Specifications for a High-Level Isolation Unit for hazardous infectious diseases in Europe: report and commentary on a consensus view of European experts participating in the EUNID project.
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Introduction

EUNID is a project funded through the European Union; Framework 6 Public Health (DG SANCO) programme. The project's aims are to identify the current facilities for the clinical management of patients with hazardous infections and, further, to define the appropriate specification for high-level isolation facilities in today's Europe. Led from the National Institute for Infectious Diseases "Lazzaro Spallanzani" in Rome, the project consists of a consortium of experts in managing patients with hazardous infections from European Member States and associated countries, who each contribute their experience and knowledge to determining appropriate standards of provision (*list of participating countries and representatives added as an acknowledgement*).

After an information gathering stage, in which all experts completed lists of available facilities, guidelines and expertise, criteria for the provision of a high-level isolation service were discussed in detail in a meeting in London in May 2006, and finalised by review and consensus in a further symposium in May 2007. Initially, two separate groups discussed and presented: a) the physical and organisational requirements for such a service and b) personal protective measures necessary for the safety of staff working in the clinical areas. At the final meeting, all aspects of a HIU provision were discussed by the entire group. This is the report and commentary on the final conclusions of the expert group.

Definition of a High Level Isolation Unit (HIU)

All participants agreed at the beginning of the project in 2004, that some patients required management in a facility with enhanced levels of biosecurity, compared with patient isolation facilities usually available in a European hospital setting. Representatives of all but one Member State would use such a facility for individual patients or a small number of patients but not for patients affected in an epidemic or large outbreak of a hazardous infection. They agreed that the use of a high-level isolation unit was less appropriate in an epidemic situation where exposure to the condition in the normal community would become increasingly likely.

Participants also agreed that a HIU could be used flexibly, with more than one level of infection containment. The level of containment could be decided, based on an individual risk assessment of the nature of the pathogen and the nature of the patient's illness.

EUNID definition of a High Level Isolation Unit
A flexible facility specifically designed to optimise infection containment and control procedures for single or a small number of patients with suspected, probable or known highly infectious diseases, providing an high standard of patient care, appropriate for the patient's condition.

Definition of a highly infectious disease (HID)

Hazardous infections were defined at the beginning of the project as those infections for which a higher level of isolation and infection control is necessary than that which is available in tertiary referral hospitals.

EUNID definition of a highly infectious disease:
"A highly infectious disease
- is transmissible from person to person,
- is life-threatening, and
- presents a severe hazard in the health care setting and in the community, requiring specific control measures"

Examples of such infections include viral haemorrhagic fevers and poxvirus infections, which are classified at hazard level 4 under the provisions of the European Biological Agents Directive [1], and therefore require special isolation and laboratory precautions. Other, or newly-emerging, infections may also be included according to their agreed risk assessment.

There was an extensive discussion of whether certain named diseases or pathogens should be included in an indicative list of HIDs. Infections specifically considered included avian influenza, SARS, pandemic influenza, multiple-drug resistant tuberculosis (MDRTB) and extended drug resistant tuberculosis (XDRTB). It was accepted by most representatives that standards of isolation for MDRTB in negative-pressure, airflow-controlled single patient rooms were available in many Western countries. The need for enhanced infection control for XDRTB cases was less clear.

EUNID consensus list of pathogens or diseases that fulfil the definition of a HID
- Human-to-human transmissible viral haemorrhagic fevers (VHFs)
- Avian influenza infection which has transmitted from human to human
- An emerging highly pathogenic influenza or other respiratory infection
- Smallpox and other highly pathogenic Orthopox infections
- Cases of an unknown emerging pathogen or suspected bioterrorist agent
- XDR-TB and some highly resistant strains of MDRTB

Specifications for HIUs in Europe.
The Group identified important headings under which the main needs for high-level isolation units could be grouped. These were:

- The appropriate number and distribution of units within each Member State
- The minimum requirements for facilities and services provided by such units
- Clinical staff numbers, training and health assessment
- The management of airflow control and potential air contamination
- Staff and patient circulation pathways within the unit
- Transport of patients and laboratory specimens outside the unit
- Requirements for patient management laboratory services
- Requirements for clinical waste handling
- Methods of decontamination of staff
- Methods of decontamination of the units and associated equipment
- Security measures to protect the unit from damage and intrusion

All members of the consensus were experienced in providing or operating a high-level isolation service. At the outset, they acknowledged that high-quality evidence for their opinions was scanty, owing to the rarity of hazardous infections, differences in the

ways in which national provisions had developed and the difficulty of performing prospective clinical studies. Much of the existing literature on the containment of pathogens concerns safety in laboratory environments, or the need for emergency measures in managing situations such as the SARS pandemic. Evidence for the effectiveness of airflow control and air filtration also mostly relates to laboratory containment of pathogens or to protection from chemical contamination, though there are reports of the success or failure of specific systems in infection control. The commentaries on the decisions of the consensus group, and the references provided, reflect the limitations of the evidence. However, the accumulated experience of the group members, and the procedures which they use, have developed along similar lines in many countries and have stood the test of time. Taken together, the available evidence and the body of experience of the group are an excellent basis on which to set achievable and effective standards.

Recommendations on the number and distribution of units in a Member State

One national Unit or dispersed units?

The EUNID consensus was that:
- The number of units per Member State (MS) should depend on size of the individual MS and the administrative structure within it;
- Units should be sited to avoid needing journey times of greater than 6 hours for sick patients requiring admission;
- Two units would be desirable for MSs with the resources to support them, to provide resilience in the service: one unit could support the other during down-time for maintenance and repairs;
- An alternative for some MSs, depending on geography and communications, would be collaboration between two adjacent MSs with one unit in each;
- A model could be hypothesised, in which a number of International collaborating units serve several MSs.

