I. Review of Scientific Data Regarding Transmission of Infectious Agents in Healthcare Settings

Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings (2007)

WHAT TO KNOW

The *Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings 2007* builds upon a series of isolation and infection prevention documents promulgated since 1970.

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Evolution of the 2007 Document

The previous documents are summarized and referenced in Table 1 and in Part I of the *1996 Guideline for Isolation Precautions in Hospitals*[1].

Objectives and methods

The objectives of this guideline are to

1. provide infection control recommendations for all components of the healthcare delivery system, including hospitals, long-term care facilities, ambulatory care, home care and hospice;
2. reaffirm Standard Precautions as the foundation for preventing transmission during patient care in all healthcare settings;
3. reaffirm the importance of implementing Transmission-Based Precautions based on the clinical presentation or syndrome and likely pathogens until the infectious etiology has been determined (Table 2); and
4. provide epidemiologically sound and, whenever possible, evidence-based recommendations.

This guideline is designed for use by individuals who are charged with administering infection control programs in hospitals and other healthcare settings. The information also will be useful for other healthcare personnel, healthcare administrators, and anyone needing information about infection control measures to prevent transmission of infectious agents. Commonly used abbreviations are provided in Abbreviations Used in the Guideline and terms used in the guideline are defined in the Glossary.

Med-line and Pub Med were used to search for relevant studies published in English, focusing on those published since 1996. Much of the evidence cited for preventing transmission of infectious agents in healthcare settings is derived from studies that used "quasi-experimental designs", also referred to as nonrandomized, pre- post-intervention study designs [2]. Although these types of studies can provide valuable information regarding the effectiveness of various interventions, several factors decrease the certainty of attributing improved outcome to a specific intervention. These include: difficulties in controlling for important confounding variables; the use of multiple interventions during an outbreak; and results that are explained by the statistical principle of regression to the mean, (e.g., improvement over time without any

intervention) [3]. Observational studies remain relevant and have been used to evaluate infection control interventions [4, 5]. The quality of studies, consistency of results and correlation with results from randomized, controlled trials when available were considered during the literature review and assignment of evidence-based categories (See Part IV: Recommendations) to the recommendations in this guideline. Several authors have summarized properties to consider when evaluating studies for the purpose of determining if the results should change practice or in designing new studies [2, 6, 7].

Changes or clarifications in terminology

This guideline contains four changes in terminology from the 1996 guideline:

- The term *nosocomial infection* is retained to refer only to infections acquired in hospitals. The term *healthcare-associated infection* (HAI) is used to refer to infections associated with healthcare delivery in any setting (e.g., hospitals, long-term care facilities, ambulatory settings, home care). This term reflects the inability to determine with certainty where the pathogen is acquired since patients may be colonized with or exposed to potential pathogens outside of the healthcare setting, before receiving health care, or may develop infections caused by those pathogens when exposed to the conditions associated with delivery of healthcare. Additionally, patients frequently move among the various settings within a healthcare system [8].

- A new addition to the practice recommendations for Standard Precautions is *Respiratory Hygiene/Cough Etiquette*. While Standard Precautions generally apply to the recommended practices of healthcare personnel during patient care, Respiratory Hygiene/Cough Etiquette applies broadly to all persons who enter a healthcare setting, including healthcare personnel, patients and visitors. These recommendations evolved from observations during the SARS epidemic that failure to implement basic source control measures with patients, visitors, and healthcare personnel with signs and symptoms of respiratory tract infection may have contributed to SARS coronavirus (SARS-CoV) transmission. This concept has been incorporated into CDC planning documents for SARS and pandemic influenza [9, 10].

- The term *"Airborne Precautions"* has been supplemented with the term "*Airborne Infection Isolation Room (AIIR)*" for consistency with the *Guidelines for Environmental Infection Control in Healthcare Facilities* [11], the *Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings 2005*[12] and the American Institute of Architects (AIA) guidelines for design and construction of hospitals, 2006. [13]

- A set of prevention measures termed *Protective Environment* has been added to the precautions used to prevent HAIs. These measures, which have been defined in other guidelines , consist of engineering and design interventions that decrease the risk of exposure to environmental fungi for severely immunocompromised allogeneic hematiopoietic stem cell transplant (HSCT) patients during their highest risk phase, usually the first 100 days post transplant, or longer in the presence of graft-versus-host disease [11, 13-15]. Recommendations for a Protective Environment apply only to acute care hospitals that provide care to HSCT patients.

Scope

This guideline, like its predecessors, focuses primarily on interactions between patients and healthcare providers. The Guidelines for the Prevention of MDRO Infection were published separately in November 2006, and are available online at Management of Multidrug-Resistant Organisms In Healthcare Settings. Several other HICPAC guidelines to prevent transmission of infectious agents associated with healthcare delivery are cited; e.g., *Guideline for Hand Hygiene*, *Guideline for Environmental Infection Control*, *Guideline for Prevention of Healthcare-Associated Pneumonia*, and *Guideline for Infection Control in Healthcare Personnel* [11, 14, 16, 17]. In combination, these provide comprehensive guidance on the primary infection control measures for ensuring a safe environment for patients and healthcare personnel.

This guideline does not discuss in detail specialized infection control issues in defined populations that are addressed elsewhere, (e.g., *Recommendations for Preventing Transmission of Infections among Chronic Hemodialysis Patients* , *Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Facilities 2005*, *Guidelines for Infection Control in Dental Health-Care Settings and Infection Control Recommendations for Patients with Cystic Fibrosis* [12, 18-20]. An exception has been made by including abbreviated guidance for a Protective Environment used for allogeneic HSCT recipients because components of the Protective Environment have been more completely defined since publication of the *Guidelines for Preventing Opportunistic Infections Among HSCT Recipients in 2000* and the *Guideline for Environmental Infection Control in Healthcare Facilities* [11, 15].

I.B. Rationale for Standard and Transmission-Based Precautions in Healthcare Settings

Transmission of infectious agents within a healthcare setting requires three elements: a source (or reservoir) of infectious agents, a susceptible host with a portal of entry receptive to the agent, and a mode of transmission for the agent. This section describes the interrelationship of these

elements in the epidemiology of HAIs.

I.B.1. Sources of infectious agents.

Infectious agents transmitted during healthcare derive primarily from human sources but inanimate environmental sources also are implicated in transmission. Human reservoirs include patients [20-28], healthcare personnel [29-3517, 36-39], and household members and other visitors [40-45]. Such source individuals may have active infections, may be in the asymptomatic and/or incubation period of an infectious disease, or may be transiently or chronically colonized with pathogenic microorganisms, particularly in the respiratory and gastrointestinal tracts. The endogenous flora of patients (e.g., bacteria residing in the respiratory or gastrointestinal tract) also are the source of HAIs [46-54].

I.B.2. Susceptible hosts.

Infection is the result of a complex interrelationship between a potential host and an infectious agent. Most of the factors that influence infection and the occurrence and severity of disease are related to the host. However, characteristics of the host-agent interaction as it relates to pathogenicity, virulence and antigenicity are also important, as are the infectious dose, mechanisms of disease production and route of exposure [55]. There is a spectrum of possible outcomes following exposure to an infectious agent. Some persons exposed to pathogenic microorganisms never develop symptomatic disease while others become severely ill and even die. Some individuals are prone to becoming transiently or permanently colonized but remain asymptomatic. Still others progress from colonization to symptomatic disease either immediately following exposure, or after a period of asymptomatic colonization. The immune state at the time of exposure to an infectious agent, interaction between pathogens, and virulence factors intrinsic to the agent are important predictors of an individuals' outcome. Host factors such as extremes of age and underlying disease (e.g., diabetes [56, 57]), human immunodeficiency virus/acquired immune deficiency syndrome [HIV/AIDS] [58, 59], malignancy, and transplants [18, 60, 61] can increase susceptibility to infection as do a variety of medications that alter the normal flora (e.g., antimicrobial agents, gastric acid suppressants, corticosteroids, antirejection drugs, antineoplastic agents, and immunosuppressive drugs). Surgical procedures and radiation therapy impair defenses of the skin and other involved organ systems. Indwelling devices such as urinary catheters, endotracheal tubes, central venous and arterial catheters [62-64] and synthetic implants facilitate development of HAIs by allowing potential pathogens to bypass local defenses that would ordinarily impede their invasion and by providing surfaces for development of biofilms that may facilitate adherence of microorganisms and protect from antimicrobial activity [65]. Some infections associated with invasive procedures result from transmission within the healthcare facility; others arise from the patient's endogenous flora [46-50]. High-risk patient populations with noteworthy risk factors for infection are discussed further in Sections I.D, I.E., and I.F.

I.B.3. Modes of transmission.

Several classes of pathogens can cause infection, including bacteria, viruses, fungi, parasites, and prions. The modes of transmission vary by type of organism and some infectious agents may be transmitted by more than one route: some are transmitted primarily by direct or indirect contact, (e.g., *Herpes simplex* virus [HSV], respiratory syncytial virus, *Staphylococcus aureus*), others by the droplet, (e.g., influenza virus, *B. pertussis*) or airborne routes (e.g., *M. tuberculosis)*. Other infectious agents, such as bloodborne viruses (e.g., hepatitis B and C viruses [HBV, HCV] and HIV are transmitted rarely in healthcare settings, via percutaneous or mucous membrane exposure. Importantly, not all infectious agents are transmitted from person to person. These are distinguished in Appendix A. The three principal routes of transmission are summarized below.

