Clinical Management of Patients Infected with Highly Pathogenic Microorganisms

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9.1 Introduction

Providing clinical care for patients suffering from high-consequence infectious disease (HCID) is challenging. Medical therapy for patients suffering from HCID may frequently be sophisticated and complex but lacking in evidence base and in extensive experience. Despite maximal intensive care treatment that is administered, including the most advanced resources, mortality among such patients is mostly very high. On the other hand, the natural impulse as a medical practitioner to provide immediate and efficient medical care to the patient may be compromised by the need for health care workers' (HCW) protection with personal protective equipment (PPE). Biological weapons agents are frequently rare, highly virulent micro-organisms causative for HCID (Table 9.1).

This chapter focuses primarily on individual patient care with a high level of both patient care and infection prevention and control. Mass casualty management strategies for HCID are discussed as well.

9.2 Initial Approach Towards an HCID Patient Potentially Requiring High Containment Isolation

The initial approach towards an HCID patient differs. Scenarios might be:

(a) *A patient turns up at a medical facility on her/his own initiative as a suspect case*

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Table 9.1 Causative agents of HCID potentially requiring high level containment

Agent	Disease(s)	US Biosafety Level (BSL) requirement[a]
Middle East respiratory syndrome coronavirus (MERS-CoV)	Middle East respiratory syndrome (MERS)	3
Severe acute respiratory syndrome coronavirus (SARS-CoV)	Severe acute respiratory syndrome (SARS)	3
Yersinia pestis	Pneumonic plague Bubonic plague Plague meningitis Plague sepsis Other forms of plague	3
Variola virus (VARV)	Smallpox	4
Monkeypox virus (MPXV)	Monkeypox	4
Crimean-Congo hemorrhagic fever virus (CCHFV)	Crimean-Congo hemorrhagic fever (CCHF)	4
Ebola Virus (EBOV) Sudan Virus (SUDV) Taï Forest Virus (TAFV) Bundibugyo Virus (BDBV)	Ebola virus disease (EVD)	4
Marburg Virus (MARV) Ravn Virus (RAVV)	Marburg virus disease (MVD)	4
Lassa virus (LASV)	Lassa fever	4
Other viruses for which US BSL requirement is 4 and which are causative of viral hemorrhagic fevers (e.g., Junín Virus, Machupo Virus)		

[a]Laboratory biosafety levels according to: https://www.cdc.gov/biosafety/publications/bmbl5/bmbl5_sect_iv.pdf

This might include the so-called "worried well" who did not encounter a significant source of infection. Particularly in the case of a mass casualty scenario, the "worried well" may slow down clinical management of genuinely affected patients [1]. Furthermore, a significant role is played by patient and staff flow as well as structural capacities of the hospital.

(b) *A patient is brought to a medical facility by ambulance as a suspected case*

This scenario is probably managed most easily. Patient and staff flow, area management, and protective measures (such as donning PPE) are regulated quite restrictively in Standard Operating Procedures (SOPs) of high-level isolation units as well as of other tertiary care hospitals.

(c) *A patient is admitted to hospital for a differential diagnosis (e.g., malaria, influenza). An HCID is diagnosed later on in the hospital or after discharge*

Secondary transmissions of HCID in Africa and the Western World frequently follow this scenario. For example,

- In May 2015, a patient travelled from Liberia via Morocco to the USA, where he was admitted to hospital due to a sore throat, fever, and tiredness. He reportedly did not indicate travel to Western Africa and was discharged home the same day. Three days later, he was re-admitted due to clinical deterioration and tested positive for Lassa virus (LASV) infection. He succumbed to Lassa fever [2].
- A patient who was initially diagnosed with malaria was medically evacuated from Togo to Germany in March 2016. After his death, his body was retrospectively tested and found to be infected with LASV. The mortician who handled the corpse contracted the virus, developed Lassa fever, was administered experimental treatment with ribavirin and favipiravir and survived [3, 4].
- In August 2016, a man presented to a university hospital in Madrid, Spain, with a history of high fever, abdominal pain, malaise, nausea, and diarrhea. His clinical condition deteriorated, he developed multi-organ failure, and died in spite of intensive care treatment. All tests for routine infections were negative. Retrospectively, he was diagnosed with Crimean-Congo hemorrhagic fever (CCHF). A nurse who had assisted with the endotracheal intubation of the index patient contracted CCHFV, was treated with ribavirin, and survived [5].

Patients might present to a health care facility of any level. It is probable that the initial physician confronted with an HCID patient sees an HCID clinical picture for the first time in her or his life. Hence it is crucial to have immediate technical support by medical professionals experienced in infectious diseases as well as reference hospitals close by. Numbers and bed capacities of high-level isolation units (HLIU) differ largely between countries [6]. During the 2013–2016 Ebola virus disease (EVD) outbreak in Western Africa, medical evacuation of non-EU/non-US citizens was an issue due to the scarcity of suitable isolation facilities in their home countries [7].

Infection prevention and control measures are crucial. Please refer to Chap. 8 for further instructions on universal precautions. The particular approach differs according to the suspected pathogen. Causative pathogens of viral hemorrhagic fevers (VHFs) such as Ebola virus (EBOV) and LASV have a relatively low stability, and fluid transmission plays the key role [8]; hence national and international guidelines on EVD recommend a safety distance of 1.5–2 m to avoid transmission via macro droplets in case PPE is not worn—such as in patient screening [9, 10]. If physical contact to the patient and/or her/his bodily fluids has to occur, wearing PPE is of utmost importance. For PPE recommendations please refer to the Sect. 9.7.

Health care facilities of any level should include the initial approach towards suspected and confirmed HCID cases in their emergency preparedness plans and SOPs. These procedures might differ largely between hospitals, depending on factors such as human resources and the architectural setup of the medical facilities.

9.3 Area Management

The location where an HCID patient receives medical care is potentially highly contaminated. PPE should be worn at any time. Areas in which there is a low risk of infection and which serve as a supply base (e.g., storage room, staff room) versus sites that are high-risk zones (places where patient care takes place) should be defined very clearly. The 2013–2016 EVD outbreak has shown that poor area management can be a significant source of infection [11].

There are different concepts of area management. For example,

- In EVD treatment centers in field settings, usually a "low-risk zone" and "high-risk zone" are defined.
- A differentiation between a red zone (contaminated patient area), a yellow zone (inner chamber), and a green zone (outer chamber/non-contaminated area) is made in the context of occupational health dealing with HCID in Germany [12].

The inner chamber ("yellow zone") allows space for PPE decontamination and doffing (Fig. 9.1).