Commentary.
Several Member States have supported one or more high-level isolation facilities over the last two or three decades. Since their inauguration there have been many advances in diagnostic facilities and infection control across Europe. Most large hospitals and tertiary referral centres possess at least one or two isolation rooms with bathroom facilities. Many now also possess rooms or hospital wards with negative pressure or airflow control.

Rapid serological and nucleic acid detection techniques have improved the speed and accuracy of diagnostic tests. It is nowadays possible for many patients at low risk of having a hazardous infection, and who present low or negligible risk to their carers, to remain in a well-equipped hospital during the 12 to 24 hours required for confirmation or exclusion of such a diagnosis.

Nevertheless, some diseases, such as variola, are potentially highly dangerous in a normal patient isolation setting. Others, including the viral haemorrhagic fevers, can progress very rapidly so that the patient develops severe haemorrhage and multiple organ failures over a period of 24 to 36 hours, rapidly becoming more difficult and hazardous to manage. Patients with a confirmed or strongly suspected diagnosis of such infections should therefore be managed in a setting where reliable facilities exist, and where there are sufficient trained and experienced staff to maintain safe management of the patient for as long as necessary.

Those who may be exposed to patients and clinical material are not only doctors and nurses, but may be laboratory workers, porters, cleaners, engineers, therapists and visitors. It is accepted that, for these reasons, for the security of the patient and carers, and to protect the public health, specialist centres for high-security infection management are necessary.

A number of Member States initially created several high-security isolation units distributed across the country. However, some were little-used, and the numbers of units slowly contracted, concentrating specialist skills into a handful of places. The availability of more than one unit per MS has proved useful for resilience, as one unit can replace another during periods of repair or refurbishment. Where there is more than one unit, a range of skills and ideas may be contributed by each, effectively improving research and development in the National resource. International collaboration could enhance this sharing of expertise.

The number of facilities in a Member State is likely to be influenced by the distribution and density of the population, and the ease or difficulty of communication and transport across the country. A balance is necessary between long-distance transport of patients and clinical specimens, and the availability of highly specialised clinical care. Small Member States found it more difficult to contemplate providing duplicated facilities. These states, and others where transport across a state border was easier than across difficult terrain (such as mountainous areas), had considered collaboration with neighbouring states.

Optimum geographic location and connections for a high-level isolation unit.

The EUNID consensus was that:
- The unit must be located alongside a tertiary (specialist referral) hospital
- It could be a stand-alone pavilion or (with appropriate engineering and operational protocols) positioned within a multi-storey building
- Critical care capabilities must be included in the design and operational policies (this should be with the collaboration of the local Critical Care experts).
- There must be expertise available for paediatric advice and support
- There must be access to advice and support from other specialties

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Commentary.

These recommendations were based on the experiences of group members with experience of caring for patients who required a range of specialist support. Support provided has included: transfusion of blood and blood products; cardiac and respiratory monitoring; invasive haemodynamic monitoring; renal dialysis; intermittent positive-pressure ventilation, and drainage of effusions. Some of the experts had undertaken assessment and management of one or more feverish children, often concurrently with an accompanying parent.

It would be difficult to provide adequate diagnostic services, management expertise and expert consultation if the HIU did not share the resources of a well-equipped hospital. Most existing units are alongside and affiliated to a University Hospital, while a few are stand-alone civilian or military hospitals with tertiary care facilities.

Should the HIU facility be reserved exclusively for patients with suspected or known HIDs?

EUNID consensus suggests that:

- A HIU may be used day to day for non-HID patients, as this would ensure that the HIU did not fall into disrepair between rare periods of use;
- The primary purpose of a HID could be made clear by a national contract
- The HID facility must be made ready to receive a HID patient within three or four hours of referral (a delay of greater than 6 hours is unacceptable)
- Adequate down-time must be provided to ensure maintenance of specialised services such as filtered ventilation systems
- Time for training of dedicated staff in the special protocols of the HID must also be guaranteed

Commentary

All participants agreed that the HIU may be used to isolate other patients when not in use for a patient with a HID. However, there must be sufficient time for dedicated staff to train in the HIU. There must also be sufficient time available for regular testing of specific facilities such as ventilation systems, autoclaves and other decontamination services.

All participants agreed that it should always be clear that the primary purpose of the facility is to be ready for the care of a HID patient. There should therefore be an absolute commitment to evacuate non-HID patients, clean the unit and prepare it for use within a time period of 3-4 hours, with a maximum delay in readiness of six hours. This can often best be achieved by having a contract within the MS, which makes this responsibility clear. For a busy HIU which is relatively regularly used, it may be preferable to use it for non-HID patients only if other isolation facilities are temporarily unavailable, and to transfer the non-HID patients to suitable alternative facilities as soon as practicable.

Should a dedicated and trained cadre of staff be attached to a HIU?

The EUNID consensus on overall staffing issues is that:
- When a HID is in use, the entry of non-essential and untrained staff should be avoided-cleaning of the HID area and transport of specimens and the patient are subject to specific control of infection protocols and should therefore be performed by the trained doctors and nurses working in the HID;
- Doctors and nurses who operate the unit should receive specific training with regular refresher training;
- Sufficient trained staff should be available to provide 24-hour availability to open and run the HIU;
- Other specialists, such as intensivist doctors and nurses, who may often be asked to support the patient, should regularly train alongside the HIU doctors and nurses, to retain their familiarity with the HIU and its protocols;
- Training should be according to agreed programmes for the different professional groups, and records should be kept of training courses attended and of satisfactory performance;
- Engineers may also require some training in the facilities and maintenance of the HID;
- Specifically trained staff are often volunteers for these specialist duties, and should be appropriately rewarded for training and working in the HIU;
- Specifically trained staff are typically also regular staff of the affiliated hospital-clear arrangements must be made to cover their other duties when they are called to work in the HIU.