I.B.3.a. Contact transmission.

The most common mode of transmission, contact transmission is divided into two subgroups: direct contact and indirect contact.

I.B.3.a.i. Direct contact transmission.

Direct transmission occurs when microorganisms are transferred from one infected person to another person without a contaminated intermediate object or person. Opportunities for direct contact transmission between patients and healthcare personnel have been summarized in the Guideline for Infection Control in Healthcare Personnel, 1998 [17] and include:

- blood or other blood-containing body fluids from a patient directly enters a caregiver's body through contact with a mucous membrane [66] or breaks (i.e., cuts, abrasions) in the skin [67].
- mites from a scabies-infested patient are transferred to the skin of a caregiver while he/she is having direct ungloved contact with the patient's skin [68, 69].
- a healthcare provider develops herpetic whitlow on a finger after contact with HSV when providing oral care to a patient without using gloves or HSV is transmitted to a patient from a herpetic whitlow on an ungloved hand of a healthcare worker (HCW) [70, 71]

I.B.3.a.ii. Indirect contact transmission.

Indirect transmission involves the transfer of an infectious agent through a contaminated intermediate object or person. In the absence of a point-source outbreak, it is difficult to determine how indirect transmission occurs. However, extensive evidence cited in the Guideline for Hand Hygiene in Health-Care Settings suggests that the contaminated hands of healthcare personnel are important contributors to indirect contact transmission [16]. Examples of opportunities for indirect contact transmission include:

- Hands of healthcare personnel may transmit pathogens after touching an infected or colonized body site on one patient or a contaminated inanimate object, if hand hygiene is not performed before touching another patient.[72, 73].
- Patient-care devices (e.g., electronic thermometers, glucose monitoring devices) may transmit pathogens if devices contaminated with blood or body fluids are shared between patients without cleaning and disinfecting between patients[74 75-77].
- Shared toys may become a vehicle for transmitting respiratory viruses (e.g., respiratory syncytial virus [24, 78, 79] or pathogenic bacteria (e.g., *Pseudomonas aeruginosa* [80]) among pediatric patients.
- Instruments that are inadequately cleaned between patients before disinfection or sterilization (e.g., endoscopes or surgical instruments) [81-85] or that have manufacturing defects that interfere with the effectiveness of reprocessing [86, 87] may transmit bacterial and viral pathogens.

Clothing, uniforms, laboratory coats, or isolation gowns used as personal protective equipment (PPE), may become contaminated with potential pathogens after care of a patient colonized or infected with an infectious agent, (e.g., MRSA [88], VRE [89], and *C. difficile* [90]. Although contaminated clothing has not been implicated directly in transmission, the potential exists for soiled garments to transfer infectious agents to successive patients.

I.B.3.b. Droplet transmission.

Droplet transmission is, technically, a form of contact transmission, and some infectious agents transmitted by the droplet route also may be transmitted by the direct and indirect contact routes. However, in contrast to contact transmission, respiratory droplets carrying infectious pathogens transmit infection when they travel directly from the respiratory tract of the infectious individual to susceptible mucosal surfaces of the recipient, generally over short distances, necessitating facial protection. Respiratory droplets are generated when an infected person coughs, sneezes, or talks [91, 92] or during procedures such as suctioning, endotracheal intubation, [93-96], cough induction by chest physiotherapy [97] and cardiopulmonary resuscitation [98, 99]. Evidence for droplet transmission comes from epidemiological studies of disease outbreaks [100-103], experimental studies [104] and from information on aerosol dynamics [91, 105]. Studies have shown that the nasal mucosa, conjunctivae and less frequently the mouth, are susceptible portals of entry for respiratory viruses [106]. The maximum distance for droplet transmission is currently unresolved, although pathogens transmitted by the droplet route have not been transmitted through the air over long distances, in contrast to the airborne pathogens discussed below. Historically, the area of defined risk has been a distance of ≤3 feet around the patient and is based on epidemiologic and simulated studies of selected infections [103, 104]. Using this distance for donning masks has been effective in preventing transmission of infectious agents via the droplet route. However, experimental studies with smallpox [107, 108] and investigations during the global SARS outbreaks of 2003 [101] suggest that droplets from patients with these two infections could reach persons located 6 feet or more from their source. It is likely that the distance droplets travel depends on the velocity and mechanism by which respiratory droplets are propelled from the source, the density of respiratory secretions, environmental factors such as temperature and humidity, and the ability of the pathogen to maintain infectivity over that distance [105]. Thus, a distance of ≤3 feet around the patient is best viewed as an *example* of what is meant by "a short distance from a patient" and should not be used as the sole *criterion* for deciding when a mask should be donned to protect from droplet exposure. Based on these considerations, it may be prudent to don a mask when within 6 to 10 feet of the patient or upon entry into the patient's room, especially when exposure to emerging or highly virulent pathogens is likely. More studies are needed to improve understanding of droplet transmission under various circumstances.

Droplet size is another variable under discussion. Droplets traditionally have been defined as being >5 µm in size. Droplet nuclei, particles arising from desiccation of suspended droplets, have been associated with airborne transmission and defined as ≤5 µm in size,[105] a reflection of the pathogenesis of pulmonary tuberculosis which is not generalizeable to other organisms. Observations of particle dynamics have demonstrated that a range of droplet sizes, including those with diameters of 30µm or greater, can remain suspended in the air [109]. The behavior of droplets and droplet nuclei affect recommendations for preventing transmission. Whereas fine airborne particles containing pathogens that are able to remain infective may transmit infections over long distances, requiring AIIR to prevent its dissemination within a facility; organisms transmitted by the droplet route do not remain infective over long distances, and therefore do not require special air handling and ventilation. Examples of infectious agents that are transmitted via the droplet route include *Bordetella pertussis* [110], influenza virus [23], adenovirus [111] , rhinovirus [104], *Mycoplasma pneumoniae* [112], SARS-associated coronavirus (SARS-CoV) [21, 96, 113], group A streptococcus [114], and *Neisseria meningitidis* [95, 103, 115]. Although respiratory syncytial virus may be transmitted by the droplet route, direct contact with infected respiratory secretions is the most important determinant of transmission and consistent adherence to Standard plus Contact Precautions prevents transmission in healthcare settings [24, 116, 117].

Rarely, pathogens that are not transmitted routinely by the droplet route are dispersed into the air over short distances. For example, although *S. aureus* is transmitted most frequently by the contact route, viral upper respiratory tract infection has been associated with increased dispersal of *S. aureus* from the nose into the air for a distance of 4 feet under both outbreak and experimental conditions and is known as the "cloud baby" and "cloud adult" phenomenon[118-120].

I.B.3.c. Airborne transmission.

Airborne transmission occurs by dissemination of either airborne droplet nuclei or small particles in the respirable size range containing infectious agents that remain infective over time and distance (e.g., spores of *Aspergillus* spp, and *Mycobacterium tuberculosis*). Microorganisms carried in this manner may be dispersed over long distances by air currents and may be inhaled by susceptible individuals who have not had face-to-face contact with (or been in the same room with) the infectious individual [121-124]. Preventing the spread of pathogens that are transmitted by the airborne route requires the use of special air handling and ventilation systems (e.g., AIIRs) to contain and then safely remove the infectious agent [11, 12]. Infectious agents to which this applies include *Mycobacterium tuberculosis* [124-127], rubeola virus (measles) [122], and varicella-zoster virus (chickenpox) [123]. In addition, published data suggest the possibility that variola virus (smallpox) may be transmitted over long distances through the air under unusual circumstances and AIIRs are recommended for this agent as well; however, droplet and contact routes are the more frequent routes of transmission for smallpox [108, 128, 129]. In addition to AIIRs, respiratory protection with NIOSH certified N95 or higher level respirator is recommended for healthcare personnel entering the AIIR to prevent acquisition of airborne infectious agents such as *M. tuberculosis* [12].

For certain other respiratory infectious agents, such as influenza [130, 131] and rhinovirus [104], and even some gastrointestinal viruses (e.g., norovirus [132] and rotavirus [133]) there is some evidence that the pathogen may be transmitted via small-particle aerosols, under natural and experimental conditions. Such transmission has occurred over distances longer than 3 feet but within a defined airspace (e.g., patient room), suggesting that it is unlikely that these agents remain viable on air currents that travel long distances. AIIRs are not required routinely to prevent transmission of these agents. Additional issues concerning examples of small particle aerosol transmission of agents that are most frequently transmitted by the droplet route are discussed below.

I.B.3.d. Emerging issues concerning airborne transmission of infectious agents.

I.B.3.d.i. Transmission from patients.

Interim Measles Infection Control [July 2019]

See Interim Infection Prevention and Control Recommendations for Measles in Healthcare Settings

The emergence of SARS in 2002, the importation of monkeypox into the United States in 2003, and the emergence of avian influenza present challenges to the assignment of isolation categories because of conflicting information and uncertainty about possible routes of transmission. Although SARS-CoV is transmitted primarily by contact and/or droplet routes, airborne transmission over a limited distance (e.g., within a room), has been suggested, though not proven [134-141]. This is true of other infectious agents such as influenza virus [130] and noroviruses [132, 142, 143]. Influenza viruses are transmitted primarily by close contact with respiratory droplets [23, 102] and acquisition by healthcare personnel has been prevented by Droplet Precautions, even when positive pressure rooms were used in one center [144] However, inhalational transmission could not be excluded in an outbreak of influenza in the passengers and crew of a single aircraft [130]. Observations of a protective effect of UV lights in preventing influenza among patients with tuberculosis during the influenza pandemic of 1957-'58 have been used to suggest airborne transmission [145, 146].