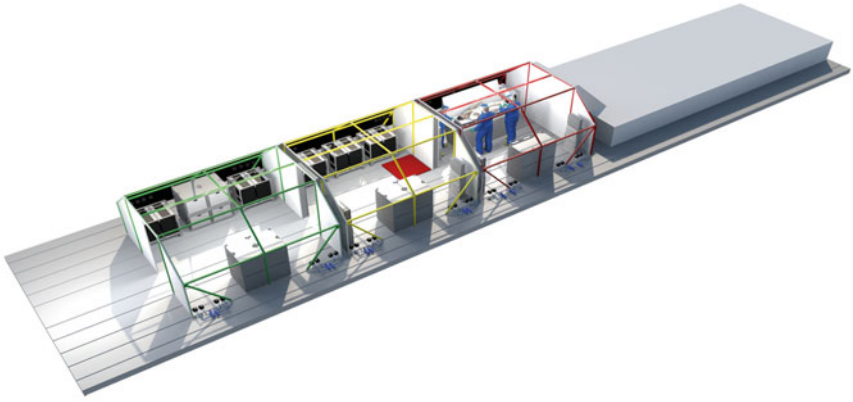

Fig. 9.1 Example of Area Management: Medical evacuation aircraft "Robert Koch". The patient is treated in the red zone by staff wearing personal protective equipment (PPE). The yellow zone is designated for PPE decontamination and doffing. Staff can don PPE and store supplies in the green zone

9.4 Supportive Treatment

Supportive treatment should be based on clear plans and guidelines, such as those for intensive care and sepsis management (http://www.survivingsepsis.org). Furthermore, national and international (WHO) specific guidelines and therapeutic recommendations for the particular disease should be consulted. Intensive care largely depends on available resources in the limited nursing setting. There are indications that intensive care may improve clinical outcomes: Out of 20 patients who were medically evacuated during the 2013–2016 EVD outbreak, 16 survived, yielding a case–fatality ratio (CFR) of 20% [13]. On the other hand, the overall case–fatality ratio for all confirmed cases in Guinea, Sierra Leone, and Liberia with recorded clinical outcomes was 63% [14]. Even more, case fatality ratios for Marburg virus disease (MVD) fluctuate between ~22% for an outbreak which occurred in West Germany in 1967 (supportive treatment and frequent blood samplings for clinical surveillance were performed at that time) and ~88% for an outbreak in Uíge/Angola in 2005 [15, 16].

One means of intensive care not listed in Table 9.2 is extracorporeal membrane oxygenation, the use of which has been documented for one case of Middle East

Table 9.2 Supportive care measures reportedly delivered at EVD treatment facilities during the 2013–2016 Western African outbreak [13, 17, 18]

Facility	Supportive care measures available
Goderich Treatment Centre (Sierra Leone)	Constant bedside nursing Continuous blood pressure/heart rate/respiratory rate monitoring Pulse oximetry Arterial and venous cannulation Nasogastric tube feeding Invasive ventilation Continuous renal replacement therapy Diagnostic biochemistry and hematology Ultrasonography Plain radiography
Mathaska Ebola Treatment Unit (Sierra Leone)	Nasogastric tube feeding Bedside ultrasound Intraosseous cannulation for intravenous fluid resuscitation
Frankfurt High-Level Isolation Unit (Germany)	Constant bedside nursing Continuous blood pressure/heart rate/respiratory rate monitoring Pulse oximetry Peripheral arterial and venous cannulation Central venous cannulation/placement of Sheldon Catheter Invasive ventilation Renal replacement therapy Diagnostic biochemistry and hematology Ultrasonography Plain radiography

respiratory syndrome (MERS) treated in France [19]. Severe acute respiratory syndrome (SARS), MERS, and pneumonic plague mainly affect the respiratory system. A long-term follow-up study indicates that patients affected by adult respiratory distress syndrome (ARDS) can benefit from extracorporeal membrane oxygenation [20]. Equipment and qualified staff are available in designated extracorporeal membrane oxygenation centers. A directory of these centers is available at https://www.elso.org/.

9.5 Specific Treatment

Specific treatment for HCID is often still experimental and/or only administered as compassionate use. This lack of progress is partly due to a lack of patients and costly large-scale clinical trials, hence precluding regular drug approval by national drug authorities. For example, the use of ribavirin as a treatment of Lassa fever is mainly based on a small clinical study without a control group performed in the 1980s [21]. However, none of the HCID dealt with in this chapter are listed as neglected tropical diseases, according to WHO [22]. Examples of specific treatments for HCID are indicated in Table 9.3.

National and international guidelines which mention specific treatments against HCID are scarce. Some of the above-mentioned specific treatments are more frequently used for treating more 'common' diseases, making available more safety data and facilitating easier drug procurement, for example:

- Antibiotics such as quinolones/tetracyclines/cotrimoxazole against bacterial infections
- Oral ribavirin against hepatitis C and
- Favipiravir against influenza.

On the other hand, drug procurement and stockpiling of rarely used drugs or those commercially undeveloped (so-called 'orphan drugs') are a challenge. The fact that synergies are not implemented but country and state authorities tend to do 'their own thing' can be detrimental for efficient stockpiling strategies [41]. Drug procurement strategies should take into account established contacts to the drug manufacturer and to the public health/drug/customs authorities and, if applicable, should also consider benefitting from the compassionate use program. For examples of such programs, please refer to [42–44].

Table 9.3 Examples of specific treatments, post-exposure prophylaxis and vaccines for HCID (all experimental)

Disease(s)	Treatment	Post-exposure prophylaxis	Vaccines	International specific treatment guidelines
Pneumonic plague	Quinolones Aminoglycosides Tetracyclines Cotrimoxazole [23, 24]	Quinolones, cotrimoxazole [23, 24]	Sub-unit vaccine based on the F1- and V-antigens [25]	WHO guidelines available [23]
Smallpox	Brincidofovir [26] Tecovirimat (ST-246) [27]	Smallpox vaccine [28]	Smallpox vaccine (WHO Emergency stockpile 'SVES' available) [29]	
Crimean–Congo hemorrhagic fever	Ribavirin [30] Favipiravir [31]			WHO guidelines in development [32]
Ebola virus disease[a]	ZMAPP [33] Favipiravir [34]	VSV-ZEBOV vaccine [35]	VSV-ZEBOV ChAd3-vaccine [36]	WHO guidelines available [37]
Lassa fever	Ribavirin [21] Favipiravir [38]	Ribavirin [39]		

For more details, please consult chapters dealing with the particular disease as well as national and international guidelines

[a]In the context of the 2013–2016 Western African EVD outbreak, research activities were mainly focused on Ebola Virus (EBOV) and did not target other ebolaviruses (SUDV, TADF, BDBV) or marburgviruses (MARV, RAVV). For future epidemics caused by filoviruses other than EBOV, there are thus still significant research gaps concerning specific treatment and vaccination [40]

9.6 Dead Body Management

Handling dead bodies is a high-risk task. Staff managing dead bodies (e.g., morticians) are rarely trained at the same level as medical practitioners, although they may be exposed to the same risks. As for EVD, the highest viral loads can be found in dead bodies [45]. Having well-trained staff and PPE available is crucial. All procedures that involve any contact with the dead body and/or body fluids should be performed while wearing PPE. All avoidable procedures (e.g., embalming) should be avoided. The body should be placed in a body bag. Cultural sensitivities should be respected when handling a dead body as the evacuation of a dead body can be traumatizing for the population. For example, during the Western African EVD outbreak, burial teams were attacked [46]. Exact procedures for decontamination of the dead body, body bag, and surroundings as well as exact burial procedures depend on the causative pathogen. For example, *Yersinia pestis*, though sensitive in aerosols, can survive in carcasses for up to 2 months at 35 °C [47]. ICRC guidelines for

dead body management in disaster contexts were updated recently [48]. A specific WHO dead body management/burial guideline for EVD is available [49].