Commentary

There was extensive discussion on the necessary staff for a HIU, and on the management and safety of staff. In most existing HIUs, the clinical staff were all volunteers. Housekeeping and hotel services for the HIU when it was not in use could be as for the rest of the affiliated hospital. However, the general experience was that

non-clinical staff such as domestic staff, phlebotomists, and porters, are more likely to have short contracts, to be temporary staff members or to be provided by outside contractors. There are many difficulties in maintaining sufficient of these to work safely in a HIU during a patient's admission. To ensure the safe running of the HIU, and adequate control of infection, it was therefore usual practice to have their tasks done by the regular clinical team during a patient admission.

All experts had found it necessary to designate a lead specialist to undertake administration, coordinate the work of the various professional groups in the HIU, supervise training protocols, liaise with occupational health services and to represent the HIU in regional and national management activities. This person was usually the most senior and experience doctor. A designated lead nurse was also important, to manage the ward and to lead in developing and maintaining nurse training programmes.

Occupational health provision is necessary to ensure safety of the staff from infection, maintain health surveillance of teams working in the HIU and to ensure a rapid and effective response if a staff member should become ill during or soon after a period of duty. For staff working in a demanding and high-pressure environment, and whose patient is often young and dangerously ill, psychological support is essential both during and after the event.

EUNID experts agreed that other specific staffing issues included:
- The need for designated Director of the HIU, usually a senior doctor;
- The need for a designated nursing director;
- Appropriate succession planning for clinical leads;
- Normal occupational health checks, according to local policy, are adequate for HIU staff;
- No special immunisations are necessary (but may be considered in special circumstances, such as admission of a patient with transmissible avian influenza;
- A daily record should be kept of all personnel who enter and work in the HIU;
- Staff health surveillance should be maintained during and for some time after the operation of the HIU;
- Psychological support for HIU staff is helpful during and at the conclusion of deployment.

How should patients be transported to the HIU after referral?

The EUNID opinion on transport of HID patients was:
- Road transport should be by an ambulance appropriate to the patient's needs and able to be effectively decontaminated by wiping, spraying or 'fogging' with an effective disinfectant, according to local policy;
- Specially constructed ambulances with controlled ventilation, though specified in some Member States, are not considered essential by most experts;
- Ambulance transport isolators might protect the vehicle and healthcare team from splash and spillage and may be used for patients with severe; haemorrhage, or other hazardous condition, but are not often essential and may compromise the care of a sick patient;
- Appropriate personal protective equipment must be used by those exposed to the HID patient in the ambulance;
- Arrangements must be in place for appropriate storage and decontamination of contaminated ambulance equipment;
- Ambulance crews must be trained in the protocols for transport of HID patients;
- A designated and secure area must be available where the ambulance can be decontaminated and wait for the crew to return to it after personal decontamination.

Commentary

Although the existing clinical facilities in Member States have evolved according to similar philosophy in each case, the requirements for safe transport of patients to the unit have been addressed quite differently. Most MSs require ambulance crews to be specially trained but not all have required the use of special vehicles. In some MSs, a special ambulance with controlled and filtered ventilation is used; some use a special ambulance with crew wearing various levels of personal protective equipment and others, again, use patient isolators to protect the crew and environment. Most experts now believe that almost all patients can be managed by ambulance personnel wearing standard personal protective equipment. In the last 40 years of ill patients with different viral haemorrhagic fevers have travelled by public airline, by air casualty transport and by road transport without secondary cases being detected. While this does not mean that a critically ill patient could safely travel in this way, it does suggest that a proper risk assessment could probably identify those few patients with late or severe disease for whom more severe infection control measures should be used.

A factor in deciding to use exceptional precautions is the difficulty of continuing them for the necessary time, the exhaustion of personnel caring for the patient, and the tendency for damage to personal suits, motors and filters when working in confined spaces. Also, if small isolators are used to transport patients, it is unpleasant for the patient and very difficult to provide appropriate care for a sick patient in such a small space.

Security of the patient and the HIU.

The EUNID consensus was:
- Security arrangements should be appropriate to the situation and requirement in a particular Member State;
- A defined entrance to the HIU is an advantage, as it allows entry and exit control;
- Important issues include ensuring privacy for the patient and safety for both those working inside and workers/visitors outside who might enter the HIU;
- Adequate communications between the HIU and outside are important, so that help can be obtained if an emergency should occur.

Should the unit have Negative pressure ventilation control?

The EUNID experts agreed that:
- Negative pressure ventilation systems provide significant protection to adjacent areas;
- A pressure gradient should be maintained in successive areas from the clean to the most contaminated zone;
- The level of negative pressure would depend on the size and design of the rooms in the unit; levels of -15 to -45 Pascals between the general hospital environment and the patient room were considered appropriate;
- According to available knowledge, an adequate number of air changes per hour should be achieved, aiming for at least 12 changes per hour (with a minimum acceptable number of six changes per hour);
- Lobbies or anterooms increase the security of airflow control and reduce the negative pressure required for adequate control of airflow direction; although not
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essential, they were considered to be a highly desirable feature of HIU isolation rooms.

Commentary

Although it is not the only route of transmission, infection of healthcare attendants by the droplet or aerosol route has been shown to occur with influenza [2], varicella [3,4], SARS [5,6], measles [7], pneumonic plague [8] and smallpox [9], and has been suspected as a rare route of transmission for Ebola, Lassa, Marburg and Crimean-Congo haemorrhagic fevers [10,11,12,13].

