

Management of Accidental Exposure to Ebola Virus in the Biosafety Level 4 Laboratory, Hamburg, Germany

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A needlestick injury occurred during an animal experiment in the biosafety level 4 laboratory in Hamburg, Germany, in March 2009. The syringe contained *Zaire ebolavirus* (ZEBOV) mixed with Freund's adjuvant. Neither an approved treatment nor a postexposure prophylaxis (PEP) exists for Ebola hemorrhagic fever. Following a risk–benefit assessment, it was recommended the exposed person take an experimental vaccine that had shown PEP efficacy in ZEBOV-infected nonhuman primates (NHPs) [12]. The vaccine, which had not been used previously in humans, was a live-attenuated recombinant vesicular stomatitis virus (recVSV) expressing the glycoprotein of ZEBOV. A single dose of 5×10^7 plaque-forming units was injected 48 hours after the accident. The vaccinee developed fever 12 hours later and recVSV viremia was detectable by polymerase chain reaction (PCR) for 2 days. Otherwise, the person remained healthy, and ZEBOV RNA, except for the glycoprotein gene expressed in the vaccine, was never detected in serum and peripheral blood mononuclear cells during the 3-week observation period.

Ebola virus is a zoonotic pathogen causing hemorrhagic fever in humans. The species *Zaire ebolavirus* (ZEBOV) and *Sudan ebolavirus* (SEBOV), as well as *Bundibugyo ebolavirus*, a proposed prototype member of a new species, have caused epidemics among humans in Africa with case fatality rates ranging from 25% to 90%. The

virus is transmitted from human to human by infectious body fluids, often in hospital settings [1–3]. Neither a vaccine, an effective treatment, nor a postexposure prophylaxis (PEP) for humans is currently available. For these reasons, experiments with Ebola virus have to be performed in biosafety level (BSL)-4 laboratories. Despite high standards of protection in these laboratories, laboratory workers are still at risk of contracting Ebola hemorrhagic fever, in particular during animal experimentation. Three laboratory accidents with Ebola virus are documented in the literature: 1 case was fatal [4], 1 case was symptomatic and survived [5], and in 1 case, there was no evidence that the accident resulted in infection [6]. Here, we report on the management of a laboratory accident with Ebola virus that occurred in the BSL-4 facility at the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany.

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CASE REPORT

A virologist working in the BSL-4 laboratory pricked herself in the finger during a mouse experiment on 12 March 2009. The syringe contained ZEBOV from culture supernatant that had been concentrated by ultracentrifugation and mixed 1:1 with incomplete Freund's adjuvant for immunization of mice. The material was injected into the animal before the accident happened. When the laboratory worker tried to recap the needle, it penetrated the cap laterally and subsequently all 3 gloves. The puncture site on the skin was visible, but it did not bleed. The wound was disinfected after leaving the laboratory. Overnight, reverse-transcription polymerase chain reaction (RT-PCR) analysis revealed that the ultracentrifuged material, before mixing with Freund's adjuvant, contained 2.6×10^{10} copies/mL ZEBOV. Traces of material in the syringe (about 2 μ L) were recovered and tested as well: it contained 1.4×10^8 copies/mL. The effect of incomplete Freund's adjuvant on Ebola virus was retrospectively tested by immunofocus assay. Mixing cell culture supernatant with adjuvant reduced the virus titer 4.4-fold. Thus, Ebola virus mixed with incomplete Freund's adjuvant essentially retains its infectivity.