9.7 Personal Protective Equipment (PPE)

For further instructions on universal precautions, please refer to the Chap. 8 in this book. PPE should be safe, user-friendly, and appropriate. Choosing the 'appropriate' PPE is complex because of to the following elements:

- National and international PPE recommendations vary. For example, during the Western African EVD outbreak, differences between PPE standards of WHO, CDC, MSF, and other actors were the subject of debate [50].
- The resources in terms of materials and qualified staff are different from place to place.
- National work security regulations differ (e.g., restricting duration of shifts).
- In the event of a possible bioweapons attack, the causative agent might be unknown (unknown pathogen or, even more complex, generally unknown chemical/biological/radiological/nuclear CBRN-spectrum agent) or multi resistant (example: multi-resistant *Y. pestis*). Particle sizes for different pathogens differ significantly, compromising the choice of the appropriate respirator. For example, if a chemical agent cannot be excluded in a scenario of a generally unknown CBRN-spectrum agent, a self-contained breathing apparatus should be considered.

Types of PPE are

- *PPE with gown/overall*, FFP2/3 (or N95/N98) respirator, double gloving, goggles/face shield and other facultative items (e.g., apron, rubber boots): This PPE is inexpensive, widely available, and WHO standards have been set for clinical care for patients infected with filoviruses such as EBOV: http://www.who.int/csr/resources/publications/ebola/ppe-guideline/en/.

  The challenge is that this PPE is composed of singular items, each of which was usually tested according to norms (in the European Union: EN standards). In practice, due to the complexity of donning, doffing, and decontaminating PPE, errors which compromised biosafety have been documented [51]. Furthermore, particular agents for decontamination (e.g., peracetic acid) cannot be used due to lack of filtering of chemical agents by FFP2/3 (or N95) respirators. Finally, because of the lack of ventilation, exhaustion due to heat is frequent and the wearing time thus limited [52].
- *Powered Air Purifying Respirator (PAPR)* is frequently used in European HLIU and, as for the EU, defined by EN standard 12,941 [53]. Depending on the exact type, they are mostly easy to don and doff. As ventilated equipment, PAPR is comfortable to wear, allowing longer working times [54]. Decontamination can be performed by, for instance, taking a shower with a decontaminating agent,

provided that this agent is compatible with the filter chosen. However, PAPR is quite expensive and hence may not be available in resource-poor settings.
- *Self-Contained Breathing Apparatus* is frequently used by fire brigades in Western countries (e.g., for intervening in smoky locations or those contaminated by chemical agents). This apparatus is heavy, complex to use, allows only very limited time of operation while wearing it, and is, according to national work security regulations, only to be used by staff who underwent a medical examination for aptitude. The choice of a self-contained breathing apparatus should hence be reserved to settings in which the presence of an agent leaking through the filters of other PPE (e.g. PAPR) cannot be excluded [54].

The choice of PPE for different procedures in environmental and health care settings should be circumscribed as clearly as possible *before* an HCID-related event takes place.

Case example 1: Choice of PPE in HLIU in Germany

The choice of PPE in Germany is mainly prescribed by regulations (e.g., Ordinance on biological substances or technical regulations for biological substances—TRBA). Annex 1 of TRBA No. 250 describes the infection prevention and control measures that have to be undertaken in an HLIU. There, PAPR according to the norm EN 12941 is set forth as mandatory. Each one of the seven German HLIU has its individual PAPR. Integrated systems as well as a combination of an overall and a ventilated hood are used.

Case example 2: Choice of PPE in mass casualty management in Israel

The type of PPE to be used in Israel by medical first responders and hospital teams in each type of emergency scenario is determined by the Israeli Ministry of Health. The decision is made based on the lethality of each agent, availability or lack of a specific effective treatment, extent of morbidity, and level of infectivity. In case of agents that are not communicable from person to person (e.g., *Bacillus anthracis*), standard droplet protection is required consisting of surgical masks, protective glasses/facial protection, and a gown while performing actions that involve aerosol exposure (e.g. suction of secretions). During pandemics, aerosol protection is required especially if the lethality of the disease is high relative to seasonal influenza. This protection includes surgical masks (to be replaced at least every 4 h); gowns over clothes; gloves to prevent contact with mucous membranes, blood secretions, and fluids; and protective goggles only when performing activities that pose a risk of spraying onto mucous membranes. In cases when aerosolization is likely, N95 masks are required (e.g., cases of airborne infection). Only very severely ill patients are treated by staff donning the strictest PPE against aerosol agents, including negative-pressure protective systems and ventilated hoods.

9.8 Decontamination and Disinfection

This chapter deals with decontamination and disinfection in the context of clinical management. For general advice on decontaminating capabilities and facilities, please refer to Chap. 6 in this book. The decontaminating agent should be chosen depending on the pathogen and site (PPE, surface, medical equipment, skin/mucous membranes or eyes, environmental decontamination). International and national recommendations concerning decontaminating agents should be taken into account, considering the pathogen (bacteria, viruses, or fungi). The 'worst-case pathogen' is *Bacillus anthracis* due to its extreme stability in most environments [55].

Concerning PPE decontamination, detailed documentation is available concerning its application and decontamination at a CBRN site ('hot zone') [56]. On the other hand, the decision of how to decontaminate PPE after having performed clinical management of HCID patients is complex: Concerning EVD, CDC currently recommends disinfection of gloved hands as well as of visibly soiled parts of the PPE. PAPR should be cleaned and disinfected in accordance with the manufacturer's recommendations [57]. As for high-level isolation units in Germany, PAPR is systematically decontaminated after use. For example, when an EVD case was cared for in Hamburg/Germany in 2014, the PPE was decontaminated after use by two shower cycles with 2% perchloric acid for 2 min, a residence time of 7 min, and rinsing off of acid residues by showering with water [17].

Surface decontamination can be complex if the surface is porous and/or if medical equipment is involved. Krauter et al. [58] discuss general decontamination strategies following a bio-contamination event.

The *decontamination of medical devices and the needed measures* are, in detail, discussed by WHO [59] and RKI [60]; differentiating between:

- non-critical equipment which neither invades the skin nor comes in contact with mucous membranes (e.g., ECG electrodes)
- semi-critical equipment which comes in contact with mucous membranes (e.g., speculum, gastroscope), and
- critical equipment which is invasive (e.g., retractors, trocars).

The relevant guidelines should be consulted to decontaminate medical devices adequately.

Decontamination of skin, mucous membranes, or eyes applies mainly in the context of immediate contamination with a bioweapons, such as *B. anthracis* spores. Please refer to Chap. 6 in this book as well as Krauter et al. [58].

Disinfection of skin, mucous membranes, or eyes is subject to universal precautions (see Chap. 8 in this book). A particular challenge can be the disinfection of mucous membranes and eyes due to their vulnerability. For disinfection of mucous membranes, the Framework Ebola Virus Disease document in Germany recommends octenidine dihydrochloride/phenoxyethanol or chlorhexidine-containing drugs or povidone–iodine complexes (7.5%) (e.g. Octenisept®, Skinsept mucosa®, Braunol®). For application on the eyes, 5% povidone–iodine complex

can be suitable [61]. A particular scenario might be an accidental exposure to bodily fluids, for instance by a splash of infective bodily fluids on unprotected skin or into the eyes, or by a needle stick injury. Medical facilities should have clear SOPs for such incidents.

For environmental decontamination, please refer to Chap. 6 in this book. This topic is furthermore discussed in detail by Franco and Bouri [55].

