guinea, Sierra Leone and Liberia) and Nigeria and these countries report the majority of Lassa fever cases [1]. In addition, human cases have been reported in Ghana (October 2001), Mali (February 2009) and Benin (November 2014) [2] [6,7]. In the past five years, notable outbreaks have been reported in Nigeria in 2012 (1 723 cases, 112 fatalities in 23 states), 2013 (232 cases, 15 fatalities in nine states) and 2014 (208 cases, 17 fatalities) and in Liberia in 2013 (12 cases, 8 fatalities, Bong county) and (14 cases, 1 fatality, Margibi county).

There is a probable risk of exposure in other rural areas of West Africa where the multimammate rat (*Mastomys natalensis* species complex) is present and maintaining the zoonotic cycle of Lassa fever [4]. Lassa virus is present in *Mastomys* species rodent populations in countries between Nigeria and Guinea [3]. The modelled zoonotic niche of Lassa virus covers 14 West African countries from Guinea-Bissau to Chad [5]. At present, there are an estimated 300 000 to 500 000 cases of Lassa fever annually in West Africa [3].

The virus is present in rodent excreta (e.g. urine, saliva and respiratory secretions). The rodent excretes the virus in urine for an extended time period and can therefore contaminate peridomestic environments where food and non-food items are poorly stored. Transmission of Lassa virus occurs most commonly through ingestion or inhalation of contaminated items. Sexual transmission is possible [2]. Airborne transmission can also occur when cleaning dust contaminated by rodent excreta. In addition, Lassa virus is transmitted from human to human by

contaminated blood. Therefore, primary prevention involves avoiding contact with items contaminated with rodent urine or faeces and implementing appropriate infection control measures in healthcare settings to minimise the risk of nosocomial transmission [2].

Rare cases have been reported among returning travellers with a history of exposure in rural areas or hospitals in countries where Lassa fever is known to be endemic (Annex 1).

Clinical diagnosis may be challenging, especially during the early phase of the disease. Laboratory diagnosis is carried out in specialised laboratories using antibody enzyme-linked immunosorbent assay (ELISA), reverse transcriptase polymerase chain reaction (RT-PCR) assay and antigen detection tests or virus isolation [2]. Differential diagnoses include severe malaria, typhoid fever, viral haemorrhagic fever, leptospirosis, typhus, tick-borne relapsing fever, non-typhoidal salmonellosis, meningococcal septicaemia and meningitis.

Laboratory infections by Lassa virus have been reported. Lassa virus is a risk group class 4 agent. Laboratory investigation of Lassa virus infection should be handled under ad-hoc biological containment conditions. Clinical specimens must be handled with universal precautions and sent to the reference laboratory in compliance with sample shipment regulations [1,6-8]. Lassa virus is susceptible to the usual disinfectants (e.g. 0.5% sodium hypochlorite, phenolic compounds, lipid solvents and detergents) and is inactivated by heat or UV irradiation [9,10]. The virus is stable as an aerosol, particularly at low relative humidity (30% RH). The biological half-life of the virus at 24°C and 32°C ranges from 10.1 to 54.6 minutes [11].

Ribavirin is effective early in the course of the illness, notably when started within the first six days of illness [12,13]. There is currently no evidence supporting the use of ribavirin as post-exposure prophylactic treatment [2]. There is no vaccine for Lassa fever but several candidates are under development and encouraging results have been seen in trials involving non human primates [14].

In areas where Lassa fever is circulating, preventive measures are based on reduction of exposure to rodent excreta with appropriate community hygiene practices (safe storage of food, waste management, avoiding the consumption of rodents and reduction of rodent populations in and around homes).

Early detection of cases reduces the risk of outbreaks related to person-to-person transmission, especially among family members and healthcare workers. In endemic areas, standard infection prevention and control precautions should be applied when caring for patients, irrespective of their diagnosis. When caring for patients with suspected or confirmed Lassa fever, measures focus on preventing contact with the patient's blood and body fluids and contaminated surfaces or materials. The risk of infection among healthcare workers can be significantly reduced through strict isolation of case(s), appropriate use of infection control precautions, such as use of personal protective equipment (masks, gloves, gowns and goggles), application of strict barrier nursing procedures and safe burial practices [15].

## Event background information

### Germany

On 25 February 2016, a 46-year-old male US citizen was flown by air-ambulance from Togo to Cologne (Germany) where he was admitted to the University hospital with suspected malaria. He presented with a severe multi-organ dysfunction syndrome and died on 26 February 2016. On 3 March 2016, the body was transferred to a funeral home specialising in conditioning corpses for repatriation flights. On 9 March 2016, Lassa fever was confirmed by the Bernhard Nocht Institute for Tropical Medicine. The patient had worked for years as a surgical physician's assistant and head of staff at a missionary hospital in the Togolese district of Oti, over 500 km north of the capital Lomé.