An infectious disease specialist at the University Medical Center Hamburg saw the patient immediately after the accident. It was decided to consult colleagues from Canada and the United States to explore possibilities for PEP and treatment. The first teleconference was held in the evening of 12 March; a second one on 13 March. Filovirus experts from the Laboratory of Virology, National Institutes of Health, Hamilton, Montana; the Boston University School of Medicine; the Public Health Agency of Canada, Winnipeg, Canada; the Special Pathogens Branch, Centers for Disease Control and Prevention, Atlanta, Georgia; the US Army Medical Research Institute of Infectious Diseases in Fort Detrick, Maryland, and the University of Texas Medical Branch, Galveston, Texas, participated in the consultations. Various possibilities for PEP and treatment, which had previously been tested in nonhuman primates (NHPs), were discussed, including recombinant nematode anticoagulant protein c2 (rNAPc2) [7], recombinant human activated protein C [8], siRNA (unpublished at the time of accident) [9], interferon (L. Hensley, unpublished data), immune therapy with neutralizing antibodies [10, 11], and experimental vaccines [12–17]. The expert panel eventually recommended postexposure vaccination with live-attenuated recombinant vesicular stomatitis virus (recVSV) expressing the glycoprotein of ZEBOV (VSV Δ G/ZEBOVGP) for the following reasons: (1) VSV Δ G/ZEBOVGP has shown PEP efficacy in NHP [12]; (2) it is well tolerated in immunocompromized NHPs [13]; (3) a similar vaccine shows PEP efficacy against Marburg virus [15] and SEBOV [18]; (4) at the time of the accident, unpublished data indicated PEP effect (33% survival) of the recVSV-based Marburg virus vaccine, even 48 hours postinfection [14]; and (5) recVSV vectors show good

safety profile in NHPs as long as the vector is not inoculated directly into the central nervous system [19]. Immediately following the first teleconference, the VSV Δ G/ZEBOVGP vaccine was shipped from Winnipeg, Canada, to Hamburg. An emergency clearance from customs was obtained in advance. The package arrived in Hamburg in the morning of 14 March. Relevant facts available on the vaccine by 14 March are listed in Table 1. While the vaccine was in transit, a risk–benefit assessment was made on whether the vaccine should be given or not based on the following considerations:

1. a visible puncture site, but not definitive evidence that the skin was fully penetrated due to the lack of bleeding;
2. the syringe looked empty when the accident happened, but material was probably in the lumen of the needle;
3. a high concentration of ZEBOV in the syringe at the start of the manipulation, but was unknown whether mixing with adjuvant affected virus infectivity (retrospectively, we found Ebola virus does retain infectivity);
4. a good safety profile of the vaccine in NHPs, but no safety data in humans, as experimental VSV vaccines have never been administered to human volunteers;
5. an unknown mechanism of PEP effect in NHPs (not clear if effect is reproducible in humans);
6. a diminished PEP efficacy of the related recVSV-based Marburg virus vaccine in NHPs when given 48 hours after inoculation compared with earlier administration [14] (but the infectious dose in our case was probably much lower than in the animal experiments, which expectedly could increase the efficacy of PEP);
7. laboratory stock rather than Good Manufacturing Practice (GMP)–made vaccine;
8. ZEBOV infection is associated with 80–90% case fatality rate [20];
9. 1 of 3 documented needlestick injuries with Ebola virus had a fatal outcome [4–6].

The risk of ZEBOV infection and fatal outcome due to the accidental exposure was considered to be low, but real. A hypothetical risk of life-threatening adverse effects due to the experimental vaccine was considered acceptable in view of the anticipated benefit and the risk of ZEBOV infection. In addition, overwhelming recVSV replication was expected to be amenable to treatment with ribavirin and type I interferon, both of which strongly inhibit VSV replication *in vitro* and *in vivo* [21–25]. Members of the Institutional Ethics Committee of the University Medical Center, who were available for evaluation of the planned interventions, also shared these views. As a result, the patient was recommended to take the experimental vaccine. A PEP and treatment protocol with informed consent was drafted and signed by the patient.

