Framework for the design and operation of high-level isolation units: consensus of the European Network of Infectious Diseases

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Patients with highly infectious diseases require safe, secure, high-quality medical care with high-level infection control, which may be most effectively delivered by specially trained staff in the setting of a high-level isolation unit (HLIU). The European Network of Infectious Diseases is a European Commission co-funded network of experts in the management of highly infectious diseases from national (or regional) centres designated for the care of this patient population. Participants took a consensus-based approach to develop a framework for the design and operation of HLIUs in Europe, covering clinical care provision, diagnostic services, transport, health and safety, and essential design and construction features, to support planning by health authorities for the safe and effective management of highly infectious diseases and preparedness for infectious disease emergencies in Europe.

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Introduction

Recent global scares involving infectious diseases—such as the release of letters containing anthrax spores in the USA in 2001 and the emergence of severe acute respiratory syndrome (SARS) in 2002—along with the continuing effort to contain highly pathogenic avian influenza A (H5N1) virus have highlighted the need to improve preparedness within Europe for emerging public-health threats.[1–6] The European Commission is funding several activities intended to improve health security, build capacity, and strengthen preparedness for response to infectious disease emergencies. These ventures include a network of biosafety level 4 (BSL4/P4) laboratories (Euronet-P4), the European Programme for Intervention Epidemiology Training, and the European Network of Infectious Diseases (EUNID).[7]

The 3-year EUNID project began in 2004, and will continue (as the European Network for Highly Infectious Diseases [EuroNHID]) for a further 3 years, until 2010. EUNID was created to exchange information, share best practice, and improve the connections between national (or regional) centres designated for the care of patients with highly infectious diseases.

EUNID includes national representatives and experts from 16 member states (Austria, Belgium, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, and the UK). Most are clinicians working in high-level isolation units (HLIU) or centres designated for referral of patients with highly infectious diseases, who have backgrounds in infectious diseases, intensive care, infection control, pulmonary medicine, occupational health, or public health.

Three network meetings were held during the project to reach consensus on specific project objectives,[8–10] which included defining a highly infectious disease,[11] archiving an inventory of relevant guidelines,[12] defining a high-level isolation unit (HLIU), identifying the key elements in the design and operation of an HLIU, and using these to develop a framework for the design and operation of HLIUs in Europe.

Since highly infectious diseases are uncommon in industrialised countries, there are few prospective randomised controlled trials on their management and a limited evidence base; therefore, EUNID took a consensus-based approach to these tasks. This report presents the framework, which provides practical guidance on the design and operation of HLIUs in Europe to support planning by public-health authorities for the management of highly infectious diseases and preparedness for infectious disease emergencies in Europe.

Methods

In 2003, national public-health authorities in countries that have, or are planning, an HLIU were contacted by the EUNID coordination team, with the help of the European Commission, and asked to suggest (although not to formally endorse) clinicians with expertise in highly infectious disease/HLIU management as national representatives. The team also co-opted additional participants, selected for their experience in one or more aspects of highly infectious disease/HLIU management, including a representative of the group that developed similar guidance in the USA.[13] Thus, the skill mix and expertise of the group represented all key aspects of highly infectious disease/HLIU management (infectious diseases, intensive care, transport, engineering and maintenance, infection control, diagnostic services, occupational health, public health, and unit management).

Group members presented details of arrangements in their countries for the management of patients with highly infectious diseases, heard (and questioned) expert presentations on HLIU management, and agreed a consensus definition of a highly infectious disease by discussion at the first network meeting in 2005.[8,11] We then inventoried national and international guidelines, and used these, with relevant legislation and representatives' responses to a questionnaire, to identify key elements in

For more on the **European Network of Infectious Diseases** see http://www.eunid.eu/

Figure: **An HLIU nearly completed at the National Institute for Infectious Diseases, Rome, Italy**
The HLIU consists of ten one-bed separate units, each one equipped with separate access from the outside, distinct pathways for entering and exiting of personnel, an independent ventilation system, autoclave, and pass-through box. The building is equipped with BSL3 and BSL4 laboratories. Additional 20 single airborne-isolation rooms are located on the second floor for quarantine.

the design and operational management of an HLIU, which were agreed by discussion at the network meeting in 2006.[9,12] These elements formed the basis for a draft framework that incorporated evidence used to support current international and national guidance and legislation. This framework, with a draft definition of an HLIU, was shared throughout the network, and revised to incorporate comments and additional evidence. We used a questionnaire that offered alternative solutions to particular design and management issues (eg, location and staffing of HLIUs, necessity for high efficiency particulate air [HEPA] filtration) to structure group discussions, clarify preferred options, and agree consensus refinements of the drafts at the third network meeting in 2007.[10] We then prepared this report, and shared it, and subsequent revisions, until the content was agreed by all.

Results

The elements of key importance in the design and operation of HLIUs in Europe are used as subheadings in this report. The framework is based on evidence, where this is available, or, where it is not, represents the collective opinion and current practice of the group.

Definition of a highly infectious disease

EUNID defines a highly infectious disease as an infection that is transmissible from person to person; is life-threatening; presents a serious hazard in the health-care setting and the community; and requires specific control measures (eg, high-level isolation).[11]

Definition of a high-level isolation unit (HLIU)

EUNID defines an HLIU as a health-care facility specifically designed to provide safe, secure, high-quality, and appropriate care, with optimal infection containment and infection prevention and control procedures, for a single patient or a small number of patients who have, or who may have, a highly infectious disease.

Function, location, and use of HLIUs

EUNID participants were unanimous about the need for provision of HLIU-based care in Europe, since there are some infections that, for the protection of health-care workers, other patients, and the community, require levels of infection control and clinical expertise that cannot easily be provided in any other setting. These include known or suspected infection with a haemorrhagic fever virus (Marburg, Ebola, Lassa, and Crimean-Congo haemorrhagic fever viruses), smallpox or other highly pathogenic orthopoxvirus, emerging highly pathogenic influenza virus or other emerging highly pathogenic respiratory virus, an unknown emerging pathogen, an engineered pathogen or a suspected bioterrorist agent, and any emerging or re-remerging infection considered by national or international authorities to require high-level containment. EUNID concurs with current guidance on extensively drug-resistant and multidrug-resistant tuberculosis, and does not regard provision of HLIU-based care for either infection as essential.[14–16]

Some countries in Europe—eg, Germany, Sweden, and the UK—have more than one HLIU; others—eg, Estonia, Luxembourg, and Spain—have centres designated for the care of patients with highly infectious diseases but do not have a purpose-built HLIU; Austria has neither, but has a cooperative agreement with centres in neighbouring countries for the transfer and care of patients with highly infectious diseases. Details of the facilities for patients with highly infectious diseases in EUNID-participating countries are available on the project website.[17]

The advantages of having more than one unit in the same country include shorter, safer, journeys for patients from the referral point to the unit, shorter times for specimen transport from the unit to the nearest BSL4 laboratory, provision of cross-cover (eg, when one unit is closed for maintenance), and the potential for a broader range of specialist research interests. Disadvantages include increased costs, less frequent use, and dispersion of clinical expertise.