Outbreaks of multi drug-resistant tuberculosis have resulted from airborne transmission, not only from patients with respiratory infections[14], but by droplets generated during the care of copiously draining abcesses [15] or during disposal of infected peritoneal dialysis fluid [16]. It has also been suggested that organisms colonising the mouth, or in dental plaque can be transmissible to others [17]. These potential exposures may be particularly important for healthcare attendants of patients who are highly dependent, suffering from severe haemorrhage or discharging body fluids heavily contaminated with hazardous pathogens.

Even the manipulation of solid clinical waste can potentially produce an airborne hazard. This is illustrated by an outbreak of multi drug-resistant tuberculosis among waste workers exposed in an industrial setting [18]. It has also been shown that small-scale compaction of clinical waste, in unsealed plastic disposal bags at the site of generation, can release aerosols of pathogenic bacteria [19]. This could represent a substantial airborne hazard in a setting where the use of disposables and the need to manage spillages may generate many tens of litres of waste daily from a single patient.

Airflow control by negative pressure. Investigation of a tuberculosis outbreak showed that the escape of expectorated pathogens from a patient's room can produce sufficient airborne contamination to infect susceptible individuals outside [14].

While directional airflow control is important in managing this problem, many workers use evidence of maintained negative pressure to indicate significant airflow from the neutral- to the negative-pressure area (ie maintaining airflow inwards from clean zones and outwards through 'dirty' zones). Ideally, inwards airflow, from clean to dirty areas should be sufficient to overcome the escape of air in vortices when hinged doors are briefly opened to permit the passage of healthcare workers[20], and the level of negative pressure should be chosen to account for this. The presence of vestibules or anterooms between the neutral- and negative- pressure areas increases the efficiency of the system. Curtains or barriers can be effective in dividing and directing airflows, but must fit closely to the ceiling and floor, to avoid escape of contaminated air outside the intended pathway [21]. Most negative pressure clinical areas are designed to provide around 2.5 [22] to 15 Pa of negative pressure between neutral and vestibule areas, and 2.5 to 40 or 45 Pa total difference between neutral areas and patient rooms.

Air changes and particle dilution

Experience in Canadian healthcare settings suggested that nosocomial transmission of tuberculosis was strongly associated with patient rooms having fewer than two air changes per hour [23]. Previous outbreak investigations support this finding [24].

Effective clearance of airborne particles from a contaminated room can be accomplished by dilution. The air-changes recommendations of CDC and HICPAC [22]

are based on investigation of the elimination of particles from a room in which there is no continuous generation of particles, no patient and no other people. However, they give a good description of the rate of particle removal from a stable environment.

The dilutional effect of air changes, with non-contaminated air replacing contaminated air, can substantially reduce airborne contamination in a defined space. While six air changes per hour has been accepted as a minimum standard, the more changes which can be achieved without causing disturbance of dust or infectious particles which have 'settled' on surfaces, the greater the reduction in contamination. This is true whatever the size of the room. However, adequate mixing of air is necessary to avoid a lack of air changes in 'dead' areas, such a room corners, alcoves or high ceilings. Twelve to 20 or 25 changes per hour are often obtainable by adequately engineered ventilation, but the surface area of any HEPA filters, which inevitably cause resistance to airflow, must be sufficient to allow passage of the required volumes of air.

Is HEPA filtration necessary for the safety of high-level isolation units?

All but one expert agreed that HEPA filtration was a requirement for high-level isolation facilities (though the second expert of the same MS recommended HEPA filters):

- Most group members agreed that HEPA filtration could protect immediately adjacent areas of the hospital buildings or the immediately local environment from any infectious particles expelled from the contaminated areas, thus providing the highest level of protection to any individual accidentally exposed in these areas
- One expert representative argued that immediate dilution when contaminated air enters the outside environment, coupled with the effect of ultraviolet irradiation from daylight, would rapidly reduce the number of contaminating viruses to an insignificant level.

Commentary.

There is a lack of high-level evidence on which to base decisions on HEPA filtration of air expelled from clinical areas.

It has been shown that the burden of aerosol within a room can be substantially reduced, compared with two air changes per hour of natural ventilation, by fixed or portable mechanical air filters [25]. However, the position of the filter units is important in achieving maximum effectiveness. Filter placement and any room dividers must be purpose-designed and closely fit the area to be protected, in order to achieve a safe and effective result [25,26]. Importantly, simply increasing the airflow through filters does not always increase the effectiveness of aerosol removal, depending on patterns of airflow and air mixing in the room. Also of relevance to the delegates' non-unanimous opinions; in one study [25], non-HEPA filters were as effective as HEPA filters. However this was for aerosolised particles (which are similar in size; around 1.3 micrometers, to bacteria or small droplets rather than to viruses or droplet nuclei. A careful study of a complex ward affected by a SARS outbreak emphasised the difficulty of achieving effective airflow control and avoiding persistence or accumulation of aerosols in all ward areas [26].

HEPA filters in the air extraction pathway can prevent the passage of airborne particles from contaminated areas to clean areas. For the best results, the air should be filtered at a point as near as possible to the source of contamination (often the patient's head), to reduce the likelihood of exposure to infectious particles by carers entering the unfiltered airflow [22,25,26].

In rare cases, air passing to the outside of a hospital building has risen up the side of the building, re-entered clinical areas and caused infection in nearby patients [3,9]. In the incidents reported, contaminated air escaped through open windows, though air expelled from an infected area through an unfiltered airflow control system could also have the same effect, if it passes up the side of a building. This is prevented in modern buildings by placement of air exhausts at the roof level. However, in some environments with many buildings of differing sizes, downdrafts can also occur. In older buildings, where ventilation outlets cannot be installed at roof level, local contamination could be prevented by filtration of potentially contaminated exhausted air.

What arrangements should be made for patient-supporting laboratory services?