9.9 Practical Case Examples: Lassa Fever and Ebola Virus Disease in Germany

1. *Ebola Virus Disease in Germany in 2014*

Health care worker (HCW) infections were an important and very sad effect of the Western African EVD outbreak. As of 31 March 2015, 815 HCW had contracted EVD. Out of 635 health care workers for whom the outcome was available, 418 (65.9%) died [62]. In total, three medically evacuated HCW were treated in HLIU in Germany in 2014, two of whom survived. The patients were administered experimental treatments and likely benefited from intensive care. Infection prevention and control was thoroughly maintained. Staff caring for the patients wore PAPR as PPE. Neither secondary infections nor imported cases occurred in Germany [17, 18]. In spite of this fortunate epidemiologic 'outcome', there was an emotional debate in Germany driven by fear [63]. Public health authorities made a tremendous effort to enhance emergency preparedness towards the disease, and an elaborate document 'Framework Ebola Virus Disease' was released led by Robert Koch Institute, Germany RKI [64]. A sophisticated medical evacuation airplane with resources for performing comprehensive intensive care measures aboard was designed, launched in November 2014 and, because of the end of the humanitarian crisis related to EVD, dismantled in [65, 66].

2. *Lassa Fever in Germany 2015*

In February 2016, a 46-year-old HCW who worked in Togo fell sick with developing fever, malaise, and a sore throat. He was admitted to a local hospital where treatment for suspected malaria was started immediately. Because of clinical deterioration he was medically evacuated from Togo to Germany nearly 2 weeks later. He was admitted to the University Hospital of Cologne, Germany. After arriving at this hospital, the clinical condition of the patient deteriorated dramatically, resulting in the patient's death shortly after hospital admission. The postmortem examination did not reveal an underlying infectious disease. Simultaneously, after histologic examination of liver specimens of the index case a viral hemorrhagic fever was suspected. Blood and liver samples were sent to the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany, for further analysis. The institute confirmed LASV infection by PCR. The body was hence cremated [67].

A mortician who handled the primary case's corpse, and who was reported to have worn gloves and did not recall being exposed to body fluids, contracted the disease. He had overlapping clinical signs of an upper respiratory tract infection at the time of contact. Eight days after exposure, a first PCR for LASV was negative. A subsequent PCR was positive and the patient was admitted to the isolation unit in Frankfurt. He received experimental treatment with ribavirin and favipiravir, clinically improved with resolving fever from the 7th day of disease onwards, and survived [4, 68].

This was the first recorded transmission of LASV infection outside Africa. The case underlines the need for rapid and robust diagnostics of HCIDs and for maintaining proper infection prevention and control measures by using PPE whenever HCIDs cannot be ruled out. The incident also demonstrated that larger outbreaks can be prevented successfully when the Health Protection Authorities (HPA) react quickly and efficiently and install effective infection control measures. Difficulties were related to the unreliableness of contact persons who did not adhere to communicated control measures, thereby provoking an increase in the number of contacts. Also, one explicit lesson learned was that information between different authorities involved should be shared rapidly, facilitated by a central coordination [69].

9.10 Role of the Public Health Sector

The interface between HCID expertise in clinical management and public health sectors should be well established. For example, for referring a patient, a health care facility might need an isolation transport ambulance—and hence the assistance of the public health service for coordination. For contact-tracing activities, the public health service requires information that is gathered by the health care facilities from affected people. HPA are responsible for responding to any problem concerning the infected patient outside of health care facilities, as well as for limiting secondary transmissions. Despite an increasing knowledge about HCID, major challenges still remain for the physicians and HPA who treat these patients.

In Germany, the Permanent Working Group of Competence and Treatment Centres for highly infectious, life-threatening diseases (STAKOB) was established in 2014. It regroups HCID experts from all seven HLIU—mainly infectious disease specialists—and from seven corresponding HPA [70]. The STAKOB members HLIU and HPA are located dispersedly on the state level to assure proximity. Additionally, specialists from the Federal Institute for Vaccines and Biomedicines, the medical services from the Federal Foreign Office, the medical service of the German Federal Armed Forces, and others participate in the activities. The STAKOB office is affiliated to the Robert Koch Institute (RKI). Regular meetings are held twice a year, and conference calls are made supplementarily and *ad hoc* in the event of an occurring crisis. In addition to professional exchange and emergency preparedness activities, STAKOB was involved in the provision of medical care to

the three EVD cases evacuated to Germany in 2014 and in the response to Lassa Fever that occurred in Germany in 2015 (see case descriptions above).

9.11 Particularities in HCID Mass Casualty Management: The Israeli Example

9.11.1 Surge Capacity

An HCID outbreak might rapidly develop andrequire management of mass casualties that may present to the hospitals. The influx of patients to the emergency departments (EDs) necessitates preparedness to expand surge capacities of the varied hospital facilities including the ED, intensive care units, inpatient departments, and laboratory capacities [71, 72]. Nevertheless, compared to natural disasters or other types of emergency situations, an HCID outbreak presents different challenges, as the patients do not necessarily present to the emergency departments simultaneously and for a short period of time but rather do so over a prolonged time span [65]. The patients may present a high risk for transmitting the infection and thus pose a risk for spreading the disease to the personnel or other patients that are hospitalized. Therefore, those managing the event need to take into account unique elements of surge capacity such as designated infrastructure and equipment (i.e., isolation facilities), communication measures, and means for infection control [65, 73].

It is recommended that establishment of a designated "biological ED" be considered, separate from the routine EDs, to facilitate safety measures and prevent potential infection of staff and other patients that present to the hospital concurrently. Regardless of the decision to operate a designated "biological ED" or admit patients in the routine ED, expansion of surge capacity of place, resources, infrastructure, and medical personnel should be instated to enable management of the numerous patients that are expected [72, 74].

The overload of inpatients may necessitate application of modifications in the hospitalization policy, compared to routine management, to optimize resource management [75, 76]. For example, the proportion of patients who require ventilation may rise to a level of 3–4 times the average number during routine periods, rendering the Intensive Care Units (ICUs) incapable of treating all the patients. Expansion of ventilation capacities is needed, based on designation of sites that consist of needed infrastructure for ventilation, such as in ambulatory surgical departments or step-down units.

Elective and ambulatory activities may be reduced and, in extreme situations, may be ceased altogether. General hospitalization guidelines may be modified, such as restricting hospitalization periods after childbirth or surgeries, and may adopt altered standards of care [76]. The resources that will be made available resulting from the modified operations can then be redirected to the HCID mass casualty management.

To overcome the shortage of hospital beds, additional facilities within the hospital may need to be involved as admitting or hospitalization sites. Hospital temporary wards may thus be installed in designated sites such as dining rooms, ambulatory

clinics, and libraries or other areas that are sufficiently spacious to be converted for this purpose. Regardless, the scope of inpatients may exceed the overall capacities of the hospitals, necessitating operation of auxiliary facilities such as geriatric hospitals, nursing homes, community clinics, or even hotels, which may be temporarily used as extension hospital sites [77, 78].

9.11.2 Triage

Triage of patients is a crucial component of managing an HCID mass casualty event to prevent overload and facilitate an effective management of resources [79]. The main objective of triage processes is to facilitate saving as many salvageable patients as possible by identifying those that will survive as a result of the administered medical attention who would otherwise not live [79, 80]. Triage during HCID events focuses on sorting those severely and critically ill patients who require immediate medical intervention from other casualties whose treatment may be delayed or administered in alternative facilities [81]. Another objective of triage in HCID situations is to use the available resources (i.e., manpower, equipment, or infrastructure) optimally to mitigate chaos and restore order, so as to resume routine operations and levels of medical care in the shortest time possible [82].