Forty-five contacts, including 33 staff of the Cologne University hospital, were placed under domestic quarantine with temperature monitoring twice a day and regular active reporting to the public health authorities.

A member of the company preparing the corpse for flight repatriation had reported presenting with flu-like symptoms before handling the corpse but stated that he had had no contact with bodily fluids during handling. A test on 11 March 2016 was negative for Lassa fever infection. However, on 15 March he developed symptoms and Lassa fever infection was laboratory-confirmed. He was transferred by a specialised ambulance to the high isolation treatment centre at the Frankfurt University Hospital. As of 19 March, the patient is showing signs of a severe virus infection, but is neither critically ill nor under intensive care treatment. Family members were admitted to the treatment centre as a precautionary measure. Further investigations regarding the exposure are ongoing.

On 18 March 2016, two additional contacts of the first case tested positive for Lassa virus IgM. However, samples were later found to have been false-positive in serology (IgM). Neither patient was ever PCR positive.

### United States

On 11 March 2016, a US citizen working as surgeon with a missionary organisation in the Oti district (same district as for the German case) was medically evacuated from Togo to the Emory University Hospital Serious Communicable Diseases Unit in Atlanta, USA. The evacuation flight was undertaken in conditions of strict isolation.

On 13 March 2016, media quoted the US CDC spokesman confirming that the patient had tested positive for Lassa infection.

### West Africa

Lassa fever is endemic in parts of West Africa including Sierra Leone, Liberia, Guinea, Nigeria and Benin. However, neighbouring countries are also at risk, as the animal reservoir for Lassa virus, the 'multimammate rat' is distributed throughout the region. Isolated cases have been reported in Côte d'Ivoire, Burkina Faso, Ghana and Mali and there is serological evidence of Lassa virus infection in Togo.

In 2016, there are ongoing outbreaks of Lassa fever in Nigeria, Benin and probably Togo. Cases are widely distributed within these countries and high case-fatality rates are reported.

As of 24 January 2016, Nigeria has reported 172 confirmed and suspected cases of Lassa fever, including 83 deaths (CFR=48%) [16]. The case-fatality rate was 60% among the 57 confirmed cases. The Ministry of Health reported more than 1 700 cases with 112 deaths in 2012, 1 195 cases with 39 deaths in 2013 and 989 cases with 36 deaths in 2014. Outbreaks generally occur during the region's dry season, typically from October–November to February, but may vary according to the environmental conditions favourable for the multimammate mice population.

Between 21 January and 14 March 2016, the authorities in Benin reported 48 cases, 11 of which were confirmed, with a case-fatality rate of 50%. Cases originated from several districts in central and eastern Benin, along the Nigerian border. The communes of Tchaourou (Borgou department) and Djougou (Donga department) were the most affected areas. Five healthcare workers have been infected, one of whom was confirmed and one probable case died. The outbreak is currently decreasing. The first outbreak of Lassa fever in Benin was reported in 2014 in Tanguiéta and Coby communes, Atakora Department, north west Benin. Between 15 October and 4 November 2014, 16 cases were recorded including nine deaths. Four healthcare workers died, two of whom presented with a confirmed Lassa virus infection [17].

In Togo, on 15 March 2016, media quoted Togo's Minister of Health who had reported on two cases of Lassa fever in the northern district of Oti, possibly referring to the two infected healthcare workers from the US, who had just been evacuated to Cologne and Atlanta respectively [18].

No cases of Lassa fever have been reported in 2016 in Sierra Leone, Liberia or Guinea.

## ECDC threat assessment for the EU

### Primary infection in European countries

The risk of primary infection with Lassa virus in community settings in Europe can be considered as non-existent since there is no endemicity for *Mastomys sp.* rodents.

### Secondary infection in European healthcare settings

The second patient reported in Germany is the seventh documented case with Lassa fever in Germany since 1974. He is the first symptomatic case of documented secondary disease transmission in Germany and the EU. A first secondary infection was documented in 2000 in a doctor who had examined an imported, symptomatic patient with Lassa fever in Germany. The doctor presented a seroconversion with specific antibodies to Lassa virus and remained asymptomatic [19].

Recent experiences with nosocomial transmission of Ebola virus in Spain and in the US confirm that even well-resourced healthcare settings with well-trained personnel are still vulnerable to the risk of secondary transmission of viral haemorrhagic fevers.