The expert group agreed that:
- Viral diagnostic tests involving concentration or culture of viruses must be performed at biosafety level 4 (BSL-4), according to the requirements of the EU Biological Agents Directive [1];
- For patient management pathology tests, optimum use should be made of near-patient testing systems;
- Routine haematology and clinical chemistry tests may be performed using laboratory auto-analysers;
- Tests which are performed by an operator at the laboratory bench (such as specimen preparation, electron microscopy preparation and agglutination tests, and including PCR tests on extracted nucleic acids) must be performed at BSL-3 or higher;
- Dried blood films (for malaria diagnosis) can be examined by an experienced operator at BSL-2;
- Protocols must exist for laboratory operator training and for adequate quality assurance of laboratory results, and appropriate records of these must be kept.

Commentary:

Most MSs provide for special reference laboratories capable of conducting viral diagnostic tests at BSL-4. Such laboratories usually provide on-call services or undertake to provide urgent testing of diagnostic specimens.

Although they have BSL-4 facilities, reference laboratories cannot undertake to carry out patient management tests of the kind usually performed in hospital clinical laboratories.

Many 'routine' haematology and clinical chemistry tests are carried out on a daily or more frequent basis when managing severely ill patients. Most hospitals now use auto-analyzers for these tests; the analysers have 'closed sampling (ie, they extract the biological sample from a closed tube, using a needle or a membrane penetration system), which prevents the generation of aerosols or the risk of spillage at the

sampling port of the machine. Effluent from the machine, a mixture of small amounts of specimen samples, reagents and, at intervals, disinfectant solution passes directly into the hospital wastewater system. Automated cross-matching systems also operate in this way. Group members agreed that these systems provide adequate assurance of laboratory safety.

There is less certainty about safety when heavily operator-dependent tests must be performed at the laboratory bench. Such tests include activities like: preparing and fractionating specimens using centrifuges, making 'wet' preparations for parasitological examination; performing urine microscopy, or agglutination and precipitation tests for serodiagnosis, performing antigen tests for malaria diagnosis or making subcultures from positive blood cultures. At least five laboratory-acquired viral haemorrhagic fever cases have been reported: two were cases of Lassa fever [27], acquired following investigation of the first case repatriated to the USA. Two cases of Sabia virus infection both resulted from exposure to open centrifuge buckets in which specimen tubes had leaked [28,29]. A needlestick-acquired Ebola infection occurred in the UK [30]. The examination of dry, fixed, slide preparations for malaria diagnosis, however, is considered safe to perform by experienced operators at BSL-2.

What arrangements should be made for specimen packaging and transport?

The packaging and transport of diagnostic specimens which may contain infectious agents is regulated by the European Agreement concerning the international carriage of dangerous goods by road. This Agreement was made under the auspices of the United Nations Economic Commission for Europe (UNECE), originally in 1957 but the latest restructured version (the orange book) came into force in 2005 (ADR 2005 edition (ECE/TRANS/175, Vol I and II and corrigenda)).

ADR 2005 applies the United Nations Classification, which places infectious substances into Class 6.2. The ADR provides guidelines on the classification, packaging, documentation, methods of road transport and training of drivers, as well as some class- and substance-specific guidelines and derogations.

A summary of requirements for transport of infectious substances is:
- Primary leak-proof containers of limited volume (usually less than 50-100 ml)
- Sufficient absorbent packaging to absorb all liquid, if it leaks
- Sealable secondary container of specified construction and strength
- Avoidance of placing any documents within the secondary container
- Appropriate outer packaging for safe handling during transport
- Appropriate labelling must be applied, including clear biohazard labelling with instructions on action in the case of loss or breakage
- Appropriate actions and documentation for the sender and the addressee
- Appropriate types of motor transport must be used
- Contingency plans must exist for handling emergencies
- Drivers must be trained in handling the packages and in contingency plans.

Some MSs use their local interpretations of the ADR. Where transport across sea is necessary (as between Britain or Malta and Continental Europe), agreed variations of the guidelines may be used.

How should medical wastes be safely handles and disposed of?

The EUNID consensus is that:

- The management of medical wastes is strongly influenced by the legislation resulting from the European Hazardous Waste Directive
- Local legislation and protocols mean that management of clinical waste varies slightly between different MSs, and MSs tend to rely on protocols which have been successful in use in that MS;
- While there is general agreement that solid wastes require safe management protocols before entering general disposal systems, it may not be necessary for all liquid wastes to be treated before disposal;
- Water from staff toilets and showers may safely enter the general liquid waste systems
- Liquid excreta from patients able to use the toilet may pass through the hospital waste system, as viruses will rapidly be diluted and degraded in this environment;
- Patient's excreta and body fluids can be solidified by adding special gel to the container before the fluid is deposited-the solidified waste can then treated as for other solid waste;
- Peritoneal dialysate is likely to be contaminated with viruses; it should be disposed of into the dirty drains system or alternatively solidified and autoclaved before disposal.
- Haemodialysis ultrafiltrate contains no, or very low levels of viruses, and the risk to hospital personnel from handling it is low; it may safely be disposed of in the normal dirty drains system
- Setting up haemodialysis equipment and rinsing of the blood compartment at the end of dialysis requires collection of virus-containing fluids; personnel should use appropriate PPE and the blood/bloodstained fluid should be solidified and autoclaved, as for other collected body fluids

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The European Hazardous Waste Directive

The European Hazardous Waste Directive [31] sets the framework within Member States of the European Community for 'provisions to control the movement of arisings of hazardous wastes'. The aim of the HWD is to provide a precise and uniform European-wide definition of hazardous waste and to ensure the correct management and regulation of such waste. It provides guidance on the categorisation of waste by degree of hazard.