The triage process may represent a significant challenge to health care personnel as it is conducted under potentially stressful circumstances when many patients present to the hospital simultaneously. As the staff are required to work under biosafety precautions and regulations, deviations from the routine mode of operation pose a complex challenge. Modifications to the routine mode of patient admittance are instated, and the staff operate while wearing personal protective gear that may be perceived as uncomfortable or daunting [83, 84].

A triage site must be defined to direct the patients to the appropriate ED. A senior internist or pediatrician (according to the designation of the site) should be appointed as Triage Medical Officer, responsible for managing the triage operations and directing each patient to the appropriate treatment site. Maintaining calm, adhering to principles of emergency response, and leading the initial sorting of the patients is a vital component of an effective emergency management of an HCID event [85].

Patients who are referred to the hospital by official agencies, such as the emergency medical services (EMS) or their primary physicians, should be directed immediately to the "biological ED"; patients who present to the hospital independently should be referred to the Biological Site according to the decision of the Triage Medical Officer.

Initial treatment in the ED is targeted to provide urgent (life-saving) treatment and to decide whether the patient requires hospitalization or may be discharged to be cared for in the community [83]. The triage must be administered strictly; patients may be referred from the ED to hospitalization only following the decision of a senior physician. Therefore, hospitals need to ensure the ongoing presence of senior staff in the ED around the clock as long as the situation persists [71].

9.11.3 Deployment of a Hospital Incident Command Center

As the significant influx of patients may overwhelm the hospital's capacities and to achieve optimal management of resources, an Incident Command Center needs to be established in an HCID epidemic [72]. The Incident Command Center is responsible for providing support to the medical teams to enable them to administer optimal medical care, despite the shortage in resources [71]. The main tasks of this Center are to update and direct the hospital's staff concerning the mode of operation, both clinically and organizationally; maintain ongoing contact with internal and external bodies; manage appropriate allocation of resources including manpower and equipment; monitor admission of patients; manage allocation of protective measures for the personnel and inpatients; and coordinate reinforcements of imaging and laboratory capacities.

9.11.4 Isolation Facilities in the Mass Casualty Management Context

Technical requirements to ensure capacity to treat patients with HCID have been defined and include components such as negative-pressure airborne infection isolation facilities and aerosol-tight doors and windows [86, 87]. Although many countries have installed such measures that allow them safely to admit and treat patients infected with biological agents, only few of them have facilities that allow for a massive influx of such patients. It is therefore expected that the surge of patients presenting to the hospitals will significantly surpass the available isolation capacities [6, 88]. Considering the high cost of installing isolation facilities that comply with the strict requirements of suitability to manage HCID events, it stands to reason that the current infrastructure will not change dramatically. Accordingly, a modified mode of operation is needed to facilitate effectively the management of a mass casualty HCID event while maintaining the safety of the staff and other inpatients of the hospital, such as designating areas in the hospital that will service exclusively HCID patients.

Miller [87] have reported that it is possible to design a temporarily designated negative-pressure isolation ward and operate it in a separate pre-determined location within the hospital. In their study, though, this site was activated over a period of only 24 h, and they have expressed some doubts as to whether such a facility may also be functional during a longer span of time.

9.11.5 Reinforcement of Resources

9.11.5.1 Staff

Reinforcement of hospital personnel should be recruited from two main sources: internal and external. Internal reinforcement should be based on a freeze of vacations, training and education programs, and participation in congresses or other activities external to the medical facility; modification/expansion of working

shifts (following agreement with the staff and/or unions); and re-direction of personnel who were formerly assigned to elective or ambulatory services to the newly established wards [89]. External reinforcement may include medical or nursing students as well as recruitment of retired personnel who are still proficient in their basic profession. The hospital should identify areas/activities that may be performed by volunteers from the community and identify such potential volunteers who are available in the vicinity of the hospital.

Those managing personnel must consider not only the number of staff needed at any point in time, over a prolonged period of days or weeks, but must also plan to cope with the fears and anxiety that often accompany outbreaks of HCID [65]. The severity of the disease, lack of effective treatments, and the potentially high transmissibility may create uncertainty among the staff concerning their safety and even distrust of the system at large and specifically the hospital administration [90].

9.11.5.2 Equipment

As the routine medical equipment and devices may be insufficient in mass casualty events, each hospital needs to plan ways of reinforcing vital means, including ventilation machines and PPE [74]. As much as possible, electronic ventilators should be used, but because of the extreme numbers of patients which may require ventilation, manual ventilators may need to be used. According to the type of pathogen, appropriate filters will need to be installed in the ventilators. Plans for procurement of relevant medications should also be developed according to the estimated number of patients expected to present to the hospital. Nonetheless, under austere conditions, some procedures may not be provided considering the scarcity of resources; for example, it may be decided that extracorporeal membrane oxygenation will not be provided during an HCID mass casualty event, despite its effective use during the 2009 H1N1 influenza pandemic [71].

Decision making concerning types and amounts of equipment that should be purchased to maintain the capacity to manage an HCID needs to consider the risk, surge capacity, and costs of stockpiling and managing the equipment [74]. A significant challenge is balancing between the need to maintain continuous preparedness while minimizing waste and the need to destroy (and consequently substitute) drugs or other materials that have expired [71, 74].

9.11.5.3 Training

Training and education are crucial for ensuring the ability of medical professionals to manage HCID mass casualty events [91]. The knowledge required of hospital personnel during an HCID epidemic encompasses both familiarity with the approach to a single/individual patient and his/her contacts and the overall organizational preparedness for mass casualties, increase of encounters of medical/nursing staff with patients, and the need to provide medical care in ambulatory and modified hospital conditions [92, 93]. Medical as well as organizational aptitude is required [77, 93]. Three main levels have been recognized as significant for inclusion in training programs for HCID events: (1) information concerning the varied biological agents, their consequences, the courses of the disease, and means to prevent and/or

mitigate its infectivity; (2) ways to develop case definitions, criteria for hospitalization, medical protocols for in-house and ambulatory care, and provision of care for patients' contacts (including staff and family members); (3) policy and decision-making processes [91, 94]. All hospital staff should be trained in the basic level of required knowledge, medical personnel need also to be trained in the second level, while managers of the EDs and the various hospital departments need to be trained in all three levels of knowledge and competencies.

HCIDs present a significant challenge to HCW because of potentially extreme working conditions, close encounters with infectious patients which may involve a substantial exposure to a lethal disease, preventive care that may be only partly effective, and high psychological pressure resulting from a dual commitment to the family and the workplace. Hospitals' training programs should accordingly focus not only on knowledge and competencies of the staff but also relate to the personnel's expected perceptions and attitudes [95, 96].

9.11.6 Crisis Communication

Risk communication is a vital component of managing a mass casualty HCID event, targeted to reduce uncertainty, confusion, and fear [87, 97].