HLIUs should be sited so that in-country patient journey and specimen transport times do not exceed 6 h, and should be colocated with a parent tertiary-care facility able to provide appropriate specialist support. A high proportion of patients with highly infectious diseases will have acquired their infections abroad, and since travellers are most likely to return home by air, a country's first HLIU should be sited in, or near to, the population centre nearest to the country's major international airport.

Formal agreements between countries for cross-border transfer of patients and specimens might solve the problem of transport across difficult terrain. Formalised

resource-sharing might also be appropriate for countries that cannot provide multiple high-level isolation facilities. Furthermore, integration of civilian and military medical services for care of highly infectious disease patients within a country could reduce unnecessary duplication.

HLIUs are expensive to build, operate, and maintain, and, if designed exclusively for the management of patients with highly infectious diseases, might be used too little to justify their costs. Costs could be offset by the development of flexible-use HLIUs, designed to offer a range of levels of infection containment; staff would then select the containment level appropriate to the patient's condition.[18] Indeed, some countries (eg, Netherlands and Italy [figure]) already use their highly infectious disease facility in this way.

The primary purpose of the HLIU is to be ready to care for patients with highly infectious diseases, so time must be allocated for training staff and for regular maintenance testing of specialised systems. This function also requires an absolute commitment formalised through a contract, with an effective standard operating procedure, to evacuate any non-highly infectious disease patients and prepare the HLIU for admission of a highly infectious disease patient within 4 h without compromising patient care. It might be preferable to admit non-highly infectious disease patients to an HLIU only when other isolation facilities are not available, and to transfer these patients from the HLIU as soon as practicable.

HLIUs are intended to provide care only for small numbers of patients. Once person-to-person transmission of a highly infectious disease is occurring within a community, HLIU-based care becomes less appropriate, so investment in an HLIU is not an alternative to planning for surge capacity or the provision of alternative care centres for use in major epidemics.[13,19]

***Panel 1:* Operational management and clinical care in HLIUs**

An HLIU should have:

- A designated HLIU director/lead clinician (usually the most senior and experienced doctor), with overall responsibility for coordination, training, liaison, and communication
- A designated HLIU nursing director/lead nurse consultant/nurse manager, responsible for ward management and training of nursing staff
- An effective mechanism for succession planning
- An HLIU-specific training programme that is mandatory for all staff who will work in, or enter, the HLIU. This programme should have standardised curricula and competencies appropriate for each professional group (eg, doctors, engineers), and should include both initial training and regular refresher training, with an accurate system for recording course attendance and performance[11]
- An audit and quality assurance programme, and a system for monitoring adverse events
- Sufficient HLIU-trained staff to provide 24-h availability to open and run the unit
- A regularly exercised standard procedure for becoming fully operational for management of a patient with a highly infectious disease within 3–4 h
- A clear and agreed method for providing cover for any usual duties (eg, anaesthetic list) that staff cannot undertake because they are working in the HLIU
- An agreed system of reward and remuneration for HLIU work and training
- A controlled access system, so that entry to the HLIU is limited to essential, HLIU-trained staff when it is in use for a patient with a highly infectious disease, and adequate supervision of any partly trained staff or other visitors who might need to enter the unit (eg, security emergency) is ensured
- An access log, documenting details of all individuals entering or leaving the unit
- An emergency evacuation protocol that is regularly tested
- A protocol, compatible with European and national legislation, for ensuring unit security
- A high-quality, secure communications systems (eg, scan-safe internet and e-mail, secure radio, emergency-assistance alarms)
- An agreed communication strategy, with a designated communication lead with responsibility for coordination with communication experts (eg, press officer) in the parent institution

Operational management and clinical care provision in HLIUs

The operational management and clinical care provision that all HLIUs should have are listed in panel 1. Most HLIUs in Europe are directed by a lead clinician (usually an infectious disease physician), and have a designated lead nurse/manager; medical care for patients with highly infectious diseases is provided by specially trained clinical teams. Participation in the team is voluntary, and access to the operational HLIU is limited to essential staff. The team undertakes the routine tasks (eg, phlebotomy, cleaning, food service, linen changing, patient or specimen transport, record keeping) that would usually be undertaken by others (phlebotomists, housekeepers, clerks, porters). This reduces the number of staff exposed to risk, improves safety, and obviates the need to recruit and maintain an HLIU-trained non-clinical team from a high turnover workforce.

EUNID participants reported that their highly infectious disease patients had needed a range of interventions, including transfusion of blood/blood products; cardiac, respiratory, and invasive haemodynamic monitoring; radiography; ultrasonography; minor surgical procedures (eg, thoracocentesis); renal dialysis; and mechanical ventilation. The participants also regarded input from critical care clinicians as essential to patient management. HLIUs should therefore be equipped to provide the level of care available in an intensive care unit, and critical care clinicians should routinely train alongside the HLIU team. Support from other specialties (eg, nephrology, paediatrics, cardiology) had also been needed, so specialist clinicians should also be pre-identified and train alongside the HLIU team. Additionally, needs for specialist non-clinical expertise (eg, to repair ventilation systems or maintain near-patient testing equipment) should be assessed, and relevant staff trained appropriately in advance. Partly trained or untrained individuals who need to enter the unit should be escorted and fully supervised throughout their visit by HLIU-trained staff.

Occupational health and safety

Occupational health care (panel 2) is needed to ensure staff fitness to work in the HLIU, to maintain health surveillance, to ensure a rapid, effective, response to any occupational exposure or illness in staff, and to provide the psychosocial support essential in such a demanding environment.

Pre-employment smallpox vaccination is not required, given the low probability of a deliberate release of smallpox, the risk of potentially severe adverse events, and the high turnover of staff, but fitness to work assessments should cover contraindications to vaccination.[20,21] This recommendation does not preclude the vaccination of individuals who may be members of the "smallpox response teams" set up in some countries in Europe as part of preparedness planning.[12]

Pathology and other diagnostic support services

Pathology and diagnostic support services required in an HLIU are shown in panel 3. Some of the isolation units in Europe designated for patients with highly infectious diseases have integral BSL3/4 laboratory facilities; others have access to BSL3 (or BSL4) facilities on the same campus.