Treatment of infectious waste in Europe

The European Hazardous Waste Directive was originally underpinned by the European Waste Catalogue (EWC 1994) and Hazardous Waste List (HWL). These have been updated, combined and significantly extended. A revised European Waste Catalogue was required for implementation by Member States on 1 Jan 2002 (EWC 2002). This new list defines hazardous waste as required by the HWD. Under the legislation, medical waste which is known, or likely to, contain pathogens is classified under hazard group H9 (infectious), and waste from the management of patients with known or suspected infectious diseases must be treated as 'special waste' (see box): identified, separately packaged and incinerated.

Special Waste defined according to hazard group H9:

Clinical (or animal healthcare) waste arising from a patient clinically
assessed or known to have a disease caused by a micro-organism
or its toxin. **Where the causal pathogen or toxin is present in the
waste**. For example:
• Waste from infectious disease cases.
• Waste from wound infections and other hospital acquired
infections.
• hygiene products from patients in with UTI infections.
• Waste from patients with diarrhoea and vomiting caused by
infectious agents or toxins. For example Norwalk and
Clostridium difficile .
• Blood contaminated dressings from a patient with HIV,
Hepatitis B, rubella, measles, mumps, influenza or other
infection that may be present in the blood.
• Respiratory materials from patients with Pulmonary
Tuberculosis, Influenza, RSV or other respiratory infections.
• Contaminated waste from provision of general healthcare care
to patients with known or suspected underlying or secondary
microbial diseases.
**Healthcare waste that may cause infection to any person (or
other living organism) coming into contact with it.**
• Non-clinical Healthcare waste where the "special
requirements" fraction has been removed following item
and/or patient specific assessment and segregation .
C52 Environment Agency Hazardous Waste: Interpretation of the definition and classification of hazardous waste
(2nd edition)

Some countries, have built on the guidance of the Directive to identify low-risk
medical (clinical) waste and to categorise it as non-hazardous [32]. This philosophy
differs from the belief in the USA that universal waste handling precautions are more
likely to ensure the safe handling of all potentially hazardous clinical waste [33].
Blenkharn [33] points out that the most common source of infection from clinical waste
is from needlestick injuries, transmitting bloodborne virus infections. However,
contamination of mucosae or intact skin, or inhalation of droplets or aerosols from
infectious material can also lead to infection.

Biological agents are categorised into 4 hazard groups, of which hazard group 4 is the
most dangerous, consisting of transmissible pathogens for which reliable prevention
and treatment is not available. Most of the infections requiring isolation in HIU are
hazard group 4 agents. Waste which may contain hazard group 4 pathogens clearly
must be handled as hazardous waste, but special provisions over and above the HWD
are not specified. Individual MSs, however have sometimes chosen to set standards
and develop national protocols. Some of these require the treatment of clinical waste
to destroy infectious agents before the waste is removed from the site where it was
generated.

Methods of disinfecting waste
Incineration usually involves burning the waste at temperatures of 450-550oC,
followed by further incineration of the resulting smoke and vapour at temperatures
around 1100oC to destroy dioxins. This has been shown to kill vegetative organisms,
cells and bacterial spores [34].
In an increasing number of countries, environmental legislation discourages
incineration of clinical waste at the site where it is generated, making it necessary to
transport waste to large, industrial incineration sites. Thus, in some circumstances,
waste may be stored, transported and handled by the lowest-paid and most transient

hospital staff, or by contractors, leaving the process at risk of a variety of mistakes and omissions [35].

There are some advantages in compacting clinical waste. The resulting bales or packages are stable and easy to pack and transport. They may also produce better burning properties than loose waste, or conduct electricity better. However, the compacting process may be hazardous, as it easily generates infectious aerosols [19,36].

Methods used to disinfect waste have included microwaving, autoclaving or electrothermal deactivation (heating by passing electrical energy through the waste). Combining compaction with chemical treatment may prevent infectious aerosol release [37], but the chemicals involved, such as hypochlorite, are themselves subject to health and safety controls when used in large quantities.

A number of studies have been carried out to evaluate methods of waste decontamination at the site where it is produced. Microwaving as a means of heat-treatment can effectively sterilise waste, but the seals on the equipment must be secure to avoid release of aerosols generated by small explosions during heating [38]. More recently, local treatment of waste has been attempted by a process of grinding the waste and then injecting the oxidising agent, ozone. This process reduced the bacterial count by a factor of 10 [39], which is not sufficient for material heavily contaminated with hazard group 4 pathogens.

There is a logistic problem with the local use of a special treatment process. This is the need to maintain the engineering systems and function of a system which may be complex, and is often not in continuous use. A lack of readily-available expertise and spare parts, together with deterioration of equipment which is not regularly used, both contribute to reduced functionality and safety. There are also difficulties in maintaining a sufficient level of staff training. For such equipment, shared use, for instance with an intensive care department or a pathology department may be a better option, if the sharing departments and the facilities are close enough to one another.

The method of choice for waste decontamination in many European countries is autoclaving, as this can be controlled by recording the time and temperature of the autoclaving process, and by measuring temperatures within the waste load to ensure that they reach levels known to destroy the pathogens. Most hospitals have a number of autoclaves in various departments, so that regular maintenance and validation is part of the hospital engineers' routine work. Although bulky, the equipment can usually be accommodated within or near to the clinical facility.

The process of autoclaving is time-consuming and uses large amounts of energy. When a HIU in the north of England suffered autoclave breakdown, three industrial skip-loads of double-bagged clinical waste were generated during a four-day patient admission. During intensive care treatment of patients in Germany [12] and London in 2000, very large amounts of clinical waste were produced. The London unit developed a policy of removing all packaging and protective plastic wrapping from disposable and other equipment in a clean area, before taking the equipment into the clinical area. Packaging and other non-clinical material, such as information leaflets, could then be disposed of in the domestic waste system. Thus the amount of clinical waste which required autoclaving was reduced by approximately half. A similar process, after an audit of waste disposal behaviour led to savings of 25 to 30% in energy expenditure in a general hospital in Saudi Arabia [40].