Reporting of hospital staff to work during HCID may be challenging, especially when they perceive a threat to their own or their families' well-being. Based on lessons identified during former HCID events, such as SARS, influenza, or EVD outbreaks, elements which impact on staff's willingness to report to work include perceived cohesiveness and sense of belonging to their team/place of work, and a feeling of a "mission" and commitment to patients and co-workers. Hospital administrators should communicate to the staff the criticality of their tasks, the perception of their contribution as vital for saving lives and for the continuous functioning of the medical facility, and its significant impact on medical consequences [98]. Risk communication should also include reference to actions that were taken to preserve their health and safety, such as preventive measures (physical protection, isolation facilities, infection control means, or preventive medications). Communicating messages during an HCID event must be based on relaying accurate and trustworthy information, conveyed calmly to avoid the creation of confusion and panic, and respectfully regarding the diversity prevailing among the population, including persons with special needs [65, 99]. Both the medical teams and the public need to be updated continually concerning the HCID event, its development, and potential consequences, as a dynamic process, transparently and credibly [98, 100].

The risk communication messages should be developed and published differentially according to the target population: the patients, medical personnel, family members of the staff or the patients, managers of interface agencies that operate in the vicinity of the hospital, decision and policy-makers, or the public at large [101]. Proactive risk communication should be adopted to achieve wide coverage. Clear, easily understandable information should be distributed concerning questions such as who should seek medical care, who needs to be vaccinated, who should

approach the hospital or alternative facilities, or what means should be used for evacuation to hospitals (e.g., ambulances or private cars) [102]. Use of a tele-information center is recommended to provide the concerned public with answers to their worries. Leaflets delineating answers to most frequently asked questions should be prepared, translated into languages of the major fractions of the local population. This information should be uploaded to the hospitals' websites to be readily available to all interested parties. Proficient spokespersons should be available to relay information and updated data to local media and, through them, to the population. The spokespersons and the administrators of the hospitals should collaborate closely with other entities and authorities that operate in the community to coordinate the messaging and ensure a synchronized risk communication policy [87, 102].

9.11.7 Reporting (Internal and External)

Effective management of an HCID event is dependent on early identification of the first patients before the outbreak reaches uncontainable magnitudes; this can only be achieved by sharing information concerning patients or suspected contacts [103, 104]. Once the outbreak has created mass casualties, the need for early detection and identification evolves into a vital need for sharing information concerning the patients, their differential diagnoses, and efficiency of treatments that were administered, in an attempt to contain the event and/or mitigate its effects [103, 105].

Patient charts should also be maintained during an HCID, similar to routine procedures. Nonetheless, additional reporting is needed to manage the situation including Epidemiological Investigation Forms that delineate the patients' details, areas where they stayed during the event, tentative diagnosis, and treatment that was administered. The hospital needs to record and report the number of patients admitted to the EDs, the number of suspected patients infected with biological agents, the number of patients hospitalized in ICUs (adult and pediatric), and the number of deaths from HCID. Aggregation and analysis of unbiased data will facilitate their interpretation and subsequently their utilization for decision making concerning ways to manage the situation [105]. The analyzed data should be further disseminated and shared transparently to promote scientific collaboration and effective systemic management [103].

9.11.8 Risk Assessment and Risk Reduction

Outbreaks of HCID which cause numerous casualties constitute a continuous global risk; as the consequences of such events may be devastating to humans and infrastructures, risk assessment and risk reduction must be intrinsic components of a holistic risk management program [106, 107]. Managing mass casualty HCID events necessitates a robust organizational and preparedness program, including vigorous

risk assessment and decision-making processes [108]. Risk assessment is vital for both planning and response phases to facilitate decision making and implementation of effective interventions [98, 109]. As the health caregivers may be at risk of being infected, either primarily by the HCID agent or from secondary transmission of the pathogen by the patients they treat, each hospital must have the capacity to identify the risk, assess its potential damage, and implement measures to reduce the risk and ensure the safety of its manpower [99].

Risk reduction in HCID events is dependent on hospital personnel's strict adherence to infection control procedures [65]. If such measures are not implemented as needed, the hospitals themselves may contribute to spreading the pathogen rather than containing or controlling its evolvement. Previous studies have shown that during the SARS outbreak in both Canada and Taiwan, over 75% of the cases could be traced back to virus transmission within hospitals [110].

9.11.9 Ethical Dilemmas

The goal of caring for patients is founded on the ethical objective to provide the optimal protection of lives, health, and welfare of the population in the most effective and successful manner. Ethical management considers presence of factors that may not be known or accurately estimated prior to the event [111], such as the biological features of the agent (lethality, epidemiology, infectivity, and sensitivity to antiviral treatments); characteristics of the population (density, scope of risk, and age distribution); and behavioral patterns of the population. Major ethical aspects which need to be considered include allocation of medical resources under austerity, limitation of civil rights, enforcing professional ethics of medical teams during an HCID event, competing commitments of health care providers to their place of work versus responsibility to their families and themselves, and integrating ethical as well as religious aspects in decision-making processes [111, 112]. Bio-ethical professionals should be involved in the decision-making processes.

References

1. Stone. The "worried well" response to CBRN events: analysis and solutions. Defense technical information center. 2007.
2. CDC. Lassa fever confirmed in death of U.S. Traveler returning from Liberia [Online]. 2015. https://www.cdc.gov/vhf/lassa/announcements/death-of-us-traveler-returning-from-liberia.html. Accessed 18 July 2017.
3. Maisa. Federal state level management of an imported Lassa fever case to North Rhine-Westphalia, Germany, March 2016. Int J Infect Dis. 2017.
4. Raabe. Favipiravir and ribavirin treatment of epidemiologically linked cases of Lassa fever. Clin Infect Dis. 2017;65:855–9.
5. Negredo. Autochtonous crimean-congo hemorrhagic fever in Spain. N Engl J Med. 2017;377:154–61.
6. Schilling S. Isolation facilities for highly infectious diseases in Europe – a cross-sectional analysis in 16 countries. PLoS One. 2014;9(10):e100401.