No consensus was reached on whether auto-analysers in the main (BSL2) hospital laboratory could safely be used for routine haematology and biochemistry on HLIU patients. The view of most participants is that their use for infectious samples is acceptable, provided the analyser is of the "closed-sampling" type (which minimises the risk of exposure to patients' blood or body fluids), and is operated by trained staff in compliance with written, regularly exercised, protocols for the safe transport, handling, tracking, and disposal of specimens.[28] The strongly held alternative view is that all potentially infectious samples from patients who might be infected with a potentially lethal pathogen (eg, a blood sample from an Ebola patient) should be handled at least under BSL3 conditions.[29]

Transport of patients to the HLIU

Transport arrangements (panel 4) for patients with highly infectious diseases in Europe vary, as do the legal regulations applicable in each country.[8,9,12,30,31] Most countries require ambulance crews to be specially trained; some require the use of specialised patient transport equipment (stretcher transport isolators),

Panel 2: **Occupational health and safety in HLIUs**

An HLIU should have:

- Infection-specific and procedure-specific protocols on infection control and prevention, including risk-assessment-based use of personal protective equipment, and a programme for testing these protocols
- An occupational health and safety programme, led by a specialist HLIU-trained occupational health physician
- An audit and quality assurance programme, and a system for incident reporting and management

HLIU personnel should:

- Have routine pre-employment health checks in accordance with local policy
- Have routine pre-employment immunisations, including hepatitis B vaccine and seasonal influenza vaccine, in accordance with local policy
- Not be offered HLIU-specific, pre-employment immunisations (eg, smallpox vaccine)
- Adhere to written local protocols for active health surveillance, which should be applied to all individuals who enter the unit while a patient with a highly infectious disease is present, or who participate in decontamination, transport, or other procedures, and should continue for a minimum of one disease incubation period after the last possible opportunity for exposure
- Have access to confidential psychological and spiritual support

Panel 3: **Diagnostic support services in HLIUs**

EUNID recommends that:

- All pathology tests on HLIU patients must be undertaken in accordance with relevant European legislation, and national legislation or guidance (eg, in the UK, EU Biological Agents Directive, Control of Substances Hazardous to Health Regulations 2002, and guidance from the Health and Safety Executive[22-25])
- Packaging and transport of patient specimens and infectious substances should conform to all relevant international, European, and national legislation[26]
- HLIU protocols for clinical procedures and diagnostic tests should clearly state how any sample obtained should be collected, handled, and transported, state in which laboratory the test should be done, and contain up-to-date contact details for that laboratory
- HLIUs should make optimum use of near-patient testing systems and have written protocols for their use and maintenance
- HLIUs should make optimum use of laboratory information management systems, including electronic test requesting
- HLIUs should have access to portable ultrasonography and radiography services (ideally, digital radiography), with dedicated or pre-identified equipment
- Staff who undertake tests on samples from HLIU patients must be fully and appropriately trained in biosafety, and subject to the HLIU occupational health programme or (if employed by a BSL4 laboratory on a distant site) its equivalent
- Laboratories that undertake tests on samples from HLIU patients should be appropriately accredited, apply appropriate and valid bio-risk minimisation procedures, participate fully in appropriate external quality assurance schemes, have adequate arrangements for internal quality control and audit, and should keep appropriate records of performance, quality improvement, and staff training[27]

Panel 4: **Transport of patients to the HLIU**

EUNID recommends that:

- The decision to transport a patient to the HLIU must be based on expert clinical risk assessment
- The appropriate transport mode and vehicle type should be determined by expert risk assessment
- Staff and others who might be exposed to the patient during the journey should wear appropriate personal protective equipment, as determined by expert risk assessment, and should be subject to the same health surveillance after the journey as potentially exposed HLIU staff
- The ambulance and any fixed equipment used must be able to be effectively decontaminated (by wiping, spraying, or fogging with an effective disinfectant, according to national policy)
- The ambulance crew must be trained in the protocol for transport of patients with highly infectious diseases
- The HLIU should have an external, securable, area for ambulance parking and decontamination, and procedures for safe decontamination of ambulance equipment, including safe storage before decontamination
- The HLIU should have an admission route from the ambulance area to the unit entrance that can be controlled and secured, and that is wide enough to permit transfer of patient, staff, and equipment
- An ambulance used to transport a highly infectious disease patient should not be returned to normal use until the vehicle (and any fixed equipment in it) has been decontaminated

Panel 5: **Ventilation systems and air handling in HLIUs**

EUNID recommends that:

- The HLIU ventilation system is independent of the other building heating, ventilation, and air conditioning systems
- Each patient room should have an anteroom
- Air flows and pressure gradients within the HLIU run from the cleanest to the most contaminated areas; with the patient room at negative air pressure relative to adjacent areas, and a suggested differential pressure gradient of more than 15 Pa between patient room and anteroom and between anteroom and the rest of the unit, and an effective ventilation rate of at least 12 air changes per h in the patient room
- Air from the HLIU is not recirculated, and exhaust air is vented 100% to the outside of the building
- Exhaust air is discharged at a site and distance from the building that minimises the risk of contamination of occupants of the building (eg, by down-draught into open windows) and the community
- HEPA filtration of exhausted air is preferable, and, if there is any possible risk of re-entry of exhaust air or of human exposure to exhausted air, obligatory
- HEPA filtration of supply air may be considered
- HEPA filters are appropriately protected by pre-filters, housed correctly, and sited for ease of safe access for maintenance[39–43]
- HLIU ventilation systems are designed to fail safe, and to minimise cross-contamination in the event of system failure in the unit or elsewhere on the site (eg, built-in redundancy—HLIU ventilation system with dual fans each capable of exhausting 100% air; air flow shutdown system independent of site system to protect against unwanted shutdown after alarm elsewhere on site; interlocking supply and exhaust systems, so that supply fan is prevented from running if exhaust fans fail)
- HLIU ventilation systems are connected to an emergency back-up power source
- Commissioning of ventilation systems includes functional ("in-use") testing
- Ventilation systems incorporate current best practice performance checking tools (eg, visual pressure check gauges, audible alarms); have a schedule for planned preventive maintenance, and that HLIUs have written protocols for performance-checking the ventilation system that comply with all relevant European and national regulations and current standards of best practice

specially constructed ambulances with controlled ventilation and HEPA filtration, or modified vehicles with additional personal protective equipment for staff. Sweden, Germany, Italy, and the UK have arrangements for, and experience of, national and international aeromedical transport. Transport in stretcher isolators is unpleasant for the patient, and limits patient care, so might be unsuitable for critically ill patients.[32,33] High-level personal protective equipment (eg, impervious suit, powered air purifying respirator) can be used for short shifts only (less than 4 h), which limits the length of journeys that can be undertaken, and the suits, motors, and filters are easily damaged. In the past 40 years, patients with symptomatic haemorrhagic fever virus infections have travelled by road, by public airline, and by unmodified air casualty transport without the detection of a secondary case,[34–36] so that it is now believed that almost all such patients can be managed by transport in standard ambulances, with appropriate personal protective equipment for staff. International guidance on epidemic-prone acute respiratory disease and recommendations on the management of suspected smallpox do not require patient transport by modified ambulance.[20,37,38] Therefore, EUNID does not consider that ambulances with controlled ventilation systems are essential, but recognises that, in some countries, national authorities regard them as desirable, and so have invested in their use. Formal arrangements, which might involve cooperation between international agencies, non-governmental organisations, and civilian and military medical services, could help to overcome the challenges of arranging an international aeromedical evacuation.

