

Single-Case Research Designs: Methods for Clinical and Applied Settings

I.A. Evolution of the 2007 Document

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. These 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

provide infection control recommendations for all components of the healthcare delivery system, including hospitals, long-term care facilities, ambulatory care, home care and hospice; reaffirm Standard Precautions as the foundation for preventing transmission during patient care in all healthcare settings; 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 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.

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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

, the Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings 2005 and the American Institute of Architects (AIA) guidelines for design and construction of hospitals, 2006 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 hematopoietic 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.

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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.

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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.

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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 29-35 17, 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.

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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 individual's 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.

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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.

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I.B.3.a. Contact transmission.

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

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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 .

or breaks (i.e., cuts, abrasions) in the skin . 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.

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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.

or pathogenic bacteria (e.g., *Pseudomonas aeruginosa*) 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.

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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 $>5 \mu\text{m}$ in size. Droplet nuclei, particles arising from desiccation of suspended droplets, have been associated with airborne transmission and defined as $\geq 5 \mu\text{m}$ in size, 105 a reflection of the pathogenesis of pulmonary tuberculosis which is not generalizable to other organisms. Observations of particle dynamics have demonstrated that a range of droplet sizes, including those with diameters of $30 \mu\text{m}$ 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" phenomenon¹¹⁸⁻¹²⁰.

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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 individual¹²¹⁻¹²⁴. 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 rhinovirus¹⁰⁴, and even some gastrointestinal viruses (e.g., norovirus¹³² and rotavirus¹³³) 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.

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

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

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 1957-1958 have been used to suggest airborne transmission 145, 146.

alert icon Interim Measles Infection Control [July 2019] See Interim Infection Prevention and Control Recommendations for Measles in Healthcare Settings

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 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

, in burn units , or in a LTCF ; Legionella sp. , Aspergillus sp.) 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

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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.

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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 fluoroquinolones, 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 facilities¹⁹⁹⁻²⁰¹. 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 and may be found at *Management of Multidrug-Resistant Organisms in Healthcare Settings* (2006).

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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 preparedness²⁰². 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:

identifying persons who may be exposed or infected; preventing transmission among patients, healthcare personnel, and visitors; providing treatment, chemoprophylaxis or vaccine to potentially large numbers of people; 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; providing adequate quantities of appropriate personal protective equipment; and 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 Nationexternal icon 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.

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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.

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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 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:

younger median age at death: 28 (range 16-48) vs. 68 years; longer duration of illness: median 14 months vs. 4-6 months; increased frequency of sensory symptoms and early psychiatric symptoms with delayed onset of frank neurologic signs; and 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.]).

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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.].

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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 approximately 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.].

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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 facilities 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., 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&.

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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 $\geq 30\%$ 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

Reference

[Qualitative Methods in Public Health: A Field Guide for Applied Research \(Jossey-Bass Public Health\)](#)

[Research Methods, Statistics, and Applications](#)