7. McLean. The politics of fear. 2017.
8. Sagripanti. Persistence in darkness of virulent alphaviruses, Ebola virus, and Lassa virus deposited on solid surfaces. Arch Virol. 2015;155:2035–9.
9. RKI. Rahmenkonzept Ebolafieber [Online]. 2014. http://www.rki.de/DE/Content/InfAZ/E/Ebola/Rahmenkonzept_Ebolafieber.html. Accessed 18 July 2017.
10. WHO. Clinical management of patients with viral haemorrhagic fever. A pocket guide for the front-line health worker. 2016.
11. Kratz. Ebola – the politics of fear. 2017.
12. BBK. Handbuch biologische Gefahrenlagen.
13. Leligdowicz. Ebola virus disease and critical illness. Crit Care. 2016;20(1):217.
14. Garske. Heterogeneities in the case fatality ratio in the West African Ebola outbreak 2013–2016. 2017.
15. Jeffs. The Médecins Sans Frontières Intervention in the Marburg Hemorrhagic Fever Epidemic, Uige, Angola, 2005. I. Lessons Learned in the Hospital. 2007.
16. Martini. Über eine bisher unbekannte, von Affen eingeschleppte Infektionskrankheit: Marburg-Virus-Krankheit. DMW. 1968.
17. Kreuels. A case of severe Ebola virus infection complicated by gram-negative septicemia. N Engl J Med. 2014;371:2394–401.
18. Wolf. Severe Ebola virus disease with vascular leakage and multiorgan failure: treatment of a patient in intensive care. Lancet. 2014;385:1428–35.
19. Guery. Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission. Lancet. 2013.
20. Linden. ECMO in ARDS: a long-term follow-up study regarding pulmonary morphology and function and health-related quality of life. Acta Anesthesiol Scand. 2009;53(4):489–95.
21. McCormick. Lassa fever. Effective therapy with ribavirin. NEJM. 1985;314(1):20–6.
22. WHO. Neglected tropical diseases [Online]. 2017. http://www.who.int/neglected_diseases/diseases/en/. Accessed 19 July 2017.
23. Poland. Treatment of plague. 1999.
24. CDC. Plague: resources for clinicians [Online]. 2015. https://www.cdc.gov/plague/healthcare/clinicians.html.
25. Titball. Vaccination against bubonic and pneumonic plague. Vaccine. 2001;19:4175–84.
26. Olson. In vitro efficacy of brincidofovir against variola virus. 2014.
27. Durrafour. Tecovirimat, a p37 envelope protein inhibitor for the treatment of smallpox infection. IDrugs. 2010;13:181–91.
28. Keckler. The effects of post-exposure smallpox vaccination on clinical disease presentation: addressing the data gaps between historical epidemiology and modern surrogate model data. Vaccine. 2013;31(45):5192–201.
29. WHO. Smallpox vaccines [Online]. 2017. http://www.who.int/csr/disease/smallpox/vaccines/en/. Accessed 19 July 2017.
30. Tignor. Ribavirin efficacy in an in vivo model of Crimean-Congo hemorrhagic fever virus (CCHF) infection. Antivir Res. 1993;22(4):309–25.
31. Oesterreich. Evaluation of Antiviral Efficacy of Ribavirin, Arbidol, and T-705 (Favipiravir) in a Mouse Model for Crimean-Congo Hemorrhagic Fever. PLoS Negl Trop Dis. 2014;8:e2804.
32. WHO. Crimean-Congo haemorrhagic fever (CCHF) [Online]. 2017. http://www.who.int/csr/disease/crimean_congoHF/en/. Accessed 19 July 2017.
33. PREVAIL. A randomized, controlled trial of ZMapp for Ebola virus infection. N Engl J Med. 2016;375:1448–56.
34. Sissoko. Experimental treatment with favipiravir for Ebola virus disease (the JIKI Trial): a historically controlled, single-arm proof-of-concept trial in Guinea. PLoS Med. 2016;13:e1001967.
35. Henao-Restepro. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. Lancet, 2015. https://doi.org/10.1016/S0140-6736(13)60982-4.

36. Santis. Safety and immunogenicity of a chimpanzee adenovirus-vectored Ebola vaccine in healthy adults: a randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study. Lancet Infect Dis. 2016;16(3):311–20.
37. WHO. Ebola publications: case management, infection prevention and control [Online]. 2017. http://www.who.int/csr/resources/publications/ebola/infection-prevention/en/. Accessed 19 July 2017.
38. Mendenhall. Effective oral favipiravir (T-705) therapy initiated after the onset of clinical disease in a model of arenavirus hemorrhagic fever. 2011.
39. Bausch. Review of the literature and proposed guidelines for the use of oral ribavirin as post-exposure prophylaxis for Lassa fever. Clin Infect Dis. 2010;51:1435–51.
40. Burk. Neglected filoviruses. FEMS Microbiol Rev. 2016;40:494–519.
41. Klafki. Debatte Schutz vor Pandemien – Tödliche Kleinstaaterei. TAZ. 2017.
42. Bedell. Global access to medicinal products: compassionate use programs. 2010.
43. BFARM. Compassionate use programmes [Online]. 2017. http://www.bfarm.de/EN/Drugs/licensing/clinicalTrials/compUse/_node.html. Accessed 19 July 2017.
44. FDA. Expanded Access (Compassionate Use) [Online]. 2017. https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm. Accessed 19 July 2017.
45. Vetter. Ebola virus shedding and transmission: review of current evidence. J Infect Dis. 2016;214:S177–84.
46. Wilson. Sierra Leone Ebola burial team attacked despite lockdown. Daily Telegraph. 2014.
47. Rakin. Yersinis pestis – Eine Bedrohung für die Menschheit. Bundesgesundheitsblatt. 2003.
48. ICRC. 2017.
49. WHO. How to conduct safe and dignified burial of a patient who has died from suspected or confirmed Ebola virus disease [Online]. 2014. http://www.who.int/csr/resources/publications/ebola/safe-burial-protocol/en/. Accessed 24 July 2017.
50. Macintyre 2015. Uncertainty, risk analysis and change for Ebolapersonal protective equipment guidelines. International Journal of Nursing Studies, 52(5), 899–903.
51. Kang. Use of personal protective equipment among health care personnel: Results of clinical observations and simulations. Am J Infect Control. 2016;45(1):17–23.
52. Coca. Physiological and subjective evaluation of PPE using a sweating thermal manikin. Extrem Physiol Med. 2015;4(Suppl 1):A27.
53. de Iaco G, Puro V, Fusco FM, Schilling S, Maltezou HC, Brouqui P, Gottschalk R, Bannister B, Brodt HR, Siikamaki H, Perronne C, Brantsaeter AB, Fjellet AL, Ippolito G. Personal protective equipment management and policies: European network for highly infectious diseases data from 48 isolation facilities in 16 European countries. Infect Control Hosp Epidemiol. 2012;33:1008–16.
54. REMM. PPE classification system from OSHA and EPA [Online]. 2017. https://www.remm.nlm.gov/osha_epa_ppe.htm. Accessed 19 July 2017.
55. Franco. Environmental decontamination following a large-scale bioterrorism attack: federal progress and remaining gaps. Biosecur Bioterror. 2010;8(2):107–17.
56. Bodurtha. Decontamination science and personal protective equipment (PPE) selection for chemical-biological-radiological-nuclear (CBRN) events. 2016.
57. CDC. Guidance on personal protective equipment (PPE) to be used by healthcare workers during management of patients with confirmed Ebola [Online]. 2015. https://www.cdc.gov/vhf/ebola/healthcare-us/ppe/guidance.html. Accessed 21 July 2017.
58. Krauter. A systematic methodology for selecting decontamination strategies following a biocontamination event. Biosecur Bioterror. 2011;9(3):262–70.
59. WHO. Decontamination and reprocessing of medical devices for healthcare facilities. 2016.
60. RKI. Hygiene requirements for the reprocessing of medical devices [Online]. 2001. https://www.rki.de/DE/Content/Infekt/Krankenhaushygiene/Kommission/Downloads/Hygiene_Requirements_Medical_Devices_2012.pdf?__blob=publicationFile. Accessed 21 July 2017.