In contrast to the strict interpretation of an airborne route for transmission (i.e., long distances beyond the patient room environment), short distance transmission by small particle aerosols generated under specific circumstances (e.g., during endotracheal intubation) to persons in the immediate area near the patient has been demonstrated. Also, aerosolized particles <100 µm can remain suspended in air when room air current velocities exceed the terminal settling velocities of the particles [109]. SARS-CoV transmission has been associated with endotracheal intubation, noninvasive positive pressure ventilation, and cardio-pulmonary resuscitation [93, 94, 96, 98, 141]. Although the most frequent routes of transmission of noroviruses are contact and food and waterborne routes, several reports suggest that noroviruses may be transmitted through aerosolization of infectious particles from vomitus or fecal material [142, 143, 147, 148]. It is hypothesized that the aerosolized particles are inhaled and subsequently swallowed.

Roy and Milton proposed a new classification for aerosol transmission when evaluating routes of SARS transmission:

1. *obligate*: under natural conditions, disease occurs following transmission of the agent only through inhalation of small particle aerosols (e.g., tuberculosis);

2. *preferential*: natural infection results from transmission through multiple routes, but small particle aerosols are the predominant route (e.g., measles, varicella); and

3. *opportunistic*: agents that naturally cause disease through other routes, but under special circumstances may be transmitted via fine particle aerosols [149].

This conceptual framework can explain rare occurrences of airborne transmission of agents that are transmitted most frequently by other routes (e.g., smallpox, SARS, influenza, noroviruses). Concerns about unknown or possible routes of transmission of agents associated with severe disease and no known treatment often result in more extreme prevention strategies than may be necessary; therefore, recommended precautions could change as the epidemiology of an emerging infection is defined and controversial issues are resolved.

I.B.3.d.ii. Transmission from the environment.

Some airborne infectious agents are derived from the environment and do not usually involve person-to-person transmission. For example, anthrax spores present in a finely milled powdered preparation can be aerosolized from contaminated environmental surfaces and inhaled into the respiratory tract [150, 151]. Spores of environmental fungi (e.g., *Aspergillus spp.*) are ubiquitous in the environment and may cause disease in immunocompromised patients who inhale aerosolized (e.g., via construction dust) spores [152, 153]. As a rule, neither of these organisms is subsequently transmitted from infected patients. However, there is one well-documented report of person-to-person transmission of *Aspergillus* sp. in the ICU setting that was most likey due to the aerosolization of spores during wound debridement [154]. A Protective Environment refers to isolation practices designed to decrease the risk of exposure to environmental fungal agents in allogeneic HSCT patients [11, 14, 15, 155-158].

Environmental sources of respiratory pathogens (eg. Legionella) transmitted to humans through a common aerosol source is distinct from direct patient-to-patient transmission.

I.B.3.e. Other sources of infection.

Transmission of infection from sources other than infectious individuals include those associated with *common environmental sources or vehicles* (e.g., contaminated food, water, or medications (e.g., intravenous fluids). Although *Aspergillus* spp. have been recovered from hospital water systems [159], the role of water as a reservoir for immunosuppressed patients remains uncertain. *Vectorborne transmission* of infectious agents from mosquitoes, flies, rats, and other vermin also can occur in healthcare settings. Prevention of vector borne transmission is not addressed in this document.

I.C. Infectious Agents of Special Infection Control Interest for Healthcare Settings

Several infectious agents with important infection control implications that either were not discussed extensively in previous isolation guidelines or have emerged recently are discussed below. These are epidemiologically important organisms (e.g., *C. difficile*), agents of bioterrorism, prions, SARS-CoV, monkeypox, noroviruses, and the hemorrhagic fever viruses. Experience with these agents has broadened the understanding of modes of transmission and effective preventive measures. These agents are included for purposes of information and, for some (i.e., SARS-CoV, monkeypox), because of the lessons that have been learned about preparedness planning and responding effectively to new infectious agents.

I.C.1. Epidemiologically important organisms.

Any infectious agents transmitted in healthcare settings may, under defined conditions, become targeted for control because they are epidemiologically important. *C. difficile* is specifically discussed below because of wide recognition of its current importance in U.S. healthcare facilities. In determining what constitutes an "epidemiologically important organism", the following characteristics apply:

- A propensity for transmission within healthcare facilities based on published reports and the occurrence of temporal or geographic clusters of > 2 patients, (e.g., *C..difficile*, norovirus, respiratory syncytial virus (RSV), influenza, rotavirus, *Enterobacter* spp; *Serratia* spp., group A streptococcus). A single case of healthcare-associated invasive disease caused by certain pathogens (e.g., group A streptococcus post-operatively [160], in burn units [161], or in a LTCF [162]; *Legionella* sp. [14, 163], *Aspergillus* sp. [164]) is generally considered a trigger for investigation and enhanced control measures because of the risk of additional cases and severity of illness associated with these infections. Antimicrobial resistance

- Resistance to first-line therapies (e.g., MRSA, VISA, VRSA, VRE, ESBL-producing organisms).

- Common and uncommon microorganisms with unusual patterns of resistance within a facility (e.g., the first isolate of *Burkholderia cepacia* complex or *Ralstonia* spp. in non-CF patients or a quinolone-resistant strain of *Pseudomonas aeruginosa* in a facility).

- Difficult to treat because of innate or acquired resistance to multiple classes of antimicrobial agents (e.g., *Stenotrophomonas maltophilia, Acinetobacter spp.*).
- Association with serious clinical disease, increased morbidity and mortality (e.g., MRSA and MSSA, group A streptococcus)
- A newly discovered or reemerging pathogen

I.C.1.a. *C. difficile*.

C. difficile is a spore-forming gram positive anaerobic bacillus that was first isolated from stools of neonates in 1935 [165] and identified as the most commonly identified causative agent of antibiotic-associated diarrhea and pseudomembranous colitis in 1977 [166]. This pathogen is a major cause of healthcare-associated diarrhea and has been responsible for many large outbreaks in healthcare settings that were extremely difficult to control. Important factors that contribute to healthcare-associated outbreaks include environmental contamination, persistence of spores for prolonged periods of time, resistance of spores to routinely used disinfectants and antiseptics, hand carriage by healthcare personnel to other patients, and exposure of patients to frequent courses of antimicrobial agents [167] . Antimicrobials most frequently associated with increased risk of *C. difficile* include third generation cephalosporins, clindamycin, vancomycin, and fluoroquinolones.

Since 2001, outbreaks and sporadic cases of *C. difficile* with increased morbidity and mortality have been observed in several U.S. states, Canada, England and the Netherlands [168-172]. The same strain of *C. difficile* has been implicated in these outbreaks [173]. This strain, toxinotype III, North American PFGE type 1, and PCR-ribotype 027 (NAP1/027) has been found to hyperproduce toxin A (16 fold increase) and toxin B (23 fold increase) compared with isolates from 12 different pulsed-field gel electrophoresis PFGE types. A recent survey of U.S. infectious disease physicians found that 40% perceived recent increases in the incidence and severity of *C. difficile* disease[174]. Standardization of testing methodology and surveillance definitions is needed for accurate comparisons of trends in rates among hospitals [175]. It is hypothesized that the incidence of disease and apparent heightened transmissibility of this new strain may be due, at least in part, to the greater production of toxins A and B, increasing the severity of diarrhea and resulting in more environmental contamination. Considering the greater morbidity, mortality, length of stay, and costs associated with *C. difficile* disease in both acute care and long term care facilities, control of this pathogen is now even more important than previously. Prevention of transmission focuses on syndromic application of Contact Precautions for patients with diarrhea, accurate identification of patients, environmental measures (e.g., rigorous cleaning of patient rooms) and consistent hand hygiene. Use of soap and water, rather than alcohol based handrubs, for mechanical removal of spores from hands, and a bleach-containing disinfectant (5000 ppm) for environmental disinfection, may be valuable when there is transmission in a healthcare facility. See Appendix A for specific recommendations.

I.C.1.b. Multidrug-resistant organisms (MDROs).

In general, MDROs are defined as microorganisms – predominantly bacteria – that are resistant to one or more classes of antimicrobial agents[176]. Although the names of certain MDROs suggest resistance to only one agent (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA], vancomycin resistant enterococcus [VRE]), these pathogens are usually resistant to all but a few commercially available antimicrobial agents. This latter feature defines MDROs that are considered to be epidemiologically important and deserve special attention in healthcare facilities[177]. Other MDROs of current concern include multidrug-resistant *Streptococcus pneumoniae* (MDRSP) which is resistant to penicillin and other broad-spectrum agents such as macrolides and fluroquinolones, multidrug-resistant gram-negative bacilli (MDR- GNB), especially those producing extended spectrum beta-lactamases (ESBLs); and strains of *S. aureus* that are intermediate or resistant to vancomycin (i.e., VISA and VRSA)[178-197 198].

MDROs are transmitted by the same routes as antimicrobial susceptible infectious agents. Patient-to-patient transmission in healthcare settings, usually via hands of HCWs, has been a major factor accounting for the increase in MDRO incidence and prevalence, especially for MRSA and VRE in acute care facilities[199-201]. Preventing the emergence and transmission of these pathogens requires a comprehensive approach that includes administrative involvement and measures (e.g., nurse staffing, communication systems, performance improvement processes to ensure adherence to recommended infection control measures), education and training of medical and other healthcare personnel, judicious antibiotic use, comprehensive surveillance for targeted MDROs, application of infection control precautions during patient care, environmental measures (e.g., cleaning and disinfection of the patient care environment and equipment, dedicated single-patient-use of non-critical equipment), and decolonization therapy when appropriate.

