Imported Lassa Fever in Germany: Surveillance and Management of Contact Persons

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This study sought to assess the risk of secondary transmission after import of Lassa fever into Europe. A total of 232 persons exposed to a case of Lassa fever imported into Germany were identified. The level of exposure was determined for 157 persons (68%), and 149 (64%) were tested serologically. High-risk or close contact was reported by 30 (19%) of 157 persons. No symptomatic secondary infections were observed. However, Lassa virus–specific immunoglobulin G antibodies were detected in a serum sample obtained from a physician who examined the index patient on day 9 of illness. The physician received ribavirin prophylaxis and did not develop symptoms of Lassa fever. On the basis of these data, the contact was classified as having a probable secondary infection. The study indicates a low risk of transmission during the initial phase of symptomatic Lassa fever, even with high-risk exposures. The risk may increase with progression of disease and increasing virus load.

Lassa fever is a viral hemorrhagic fever that is endemic in west Africa. The disease results from transmission of Lassa virus ( Arenaviridae family) from its natural host, the African rodent Mastomys natalensis, to humans. Lassa virus can also be transmitted from human to human, in contrast to other hemorrhagic fever viruses, such as yellow fever virus or dengue fever virus. In Africa, secondary infections often occur in hospitals under conditions of poor hygiene and cause epidemics with high mortality rates [1, 2]. As a result of an incubation period of up to 3 weeks, the virus may be imported into other regions of the world while the infected person is asymptomatic or shows early, nonspecific signs of Lassa fever.

To date, ∼20 cases of imported Lassa fever have been reported worldwide [3]. Investigations to assess the risk of secondary infection were undertaken in cases of Lassa fever imported into the United States and Great Britain [4–6]. No clinically apparent secondary cases were observed, and serological testing of a subgroup of contacts revealed no asymptomatic infections. Therefore, the risk of human-to-human transmission due to imported Lassa fever was considered to be low, and relaxed guidelines for management have been published [5]. Ribavirin, which is therapeutically effective if administered early during infection [7], has been used for postexposure prophylaxis [5].

Four cases of Lassa fever were imported into Europe in the year 2000, all of which were fatal. Still, every case receives great attention because of the possibility of secondary infections in contact persons. Furthermore, the debate on the use of hemorrhagic fever viruses as biological warfare emphasizes the need for data on the spread of these agents from human to human in Europe. The present study reports the epidemiological and virological investigation of 157 contact persons with...
different levels of exposure to a symptomatic patient with Lassa fever in Germany in January 2000.

INDEX PATIENT

The index patient had been symptomatic with fever and cough for 5 days when she boarded a commercial flight from Abidjan, Ivory Coast, via Lisbon to Germany. She was admitted to a local hospital the same day. After clinical deterioration, the patient was transferred to a specialized hospital on day 9 after the onset of symptoms (4 days after hospitalization), and 1 day later, Lassa fever was diagnosed by PCR and viral culture [8]. Appropriate isolation and surveillance measures were initiated. She died of hemorrhage and organ failure on day 14 of illness [9]. The viral RNA concentration in serum, as measured by real-time PCR, was initially $10^{5}$–$10^{6}$ RNA copies/mL and was increasing to $>10^8$ copies/mL concomitant with disease progression [10]. Furthermore, Lassa viral RNA was detected in a throat washing on day 10 of illness.

SURVEILLANCE AND MANAGEMENT OF CONTACTS

Epidemiological studies. A total of 232 contact persons were identified, and their level of exposure was assessed through interviews conducted by 22 local health departments in 7 states of Germany by means of a standardized questionnaire. Serological testing to identify asymptomatic infections started 3 weeks after the end of the incubation period. Serum samples obtained from contact persons were screened for IgG antibodies to Lassa virus by indirect immunofluorescence by using Vero cells infected with Lassa virus strain AV that had been isolated from the index patient [8]. Complete information was obtained for 157 (68%) of 232 identified contacts, and 149 patients (64%) were involved in care of the patient or handling of specimens obtained from contact persons were screened for IgG antibodies to Lassa virus by indirect immunofluorescence by using Vero cells infected with Lassa virus strain AV that had been isolated from the index patient [8]. Complete information was obtained for 157 (68%) of 232 identified contacts, and 149 patients (64%) were tested serologically (table 1).