Ventilation systems, air handling, and airborne infection isolation

Controlled ventilation systems (panel 5) reduce the risk of infection with obligate airborne pathogens.[14,44–47] Although most highly infectious diseases are not primarily transmitted by the airborne route, the risk of opportunistic airborne transmission of SARS and influenza infections, through exposure to droplet nuclei during aerosol-generating procedures, might be increased in poorly ventilated environments. Therefore, WHO suggests that airborne isolation precautions could be used when aerosol-generating procedures are undertaken

on these patients, and also recommends that inpatients with an acute respiratory disease caused by a novel pathogen with potential for high public-health impact should be managed in airborne isolation until routes of transmission have been clarified.[37,44–50] Airborne transmission of smallpox can occur; therefore, all guidelines recommend airborne infection isolation for suspected cases.[12,20,37,51] European legislation on containment measures for patients who have, or who may have, an infection with a group 3 or group 4 biological agent has been interpreted in supplemental legislation in some countries as requiring airborne infection isolation for all these infections, which include viral haemorrhagic fevers.[22,51–53] Furthermore, flexible-use HLIUs may be used to care for patients with tuberculosis, measles, or chickenpox (all of which require airborne infection isolation) or to isolate laboratory technicians after occupational exposure to a pathogen of unknown transmissibility. EUNID therefore recommends that HLIUs be designed for airborne infection containment.[15,17,39–42]

Directional airflow, where air flows from less contaminated ("clean") areas to more contaminated ("dirty") areas contains infection at source. In mechanically ventilated systems this is achieved by engineering pressure gradients by manipulating supply and exhaust air so that the patient room is maintained at negative air pressure relative to adjacent areas. Minimum recommended air pressure differentials for airborne isolation rooms vary from 2·5 Pa to 30 Pa. There is no direct evidence to link increases in the pressure gradient above 10 Pa with reduction in risk of infection. Some countries (eg, Sweden, Japan, and Australia) require that airborne infection isolation rooms have an anteroom,[39,43,54] whereas other countries do not, but recognise that anterooms may increase ventilation system efficiency.[40] Anterooms also provide a controlled environment in which to put on and remove personal protective equipment, prepare clinical equipment, and store immediately necessary supplies.

High, effective ventilation rates reduce the concentration of contaminating airborne particles by dilution, since contaminated air is replaced by clean air. Standards have evolved through convention, coupled with application of experimental work on concentration decay rates of airborne particles: the relation between incremental increases in air change rates and reduction in infection risk has not been assessed.[39,40] Recent guidelines define an adequately ventilated airborne infection isolation room (or airborne precaution room) as one that has more than 12 air changes per h, although newer HLIUs have rates that substantially exceed this.[14,37,39,41]

Some guidelines recommend that ventilation system design should ensure that clean air flows from parts of the room where carers are likely to work, across the infectious source, and into the exhaust.[41] This arrangement might not be achievable at lower air exchange rates, and others have suggested, in a full review of isolation room design, that the best strategy is to achieve effective mixing and the highest contaminant dilution rate consistent with maintaining thermal comfort.[39] Achieving high air exchange rates and maintaining higher-range pressure differentials requires rooms designed and constructed for "air envelope tightness"—ie, with as little unplanned leakage as possible—with controlled leakage paths, and specially designed doors. To maximise source containment, exhaust registers (air outlet points) should be located as close to the patient's head as possible.

European legislation on worker protection specifies a mandatory set of containment measures, including HEPA filtration, for laboratories working with group 3 or group 4 biological agents, but is less prescriptive about containment in patient isolation facilities, requiring only that containment measures be selected from the list of measures mandated for laboratories.[22,52,53] In some European countries this has been interpreted as mandating HEPA filtration of both supply and exhaust air in high-level isolation facilities. Consequently, some isolation facilities in Europe have HEPA-filtered supply air, despite a lack of evidence to support the need for it.

In an outbreak in Germany, smallpox virus was thought to have been carried on air currents, from a window in an isolation room, up the outside of the building, and into other clinical areas, where patients became infected.[51] Building regulations and codes now require that ventilation systems are designed to prevent re-entry of exhaust air, and that exhausts are not located near areas that might be populated, or within the building's air recirculation zone. Exhaust air from HLIUs must be 100% exhausted to the outside, and not recirculated. Although HEPA filters in theory provide additional protection, their use increases the complexity

***Panel 6:* Safe management of clinical waste in HLIUs**

EUNID recommends that:

- Procedures for management of clinical waste must comply with all relevant European and national legislation
- Unit procedures should incorporate waste-reduction measures (eg, removal of packaging from equipment in a "clean" area before transfer of the equipment into the clinical area)
- Solid waste should be decontaminated before disposal; autoclaving (with verification testing) is the preferred method
- Procedures for handling and disposal of liquid waste should be determined by risk assessment. Suggested methods include: direct disposal into the dirty drain system, autoclaving after solidification, or chlorine decontamination before disposal

and cost of the system. HLIUs in France, Germany, Italy, Sweden, and the UK have HEPA-filtered exhaust air, as do newly built isolation wards in Denmark, Finland, and Estonia; isolation units in Greece and Ireland do not.

Safe management of clinical waste

The greatest hazard from clinical waste (panel 6) is percutaneous exposure to contaminated needles or other sharp objects.[55] Workers can also be at risk of airborne infection: an outbreak of tuberculosis in waste workers exposed in an industrial setting has been reported, and even small-scale compaction of waste can generate pathogen-containing aerosols.[56,57]

The European Hazardous Waste Directive and related regulations set the framework for the management and disposal of clinical (medical) waste in Europe. Waste from the management of patients with a known or suspected infectious disease, where the causal pathogen or toxin is present in the waste, must be identified, separately packaged, and incinerated.[58] Related national legislation varies somewhat from country to country. Increasingly, environmental legislation discourages incineration on-site in health facilities, making it necessary to transport waste to industrial incineration sites. Some countries in Europe have national standards that require that clinical waste be treated to destroy infectious agents before the waste is removed from the site where it was generated; others, however, have defined and identified "low-risk" clinical waste, and categorised it as non-hazardous, although universal waste-handling precautions may be more likely to ensure safety.[40,55]

Solid wastes generated in an HLIU require decontamination before disposal. Most HLIUs achieve this by autoclaving. The process is easily controllable, and hospital engineers are usually experienced in equipment maintenance and validation. However, autoclaving is time consuming, and energy inefficient. Large quantities of clinical waste are generated during the care of patients with highly infectious diseases, especially when critically ill: a 4-day admission of a single patient with suspected Lassa fever in an HLIU in the UK generated three industrial skip loads of double-bagged clinical waste. One HLIU has a protocol for removing all packaging and protective wrapping from disposable and other equipment in a clean area, before taking the equipment into the clinical area. Packaging and other discarded materials (eg, information leaflets) are disposed of as domestic waste (which may include recycling), cutting the quantity of waste needing autoclaving by about a half. A similar process led to savings of 25–30% in energy expenditure in a hospital in Saudi Arabia.[59] Alternatives to autoclaving include microwave treatment, compaction combined with chemical treatment, which reduces the risks of aerosols but requires the use of chemicals that pose their own risks, and grinding combined with ozone injection, which is unsuitable for waste that might contain group 4 pathogens.[60–62] Local use of special treatment processes has disadvantages: a scarcity of maintenance expertise, greater system complexity, deterioration of equipment through infrequent, intermittent use, and difficulties in obtaining spare parts could all contribute to reduced system functionality and safety.