The prevention and control of MDROs is a national priority – one that requires that all healthcare facilities and agencies assume responsibility and participate in community-wide control programs[176, 177]. A detailed discussion of this topic and recommendations for prevention was published in 2006 may be found at Management of Multidrug-Resistant Organisms in Healthcare Settings (2006).

I.C.2. Agents of bioterrorism.

CDC has designated the agents that cause anthrax, smallpox, plague, tularemia, viral hemorrhagic fevers, and botulism as Category A (high priority) because these agents can be easily disseminated environmentally and/or transmitted from person to person; can cause high mortality and have the potential for major public health impact; might cause public panic and social disruption; and require special action for public health preparedness[202]. General information relevant to infection control in healthcare settings for Category A agents of bioterrorism is summarized in Table 3. Consult [This link is no longer active: www.bt.cdc.gov. Similar information may be found at CDC Emergency Preparedness and Response: Bioterrorism Accessed May 2016.] for additional, updated Category A agent information as well as information concerning Category B and C agents of bioterrorism and updates. Category B and C agents are important but are not as readily disseminated and cause less morbidity and mortality than Category A agents.

Healthcare facilities confront a different set of issues when dealing with a suspected bioterrorism event as compared with other communicable diseases. An understanding of the epidemiology, modes of transmission, and clinical course of each disease, as well as carefully drafted plans that provide an approach and relevant websites and other resources for disease-specific guidance to healthcare, administrative, and support personnel, are essential for responding to and managing a bioterrorism event. Infection control issues to be addressed include:

1. identifying persons who may be exposed or infected;
2. preventing transmission among patients, healthcare personnel, and visitors;
3. providing treatment, chemoprophylaxis or vaccine to potentially large numbers of people;
4. protecting the environment including the logistical aspects of securing sufficient numbers of AIIRs or designating areas for patient cohorts when there are an insufficient number of AIIRs available;
5. providing adequate quantities of appropriate personal protective equipment; and
6. identifying appropriate staff to care for potentially infectious patients (e.g., vaccinated healthcare personnel for care of patients with smallpox).

The response is likely to differ for exposures resulting from an intentional release compared with naturally occurring disease because of the large number persons that can be exposed at the same time and possible differences in pathogenicity.

A variety of sources offer guidance for the management of persons exposed to the most likely agents of bioterrorism. Federal agency websites (e.g., [This link is no longer active: www.usamriid.army.mil/publications/index.html. Similar information may be found at USAMRIID: Biodefense Solutions to Protect our Nation Accessed May 2016.], [This link is no longer active: www.bt.cdc.gov. Similar information may be found at CDC Emergency Preparedness and Response: Bioterrorism Accessed May 2016.]). and state and county health department web sites should be consulted for the most up-to-date information. Sources of information on specific agents include: anthrax [203]; smallpox [204-206]; plague [207, 208]; botulinum toxin [209]; tularemia [210]; and hemorrhagic fever viruses: [211, 212].

I.C.2.a. Pre-event administration of smallpox (vaccinia) vaccine to healthcare personnel.

Vaccination of personnel in preparation for a possible smallpox exposure has important infection control implications [213-215]. These include the need for meticulous screening for vaccine contraindications in persons who are at increased risk for adverse vaccinia events; containment and monitoring of the vaccination site to prevent transmission in the healthcare setting and at home; and the management of patients with vaccinia-related adverse events [216, 217]. The pre-event U.S. smallpox vaccination program of 2003 is an example of the effectiveness of carefully developed recommendations for both screening potential vaccinees for contraindications and vaccination site care and monitoring. Approximately 760,000 individuals were vaccinated in the Department of Defense and 40,000 in the civilian or public health populations from December 2002 to February 2005, including approximately 70,000 who worked in healthcare settings. There were no cases of eczema vaccinatum, progressive vaccinia, fetal vaccinia, or contact transfer of vaccinia in healthcare settings or in military workplaces [218, 219]. Outside the healthcare setting, there were 53 cases of contact transfer from military vaccinees to close personal contacts (e.g., bed partners or contacts during participation in sports such as wrestling [220]). All contact transfers were from individuals who were not following recommendations to cover their vaccination sites. Vaccinia virus was confirmed by culture or PCR in 30 cases, and two of the confirmed cases resulted from tertiary transfer. All recipients, including one breast-fed infant, recovered without complication. Subsequent studies using viral culture and PCR techniques have confirmed the effectiveness of semipermeable dressings to contain vaccinia [221-224]. This experience emphasizes the importance of ensuring that newly vaccinated healthcare personnel adhere to recommended vaccination-site care, especially if they are to care for high-risk patients. Recommendations for pre-event smallpox vaccination of healthcare personnel and vaccinia-related infection control recommendations are published in the MMWR [216, 225] with updates posted on the CDC bioterrorism web site [205].

I.C.3. Prions.

Creutzfeldt-Jakob disease (CJD) is a rapidly progressive, degenerative, neurologic disorder of humans with an incidence in the United States of approximately 1 person/million population/year [226, 227] (Creutzfeldt-Jakob Disease, Classic (CJD) [Current version of this document may differ

from original.]). CJD is believed to be caused by a transmissible proteinaceous infectious agent termed a prion. Infectious prions are isoforms of a host-encoded glycoprotein known as the prion protein. The incubation period (i.e., time between exposure and and onset of symptoms) varies from two years to many decades. However, death typically occurs within 1 year of the onset of symptoms. Approximately 85% of CJD cases occur sporadically with no known environmental source of infection and 10% are familial. Iatrogenic transmission has occurred with most resulting from treatment with human cadaveric pituitary-derived growth hormone or gonadotropin [228, 229], from implantation of contaminated human dura mater grafts [230] or from corneal transplants [231]). Transmission has been linked to the use of contaminated neurosurgical instruments or stereotactic electroencephalogram electrodes [232, 233 , 234 , 235].

Prion diseases in animals include scrapie in sheep and goats, bovine spongiform encephalopathy (BSE, or "mad cow disease") in cattle, and chronic wasting disease in deer and elk [236]. BSE, first recognized in the United Kingdom (UK) in 1986, was associated with a major epidemic among cattle that had consumed contaminated meat and bone meal.

The possible transmission of BSE to humans causing variant CJD (vCJD) was first described in 1996 and subsequently found to be associated with consumption of BSE-contaminated cattle products primarily in the United Kingdom. There is strong epidemiologic and laboratory evidence for a causal association between the causative agent of BSE and vCJD [237]. Although most cases of vCJD have been reported from the UK, a few cases also have been reported from Europe, Japan, Canada, and the United States. Most vCJD cases worldwide lived in or visited the UK during the years of a large outbreak of BSE (1980-96) and may have consumed contaminated cattle products during that time (Creutzfeldt-Jakob Disease, Classic (CJD) [Current version of this document may differ from original.]). Although there has been no indigenously acquired vCJD in the United States, the sporadic occurrence of BSE in cattle in North America has heightened awareness of the possibility that such infections could occur and have led to increased surveillance activities. Updated information may be found on the following website: Creutzfeldt-Jakob Disease, Classic (CJD) [Current version of this document may differ from original.]. The public health impact of prion diseases has been reviewed [238].

vCJD in humans has different clinical and pathologic characteristics from sporadic or classic CJD [239], including the following:

1. younger median age at death: 28 (range 16-48) vs. 68 years;
2. longer duration of illness: median 14 months vs. 4-6 months;
3. increased frequency of sensory symptoms and early psychiatric symptoms with delayed onset of frank neurologic signs; and
4. detection of prions in tonsillar and other lymphoid tissues from vCJD patients but not from sporadic CJD patients [240].

Similar to sporadic CJD, there have been no reported cases of direct human-to-human transmission of vCJD by casual or environmental contact, droplet, or airborne routes. Ongoing blood safety surveillance in the U.S. has not detected sporadic CJD transmission through blood transfusion [241-243]. However, bloodborne transmission of vCJD is believed to have occurred in two UK patients [244, 245]. The following FDA websites provide information on steps that are being taken in the US to protect the blood supply from CJD and vCJD: [This link is no longer active: http://www.fda.gov/cber/gdlns/cjdvcjd.htm. Similar information may be found at Guidance for Industry: Revised Preventive Measuresexternal icon, accessed May 2016.]; [This link is no longer active: http://www.fda.gov/cber/gdlns/cjdvcjdq&a.htm. Similar information may be found at Questions and Answers on Guidance for Industry: Revised Preventive Measuresexternal icon, accessed May 2016.].

Standard Precautions are used when caring for patients with suspected or confirmed CJD or vCJD. However, special precautions are recommended for tissue handling in the histology laboratory and for conducting an autopsy, embalming, and for contact with a body that has undergone autopsy [246]. Recommendations for reprocessing surgical instruments to prevent transmission of CJD in healthcare settings have been published by the World Health Organization (WHO) and are currently under review at CDC.

Questions concerning notification of patients potentially exposed to CJD or vCJD through contaminated instruments and blood products from patients with CJD or vCJD or at risk of having vCJD may arise. The risk of transmission associated with such exposures is believed to be extremely low but may vary based on the specific circumstance. Therefore consultation on appropriate options is advised. The United Kingdom has developed several documents that clinicians and patients in the US may find useful ([This link is no longer active: http://www.hpa.org.uk/infections/topics_az/cjd/information_documents.htm. Similar information may be found at Health Protection Agency: Creutzfeldt-Jakob Disease (CJD)external icon, accessed May 2016.]).