Contact persons were assigned to 3 categories: (1) “high-risk contacts,” defined as persons with unprotected exposure of skin or mucous membranes to blood or secretions of the index patient, including intimate contact (such as kissing), or unprotected handling of specimens obtained from the patient; (2) “close contacts,” defined as persons with direct physical contact with the index patient; and (3) “casual contacts,” defined as persons who were in the same room with the index patient or who traveled on the same flight. Hospital staff members who were involved in care of the patient or handling of specimens and who used gloves and barrier techniques were assigned to group 3. Symptomatic secondary infections were not observed in any group.

High-risk exposures were reported by 18 contacts. Of these, 3 reported unprotected skin exposure to blood, 2 in the first and 1 in the second hospital. Exposure of unprotected skin to urine and stool was reported by 3 health care workers in the second hospital. Kissing of the patient was reported by 4 persons to have occurred before day 9 of illness. The remaining contact persons were hospital staff who reported unprotected handling of specimens of blood or other body fluids, mainly in the first hospital. The results of serological tests were negative for all persons with high-risk exposure.

Close physical contact was reported by 12 health care workers and family members. Lassa virus–specific antibodies were detected in the serum specimen obtained from a physician who reported a close contact on day 9 (see below). All other exposures occurred before day 9, and the contact persons were found to have negative results of serological testing.

No evidence of transmission was found among any casual contacts. The negative serological test results for all airplane passengers, including 19 persons who were seated within 2 rows of the index patient, indicate a very low risk of transmission under the conditions of a 3-h flight in a civil aircraft.

Probable secondary case. The physician who had positive results of serological tests had performed a physical examination of the patient after she had been transferred to the second hospital. The doctor inserted an intravenous line, obtained blood samples, and administered an infusion. Gloves and a protective mask were not used. Contamination of skin with blood from the patient was not recalled. The examination included inspection of the throat, and there was exposure to cough of the patient. The physician initiated ribavirin prophylaxis when Lassa fever was diagnosed in the index person ∼36 h after exposure and did not develop symptoms of the disease.

The contact person had never traveled to Africa, nor did she have antibodies to the Lassa virus–related lymphocytic choriomeningitis virus (LCMV), as determined by immunofluorescence testing. This excludes previous infection with Lassa virus or any other Lassa virus–related African arenavirus, as well as infection with the sole arenavirus known to be endemic in central Europe, LCMV, which may elicit antibodies that cross-react with Lassa virus. The Lassa virus–specific IgG titer was 1:320; the IgM titer was <1:20. The IgG response was found to be specific for the Lassa virus strain isolated from the

<table>
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<td>1 (2)</td>
<td>2 (4)</td>
<td>8 (4)</td>
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<td>62 (53)</td>
<td>0 (0)</td>
<td>13 (27)</td>
<td>75 (32)</td>
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Table 1. Identified contact persons and study population.
index patient (strain AV; figure 1A), because no reactivity was detected by immunofluorescence if the cells that were used for this assay had been infected with a laboratory Lassa virus strain (strain Josiah; figure 1C), which differs from strain AV by 6%–8% in the amino acid sequence [8].

Neutralizing antibodies against Lassa virus AV were not detected by plaque reduction testing [11] of serum samples obtained 1, 5, and 10 months after exposure. Absence of both IgM and neutralizing antibodies has been reported in patients with Lassa fever [11, 12]. The immunofluorescence pattern of the Lassa virus–specific IgG of the physician (figure 1A) perfectly matched the pattern produced by a monoclonal antibody to Lassa virus nucleoprotein (figure 1B), suggesting that nucleoprotein is the target of the physician’s antibodies. The reactivity to nucleoprotein was confirmed by a recombinant immunofluorescence assay. The nucleoprotein gene of Lassa virus AV was cloned into a plasmid and expressed in cell culture. IgG antibodies of the physician reacted with the recombinant nucleoprotein (figure 1E) similar to the nucleoprotein–specific monoclonal antibody (figure 1F). These data demonstrate an IgG response of the contact person to the putative infecting Lassa virus strain AV. An IgG seroconversion could not be demonstrated because of the lack of serum samples obtained early after exposure. Taking the laboratory data together, and considering the lack of clinical symptoms, the contact was classified as having a probable but not confirmed secondary infection.

Ribavirin prophylaxis. Prophylaxis with orally administered ribavirin (10 mg/kg 4 times per day for 5–8 days) was started for 16 high-risk and close-contact persons after the diagnosis in the index patient was established. There were temporary side effects reported, including skin rash, tachycardia, myalgia, diarrhea, and abdominal pain. In 1 case, there may have been an association between ribavirin and worsening of a preexisting tachyarrhythmia. A reversible increase in bilirubin levels and a decrease in the hemoglobin level occurred in 11 and 9 persons, respectively. One person stopped prophylaxis after 4 days because of jaundice, and another experienced an increase in the lipase level.