Lassa fever cases had never been reported in Togo and therefore this was not considered initially as a differential diagnosis. However, the list of countries reporting Lassa fever cases has been extended in recent years. As a result, Lassa fever should be considered as a differential diagnosis for any patient presenting with suggestive symptoms originating from West African countries.

Transmission of Lassa virus mainly occurs through contact with bodily fluids or droplets. The role of sexual transmission is unclear and use of a condom for two months has been recommended [7]. The risk level for secondary transmission depends on the closeness and duration of contact, on the type of activity performed by medical staff, as well as people handling or preparing the body of a person infected by Lassa fever (i.e. undertakers), and the type of personal protective equipment used (see Table 1). Therefore, healthcare personnel involved in invasive care procedures are at increased risk of exposure, especially as regards aerosolisation of patients' bodily fluids – e.g. during endotracheal suction or bronchoscopy ('Aerosol Generating Procedures - AGP') [20-22].

**Table 1. Risk stratification\* in transmission of viral haemorrhagic fever [20]**

Risk level	Type of contact
Very low or no recognised risk	Casual contact with a feverish, ambulant, non-diagnosed case. Examples: sharing a seating area or public transportation; receptionist tasks.
Low risk	Close face-to-face contact with a feverish and ambulant non-diagnosed case. Example: physical examination, measuring temperature and blood pressures.
Moderate risk	Close face-to-face contact without appropriate personal protective equipment (including eye protection) with a patient who is coughing or vomiting, has nosebleeds or who has diarrhoea.
High risk	Percutaneous, needle stick or mucosal exposure to virus-contaminated blood, bodily fluids, tissues or laboratory specimens in severely ill or known positive patients

Adapted from [23].

\* Risk stratification in household contacts is entirely on a case-by-case basis.

### Biosafety and laboratory investigation

Compliance with universal precautions for handling biological samples of suspect viral haemorrhagic fever case and shipment regulations is required [8]. Laboratory investigations should be handled under ad hoc biological containment conditions.

### Travellers coming from affected countries

The risk of a traveller coming from affected areas becoming infected with Lassa virus and developing the disease upon entering the EU is very low but has been reported in the past (Annex 1). There is a possibility that persons who have been exposed to Lassa fever and developed symptoms may board a commercial flight to seek medical attention in the EU. It is highly likely that such patients would seek immediate medical attention upon arrival in the EU and then be isolated to prevent further transmission.

WHO does not recommend applying travel or trade restrictions to countries affected by Lassa fever outbreaks.

### Visiting family and friends

The risk of exposure to Lassa virus is higher among visitors to rural areas, where living conditions are basic. Therefore, the risk of coming into contact with infected rodents tends to be higher among travellers visiting family and friends than among tourists or business travellers.

### Aircraft passengers exposed to a Lassa fever case during a flight

The possibility of transmission to co-passengers and crew on board an aircraft should be assessed using the ECDC RAGIDA guidelines [24]. To date, Lassa fever infection has not been reported among passengers seated close to a sick patient during an intercontinental flight (Annex 1).

## Conclusions and options for response

The two imported cases of Lassa fever recently reported from Togo indicate a geographical spread of the disease to areas where it had not been recognised previously. Delays in the identification of viral haemorrhagic fevers pose a risk to healthcare facilities. Therefore, Lassa fever should be considered for any patient presenting with suggestive symptoms originating from West African countries (from Guinea to Nigeria) particularly during the dry season (November to May), a period of increased transmission, and even if a differential diagnosis such as malaria, dengue or yellow fever is laboratory-confirmed.

Case ascertainment should involve asking about consumption of foods and drinks contaminated by rodent urine or droppings and exposure to *Mastomys* rodents or to patients presenting with haemorrhagic fever.

### Prevention of nosocomial transmission

Patients suspected of viral haemorrhagic fever should be placed in ad-hoc isolation, and cared for using appropriate personal protective equipment (PPE) [20-22]. Once diagnosis is confirmed, the patient should be transported to a specialised treatment centre, the competent public health authority should be notified immediately and contact tracing should be systematically initiated.

In nosocomial settings with adequate barrier nursing and prevention and control measures, the secondary attack rate for Lassa fever is extremely low.

### Laboratory

Testing of samples for Lassa virus should be performed under BSL-4 laboratories. Sufficient capacity exists in the EU for testing purposes, however given the wide genetic diversity of circulating Lassa viruses, laboratory protocols for RT-PCR detection should be revised periodically [25-27].