Health-care workers are at risk of infection from exposure caused by splash, spillage, or aerosol generation during handling or disposal of infected fluids, and there is a theoretical risk for engineers or others working on drainage or sewage systems within or close to the unit. Guidance in the USA recommends disposal of liquid waste (eg, blood, urine, vomit) without pretreatment by pouring into the sanitary sewer.[13] A unit in the UK converts all liquid waste from the patient to a gel by use of specially formulated absorbent crystals that are added as degradable sachets to disposable containers/urinals immediately before use. The gel is then managed as solid waste by autoclaving. This procedure avoids contamination of the drainage system with high concentrations of viruses, and protects health-care workers from the risk of spillage. The unit uses this method for peritoneal dialysate (which can contain high concentrations of virus, even if not blood-stained[63]), and for fluids collected when setting up haemodialysis equipment or rinsing the blood compartment at the end of the session,[64] but haemodialysis ultrafiltrate (likely to contain no, or very low, concentrations of virus because particles of more than 7 nm diameter will be retained by the filtration membrane[64–67]) is disposed of directly into the dirty drains system. Alternative decontamination methods include chemical disinfection, although the chemicals used might be ineffective in the presence of organic matter and are potentially hazardous to health-care workers, and heat treatment, which requires storage of wastes until treated and needs complex equipment and engineering controls.

EUNID participants did not reach a consensus on the need to decontaminate liquid waste before disposal. Most would recommend direct disposal of excreta into the dirty drains system without additional safety measures (eg, pre-addition of hypochlorite), because any significant concentrations of virus would be rapidly diluted within the hospital wastewater system and degraded by agents used for routine cleaning, and the theoretical risk to workers undertaking repairs could be managed by using properly trained, supervised, and equipped maintenance staff. A few participants advise more caution, and would recommend that untreated body fluids (including urine, faeces, haemodialysis ultrafiltrate) should not be disposed of into the dirty drain system, arguing that their approach provides maximum protection and would also be of benefit in the event of the emergence of a new, highly infectious pathogen in the period before the pathogen's

Panel 7: **Decontamination of equipment and environmental hygiene in HLIUs**

EUNID recommends that:

- HLIU equipment should be selected with decontamination in mind
- If an item of equipment cannot safely be decontaminated for reuse, a disposable alternative should be selected
- The HLIU should maintain an inventory of all unit equipment, which states the usual method of decontamination/disposal of each item (eg, bed linen, smallpox—double leak proof bag, autoclave or incinerate on site; bed linen, viral haemorrhagic fever—alginate bag, leak proof container, hot wash laundry cycle; bed frame—wipe down with approved hospital detergent/disinfectant, clean with water, dry)
- Staff undertaking cleaning or decontamination should wear appropriate personal protective equipment and be appropriately trained[11,18,40]
- Patient care equipment (eg, mechanical ventilator, pressure-control mattress) can be decontaminated according to standard national/local protocols. Large, complex equipment that has been contaminated might require decontamination on site before disassembly, and a fumigation method may sometimes be appropriate.[13] In each case, a risk assessment should determine whether staff can safely disassemble the equipment before the separate parts are autoclaved
- Standard national/local hospital protocols are used for cleaning and decontamination of environmental surfaces (eg, hospital detergent/disinfectant designed for general housekeeping purposes for routine cleaning of clinical area; hypochlorite 1% solution for heavily contaminated clinical areas)
- Formaldehyde fumigation of clinical areas is not necessary
- Spillages of blood and other potentially infectious material should be promptly cleaned and decontaminated

transmission and capacity for environmental survival were fully understood. However, the group agreed unanimously that treatment of water resulting from washing or showering by unit personnel (or an ambulant, continent, patient) was not required.

Decontamination of equipment and environmental hygiene

HLIU cleaning and decontamination protocols (panel 7) should cover patients' likely primary diagnoses and health-care-associated infections (eg, *Clostridium difficile*, meticillin-resistant *Staphylococcus aureus*).

Environmental survival of pathogens for which HLIU-based care is recommended is such that extraordinary methods of decontamination will not usually be necessary; an exception might be the need to use a fumigation method to decontaminate large, complex equipment.[13,18,40]

HLIU design and construction requirements

The design and construction requirements for HLIUs are listed in panel 8 and panel 9. Since HLIUs are specifically designed to provide high-level infection control and best possible patient care without compromising the safety of carers or the community, the design and construction values must be specified to ensure this. We suggest that planners seek early advice from clinicians and managers in existing HLIUs. Unit design should also minimise the stressful effects of isolation on the patient, and provide a good working environment for staff.

Conclusion

HLIUs are designed to provide optimum medical care for patients with highly infectious diseases, while at the same time protecting health-care workers, other patients, and the wider community from infection. The renewed interest in biodefence-related research, fuelled by fear of bioterrorism, has meant that more laboratories are working with group 4 pathogens than at any time in the past 50 years, which has increased the likelihood that occupationally acquired infections requiring HLIU-based care will occur.[68] In 2004, for example, a laboratory technician in the USA was admitted to an HLIU for observation after occupational exposure to Ebola virus, and a Russian laboratory worker died of occupationally acquired Ebola haemorrhagic fever.[69] Laboratory personnel working on newly emergent infections can also be at risk of infection, and might, if diagnosis and containment is delayed, transmit infection to others.[70] Infections caused by hazardous pathogens or by newly emerging infections of unknown transmissibility are likely to occur, or be imported, too infrequently in Europe to generate widespread experience or confidence in their management, but sufficiently often enough to justify the maintenance of centres of expertise where they can be most effectively and safely managed.[71–75]

This framework for the design and operation of these centres in European countries was developed by consensus by a multinational, multidisciplinary expert group. Strongly opposed positions emerged on only two issues: the management of routine clinical samples and the disposal of liquid clinical waste. In each case, the options expressed represent current practice in at least one of the isolation facilities for patients with highly infectious diseases in Europe; in neither case is there evidence to determine which option is the safest. The more cautious positions rely on a stricter application of the precautionary principle, or have been required by a more conservative interpretation, at national level, of European legislation, but are more costly and complex to implement, and are not recommended by similar clinical guidance elsewhere.[13,28]

There are other areas of uncertainty, including the optimum air exchange rate, optimum mode of patient transport, and the necessity for HEPA filtration of exhaust

air. Future research could provide definitive answers, and could also provide innovative design and engineering solutions that reduce costs, simplify maintenance, maximise energy efficiency, or improve health-care worker or patient comfort without compromising safety.