CONCLUSION AND DISCUSSION

The negative results of serological tests for Lassa virus for casual contacts, including passengers sitting next to the index patient in the airplane for hours, close contacts, and even high-risk contacts who were exposed to the index patient before day 9 of illness, suggest a minute risk for transmission during the initial phase of symptomatic Lassa fever. This is in agreement with the findings of previous studies, which have not detected secondary transmissions by surveillance and serological testing of selected contacts [4–6]. In contrast to these investigations,
a probable transmission was identified in a person who had a close contact on day 9 of illness. Even though the transmission could not definitively be proven according to serological criteria for acute infection (IgM detection or increase in IgG titer), the possibility that a transmission took place should be taken into consideration in the future management of imported Lassa fever.

Additional aspects that are consistent with an increased risk of transmission at the later phase of illness are the increase in viral RNA concentration in serum of the index patient after day 8 and the detection of Lassa viral RNA in saliva on day 10 [10], which offers the possibility that the virus is transmitted by coughing. Lassa virus can be transmitted via air between laboratory animals [13], and aerosol stability of Lassa virus has been proven experimentally [14]. However, there is so far no evidence that aerosols play a role in human-to-human transmission of Lassa virus.

Our findings emphasize that existing guidelines for the treatment of patients with imported Lassa fever as well as contacts [3, 5, 15] are reasonable, and that there is no reason to ease the rules. Patients with Lassa fever should be isolated in the clinical setting and treated by the use of barrier nursing techniques or protective respirators [15], as was done for the described patient [9]. The importance of universal precautions for control of nosocomial infections was underlined by the relatively high number of hospital staff who were found to be at risk because of unprotected contacts before the diagnosis was established.

There are 2 aspects that may be considered in the risk assessment of exposures in the future in light of the data. First, contacts who “perceived skin or mucosal contact with patient’s aerosolized sputum after a sneeze or cough” [5, p. 1121] were classified as medium risk in a previous [5] as well as in the current study. It seems advisable to classify these exposures as high risk. Second, the lack of transmission during the early phase of disease, despite high-risk exposures, and a likely transmission in the late phase, when the Lassa virus RNA concentration in serum was increasing, are consistent with a time-dependent increase in the risk of transmission parallel to disease progression. Thus, in addition to the degree of exposure, the stage of illness and/or the level of viremia at the time of exposure should be included in the risk assessment of transmission. The present study found no evidence of transmission as long as the viral RNA concentration was 10⁵–10⁶ RNA copies/mL serum. Recently developed real-time PCR protocols allow determination of the Lassa virus RNA concentration within a few hours [16]. Information on the virus concentration in serum and saliva could lower the number of contact persons that have to be observed or considered for prophylaxis.

Ribavirin is therapeutically effective for Lassa fever [7] and has been used for postexposure prophylaxis [5]. Prophylactic efficacy was observed with Lassa virus–exposed monkeys [17] but has not been demonstrated by clinical studies involving humans. The decision to administer ribavirin as prophylaxis is complicated by the side effects of the drug. In the 16 contact persons who received ribavirin in the current study, adverse events were observed in temporal association with ribavirin administration, although a causal relationship with the drug is not proven. With one possible exception, all were reversible. The most common adverse events—elevated bilirubin level and a decrease in the hemoglobin level—are known side effects of the drug [7, 18]. Therefore, monitoring of blood parameters is required, as has been noted previously [5, 7]. Mitochondrial toxicity resulting in pancreatitis or liver injury has been demonstrated in association with other nucleoside analogue drugs [19]. Jaundice and an elevated lipase level, as observed in 2 persons, are compatible with such toxicity. Observations of patients treated with ribavirin for other infections have suggested, but not definitively proven, similar toxicity associated with ribavirin [18]. Nevertheless, considering that a case of Lassa fever has presumably been prevented, we think that the administration of ribavirin in this situation was justified.

In conclusion, the present investigation demonstrates that Lassa virus is not easily transmitted from human to human outside of areas of endemicity, and, therefore, imported cases are unlikely to cause epidemics in Europe.

Acknowledgments

We thank the public health officials at the community and state level, for their commitment and collaboration; Gabrielle Rietdorf, for excellent technical assistance; and both reviewers, for their valuable suggestions on the article in manuscript.

References