I.C.4. Severe Acute Respiratory Syndrome (SARS).

SARS is a newly discovered respiratory disease that emerged in China late in 2002 and spread to several countries [135, 140]; Mainland China, Hong Kong, Hanoi, Singapore, and Toronto were affected significantly. SARS is caused by SARS CoV, a previously unrecognized member of the coronavirus family [247, 248]. The incubation period from exposure to the onset of symptoms is 2 to 7 days but can be as long as 10 days and uncommonly even longer [249]. The illness is initially difficult to distinguish from other common respiratory infections. Signs and symptoms

usually include fever >38.0°C and chills and rigors, sometimes accompanied by headache, myalgia, and mild to severe respiratory symptoms. Radiographic finding of atypical pneumonia is an important clinical indicator of possible SARS. Compared with adults, children have been affected less frequently, have milder disease, and are less likely to transmit SARS-CoV [135, 249-251]. The overall case fatality rate is approximately 6.0%; underlying disease and advanced age increase the risk of mortality (WHO Update 49 – SARS case fatality ratio, incubation periodexternal icon).

Outbreaks in healthcare settings, with transmission to large numbers of healthcare personnel and patients have been a striking feature of SARS; undiagnosed, infectious patients and visitors were important initiators of these outbreaks [21, 252-254]. The relative contribution of potential modes of transmission is not precisely known. There is ample evidence for droplet and contact transmission [96, 101, 113]; however, opportunistic airborne transmission cannot be excluded [101, 135-139, 149, 255]. For example, exposure to aerosol-generating procedures (e.g., endotracheal intubation, suctioning) was associated with transmission of infection to large numbers of healthcare personnel outside of the United States [93, 94, 96, 98, 253].Therefore, aerosolization of small infectious particles generated during these and other similar procedures could be a risk factor for transmission to others within a multi-bed room or shared airspace. A review of the infection control literature generated from the SARS outbreaks of 2003 concluded that the greatest risk of transmission is to those who have close contact, are not properly trained in use of protective infection control procedures, do not consistently use PPE; and that N95 or higher respirators may offer additional protection to those exposed to aerosol- generating procedures and high risk activities [256, 257]. Organizational and individual factors that affected adherence to infection control practices for SARS also were identified [257].

Control of SARS requires a coordinated, dynamic response by multiple disciplines in a healthcare setting [9]. Early detection of cases is accomplished by screening persons with symptoms of a respiratory infection for history of travel to areas experiencing community transmission or contact with SARS patients, followed by implementation of Respiratory Hygiene/Cough Etiquette (i.e., placing a mask over the patient's nose and mouth) and physical separation from other patients in common waiting areas.The precise combination of precautions to protect healthcare personnel has not been determined. At the time of this publication, CDC recommends Standard Precautions, with emphasis on the use of hand hygiene, Contact Precautions with emphasis on environmental cleaning due to the detection of SARS CoV RNA by PCR on surfaces in rooms occupied by SARS patients [138, 254, 258], Airborne Precautions, including use of fit-tested NIOSH-approved N95 or higher level respirators, and eye protection [259]. In Hong Kong, the use of Droplet and Contact Precautions, which included use of a mask but not a respirator, was effective in protecting healthcare personnel[113]. However, in Toronto, consistent use of an N95 respirator was slightly more protective than a mask [93]. It is noteworthy that there was no transmission of SARS-CoV to public hospital workers in Vietnam despite inconsistent use of infection control measures, including use of PPE, which suggests other factors (e.g., severity of disease, frequency of high risk procedures or events, environmental features) may influence opportunities for transmission [260].

SARS-CoV also has been transmitted in the laboratory setting through breaches in recommended laboratory practices. Research laboratories where SARS-CoV was under investigation were the source of most cases reported after the first series of outbreaks in the winter and spring of 2003 [261, 262]. Studies of the SARS outbreaks of 2003 and transmissions that occurred in the laboratory re-affirm the effectiveness of recommended infection control precautions and highlight the importance of consistent adherence to these measures.

Lessons from the SARS outbreaks are useful for planning to respond to future public health crises, such as pandemic influenza and bioterrorism events. Surveillance for cases among patients and healthcare personnel, ensuring availability of adequate supplies and staffing, and limiting access to healthcare facilities were important factors in the response to SARS that have been summarized [9]. Guidance for infection control precautions in various settings is available at [This link is no longer active: www.cdc.gov/ncidod/sars. Similar information may be found at CDC Severe Acute Respiratory Syndrome (SARS), accessed May 2016.].

I.C.5. Monkeypox.

Monkeypox is a rare viral disease found mostly in the rain forest countries of Central and West Africa. The disease is caused by an orthopoxvirus that is similar in appearance to smallpox but causes a milder disease. The only recognized outbreak of human monkeypox in the United States was detected in June 2003 after several people became ill following contact with sick pet prairie dogs. Infection in the prairie dogs was subsequently traced to their contact with a shipment of animals from Africa, including giant Gambian rats [263]. This outbreak demonstrates the importance of recognition and prompt reporting of unusual disease presentations by clinicians to enable prompt identification of the etiology; and the potential of epizootic diseases to spread from animal reservoirs to humans through personal and occupational exposure [264].

Limited data on transmission of monkeypox are available. Transmission from infected animals and humans is believed to occur primarily through direct contact with lesions and respiratory secretions; airborne transmission from animals to humans is unlikely but cannot be excluded, and may have occurred in veterinary practices (e.g., during administration of nebulized medications to ill prairie dogs [265]). Among humans, four instances of monkeypox transmission within hospitals have been reported in Africa among children, usually related to sharing the same ward or bed [266, 267]. Additional recent literature documents transmission of Congo Basin monkeypox in a hospital compound for an extended number of generations [268].

There has been no evidence of airborne or any other person-to-person transmission of monkeypox in the United States, and no new cases of monkeypox have been identified since the outbreak in June 2003 [269]. The outbreak strain is a clade of monkeypox distinct from the Congo Basin clade and may have different epidemiologic properties (including human-to-human transmission potential) from monkeypox strains of the Congo Basin [270]; this awaits further study. Smallpox vaccine is 85% protective against Congo Basin monkeypox [271]. Since there is an associated case fatality rate of ≤10%, administration of smallpox vaccine within 4 days to individuals who have had direct exposure to patients or animals with monkeypox is a reasonable consideration [272]. For the most current information, see CDC Monkeypox [Current version of this document may differ from original.].

I.C.6. Noroviruses.

Noroviruses, formerly referred to as Norwalk-like viruses, are members of the *Caliciviridae* family. These agents are transmitted via contaminated food or water and from person-to-person, causing explosive outbreaks of gastrointestinal disease [273]. Environmental contamination also has been documented as a contributing factor in ongoing transmission during outbreaks [274, 275]. Although noroviruses cannot be propagated in cell culture, DNA detection by molecular diagnostic techniques has facilitated a greater appreciation of their role in outbreaks of gastrointestinal disease [276]. Reported outbreaks in hospitals [132, 142, 277], nursing homes [275, 278-283], cruise ships [284, 285], hotels [143, 147], schools [148], and large crowded shelters established for hurricane evacuees [286], demonstrate their highly contagious nature, the disruptive impact they have in healthcare facilities and the community, and the difficulty of controlling outbreaks in settings where people share common facilites and space. Of note, there is nearly a 5 fold increase in the risk to patients in outbreaks where a patient is the index case compared with exposure of patients during outbreaks where a staff member is the index case [287].

The average incubation period for gastroenteritis caused by noroviruses is 12-48 hours and the clinical course lasts 12-60 hours [273]. Illness is characterized by acute onset of nausea, vomiting, abdominal cramps, and/or diarrhea. The disease is largely self-limited; rarely, death caused by severe dehydration can occur, particularly among the elderly with debilitating health conditions.

The epidemiology of norovirus outbreaks shows that even though primary cases may result from exposure to a fecally-contaminated food or water, secondary and tertiary cases often result from person-to-person transmission that is facilitated by contamination of fomites [273, 288] and dissemination of infectious particles, especially during the process of vomiting [132, 142, 143, 147, 148, 273, 279, 280]. Widespread, persistent and inapparent contamination of the environment and fomites can make outbreaks extremely difficult to control [147, 275, 284].These clinical observations and the detection of norovirus DNA on horizontal surfaces 5 feet above the level that might be touched normally suggest that, under certain circumstances, aerosolized particles may travel distances beyond 3 feet [147]. It is hypothesized that infectious particles may be aerosolized from vomitus, inhaled, and swallowed. In addition, individuals who are responsible for cleaning the environment may be at increased risk of infection. Development of disease and transmission may be facilitated by the low infectious dose (i.e., <100 viral particles) [289] and the resistance of these viruses to the usual cleaning and disinfection agents (i.e., may survive ≤10 ppm chlorine) [290-292]. An alternate phenolic agent that was shown to be effective against feline calicivirus was used for environmental cleaning in one outbreak [275, 293]. There are insufficient data to determine the efficacy of alcohol-based hand rubs against noroviruses when the hands are not visibly soiled [294]. Absence of disease in certain individuals during an outbreak may be explained by protection from infection conferred by the B histo-blood group antigen [295]. Consultation on outbreaks of gastroenteritis is available through CDC's Division of Viral and Rickettsial Diseases [296].