The patient voluntarily agreed on being hospitalized on 13 March. The responsible public health authorities, infectious

Table 1. Facts on the recVSV Vaccine as Summarized in the PEP Protocol Signed by the Patient

Category	Comment
Origin of VSVΔG/ZEBOVGP vaccine	Vaccine stock was prepared in January 2005 and has since been stored in liquid nitrogen; concentration 2×10^7 plaque-forming units/mL. Grown on Vero E6 cells, harvested 2 days post infection and clarified of cells. Stock had been passaged 2 times after initial plasmid DNA transfection. Growth medium was DMEM, supplemented with 2% FBS, penicillin G, and streptomycin. Prior to freezing, FBS was added to a final concentration of 10%. Vaccine was provided by the Canadian Science Centre for Human and Animal Health, Public Health Agency of Canada, Winnipeg, Canada.
Side effects	About 80 monkeys were inoculated so far with the recVSV vaccines. The investigators have never observed any side effects in the monkeys, including monkeys that were severely immunocompromised [12–15, 18]. Known side effect of recVSV vaccines is neurovirulence upon intracranial inoculation of nonhuman primates (NHPs) [19]. No data on side effects in humans were available, as VSV vaccines have never been administered to human volunteers.
Dosage	NHPs of 3–10 kg were injected intramuscularly with $1\text{--}2 \times 10^7$ plaque-forming units of recVSV vaccine, including VSVΔG/ZEBOVGP [12–15, 18]. As the safety profile in humans is not known, only minimal dosage adjustment for humans was recommended (5×10^7 plaque-forming units).
Virological parameters	A transient recVSV viremia occurred in about half of the NHPs. The highest recVSV viremia was seen on day 2. In animals with a transient recVSV viremia, the level is usually less than 10^3 plaque-forming units/mL of plasma [13].
Treatment of recVSV-associated disease	Ribavirin and type I interferon inhibit VSV replication in cell culture and mice [21–25]. Therefore, both drugs would be used to treat overwhelming recVSV replication.
Combination with other treatments	Co-administration of activated protein C treatment had a negative effect on VSVΔG/ZEBOVGP efficacy in NHPs (T.W. Geisbert and L.E. Hensley, unpublished observations). Although the reason for this interference was not known, it was recommended not to use drugs with effects on the clotting system and the inflammatory response, including rNAPc2, in combination with the recVSV vaccine.

NOTE: DMEM = Dulbecco's modified Eagle's medium; FBS = fetal bovine serum; recVSV = recombinant vesicular stomatitis virus; NHPs = nonhuman primates; rNAPc2 = recombinant nematode anticoagulant protein c2.

disease specialists, and virologists considered the risk of virus transmission during the incubation period extremely low, as available epidemiological evidence indicates that Ebola virus is spread by ill or deceased patients through direct contact with infectious body fluids [1–3]. It was agreed that surveillance on a regular infectious disease ward in a single room with anteroom and negative pressure is appropriate. Standard barrier nursing precautions were implemented (gown, gloves, N95 mask, eye protection). It was also taken into account that this level of isolation is less stressful to the patient and the hospital staff. A maximum incubation period of 21 days was assumed and, therefore, surveillance was foreseen for this period of time. Daily monitoring during this period included (1) body temperature; (2) D-dimer level, which is an early marker of Ebola hemorrhagic fever in NHPs [7] and is increased in humans with Ebola hemorrhagic fever [26]; (3) hematology and blood chemistry; and (4) Ebola virus in plasma and peripheral blood mononuclear cells (PBMCs) using real-time RT-PCR [27, 28]. PBMCs were tested because the virus was detected in these cells in asymptomatic Ebola virus infections [29]. Fever, a rise in the D-dimer level, or the detection of Ebola virus RNA by RT-PCR were defined as independent indications of Ebola virus infection. If any of these showed a positive indication, the patient would have to be transferred to the Biocontainment Patient Care Unit (BPCU) of the University Medical Center (Figure 1). Isolation in the BPCU was required twice during the observation period for the reasons given below. The BPCU was located in a separate

building and included a single patient room with 2 airlocks. It had an independent ventilation system and was maintained under negative pressure. Exhaust air underwent high efficiency particulate air (HEPA) filtration. Staff was specifically trained and dressed in biosafety suits equipped with HEPA filters. A disinfectant shower enabled transfer of specimens out of the unit for laboratory analysis. All waste was treated in an autoclave. Personal protective equipment was decontaminated in the disinfectant shower before leaving the unit. Routine laboratory investigations were performed by the Clinical Chemistry Department without special precautions, as soon as a negative PCR result for a parallel sample had been communicated. If PCR results were not available in a timely manner, point of care diagnostics was performed within the BPCU.