Health-care systems, clinical services and training, and health and safety legislation vary between countries, and it should not be expected, and may not be desirable, that risk assessments, risk management solutions, and operational policies for HLIUs in Europe will be completely standardised. For public-health authorities and individual countries to develop and maintain effective, flexible, high-quality services, and improve regional capacity to respond to health threats, a collaborative approach to the design, operation, maintenance, audit, and oversight of these specialist services is required. This

Panel 8: Overall design and construction requirements for HLIUs

The HLIU should:

- Be colocated with a tertiary referral hospital, either in an entirely separate building on the same site, or as a separate unit (with a secure, controllable, entrance/exit route) within the hospital
- Be designed and constructed in compliance with relevant European, national, and local regulations and codes
- Have a separate, securable, entrance; double, inter-locking doors are ideal
- Be designed internally so that movement of "clean" and "contaminated" staff, patients, and equipment through the unit ensures segregation of "clean" and "dirty" areas
- Have integral autoclave facilities, or safe access to pre-identified, dedicated autoclave facilities
- Have an integral BSL3 or equivalent laboratory, or access to one in close proximity on the same campus
- Have an adequate storage area for large equipment
- Have adequate storage space for supplies of personal protective equipment, pharmaceuticals (including controlled drugs), and clinical supplies
- Have a sealable area for decontamination of large equipment
- Have a designated area for handling and packaging clinical waste
- Have an area for the temporary safe-keeping of deceased patients, large enough to contain and decontaminate trolleys, sealable coffins, and other mortuary equipment
- Have a staff rest area
- Have a staff office area
- Have staff changing and showering facilities
- Have a decontamination shower
- Be designed and constructed for ease of cleaning and decontamination (eg, seamless floors and walls, solid horizontal surfaces)
- Have building, electrical, ventilation, and other systems that are designed and constructed for easy and safe access for maintenance
- Have a safe, securable pathway for emergency evacuation of staff and patients
- Have a connection to an emergency power-generating system
- Have standard life-safety systems (eg, automatic sprinkler systems) that are compliant with current European, national, and local regulation, with an independent airflow shutdown system

Panel 9: Design and construction requirements for high-level patient isolation rooms

Patient isolation rooms in the HLIU should:

- Be large enough to contain the specialist equipment (eg, mechanical ventilator, haemofiltration machine, monitoring equipment) needed for critical care, and to allow free movement by staff wearing personal protective equipment
- Have a self-closing door, with well-fitted, durable, door seals
- Have a non-hand operated wash basin for clinical use in the patient's room
- Have a non-hand operated wash basin for clinical use in the anteroom
- Have an en-suite bathroom (toilet, hand basin, and shower); entrance to bathroom should be from within the patient's room, not the anteroom
- Have a system for visually monitoring the patient and room from the outside, which is flexible enough to maintain patient privacy, dignity, and safety
- Have a high-quality patient–clinician communication system
- Have a high-quality clinician–clinician communication system
- Have an emergency alarm system so that help can be summoned immediately if need be
- Have an anteroom (or equivalent designated area) large enough to store immediately necessary personal protective equipment and clinical supplies (eg, intravenous fluids and tubing, syringes, dressings, specimen containers)
- Have an adequate area for packaging clinical specimens and for decontaminating outer specimen containers
- Be designed and constructed for ease of cleaning and decontamination
- Have sealed windows
- Be designed and constructed to be as airtight as possible (ie, monolithic ceilings, tightly fitting doors and windows, door grill designed for a controlled air path); other design features that enhance the functionality of the ventilation system may also be desirable (eg, interlocking door system, with clinician controlled override function, which ensures that the patient room–anteroom door and anteroom–corridor door cannot both be opened at the same time)

Search strategy and selection criteria

Data published up to December, 2007, were obtained by searches of PubMed, Medline, and ProMed, and from review of the references listed in retrieved articles. Search terms included "patient isolation", "airborne transmission", "infection control", "occupational health", "patient transfer", "ventilation", "waste management", "decontamination", and "hospital design and construction", and "Lassa fever", "Ebola", "haemorrhagic fever", "Marburg virus", "haemorrhagic fever, Crimean", "smallpox", "monkey pox", "SARS virus", "extensively drug resistant tuberculosis", and "avian influenza". Abstracts of articles in English, French, German, Italian, and Spanish languages were read and considered, and we also reviewed relevant national guidelines, supplied (and if necessary translated) by EUNID participants.[12] No data restrictions were placed on our searches.

approach should be taken from member state to member state, or more broadly across the European Union in a way that makes the most of existing expertise.

EuroNHID will expand on EUNID's work (intended to complement, rather than duplicate, the work of the European Centre for Disease Prevention and Control), and will seek the opinion of the European Union of Medical Specialists on this framework. Furthermore, EuroNHID will explore, through the Public Health Executive Agency, other mechanisms by which this framework might be adopted as a standard for HLIUs in Europe.

Conflicts of interest

We declare that we have no conflicts of interest.

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References

1 Jernigan JA, Stephens DS, Ashford DA, et al. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. *Emerg Infect Dis* 2001; **7:** 933–44.

2 Hughes JM, Gerberding JL. Anthrax bioterrorism: lessons learned and future directions. *Emerg Infect Dis* 2002; **8:** 1013–14.

3 National Advisory Committee on SARS and Public Health. Learning from SARS: renewal of public health in Canada. Ottawa, Canada: Health Canada, 2003.

4 WHO. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. Based on data as of 31 December 2003. http://www.who.int/csr/sars/country/table2004_04_21/en/index.html (accessed Oct 20, 2008).

5 Mounier-Jack S, Coker RJ. How prepared is Europe for pandemic influenza? Analysis of national plans. *Lancet* 2006; **367:** 1405–11.

6 Nicoll A, Kaiser R. Limitations of recently published review of national influenza pandemic plans in Europe. *Euro Surveill* 2006; **11**: E060427.3. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2950 (accessed Oct 20, 2008).

7 Commission of the European Communities. Programme of cooperation on preparedness and response to biological and chemical agent attacks, [health security], Dec 17, 2001. http://www.europa.eu.int/comm/health/ph_threats/Bioterrorisme/bioterrorism01_en.pdf (accessed Oct 20, 2008).

8 EUNID. European Network of Infectious Disease Physicians report of the first annual meeting, May 27–28, 2005, Rome, Italy. http://www.eunid.com/privato/upload_folder/Final%20EUNID2005%20meeting%20report.pdf (accessed Oct 20, 2008).

9 EUNID. European Network for Infectious Diseases report of the second annual meeting, April 7–8, 2006, London, UK. http://www.eunid.com/privato/upload_folder/EUNID%20meeting%20report%20-%20London%202006.pdf (accessed Oct 20, 2008).