I.C.7. Hemorrhagic fever viruses (HFV).

The hemorrhagic fever viruses are a mixed group of viruses that cause serious disease with high fever, skin rash, bleeding diathesis, and in some cases, high mortality; the disease caused is referred to as viral hemorrhagic fever (VHF). Among the more commonly known HFVs are Ebola and Marburg viruses (Filoviridae), Lassa virus (Arenaviridae), Crimean-Congo hemorrhagic fever and Rift Valley Fever virus (Bunyaviridae), and Dengue and Yellow fever viruses (Flaviviridae) [212, 297]. These viruses are transmitted to humans via contact with infected animals or via arthropod vectors. While none of these viruses is endemic in the United States, outbreaks in affected countries provide potential opportunities for importation by infected humans and animals. Furthermore, there are concerns that some of these agents could be used as bioweapons [212]. Person-to-person transmission is documented for Ebola, Marburg, Lassa and Crimean-Congo hemorrhagic fever viruses. In resource-limited healthcare settings, transmission of these agents to healthcare personnel, patients and visitors has been described and in some outbreaks has accounted for a large proportion of cases [298-300]. Transmissions within households also have occurred among individuals who had direct contact with ill persons or their body fluids, but not to those who did not have such contact [301].

Evidence concerning the transmission of HFVs has been summarized [212, 302]. Person-to-person transmission is associated primarily with direct blood and body fluid contact. Percutaneous exposure to contaminated blood carries a particularly high risk for transmission and increased mortality [303, 304]. The finding of large numbers of Ebola viral particles in the skin and the lumina of sweat glands has raised concern that transmission could occur from direct contact with intact skin though epidemiologic evidence to support this is lacking [305]. Postmortem handling of infected bodies is an important risk for transmission [301, 306, 307]. In rare situations, cases in which the mode of transmission was unexplained among individuals with no known direct contact , have led to speculation that airborne transmission could have occurred [298]. However, airborne

transmission of naturally occurring HFVs in humans has not been seen. In one study of airplane passengers exposed to an in-flight index case of Lassa fever, there was no transmission to any passengers[308].

In the laboratory setting, animals have been infected experimentally with Marburg or Ebola viruses via direct inoculation of the nose, mouth and/or conjunctiva [309, 310] and by using mechanically generated virus-containing aerosols [311, 312]. Transmission of Ebola virus among laboratory primates in an animal facility has been described [313]. Secondarily infected animals were in individual cages and separated by approximately 3 meters. Although the possibility of airborne transmission was suggested, the authors were not able to exclude droplet or indirect contact transmission in this incidental observation.

Guidance on infection control precautions for HVFs that are transmitted person-to-person have been published by CDC [1, 211] and by the Johns Hopkins Center for Civilian Biodefense Strategies [212]. The most recent recommendations at the time of publication of this document were posted on the CDC website on 5/19/05 [314]. Inconsistencies among the various recommendations have raised questions about the appropriate precautions to use in U.S. hospitals. In less developed countries, outbreaks of HFVs have been controlled with basic hygiene, barrier precautions, safe injection practices, and safe burial practices [299, 306]. The preponderance of evidence on HFV transmission indicates that Standard, Contact and Droplet Precautions with eye protection are effective in protecting healthcare personnel and visitors who may attend an infected patient. Single gloves are adequate for routine patient care; double-gloving is advised during invasive procedures (e.g., surgery) that pose an increased risk for blood exposure. Routine eye protection (i.e. goggles or face shield) is particularly important. Fluid-resistant gowns should be worn for all patient contact. Airborne Precautions are not required for routine patient care; however, use of AIIRs is prudent when procedures that could generate infectious aerosols are performed (e.g., endotracheal intubation, bronchoscopy, suctioning, autopsy procedures involving oscillating saws). N95 or higher level respirators may provide added protection for individuals in a room during aerosol-generating procedures (Table 3, Appendix A). When a patient with a syndrome consistent with hemorrhagic fever also has a history of travel to an endemic area, precautions are initiated upon presentation and then modified as more information is obtained (Table 2). Patients with hemorrhagic fever syndrome in the setting of a suspected bioweapon attack should be managed using Airborne Precautions, including AIIRs, since the epidemiology of a potentially weaponized hemorrhagic fever virus is unpredictable.

I.D. Transmission Risks Associated with Specific Types of Healthcare Settings

Numerous factors influence differences in transmission risks among the various healthcare settings. These include the population characteristics (e.g., increased susceptibility to infections, type and prevalence of indwelling devices), intensity of care, exposure to environmental sources, length of stay, and frequency of interaction between patients/residents with each other and with HCWs. These factors, as well as organizational priorities, goals, and resources, influence how different healthcare settings adapt transmission prevention guidelines to meet their specific needs [315, 316]. Infection control management decisions are informed by data regarding institutional experience/epidemiology, trends in community and institutional HAIs, local, regional, and national epidemiology, and emerging infectious disease threats.

I.D.1. Hospitals.

Infection transmission risks are present in all hospital settings. However, certain hospital settings and patient populations have unique conditions that predispose patients to infection and merit special mention. These are often sentinel sites for the emergence of new transmission risks that may be unique to that setting or present opportunities for transmission to other settings in the hospital.

I.D.1.a. Intensive care units.

Intensive care units (ICUs) serve patients who are immunocompromised by disease state and/or by treatment modalities, as well as patients with major trauma, respiratory failure and other life-threatening conditions (e.g., myocardial infarction, congestive heart failure, overdoses, strokes, gastrointestinal bleeding, renal failure, hepatic failure, multi-organ system failure, and the extremes of age). Although ICUs account for a relatively small proportion of hospitalized patients, infections acquired in these units accounted for >20% of all HAIs [317]. In the National Nosocomial Infection Surveillance (NNIS) system, 26.6% of HAIs were reported from ICU and high risk nursery (NICU) patients in 2002 (NNIS, unpublished data). This patient population has increased susceptibility to colonization and infection, especially with MDROs and *Candida* sp. [318, 319], because of underlying diseases and conditions, the invasive medical devices and technology used in their care (e.g., central venous catheters and other intravascular devices, mechanical ventilators, extracorporeal membrane oxygenation (ECMO), hemodialysis/-filtration, pacemakers, implantable left ventricular assist devices), the frequency of contact with healthcare personnel, prolonged length of stay, and prolonged exposure to antimicrobial agents [320-331]. Furthermore, adverse patient outcomes in this setting are more severe and are associated with a higher mortality [332]. Outbreaks associated with a variety of bacterial, fungal and viral pathogens due to common-source and person-to-person transmissions are frequent in adult and pediatric ICUs [31, 333-336, 337&, 338].

I.D.1.b. Burn units.

Burn wounds can provide optimal conditions for colonization, infection, and transmission of pathogens; infection acquired by burn patients is a frequent cause of morbidity and mortality [320, 339, 340]. In patients with a burn injury involving ≥30% of the total body surface area (TBSA), the risk of invasive burn wound infection is particularly high [341, 342]. Infections that occur in patients with burn injury involving <30% TBSA are usually associated with the use of invasive devices. Methicillin-susceptible *Staphylococcus aureus*, MRSA, enterococci, including VRE, gram-negative bacteria, and candida are prevalent pathogens in burn infections [53, 340, 343-350] and outbreaks of these organisms have been reported [351-354]. Shifts over time in the predominance of pathogens causing infections among burn patients often lead to changes in burn care practices [343, 355-358]. Burn wound infections caused by *Aspergillus* sp. or other environmental molds may result from exposure to supplies contaminated during construction [359] or to dust generated during construction or other environmental disruption [360].

Hydrotherapy equipment is an important environmental reservoir of gram-negative organisms. Its use for burn care is discouraged based on demonstrated associations between use of contaminated hydrotherapy equipment and infections. Burn wound infections and colonization, as well as bloodstream infections, caused by multidrug-resistant *P. aeruginosa* [361], *A. baumannii* [362], and MRSA [352] have been associated with hydrotherapy; excision of burn wounds in operating rooms is preferred.

Advances in burn care, specifically early excision and grafting of the burn wound, use of topical antimicrobial agents, and institution of early enteral feeding, have led to decreased infectious complications. Other advances have included prophylactic antimicrobial usage, selective digestive decontamination (SDD), and use of antimicrobial-coated catheters (ACC), but few epidemiologic studies and no efficacy studies have been performed to show the relative benefit of these measures [357].

There is no consensus on the most effective infection control practices to prevent transmission of infections to and from patients with serious burns (e.g., single-bed rooms [358], laminar flow [363] and high efficiency particulate air filtration [HEPA] [360] or maintaining burn patients in a separate unit without exposure to patients or equipment from other units [364]). There also is controversy regarding the need for and type of barrier precautions for routine care of burn patients. One retrospective study demonstrated efficacy and cost effectiveness of a simplified barrier isolation protocol for wound colonization, emphasizing handwashing and use of gloves, caps, masks and plastic impermeable aprons (rather than isolation gowns) for direct patient contact [365]. However, there have been no studies that define the most effective combination of infection control precautions for use in burn settings. Prospective studies in this area are needed.

I.D.1.c. Pediatrics.