If an Ebola virus infection would have been diagnosed in the patient, the expert panel recommended treatment with rNAPc2, an inhibitor of factor VIIa/tissue factor that has shown some therapeutic potential in NHPs infected with Ebola virus [7] and already undergone phase II studies for other medical conditions [30]. ARCA Biopharma generously released a batch of rNAPc2 on 13 March, which arrived in Hamburg on 15 March. In addition, Ebola virus-specific small interfering RNA (siRNA) preparations were provided by Tekmira Pharmaceuticals and arrived in Hamburg on 14 March. This siRNA had shown PEP effects in NHPs (unpublished at the time of accident) [9].

The VSVΔG/ZEBOVGP vaccine was administered on 14 March, 48 hours after the accident: a single dose of 2.5 mL

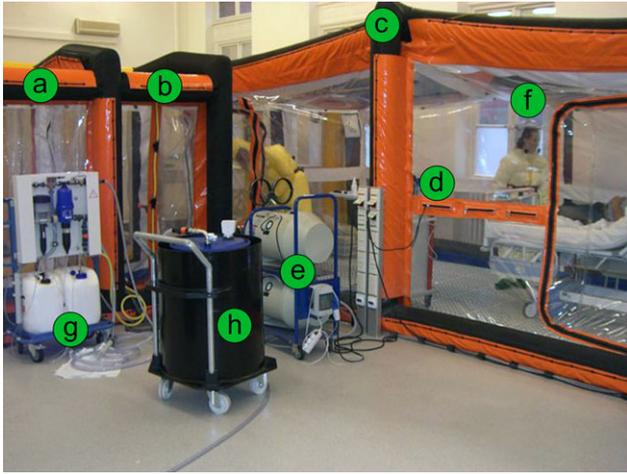


Figure 1. Biocontainment Patient Care Unit at the University Medical Center Hamburg used for isolation of the patient. The unit consists of 3 rooms: airlock 1 (a), airlock 2 (b), and the main room with a bed for a patient (c), which are separated by airtight "doors." It is maintained under negative pressure with an increasing pressure gradient from airlock 1 to the patient room. Equipment for patient care is placed outside the unit and cables or flexible tubes for artificial ventilation or suction are passed through the wall of the unit (d). Exhaust air is filtered through HEPA filters (e). Staff are wearing full-face respirators with a HEPA filter in combination with biohazard protective suits (f). The unit is entered via airlocks 1 and 2. Before exiting the unit, the suit is decontaminated in a chemical shower in airlock 2. The shower applies foam on the surface of the suit consisting of peracetic acid and alcapur that is mixed outside the unit (g). Exposure time is 12 minutes. Thereafter, the person leaves the unit through airlock 1 and undresses. The remaining decontamination fluid is pumped out of airlock 2 and stored in a barrel outside the unit (h) until the peracetic acid is decomposed and can be fed into the wastewater system.

undiluted and unfiltered virus stock (2×10^7 plaque-forming units/mL) was injected intramuscularly in the deltoid (1.25 mL each side = 5×10^7 plaque-forming units total dose). For safety reasons, the dose given to NHPs [12] was only minimally increased (2.5 fold). Anesthesiology team was on standby in case of serious anaphylactic reactions. However, neither local nor systemic adverse reactions were observed on the day of administration. The next day (day 3 after the accident), the patient developed fever and myalgia (Figure 2). The symptoms were not treated. As it could not be decided if the fever was an adverse effect of the vaccine or a sign of an Ebola virus infection, the patient was transferred to the BPCU. The ZEBOV GP gene-specific real-time RT-PCR [28] and a VSV-specific specific real-time RT-PCR (primer VSV-F1 GACCTTGATCCTT-GAAAGCC, primer VSV-R1 CATTGTGTTCTGCCACTC, and probe FAM-TGCTTCCAGAACCAGCGCAGATGACAAA-BBQ) were positive with plasma samples from days 3 and 4. The cycle threshold (Ct) values were high: VSV RT-PCR day 3: Ct 34; day 4 morning: Ct 32; day 4 evening: Ct 34; ZEBOV GP RT-PCR day 3: Ct 31; day 4 morning: Ct 33; day 4 evening: Ct 35. (Note: The Ct is the PCR cycle at which the sample reaches the