10 EUNID. European Network for Infectious Diseases report of the third annual meeting, May 24, 2007, Rome, Italy. http://ec.europa.eu/health/ph_projects/2003/action2/docs/2003_2_04_frep_a4_en.pdf (accessed Oct 20, 2008).

11 Baka A, Fusco FM, Puro V, et al. A curriculum for training healthcare workers in the management of highly infectious diseases. *Euro Surveill* 2007; **12:** E5–6. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=716 (accessed Oct 20, 2008).

12 EUNID. Compendium of national guidelines on highly infectious diseases. http://www.eunid.com/privato/partners/guidelines2.asp (accessed Dec 22, 2007).

13 Smith PW, Anderson AO, Christopher GW, et al. Designing a biocontainment unit to care for patients with serious communicable diseases: a consensus statement. *Biosecur Bioterror* 2006; **4:** 351–65.

14 CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care facilities, 1994. *MMWR Recomm Rep* 1994; **43:** 1–132.

15 Jensen PA, Lambert LA, Iademarco MF, Ridzon R. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR Recomm Rep* 2005; **54:** 1–141.

16 National Collaborating Centre for Chronic Conditions. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London: Royal College of Physicians, 2006.

17 EUNID. Highly infectious diseases and isolation room capabilities in European countries. http://www.eunid.eu/privato/upload_folder/Inventory%20of%20isolation%20facilities%20in%20EUNID%20countries.pdf (accessed Oct 20, 2008).

18 Siegel JD, Rhinehart E, Jackson M, Chiarello L. Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings, June 2007. http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/Isolation2007.pdf (accessed Oct 20, 2008).

19 Department of Health. Guidelines for smallpox response and management in the post-eradication era (smallpox plan). Appendix 5: specification for smallpox care centres. London: Department of Health, 2003.

20 Henderson DA, Inglesby TV, Bartlett JG, et al. Working Group on Civilian Biodefense. Smallpox as a biological weapon: medical and public health management. *JAMA* 1999; **281:** 2127–37.

21 Neff J, Modlin J, Birkhead GS, et al. Monitoring the safety of a smallpox vaccination program in the United States: report of the joint Smallpox Vaccine Safety Working Group of the advisory committee on immunization practices and the Armed Forces Epidemiological Board. *Clin Infect Dis* 2008; **46** (suppl 3)**:** S257–70.

22 European Commission. Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work. *Official Journal of the European Communities* 2000; L 262/21-45. http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:262:0021:0045:EN:PDF (accessed Oct 20, 2008).

23 Anon. Control of Substances Hazardous to Health Regulations 2002 (as amended) SI 2002/2677. London: The Stationery Office, London, 2002.

24 Advisory Committee on Dangerous Pathogens. Biological agents: managing the risks in laboratories and healthcare premises. London: Health and Safety Executive, 2006. http://www.advisorybodies.doh.gov.uk/acdp/managingtherisks.pdf (accessed Oct 20, 2008).

25 Advisory Committee on Dangerous Pathogens. Management and control of viral haemorrhagic fevers. December, 1996. London: The Stationery Office, 1996.

26 WHO. Guidance on regulations for the transport of infectious substances 2007–2008. Geneva: World Health Organization, 2007. WHO/CDS/EPR/2007.2.

27 WHO. Laboratory biosafety manual, 3rd edition. Geneva: World Health Organization, 2004. WHO/CDS/CSR/LYO/2004.11.

28 CDC. Interim guidance for managing patients with suspected viral haemorrhagic fever in US hospitals. http://www.cdc.gov/ncidod/dhqp/bp_vhf_interimGuidance.html (accessed Oct 20, 2008).

29 American Society for Microbiology. Sentinel laboratory guidelines for suspected agents of bioterrorism. Clinical laboratory bioterrorism readiness plan. August, 2006. http://www.asm.org/ASM/files/LeftMarginHeaderList/DOWNLOADFILENAME/000000001204/BTtemplateRevised8-10-6.pdf (accessed Oct 20, 2008).

30 Wirtz A, Niedrig A, Fock R. Management of patients with suspected viral haemorrhagic fever and other potentially lethal contagious infections in Germany. *Euro Surveill* 2002; **7:** 36–42. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=341 (accessed Oct 20, 2008).

31 Ippolito G, Nicastri E, Capobianchi M, Di Caro A, Petrosillo N, Puro V. Hospital preparedness and management of patients affected by viral haemorrhagic fever or smallpox at the Lazzaro Spallanzani Institute, Italy. *Euro Surveill* 2005; **10:** 36–39. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=523 (accessed Oct 20, 2008).

32 Trexler PC. An isolator system for the maintenance of aseptic environments. *Lancet* 1973; **1:** 91–93.

33 Christopher GW, Eitzen EM. Air evacuation under high level biosafety containment: the aeromedical isolation team. *Emerg Infect Dis* 1999; **5:** 241–46.

34 Haas WH, Breuer T, Pfaff G, et al. Imported Lassa fever in Germany: surveillance and management of contact persons. *Clin Infect Dis* 2003; **36:** 1254–58.

35 Zweighaft RM, Fraser DW, Hattwick MA, et al. Lassa fever: response to an imported case. *N Engl J Med* 1977; **297:** 803–07.

36 Formenty P, Hatz C, Le Guenno B, Stoll A, Rogenmoser P, Wildmer A. Human infection due to Ebola virus, subtype Côte d'Ivoire: clinical and biologic presentation. *J Infect Dis* 1999; **179** (suppl 1)**:** S48–53.

37 WHO. Infection prevention and control of epidemic- and pandemic-prone acute respiratory diseases in health care. WHO interim guidelines, June 2007. Geneva: World Health Organization. WHO/CDS/EPR/2007.6. http://www.who.int/csr/resources/publications/WHO_CD_EPR_2007_6/en/index.html (accessed Oct 20, 2008).

38 WHO. Public health response to biological weapons: WHO guidance (2004). Geneva: World Health Organization, 2004.

39 Rydock JP, Eian PK, Lindqvist C, Welling I, Lingaas E. Best practice in design and testing of isolation rooms in Nordic hospitals. TR564, Nordic Innovation Centre, Oslo, September 2004. http://www.nordicinnovation.net/_img/nt_tech_rep564teksti.pdf (accessed Oct 20, 2008).

40 CDC. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). *MMWR Recomm Rep* 2003; **52:** 1–42.

41 American Institute of Architects. Guidelines for design and construction of hospital and health care facilities: 2006 edition. Washington, DC: American Institute of Architects, 2006.

42 American Society of Heating, Refrigerating and Air-Conditioning Engineers, Inc. HVAC design manual for hospitals and clinics Atlanta, USA: ASHRAE, 2003.

43 Department of Human Services, Victoria. Victorian Advisory Committee on Infection Control. Guidelines for the classification and design of isolation rooms in healthcare facilities. Department of Human Services: Melbourne, Victoria, 2007.

44 Roy CJ, Milton DK. Airborne transmission of communicable infection—the elusive pathway. *N Engl J Med* 2004; **350:** 1710–12.