Studies of the epidemiology of HAIs in children have identified unique infection control issues in this population [63, 64, 366-370]. Pediatric intensive care unit (PICU) patients and the lowest birthweight babies in the high-risk nursery (HRN) monitored in the NNIS system have had high rates of central venous catheter-associated bloodstream infections [64, 320, 369-372]. Additionally, there is a high prevalence of community-acquired infections among hospitalized infants and young children who have not yet become immune either by vaccination or by natural infection. The result is more patients and their sibling visitors with transmissible infections present in pediatric healthcare settings, especially during seasonal epidemics (e.g., pertussis [36, 40, 41], respiratory viral infections including those caused by RSV [24], influenza viruses [373], parainfluenza virus [374], human metapneumovirus [375], and adenoviruses [376]; rubeola [measles] [34], varicella [chickenpox] [377], and rotavirus [38, 378]).

Close physical contact between healthcare personnel and infants and young children (eg. cuddling, feeding, playing, changing soiled diapers, and cleaning copious uncontrolled respiratory secretions) provides abundant opportunities for transmission of infectious material. Practices and behaviors such as congregation of children in play areas where toys and bodily secretions are easily shared and family members rooming-in with pediatric patients can further increase the risk of transmission. Pathogenic bacteria have been recovered from toys used by hospitalized patients [379]; contaminated bath toys were implicated in an outbreak of multidrug-resistant *P. aeruginosa* on a pediatric oncology unit [80]. In addition, several patient factors increase the likelihood that infection will result from exposure to pathogens in healthcare settings (e.g., immaturity of the neonatal immune system, lack of previous natural infection and resulting immunity, prevalence of patients with congenital or acquired immune deficiencies, congenital anatomic anomalies, and use of life-saving invasive devices in neontal and pediatric intensive care units) [63]. There are theoretical concerns that infection risk will increase in association with innovative practices used in the NICU for the purpose of improving developmental outcomes, Such factors include co-bedding [380] and kangaroo care [381] that may increase opportunity for skin-to-skin exposure of multiple gestation infants to each other and to their mothers, respectively; although infection risk smay actually be reduced among infants receiving kangaroo care [382]. Children who attend child care centers [383, 384] and pediatric rehabilitation units [385] may increase the overall burden of antimicrobial resistance (eg. by contributing to the reservoir of community-associated MRSA [CA-MRSA]) [386-391]. Patients in chronic care facilities may have increased rates of colonization with resistant GNBs and may be sources of introduction of resistant organisms to acute care settings [50].

I.D.2. Non-acute healthcare settings.

Healthcare is provided in various settings outside of hospitals including facilities, such as long-term care facilities (LTCF) (e.g., nursing homes), homes for the developmentally disabled, settings where behavioral health services are provided, rehabilitation centers and hospices[392]. In addition, healthcare may be provided in nonhealthcare settings such as workplaces with occupational health clinics, adult day care centers, assisted living facilities, homeless shelters, jails and prisons, school clinics and infirmaries. Each of these settings has unique circumstances and

population risks to consider when designing and implementing an infection control program. Several of the most common settings and their particular challenges are discussed below. While this Guideline does not address each setting, the principles and strategies provided may be adapted and applied as appropriate.

I.D.2.a. Long-term care.

The designation LTCF applies to a diverse group of residential settings, ranging from institutions for the developmentally disabled to nursing homes for the elderly and pediatric chronic-care facilities [393-395]. Nursing homes for the elderly predominate numerically and frequently represent long-term care as a group of facilities. Approximately 1.8 million Americans reside in the nation's 16,500 nursing homes [396]. Estimates of HAI rates of 1.8 to 13.5 per 1000 resident-care days have been reported with a range of 3 to 7 per 1000 resident-care days in the more rigorous studies [397-401]. The infrastructure described in the Department of Veterans Affairs nursing home care units is a promising example for the development of a nationwide HAI surveillance system for LTCFs [402].

LCTFs are different from other healthcare settings in that elderly patients at increased risk for infection are brought together in one setting and remain in the facility for extended periods of time; for most residents, it is their home. An atmosphere of community is fostered and residents share common eating and living areas, and participate in various facility-sponsored activities [403, 404]. Since able residents interact freely with each other, controlling transmission of infection in this setting is challenging [405]. Residents who are colonized or infected with certain microorganisms are, in some cases, restricted to their room. However, because of the psychosocial risks associated with such restriction, it has been recommended that psychosocial needs be balanced with infection control needs in the LTCF setting [406-409]. Documented LTCF outbreaks have been caused by various viruses (e.g., influenza virus [35, 410-412], rhinovirus [413], adenovirus [conjunctivitis] [414], norovirus [278, 279 275, 281]) and bacteria (e.g., group A streptococcus [162], *B. pertussis* [415], non-susceptible *S. pneumoniae* [197, 198], other MDROs, and *Clostridium difficile* [416]) These pathogens can lead to substantial morbidity and mortality, and increased medical costs; prompt detection and implementation of effective control measures are required.

Risk factors for infection are prevalent among LTCF residents [395, 417, 418]. Age-related declines in immunity may affect responses to immunizations for influenza and other infectious agents, and increase susceptibility to tuberculosis. Immobility, incontinence, dysphagia, underlying chronic diseases, poor functional status, and age-related skin changes increase susceptibility to urinary, respiratory and cutaneous and soft tissue infections, while malnutrition can impair wound healing [419-423]. Medications (e.g., drugs that affect level of consciousness, immune function, gastric acid secretions, and normal flora, including antimicrobial therapy) and invasive devices (e.g., urinary catheters and feeding tubes) heighten susceptibility to infection and colonization in LTCF residents [424-426]. Finally, limited functional status and total dependence on healthcare personnel for activities of daily living have been identified as independent risk factors for infection [401, 417, 427] and for colonization with MRSA [428, 429] and ESBL-producing *K. pneumoniae* [430]. Several position papers and review articles have been published that provide guidance on various aspects of infection control and antimicrobial resistance in LTCFs [406-408, 431-436]. The Centers for Medicare and Medicaid Services (CMS) have established regulations for the prevention of infection in LTCFs [437].

Because residents of LTCFs are hospitalized frequently, they can transfer pathogens between LTCFs and healthcare facilities in which they receive care [8, 438-441]. This is also true for pediatric long-term care populations. Pediatric chronic care facilities have been associated with importing extended-spectrum cephalosporin-resistant, gram-negative bacilli into one PICU [50]. Children from pediatric rehabilitation units may contribute to the reservoir of community-associated MRSA [385, 389-391].

I.D.2.b. Ambulatory care.

In the past decade, healthcare delivery in the United States has shifted from the acute, inpatient hospital to a variety of ambulatory and community-based settings, including the home. Ambulatory care is provided in hospital-based outpatient clinics, nonhospital-based clinics and physician offices, public health clinics, free-standing dialysis centers, ambulatory surgical centers, urgent care centers, and many others. In 2000, there were 83 million visits to hospital outpatient clinics and more than 823 million visits to physician offices [442]; ambulatory care now accounts for most patient encounters with the health care system [443]. In these settings, adapting transmission prevention guidelines is challenging because patients remain in common areas for prolonged periods waiting to be seen by a healthcare provider or awaiting admission to the hospital, examination or treatment rooms are turned around quickly with limited cleaning, and infectious patients may not be recognized immediately. Furthermore, immunocompromised patients often receive chemotherapy in infusion rooms where they stay for extended periods of time along with other types of patients.

There are few data on the risk of HAIs in ambulatory care settings, with the exception of hemodialysis centers [18 , 444, 445]. Transmission of infections in outpatient settings has been reviewed in three publications [446-448]. Goodman and Solomon summarized 53 clusters of infections associated with the outpatient setting from 1961-1990 [446]. Overall, 29 clusters were associated with common source transmission from contaminated solutions or equipment, 14 with person-to-person transmission from or involving healthcare personnel and ten associated with airborne or droplet transmission among patients and healthcare workers. Transmission of bloodborne pathogens (i.e., hepatitis B and C viruses and, rarely, HIV) in outbreaks, sometimes involving hundreds of patients, continues to occur in ambulatory settings. These outbreaks often are related to common source exposures, usually a contaminated medical device, multi-dose vial, or intravenous solution [82, 449-453]. In all cases,

transmission has been attributed to failure to adhere to fundamental infection control principles, including safe injection practices and aseptic technique.This subject has been reviewed and recommended infection control and safe injection practices summarized [454].

Airborne transmission of *M.tuberculosis* and measles in ambulatory settings, most frequently emergency departments, has been reported [34, 127, 446, 448, 455-457]. Measles virus was transmitted in physician offices and other outpatient settings during an era when immunization rates were low and measles outbreaks in the community were occurring regularly [34, 122, 458]. Rubella has been transmitted in the outpatient obstetric setting [33]; there are no published reports of varicella transmission in the outpatient setting. In the ophthalmology setting, adenovirus type 8 epidemic keratoconjunctivitis has been transmitted via incompletely disinfected ophthalmology equipment and/or from healthcare workers to patients, presumably by contaminated hands [17, 446, 448, 459-462].

If transmission in outpatient settings is to be prevented, screening for potentially infectious symptomatic and asymptomatic individuals, especially those who may be at risk for transmitting airborne infectious agents (e.g., *M. tuberculosis,* varicella-zoster virus, rubeola [measles]), is necessary at the start of the initial patient encounter. Upon identification of a potentially infectious patient, implementation of prevention measures, including prompt separation of potentially infectious patients and implementation of appropriate control measures (e.g., Respiratory Hygiene/Cough Etiquette and Transmission-Based Precautions) can decrease transmission risks [9, 12]. Transmission of MRSA and VRE in outpatient settings has not been reported, but the association of CA-MRSA in healthcare personnel working in an outpatient HIV clinic with environmental CA-MRSA contamination in that clinic, suggests the possibility of transmission in that setting [463]. Patient-to-patient transmission of *Burkholderia species* and *Pseudomonas aeruginosa* in outpatient clinics for adults and children with cystic fibrosis has been confirmed [464, 465].