**Post exposure prophylaxis**

Intravenously administered ribavirin is the treatment for confirmed cases of infection with Lassa virus. Risk/benefit considerations need to be drawn carefully on a case-by-case basis. In particular, this applies to cases presenting relative contraindications for the use of ribavirin [13].

There is currently no evidence supporting the use of ribavirin as a post-exposure prophylaxis (PEP). Oral administration of ribavirin is currently only recommended as a precautionary measure for PEP in the event of 'high-risk exposure' to Lassa virus after a risk-benefit analysis [13].

**Advice to travellers**

Travellers to West Africa should be informed of the risk of exposure to Lassa fever virus, particularly in areas currently experiencing outbreaks. The risk is higher in rural areas where living conditions are basic.

Travellers should avoid consumption of foods and drink contaminated by rodent droppings, exposure to rodents or to patients presenting with haemorrhagic fever.

People travelling to these regions to provide care should be aware of the risk of exposure and should apply appropriate personal protective measures.



## Annex 1

**Table 2. Imported and nosocomial cases of Lassa virus disease, EU and USA, 2000–2015**

Year	Month	Country	Occupation	Age	Country of infection	Medical evacuation	Travel history and hospitalization	Lassa confirmed date post symptoms onset	Fatality (number of day post onset)	Ribavirin treatment	Contact tracing	References
2000	January	Germany	Student	23	Ivory Coast, Ghana and Burkina Faso	No	Travel on day three via Morocco or Portugal in local hospital and day nine in reference hospital.	10 days	Yes (15)		232 contacts including 18 at high risk	[28,29]
2000	January	Germany	Physician	NA	Germany		Physical examination of Lassa patient on day nine. Asymptomatic.	Seroconversion	No	Yes	Unknown	[19]
2000	February	Netherlands	Surgeon	48	Sierra Leone (Kenema county)	No	Travel on day four to the Netherlands via Abidjan, then hospitalised on day five and Lassa fever suspected on day nine.	11 days	Yes (14)	Unknown	Contact tracing (airline contact)	[30]
2000	July	United Kingdom	Aid worker	50	Sierra Leone	Yes	Hospitalised in Freetown on day eight, then travel on day 13 to UK, hospitalised in local hospital, followed by a transfer to reference hospital.	n/a	Yes (30)		125 contacts including ten high-risk contacts.	[31,32]
2003	January	United Kingdom	Soldier	Unknown	Sierra Leone	N/A	Hospitalised in a reference hospital.	n/a	No	Unknown	Yes	[33]
2004	August	USA	Business man	38	Sierra Leone and Liberia	No	Air-travel to US via UK on day three and hospitalised on day five. Lassa suspected around day eight.	Yes (post-mortem)	Yes (9)	No	Yes, 188 contacts including five at high risk.	[1,34]
2006	July	Germany		68	Sierra Leone	No	On day five, air travel to Belgium via Cote d'Ivoire and connection to Frankfurt. Hospitalised on day six. Lassa investigated on day 11. Transfer to reference hospital on day 16 where Lassa was investigated. The patient had underlying medical conditions.	8-10 days post arrival	No	Unknown	Yes	[35]
2009	January	United Kingdom	Retired	66	Nigeria, sick since 2 days	No	Hospitalised in London on day four and transferred to reference hospital on day 16 and then investigated for Lassa.	15 days post arrival	Yes (24)	Yes from day 17	328 persons, none at high risk.	[6,36]
2009	February	United Kingdom	Engineer	24	Mali (close to Ivory Coast border)	Yes	Hospitalised on day 11 in reference hospital. Standard universal infection control precautions were followed and visitors admitted (Lassa not suspected)	11 days	Yes (11)		123 persons including seven considered at high risk (healthcare workers and family members)	[6,36,37]
2010	January	USA	Traveller	47	Liberia	No	Onset of disease on day of travel. Hospitalised. Lassa	6 days	No	No	140 persons, none at high risk	[38]
2011	March	Sweden	Aid worker	30s	West Africa	Yes	Medical transport by medical flight in Sweden Intensive care unit.	Unknown	Unknown	Unknown	Unknown	[39]
2014	March	USA	Unknown	Unknown	West Africa	No	Hospitalised in Minnesota after a trip to West Africa via New York City to Minneapolis	Unknown	Unknown	Unknown	Yes	[40]
2015	May	USA	Mining industry worker	55	West Africa	No	Returning from West Africa via Morocco to New York (New Jersey, USA)	Unknown	Yes (3 days after hospitalisation)	Unknown	Yes	[41]

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