Safe handling of liquid wastes

Current knowledge about virus survival in waste waters.

Most of the liquid waste from general hospital units is discharged into the local wastewater collection. Wastewater is treated, by one or more of several methods, to reduce its content of infectious agents to a level acceptable for release of the treated water. Treated wastewater may then be discharged into recreational areas or drinking water catchment areas.

It is widely known that wastewaters, even from domestic sources, carry a significant load of potentially pathogenic organisms, mostly of human origin [41].

Many species of virus can survive for some time in untreated wastewater, but these are mostly non-enveloped viruses, adapted for survival in the human bowel. They include the whole range of enteroviral human pathogens, such as Coxsackie viruses, reoviruses, vaccine-derived polioviruses and occasionally wild polioviruses, enteric strains of adenoviruses, noroviruses, hepatitis A virus and hepatitis E virus. Small outbreaks of viral infections have been related to locally-prevalent types of virus in sewage [42,43].

In contrast to the situation with non-enveloped enteric pathogens, there is little evidence that infectious enveloped viruses survive for more than a few hours in the wastewater environment. In a study of waste waters from two hospitals receiving SARS patients in Beijing [44], no living SARS virus could be demonstrated in hospital sewage samples, though SARS coronavirus RNA could be demonstrated before sewage treatment. Significant survival of live virus could be achieved in 'spiked' sewage samples, but survival was only for two days at 20oC. Chilling the sewage to 4oC permitted more prolonged survival of virus, as for other pathogens.

Most types of sewage treatment cause the rapid decline of virus numbers in the solid phase (sludge) of sewage [45].

The effect on wastewaters of one or two patients in an isolation unit.
The situation with one or two highly infectious patients in a specialist unit is very different from the effect of many excreters in a domestic or general hospital setting. Patients with viral haemorrhagic fevers usually excrete large amounts of virus in stools and urine, and have heavily-contaminated blood and other body fluids. Disposal of dressings and receptacles containing such infectious fluids fall within the requirements of the HWD.

Liquid wastes not contained in absorbent dressings.
The significant hazards of liquid waste disposal mainly result from:
1. a risk to healthcare workers handling and disposing of infected fluids within the high-security unit (from splash, spillage or aerosol generation);
2. a smaller or theoretical risk to engineers and workmen undertaking urgent repairs and maintenance to sewage and effluent drainage systems within or immediately adjacent to the high-security unit.

Virus concentrations in liquid waste can be reduced by the addition of chemical disinfectants. However, this can itself cause an additional hazard to healthcare workers who handle large volumes of disinfectants. Additionally, disinfectants' effects may be significantly reduced by the presence of organic matter.

Another option is to deactivate the viruses by heat treatment of the liquid waste. This process consumes large amounts of energy. It also requires complex equipment and engineering controls, as waste must be stored until treated, heat distribution must be even and adequate, and the waste must be agitated by an impeller to ensure this. The liquid waste containers, impellers and control systems must be regularly maintained and validated.

Handling of liquid waste can be simplified by using a medical product, Vernagel®, which irreversibly absorbs large volumes of fluid, converting it to a gel from which the fluid cannot be released, once absorbed. Vernagel® crystals can be added to blood, vomit, urine and other fluids. The resulting gel can be bagged or binned, and is easily autoclaved because of its high fluid content. There is no risk of spillage once a fluid has been converted to gel. The absorbent crystals can be added, as degradable sachets, to disposable containers or urinals before the fluid is introduced. In the London high-security unit, all fluids originating from the patient are converted to gel and autoclaved. This avoids contamination of the drainage system with high concentrations of viruses, and protects healthcare workers from the risk of spillage.

Fluids produced and handled during kidney support procedures.
Knowledge about hazard Group 3 viruses, such as hepatitis B and hepatitis C viruses, suggests that viral contamination of **peritoneal dialysate** occurs, in proportion to the patient's level of viraemia, even in the absence of blood contamination [46], though Caramelo et al [47] did not show the presence of virus using older PCR techniques.
Ultrafiltrate and dialysis fluid from **haemodialysis techniques** has not been shown to contain viruses [48, 49]. However, contamination of the dialysate can occur during setting-up or rinsing of the blood compartment [50], and the procedure results in the collection of virus-containing blood and blood-contaminated fluids.

Waste from urinals and toilets

Discharge of urine and faeces by the normal route, using urinals and toilets connected to the hospital wastewater system could lead to the presence of significant concentrations of viruses in local drainage systems within the high-security unit. However, these would be minimised by the use of normal, hypochlorite-containing cleaning agents. They would quickly be diluted to very low concentrations after entering the hospital wastewater system, and concentrations would further decline as virus particles are destroyed by regular cleaning of the facilities with hypochlorite-containing cleaning agents and by the hostile environment of waste waters. Because of this, both the UK and the USA made the decision that urine and faeces generated by smallpox cases, should they occur, could be disposed in the toilet and wastewater systems without special treatment [51, 52]. Nevertheless, a policy must be available for special circumstances, such as the emergency repair of drains and pipe work in the unit. Appropriate supervision and personal protective equipment must be available for workers performing these tasks.

Waste from showers and handwashing.
Enveloped viruses are readily destroyed by the action of soaps and detergents. Even without exposure to these agents, the viruses survive only for a short time in the environment. These effects are combined with a major dilution effect from the water used for washing and rinsing. There is therefore no requirement for any special management of water resulting from washing or showering of the unit staff (or even of an ambulant, continent patient who uses a shower).