See Interim Infection Prevention and Control Recommendations for Measles in Healthcare Settings

I.D.2.c. Home care.

Home care in the United States is delivered by over 20,000 provider agencies that include home health agencies, hospices, durable medical equipment providers, home infusion therapy services, and personal care and support services providers. Home care is provided to patients of all ages with both acute and chronic conditions. The scope of services ranges from assistance with activities of daily living and physical and occupational therapy to the care of wounds, infusion therapy, and chronic ambulatory peritoneal dialysis (CAPD).

The incidence of infection in home care patients, other than those associated with infusion therapy is not well studied [466-471]. However, data collection and calculation of infection rates have been accomplished for central venous catheter-associated bloodstream infections in patients receiving home infusion therapy [470-474] and for the risk of blood contact through percutaneous or mucosal exposures, demonstrating that surveillance can be performed in this setting 4[75]. Draft definitions for home care associated infections have been developed [476].

Transmission risks during home care are presumed to be minimal. The main transmission risks to home care patients are from an infectious healthcare provider or contaminated equipment; providers also can be exposed to an infectious patient during home visits. Since home care involves patient care by a limited number of personnel in settings without multiple patients or shared equipment, the potential reservoir of pathogens is reduced. Infections of home care providers, that could pose a risk to home care patients include infections transmitted by the airborne or droplet routes (e.g., chickenpox, tuberculosis, influenza), and skin infestations (e.g., scabies [69] and lice) and infections (e.g.,impetigo) transmitted by direct or indirect contact. There are no published data on indirect transmission of MDROs from one home care patient to another, although this is theoretically possible if contaminated equipment is transported from an infected or colonized patient and used on another patient. Of note, investigation of the first case of VISA in homecare [186] and the first 2 reported cases of VRSA [178, 180, 181, 183] found no evidence of transmission of VISA or VRSA to other home care recipients. Home health care also may contribute to antimicrobial resistance; a review of outpatient vancomycin use found 39% of recipients did not receive the antibiotic according to recommended guidelines [477].

Although most home care agencies implement policies and procedures to prevent transmission of organisms, the current approach is based on the adaptation of the 1996 Guideline for Isolation Precautions in Hospitals 1 as well as other professional guidance [478, 479]. This issue has been very challenging in the home care industry and practice has been inconsistent and frequently not evidence-based. For example, many home health agencies continue to observe "nursing bag technique," a practice that prescribes the use of barriers between the nursing bag and environmental surfaces in the home [480.] While the home environment may not always appear clean, the use of barriers between two non-critical surfaces has been questioned [481, 482]. Opportunities exist to conduct research in home care related to infection transmission risks [483].

I.D.2.d. Other sites of healthcare delivery.

Facilities that are not primarily healthcare settings but in which healthcare is delivered include clinics in correctional facilities and shelters. Both settings can have suboptimal features, such as crowded conditions and poor ventilation. Economically disadvantaged individuals who may have chronic illnesses and healthcare problems related to alcoholism, injection drug use, poor nutrition, and/or inadequate shelter often receive their primary healthcare at sites such as these [484]. Infectious diseases of special concern for transmission include tuberculosis, scabies, respiratory infections (e.g., N. meningitides, S. pneumoniae), sexually transmitted and bloodborne diseases (e.g.,HIV, HBV, HCV, syphilis, gonorrhea),

hepatitis A virus (HAV), diarrheal agents such as norovirus, and foodborne diseases [286, 485-488]. A high index of suspicion for tuberculosis and CA-MRSA in these populations is needed as outbreaks in these settings or among the populations they serve have been reported [489-497].

Patient encounters in these types of facilities provide an opportunity to deliver recommended immunizations and screen for *M. tuberculosis* infection in addition to diagnosing and treating acute illnesses [498]. Recommended infection control measures in these non-traditional areas designated for healthcare delivery are the same as for other ambulatory care settings. Therefore, these settings must be equipped to observe Standard Precautions and, when indicated, Transmission-based Precautions.

I.E. Transmission Risks Associated with Special Patient Populations

As new treatments emerge for complex diseases, unique infection control challenges associated with special patient populations need to be addressed.

I.E.1. Immunocompromised patients.

Patients who have congenital primary immune deficiencies or acquired disease (eg. treatment-induced immune deficiencies) are at increased risk for numerous types of infections while receiving healthcare and may be located throughout the healthcare facility. The specific defects of the immune system determine the types of infections that are most likely to be acquired (e.g., viral infections are associated with T-cell defects and fungal and bacterial infections occur in patients who are neutropenic). As a general group, immunocompromised patients can be cared for in the same environment as other patients; however, it is always advisable to minimize exposure to other patients with transmissible infections such as influenza and other respiratory viruses [499, 500]. The use of more intense chemotherapy regimens for treatment of childhood leukemia may be associated with prolonged periods of neutropenia and suppression of other components of the immune system, extending the period of infection risk and raising the concern that additional precautions may be indicated for select groups [501, 502]. With the application of newer and more intense immunosuppressive therapies for a variety of medical conditions (e.g., rheumatologic disease [503, 504], inflammatory bowel disease [505]), immunosuppressed patients are likely to be more widely distributed throughout a healthcare facility rather than localized to single patient units (e.g., hematology-oncology). Guidelines for preventing infections in certain groups of immunocompromised patients have been published [15, 506, 507].

Published data provide evidence to support placing allogeneic HSCT patients in a Protective Environment [15, 157, 158]. Also, three guidelines have been developed that address the special requirements of these immunocompromised patients, including use of antimicrobial prophylaxis and engineering controls to create a Protective Environment for the prevention of infections caused by *Aspergillus* spp. and other environmental fungi [11, 14, 15]. As more intense chemotherapy regimens associated with prolonged periods of neutropenia or graft-versus-host disease are implemented, the period of risk and duration of environmental protection may need to be prolonged beyond the traditional 100 days [508].

I.E.2. Cystic fibrosis patients.

Patients with cystic fibrosis (CF) require special consideration when developing infection control guidelines. Compared to other patients, CF patients require additional protection to prevent transmission from contaminated respiratory therapy equipment [509-513]. Infectious agents such as *Burkholderia cepacia* complex and *P. aeruginosa* [464, 465, 514, 515] have unique clinical and prognostic significance. In CF patients, *B. cepacia* infection has been associated with increased morbidity and mortality [516-518], while delayed acquisition of chronic *P.aeruginosa* infection may be associated with an improved long-term clinical outcome [519, 520].

Person-to-person transmission of *B. cepacia* complex has been demonstrated among children [517] and adults [521] with CF in healthcare settings [464, 522], during various social contacts [523], most notably attendance at camps for patients with CF [524], and among siblings with CF [525]. Successful infection control measures used to prevent transmission of respiratory secretions include segregation of CF patients from each other in ambulatory and hospital settings (including use of private rooms with separate showers), environmental decontamination of surfaces and equipment contaminated with respiratory secretions, elimination of group chest physiotherapy sessions, and disbanding of CF camps [97, 526]. The Cystic Fibrosis Foundation published a consensus document with evidence-based recommendations for infection control practices for CF patients [20].

I.F. New Therapies Associated with Potentially Transmissible Infectious Agents

I.F.1. Gene therapy.

Gene therapy has has been attempted using a number of different viral vectors, including nonreplicating retroviruses, adenoviruses, adeno-associated viruses, and replication-competent strains of poxviruses. Unexpected adverse events have restricted the prevalence of gene therapy

protocols.

The infectious hazards of gene therapy are theoretical at this time, but require meticulous surveillance due to the possible occurrence of in vivo recombination and the subsequent emergence of a transmissible genetically altered pathogen. Greatest concern attends the use of replication-competent viruses, especially vaccinia. As of the time of publication, no reports have described transmission of a vector virus from a gene therapy recipient to another individual, but surveillance is ongoing. Recommendations for monitoring infection control issues throughout the course of gene therapy trials have been published [527-529].

I.F.2. Infections transmitted through blood, organs and other tissues.

The potential hazard of transmitting infectious pathogens through biologic products is a small but ever present risk, despite donor screening. Reported infections transmitted by transfusion or transplantation include West Nile Virus infection [530] cytomegalovirus infection [531], Creutzfeldt-Jacob disease [230], hepatitis C [532], infections with *Clostridium* spp.[533] and group A streptococcus [534], malaria [535], babesiosis [536], Chagas disease [537], lymphocytic choriomeningitis [538], and rabies [539, 540]. Therefore, it is important to consider receipt of biologic products when evaluating patients for potential sources of infection.

I.F.3. Xenotransplantation.

The transplantation of nonhuman cells, tissues, and organs into humans potentially exposes patients to zoonotic pathogens. Transmission of known zoonotic infections (e.g., trichinosis from porcine tissue), constitutes one concern, but also of concern is the possibility that transplantation of nonhuman cells, tissues, or organs may transmit previously unknown zoonotic infections (xenozoonoses) to immunosuppressed human recipients. Potential infections that might accompany transplantation of porcine organs have been described [541]. Guidelines from the U.S. Public Health Service address many infectious diseases and infection control issues that surround the developing field of xenotransplantation, [542] work in this area is ongoing.

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Part II. Fundamental Elements

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