45 Menzies R, Fanning A, Yuna L, FitzGerald M. Hospital ventilation and risk for tuberculosis infection in Canadian health care workers. *Ann Intern Med* 2000; **133:** 779–89.

46 Hutton MD, Stead WW, Cauthen GM, Bloch AB, Ewing WM. Nosocomial transmission of tuberculosis associated with a draining abscess. *J Infect Dis* 1990; **161:** 286–95.

47 Matlow AG, Harrison A, Monteath A, Roach P, Balfe JW. Nosocomial transmission of tuberculosis (TB) associated with care of an infant with peritoneal TB. *Infect Control Hosp Epidemiol* 2000; **21:** 223.

48 Booth TF, Kournikakis B, Bastien N, et al. Detection of airborne severe acute respiratory syndrome (SARS) coronavirus and environmental contamination in SARS outbreak units. *J Infect Dis* 2005; **191:** 1472–77.

49 Moser MR, Bender TR, Margolis HS, Noble GR, Kendal AP, Ritter DG. An outbreak of influenza aboard a commercial airliner. *Am J Epidemiol* 1979; **110:** 1–6.

50 Alford RH, Kasel JA, Gerone PJ, Knight V. Human influenza resulting from aerosol inhalation. *Proc Soc Exp Biol Med* 1966; **122:** 800–04.

51 Wehrle PF, Posch J, Richter KH, Henderson DA. An airborne outbreak of smallpox in a German hospital and its significance with respect to other recent outbreaks in Europe. *Bull World Health Organ* 1970; **43:** 669–79.

52 Anon. Council Directive 90/679/EEC of 26 November 1990 on the protection of workers from risks related to exposure to biological agents at work (seventh individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC. *Official Journal of the European Communities* 1990; L 374/1. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31990L0679:EN:HTML (accessed Oct 29, 2008).

53 Anon. Council Directive 93/88/EEC of 12 October 1993 amending Directive 90/679/EEC. *Official Journal of the European Communities* 1993; L 268/271. http://www.biosafety.be/GB/Dir.Eur.GB/Other/93_88/TC.html (accessed Oct 29, 2008).

54 Swedish Association for Hospital Hygiene. Building design and hospital hygiene: Hospital hygiene aspects of new, remodelled and renovated hospital areas 2003 (in Swedish). http://www.sfvh.nu/dokument/nybov.pdf (accessed Oct 29, 2008).

55 Blenkharn JI. Lowering standards of clinical waste management: do the hazardous waste regulations conflict with the CDC's universal/standard precautions? *J Hosp Infect* 2006; **62:** 467–72.

56 Johnson KR, Braden CR, Cairns KL, et al. Transmission of *Mycobacterium tuberculosis* from medical waste. *JAMA* 2000; **284:** 1683–88.

57 Emery R, Sprau D, Lao YJ, Pryor W. Release of bacterial aerosols during infectious waste compaction: an initial hazard evaluation for healthcare workers. *Am Ind Hyg Assoc J* 1992; **53:** 339–45.

58 European Commission. Summary of EU waste legislation. http://europa.eu/scadplus/leg/en/s15002.htm (accessed Oct 20, 2008).

59 Alumneef M, Memish ZA. Effective medical waste management: it can be done. *Am J Infect Control* 2003; **31:** 188–92.

60 Hoffman PN, Hanley MJ. Assessment of microwave-based clinical waste decontamination unit. *J Appl Microbiol* 1994; **77:** 607–12.

61 Coronel B, Duroselle P, Behr H, Moskovetchenko JF, Freney J. In situ decontamination of medical wastes using oxidative agents: a 16-month study in a polyvalent intensive care unit. *J Hops Infect* 2002; **50:** 207–12.

62 Jette LP, Lapierre S. Evaluation of a mechanical/chemical infectious waste disposal system. *Infect Control Hosp Epidemiol* 1992; **13:** 387–93.

63 Cusumano AM, Poratto F, del Pino N, Fernandez JL, Vilches A. Identification of hepatitis C virus RNA in peritoneal dialysis fluid of patients with viraemia. *Perit Dial Int* 2005; **25:** 478–82.

64 Froio N, Nicastri E, Comandini UV, et al. Contamination by hepatitis B and C viruses in the dialysis setting. *Am J Kidney Dis* 2003; **42:** 546–50.

65 Noiri E, Nakao A, Oya A, Fujita T, Kimura S. Hepatitis C virus in blood and dialysate in hemodialysis. *Am J Kidney Dis* 2001; **37:** 38–42.

66 Hayashi H, Okuda K, Yokosuka O, et al. Adsorption of hepatitis C virus particles onto the dialyser membranes. *Artif Organs* 1997; **21:** 1056–59.

67 Kwan BC, Leung CB, Szeto CC, et al. Severe acute respiratory syndrome in dialysis patients. *J Am Soc Nephrol* 2004; **15:** 1883–88.

68 Rusnak JM, Kortepeter MG, Aldis J, Boudreau E. Experience in the medical management of potential laboratory exposures to agents of bioterrorism on the basis of risk assessment at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID). *J Occup Environ Med* 2004; **46:** 801–11.

69 ProMed Mail. Ebola, lab accident death—Russia (Siberia) (04). Aug 23, 2004. Archive number 20040823.2350. http://www.promedmail.org/pls/otn/f?p=2400:1001:::NO::F2400_P1001_BACK_PAGE,F2400_P1001_PUB_MAIL_ID:1000%2C26482 (accessed Oct 20, 2008).

70 Lim PL, Kurup A, Gopalakrishna G. Laboratory-acquired severe acute respiratory syndrome. *N Engl J Med* 2004; **350:** 1740–45.

71 Radun D, Niedrig M, Ammon A, Stark K. SARS: retrospective cohort study among German guests of the Hotel 'M', Hong Kong. *Euro Surveill* 2003; **8:** 228–30. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=436&LanguageId=1 (accessed Oct 20, 2008).

72 Issartel B, Lesens O, Chidiac C, et al. Suspected SARS patients hospitalised in French isolation units during the early SARS epidemic: the French experience. *Euro Surveill* 2005; **10:** 9–43. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=524 (accessed Oct 20, 2008).

73 Donoso Mantke O, Schmitz H, Zeller H, Heyman P, Papa A, Niedrig M. Quality assurance for the diagnostics of viral diseases to enhance the emergency preparedness in Europe. *Euro Surveill* 2005; **10:** 102–06. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=545 (accessed Oct 20, 2008).

74 ProMed Mail. Lassa fever—Europe ex Sierra Leone (02). Archive number 20060724.2045. http://www.promedmail.org/pls/otn/f?p=2400:1001:::NO::F2400_P1001_BACK_PAGE,F2400_P1001_PUB_MAIL_ID:1000%2C33712 (accessed Oct 20, 2008).

75 Macher AM, Wolfe MS. Historical Lassa fever reports and 30-year clinical update. *Emerg Infect Dis* 2006; **12:** 835–37.