61. RKI. Measures regarding disinfection and waste management as pertaining to an at least probable case of Ebola virus infection in Germany [Online]. 2015. http://www.rki.de/EN/Content/infections/epidemiology/outbreaks/Ebola_virus_disease/Ebola_disinfection.pdf?__blob=publicationFile. Accessed 21 July 2017.
62. WHO. Health care worker infections in Guinea, Liberia and Sierra Leone. A preliminary report. [Online]. 2015. http://www.who.int/csr/resources/publications/ebola/health-worker-infections/en/. Accessed 9 Apr 2018.
63. Sorge. Panik, Schlagzeilen und Leichenbeschau. Cicero. 2014.
64. Schmiedel. Ebolafieber in Westafrika und in Deutschland. Bundesgesundheitsblatt. 2015.
65. May. Catastrophic events versus infectious disease outbreak: distinct challenges for emergency planning. Reason Pap. 2015;37:54–64.
66. Lufthansa. Lufthansa hands over "Robert Koch" evacuation aircraft [Online]. 2014. https://www.lufthansa-technik.com/press-releases-content/-/asset_publisher/9Mf5/content/id/1563897. Accessed 24 July 2017.
67. Kochanek LF. Transmission and control of Lassa fever outside of Africa Accepted article – to be published. 2017.
68. WHO. Lassa fever – Germany [Online]. 2016. http://www.who.int/csr/don/23-march-2016-lassa-fever-germany/en/. Accessed 21 July 2017.
69. Maisa. Federal state level management of an imported Lassa Fever case to North Rhine-Westphalia, 2016. 2016.
70. Gottschalk. Seltene hochkontagiöse und lebensbedrohliche Erkrankungen. Bundesgesundheitsblatt. 2015;58:655–6.
71. Hick. Allocating scarce resources in disasters: emergency department principles. Ann Emerg Med. 2012;59:177–87.
72. Waseem. Impact of operational staging to improve patient throughput in an inner-city emergency department during the novel H1N1 influenza surge: a descriptive study. Pediatr Emerg Care. 2012;28:39–42.
73. Therrien. Bridging complexity theory and resilience to develop surge capacity in health systems. J Health Organ Manag. 2017;31:96–109.
74. Rebmann. Best practices for healthcare facility and regional stockpile maintenance and sustainment: a literature review. Health Secur. 2017;15(4):409–17.
75. Bar-El. Moral dilemmas faced by hospitals in time of war: the Rambam Medical Center during the Second Lebanon War. Med Health Care Philos. 2014;17:155–60.
76. Timbie. Systematic review of strategies to manage and allocate scarce resources during mass casualty events. Ann Emerg Med. 2013;61:677–89.
77. Alfred. Preparing for disasters: education and management strategies explored. Nurse Educ Pract. 2015;15:82–9.
78. Bruria. Case study–Israel. Dordrecht: Springer; 2013.
79. Culley. A review of the literature on the validity of mass casualty triage systems with a focus on chemical exposures. Am J Disaster Med. 2014;9:137.
80. Albanese. Clinical guidelines for responding to chemical, biological, radiological, nuclear and trauma/burn mass casualty incidents: quick reference guides for emergency department staff. J Bus Contin Emer Plan. 2014;8:122–33.
81. DOH U. Chapter 2: Health and medical care delivery in a mass casualty event. 2011.
82. Curnow. Mass casualty triage performance assessment tool. No. ARI/FB-RP-2015-02. Army Research Institute for the Behavioral and Social Sciences Fort Belvoir, VA, 2015. 2014.
83. Barilan. Triage in disaster medicine: ethical strategies in various scenarios. Dordrecht: Springer; 2014. p. 49–63.
84. Landsdowne. Recent advances in medical device triage technologies for chemical, biological, radiological, and nuclear events. Prehosp Disaster Med. 2015;30(3):320–3.
85. Russo. Mass casualty disasters: who should run the show? J Emerg Med. 2015;48:685–92.
86. Bannister B. Framework for the design and operation of high level isolation units: consensus of the European network of infectious diseases. Lancet Inf Dis. 2009;9(1):45–56.

87. Miller. Implementing a negative-pressure isolation ward for a surge in airborne infectious patients. Am J Infect Control. 2017;45:652–9.
88. Rubinson. Augmentation of hospital critical care capacity after bioterrorist attacks or epidemics: recommendations of the working group on emergency mass critical care. Crit Care Med. 2005;33:2393.
89. Kearns. Hospital bioterrorism planning and burn surge. Biosecurity Bioterrorism Biodefense Strateg Pract Sci. 2014;12:20–8.
90. Gonsalves. Panic, paranoia, and public health—the AIDS epidemic's lessons for Ebola. N Engl J Med. 2014;371:2348–9.
91. Djalali. TIER competency-based training course for the first receivers of CBRN casualties: a European perspective. Eur J Emerg Med. 2016;24:371–6.
92. Lewis. Mass casualty incident management preparedness: a survey of the American College of Surgeons Committee on Trauma. Am Surgeion. 2016;82:1227–31.
93. Siegel. Prioritization of pediatric chemical, biological, radiologic, nuclear, and explosive disaster preparedness education and training needs. Clin Pediatr Emerg Med. 2014;48:685–92.
94. Pesiridis. Development, implementation and evaluation of a disaster training programme for nurses: a switching replications randomized controlled trial. Nurse Educ Pract. 2015;15:63–7.
95. Kim JH. Learning from UK disaster exercises: policy implications for effective emergency preparedness. Disasters. 2014;38:846–57.
96. Quevillon. Helping the helpers: assisting staff and volunteer workers before, during, and after disaster relief operations. J Clin Psychol. 2016;72(12):1348–63.
97. Barry. A literature review on effective risk communication for the prevention and control of communicable diseases in Europe. J Health Commun. 2013:1–19.
98. Kern. Global epidemics, pandemics, terrorism: risk assessment and European responses. ISPSW Strateg Ser. 2016.
99. Penta. Of earthquakes and epidemics: examining the applicability of the all-hazards approach in public health emergencies. Risk Hazards Crisis Public Policy. 2017;8:48–67.
100. Barrelet. Unresolved issues in risk communication research: the case of the H1N1 pandemic (2009–2011). Influenza Other Respir Viruses. 2013;7(s2):114–9.
101. Farrar. The Ebola emergency—immediate action, ongoing strategy. N Engl J Med. 2014;371:1481–95.
102. Dickmann. Biological risks to public health: lessons from an international conference to inform the development of national risk communication strategies: report of an international conference on risk communication strategies before, during, and after public health emergencies, Rabat, Morocco, October 22–23, 2015. Health Secur. 2016;14:433–40.
103. Fisman. Nuanced risk assessment for emerging infectious diseases. Lancet. 2014;383:189.
104. Ruggiero. CBRN communication scorecard. Behavior and communication in CBRN crisis: findings and recommendations in case of chemical, biological, radiological, and nuclear attacks on society. Lengerich: Pabst Science; 2015.
105. Lipsitch. If a global catastrophic biological risk materializes, at what stage will we recognize it? Health Secur. 2017;15. https://doi.org/10.1089/hs.2017.0037
106. Jansen. Biological warfare, bioterrorism, and biocrime. Clin Microbiol Infect. 2014;20:488–96.
107. Lioy. Preparedness and response to chemical and biological threats: the role of exposure science. Ann N Y Acad Sci. 2016;1378:108–17.
108. Watson. Expert views on biological threat characterization for the US government: a delphi study. Risk Anal. 2017;37(12):2389–404.
109. Rainisch. Modeling tool for decision support during early days of an anthrax event. Emerg Infect Dis. 2017;23:46.
110. Grow. The challenge of hospital infection control during a response to bioterrorist attacks. Biosecurity Bioterrorism Biodefense Strateg Pract Sci. 2003;1:215–20.

111. Lor. Key ethical issues discussed at CDC-sponsored international, regional meetings to explore cultural perspectives and contexts on pandemic influenza preparedness and response. Int J Health Policy Manag. 2016;5:653.
112. WHO. Guidance for managing ethical issues in infectious disease outbreaks. [Online]. 2016. http://apps.who.int/iris/handle/10665/250580. Accessed 22 Aug 2017.