detection level. The higher the Ct, the lower the amount of virus RNA in the sample. A Ct above 30 indicates low viremia, around 10^3 – 10^4 genome copies/mL plasma.) The Ebola virus-specific L gene PCR [27] was negative, indicating that the signals from VSV and ZEBOV GP RT-PCR originated from low-level viremia of the recVSV rather than from ZEBOV replication. All 3 PCR assays remained negative during the rest of the observation period. The temperature returned to normal in the evening of day 3. Blood chemistry, coagulation, and hematology parameters were in the normal range. As no disease developed and fever and positive PCR signals could not be attributed to Ebola virus infection, the public health authorities released the patient from BPCU. On day 7, surveillance was continued on the regular infectious disease ward as described above. A slow increase in the D-dimer level starting day 9 led again to the decision to transfer the patient to the BPCU on day 11 (Figure 2). However, as no signs or symptoms developed, and other laboratory parameters remained normal—except for a slight elevation of the fibrinogen level—and all PCR assays remained negative, it was decided to retransfer the patient to the regular infectious disease ward on day 14. The elevation of the D-dimer level, as measured by Siemens Innovance assay, persisted. However, it could not be confirmed by 2 other D-dimer assays (Triage and bioMérieux Vidas), and the exact cause of this elevation has not been determined. No signs of thrombosis were detected by physical examination and Doppler sonography. The remaining clinical course was uneventful and the patient was discharged from hospital on day 21.

CONCLUSIONS

A key beneficial factor in the medical management of this accidental exposure to Ebola virus has been the immediate communication with the scientific community. Several ad hoc teleconferences were held, complemented by extensive e-mail communication, to support decision making of the team in Hamburg. Within a few hours after the accident, the way forward was defined based on the knowledge of leading experts in the field. Unpublished data were shared and investigational vaccines and drugs were provided in a completely unbureaucratic way [31].

One may ask why the team in Hamburg chose this ad hoc procedure and not activated a defined operational plan to manage the patient. The Bernhard Nocht Institute followed a general operational plan for the management of accidental laboratory exposures, which included agreements with the Infectious Diseases Unit at the University Medical Center. Both virologists and clinicians in Hamburg had been aware of experimental treatment options as published in the literature. However, like other BSL-4 facilities or infectious diseases units, which do not work on filovirus vaccines and therapeutics in NHPs or have contributed to field missions in filovirus