Environmental decontamination of the HIU during and after use?

The EUNID experts agreed that:

- Dedicated or identified equipment should be chosen with decontamination in mind, and can be decontaminated in the usual ways for complex equipment such as ventilators used in intensive care;
- For surfaces, regular cleaning and terminal cleaning with detergent-containing agents is adequate;
- Heavily-contaminated areas may be cleaned with hypochlorite 1% solution, followed by cleaning with water and drying
- Extra-ordinary methods such as formaldehyde fumigation are not required for the patient environment;
- Safer, more locally-effective measures such as ozone or hydrogen peroxide generation could be evaluated for use in decontaminating large ward areas.
- Large, complex equipment which has been contaminated may require decontamination before being disassembled for disposal; a fumigation method may be appropriate in this situation-a risk assessment should be made in each case to determine whether disassembly can be carried out by staff using appropriate PPE, and the separate parts then autoclaved;
- A list should be maintained of all equipment and its usual method of decontamination/disposal.

Comment
The short survival of viruses, in medical waste and in the environment, has already been discussed. The group agreed that, if spillages are adequately managed and surfaces are regularly cleaned to avoid build-up of contaminated material, the general environment of the Isolation Unit will not accumulate hazardous levels of contamination. When the patient has left the Unit, final (terminal) cleaning may be carried out according to the usual hospital protocol. In case of residual local contamination or contamination of equipment, personnel who perform the cleaning process should work according to an appropriate operational policy, and should wear personal protective equipment which is disposed of as clinical waste after use.

For any patient who has had a complicated illness, requiring high-level and complex care, there is a risk of colonization or infection with a resistant organism. This should not be forgotten when cleaning processes are planned.

All tertiary referral hospitals have existing policies for the cleaning and decontamination of complex, re-usable equipment, such as ventilators, pressure-control mattresses and beds. Some hospitals make regular or intermittent use of free-radical based cleansing of accumulated pathogens from complex areas, such as wards containing beds and furniture. These procedures are currently under evaluation, but it is suspected that the presence of equipment may prevent the active disinfectant from reaching all areas of the room.

It is nowadays accepted that viruses suspended in, or exposed to the air have a short survival time. Harper investigated the survival of four different viruses in aerosols released into a laboratory environment. He showed that vaccinia virus was the most persistent, but that the concentration of this virus fell by a factor of 10 in the first 24 hours after release [53], others [54] demonstrated a five- to ten-fold decline in recoverable yellow fever virus and 'psittacosis agent' in only 60 minutes, though smallpox virus numbers declined more slowly. The Group agreed, therefore that there was no strong evidence to support the use of severe decontamination measures such as formaldehyde fumigation of clinical areas.

Requirements for the building structure and facilities

The structure and organisation of the HIU must be carefully specified to ensure the safe provision of patient care, infection control, clinical waste management, decontamination of equipment and rooms, and environmental hygiene. The security of the building and personnel must also be assured. The expert group considered two main aspects of building provision: the patient care areas, and the additional areas required for special use.

Many member States already have published guidelines or regulations for the provision of various levels of patient care. However, only a minority have nationally-agreed standards for the provision of HIU facilities.

Important building issues identified by the EUNID experts included:

Requirements for patient rooms:
- Patient rooms sufficiently large to contain specialist equipment, used by staff wearing personal protective equipment;
- Toilet and shower ensuite for ambulant patients;
- High quality patient-nurse communication system
- System for rapid communication between clinical area and outside
- Lobbies or anterooms to enhance airflow controls;
- Lobbies or anterooms for storage of PPE, towels and immediately required clinical equipment.;
- Adequate area for packaging clinical specimens and decontaminating outer containers;
- Wall, ceiling and floor areas covered with sealed, cleanable surfaces

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Requirements for the building itself:
- A separate entrance to the HIU area, which could be secure if appropriate
- An adequate and controllable pathway through the hospital grounds and building for the patient to approach and enter;
- Sufficient area for ambulance parking, and cleaning when needed;
- An appropriate pathway for the circulation of clean and contaminated staff, patients and equipment, ensuring segregation of clean and dirty areas;
- A designated area for handling and packaging clinical waste;
- Identified or dedicated autoclave facilities;
- Patient management pathology laboratory nearby or in the HIU
- Adequate space for decontamination of large equipment (which may be sealable for fumigation, if required in exceptional circumstances);
- An area for the temporary safe keeping and preparation of deceased patients, which should be large enough for mortuary staff to place the patient in a sealed coffin and decontaminate coffins, trolleys and other equipment;
- All wall, ceiling and floor surfaces in dirty areas covered with sealed, cleanable coverings;
- Showering and changing facilities between dirty and clean areas, including decontamination showers where necessary;
- Adequate storage area for large equipment;
- A staff rest area and staff office

Other issues identified by the consensus group.
The Group identified some activities for which little or no evidence is available, but which may be very useful in ensuring the smooth and safe running of the HIU.

Harmonisation of standards and operational policies.

The group identified several further areas in which collaboration may be helpful:
- Operational policies and risk management protocols;
- Training and exercises in operational techniques;
- Collaboration with emergency services such as the fire response services, in case of an emergency;
- Occupational health and safety needs;
- Adverse event monitoring systems;
- Audit and quality assurance.

It is unlikely that identical risk assessments, risk management solutions and operational policies for High-Level Isolation facilities will appropriate in each Member State. Medical training, medical services and patient transport, as well as health and safety policies vary slightly from MS to MS. However, a collaborative approach to developing and maintaining these specialist services will enhance the ability of individual MSs to design effective and flexible services. It will also enhance the ability of European Nations to respond in a coordinated way to any international contingencies which may arise. Further programmes of work are planned in order to achieve this.

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