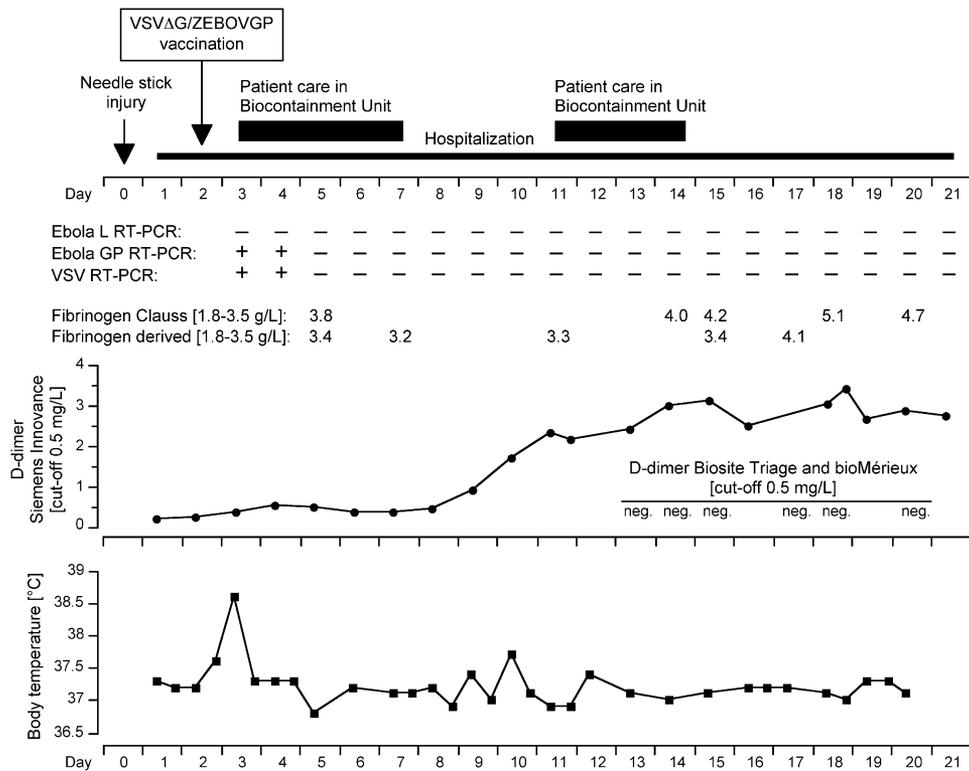


Figure 2. Monitoring of clinical, biochemical, and virological parameters during the observation period of 3 weeks. The timeline with key events is shown on top. The period of hospitalization is depicted by the horizontal bar. PCR results are indicated as positive (+) or negative (-). D-dimer levels and body temperature are shown below.

outbreaks, they lacked the personal experience with this matter, the access to unpublished data, and the link to suppliers of investigational drugs and vaccines for making a choice among the different options. While a comprehensive set of general recommendations for the management of accidental laboratory exposures in BSL-3 and BSL-4 laboratories is available [32], there are no pathogen-specific recommendations for medical treatment of a case, especially for filoviruses. The BSL-4 laboratory community should consider establishing such recommendations. However, we think that they may not replace the consultation of experts in an emergency situation to take advantage of unpublished observations and personal networks among experts, companies, and governmental agencies. Nowadays, ad hoc communication is greatly facilitated by mobile and Internet technologies. Another issue is the supply of experimental drugs or vaccines in an emergency. Laboratory and health care workers exposed to highly pathogenic viruses would benefit from the availability of GMP-made vaccines or drugs for PEP and therapy that have gone through at least extensive efficacy and safety testing in NHPs. Ideally, vaccines or drugs for PEP should be stockpiled at each BSL-4 laboratory to circumvent delays due to shipment and potential bureaucratic hurdles.

Another important aspect has been the rational decision making by the public health authorities in Hamburg, which facilitated a flexible case management based on constant

monitoring of the situation. In particular, the fact that the patient was not requested to stay for the whole 3-week observation period in the BPCU improved and simplified the care, reduced the psychological stress for the patient, and facilitated communication of the patient with staff, relatives, and colleagues. Indeed, the patient reflected that the stay within the BPCU was associated with a high level of stress.

The accident led to a review of the operating procedures for the BSL-4 facility. While the safe deposition of needles was requested in the operating procedures, recapping was not explicitly prohibited. Investigation of the case by the regulatory authorities revealed a gap in the operating procedures but no misconduct. The manuals have been revised accordingly and the laboratorians made specifically aware of the correct procedures.

Finally, the question remains whether the patient had been infected with Ebola virus or not. Investigation of the patient's serum samples revealed high IgG titers to VSV and robust IgG titers to Ebola virus GP. No further serological evidence could be obtained that would support an Ebola virus infection (unpublished data). The serological data suggest that the patient was either not infected with Ebola virus, which is considered more likely, or that the vaccine reduced virus replication to an extent that the development of a proper humoral immune response to the virus was prevented. The Ebola virus GP antibody titers are most likely a result of the vaccination.

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