CLINICAL MICROBIOLOGY REVIEWS, July 1995, p. 389–405 Vol. 8, No. 3
0893-8512/95/$04.00+0

Laboratory-Associated Infections and Biosafety

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INTRODUCTION

An estimated 500,000 workers in the United States are employed in laboratories that range in size and complexity from large, comprehensive research and clinical laboratories to the physician's office laboratory. These workers are exposed to a variety of potential occupational health risks that include infectious materials and cultures, radiation, toxic and flammable chemicals, and mechanical and electrical hazards. Although all occupational hazards are important, this report will concentrate on the biological hazards present in clinical, research, and industrial production laboratories.

The potential risk of infection by a pathogenic microorganism because of employment in a clinical, research, or industrial laboratory raises a series of questions. (i) What is the actual incidence of laboratory-acquired infections in these laboratories? (ii) Which microorganisms are associated most frequently with laboratory infections? (iii) Why do laboratory infections occur? (iv) How effective are safety measures? (v) How can laboratory infections be prevented? This review will attempt to address these questions.

The actual risk of a laboratory-acquired infection is difficult to measure because there is no systematic reporting system at the state, federal, or professional society level that monitors the number of laboratory workers and infections associated with the workplace. Also, surveillance data on laboratory-associated infections are difficult to collect because the infections are often subclinical and have an atypical incubation period and route of infection and laboratory directors may not report incidents for fear of reprisal or embarrassment. The available data are limited to published anecdotal reports, selected outbreaks with a specific microorganism, retrospective questionnaire-based surveys, and information presented at meetings related to laboratory-acquired infections and biosafety. Because a reliable estimate of the current risk or the magnitude of the problem is not available, control measures are proposed and implemented on the basis of data collected years ago, data based on experience with one infectious agent and applied to other microorganisms, data derived from the knowledge of the transmission of an infectious agent outside the laboratory, and analysis of potential safety problems by job safety analysis (131) or the concept of hazard analysis critical control point (72, 117). This approach to the management of infectious risks is necessary, but the historical data may not necessarily apply in the current laboratory environment of rapidly expanding work loads and new technologies. However, until a systematic survey of laboratory-associated infections is implemented, laboratorians must rely on the available information and their knowledge of the pathogenicity and methods of transmission of infectious agents for managing biological hazards in the workplace.

The control measures used in the laboratory are designed to protect employees from exposure to infectious agents and to protect the public through the safe disposal of infectious wastes. Therefore, a safety program must address the cultivation, storage, and disposal of biohazardous materials; the facility operation; employee education; and medical surveillance of laboratory workers. The development of programs to minimize risks associated with the handling and disposal of infectious agents is based on an understanding of the pathogenicity of the agent, the susceptibility of the host, and, most importantly, the method of transmission of the infectious agent. Most risks from biological hazards can be reduced through the use of appropriate microbiological procedures and techniques, containment devices and facilities, and protective barriers. The foundation of all safety programs is the training of workers so that they understand the need for safety procedures and follow them. Acceptance of safety procedures by employees is greatest when the precautions required are commensurate with the potential risk. Although absolute safety in the laboratory is not possible, it is the joint responsibility of both laboratory management and employees to develop and adhere to safety programs that reduce the risk of laboratory-acquired infections and laboratory accidents. Pike (111) concluded in 1979 that "the knowledge, the techniques, and the equipment necessary to prevent most laboratory infections are available." His conclusion is applicable today.

HISTORICAL PERSPECTIVE

Experience shows that the recognition and isolation of a new infectious agent is often followed by a report of a laboratory-acquired infection caused by the new isolate (82). The risk of exposure to infectious agents tends to be lower in laboratory workers than other groups of health care workers (HCW), but the risk of laboratory-associated infection in employees of clinical and research laboratories is greater than in the general population, suggesting that unique risks are associated with the laboratory work site (80).

To assess the risk of infection associated with employment in a research or clinical laboratory, Sulkin and Pike began to collect data in 1949 from literature and mail surveys (135). By 1979, Pike had compiled the most comprehensive review to date dealing with laboratory-associated infections in the United States and the rest of the world (111). His collection of these data, identification of potential infectious hazards in the laboratory, and suggestions for reducing the risk of infection formed the cornerstone for the current approach to the prevention of laboratory-acquired infections. Pike's efforts and those of other investigators increased the awareness of the occupational risks associated with employment in a clinical or research microbiology laboratory (12, 70, 137). The weaknesses of these data are that a large percentage of the infections reported by Pike occurred in research and animal laboratories and may not relate directly to the clinical laboratory and that they do not provide the denominator data necessary to calculate the actual risk or incidence of infection for all laboratory workers. Pike's early conclusions on laboratory-associated infections are supported by the documentation of the current infectious risks associated with exposure to blood and blood products.

The laboratory-acquired infections reported by Pike were due primarily to bacteria, viruses, and rickettsiae. The recognition that the primary route of transmission of many of these agents was by aerosols led to the development and use of laminar-flow biological safety cabinets, which may explain in part the perceived shift from bacteria and rickettsiae as the chief causes of laboratory-associated infections to viruses that are blood borne and transmitted primarily through contact (80). The other factors affecting this shift to viral infections in laboratory workers include the availability of antibiotics for the early treatment of bacterial and rickettsial infections, increased implementation of laboratory safety programs, and increased exposure of laboratory workers to blood and body fluids through greater reliance by other HCW on laboratory testing for patient management.

The advent of the AIDS epidemic in the early 1980s and the associated rise in tuberculosis infections has renewed interest in laboratory safety and safety programs for all HCW. The safety concerns of HCW, especially for exposure to human immunodeficiency virus (HIV) in the workplace, led to the passage of far-reaching legislation and guidelines that reduce the potential exposure of employees to blood-borne pathogens

TABLE 1. Most frequently reported laboratory-acquired infections in the United States and Great Britain

Infection	Total no. (%) of cases reported for:			
	U.S.[a]	U.S. and world[b]	Great Britain[c,d]	NADC[e]
Brucellosis	274 (9.4)	423 (10.8)	2 (2.1)	18 (52.9)
Q fever	184 (6.3)	278 (7.1)	0	
Typhoid fever	292 (10.0)	256 (6.5)	3 (3.2)	
Hepatitis	126 (4.3)	234 (6.0)	19 (20.0)	
Tularemia	129 (4.4)	225 (5.7)	0	
Tuberculosis	174 (6.0)	176 (4.5)	24 (25.3)	4 (11.8)
Dermatomycosis	84 (2.9)	161 (4.1)	0	2 (5.9)
Venezuelan equine encephalitis	118 (4.1)	141 (3.6)	0	
Typhus	82 (2.8)	124 (3.2)	0	
Psittacosis	70 (2.4)	116 (3.0)	0	4 (11.8)
Coccidioidomycosis	108 (3.7)	93 (2.4)	0	
Streptococcal infections	67 (2.3)	78 (2.0)	3 (3.2)	
Histoplasmosis	81 (2.8)	71 (1.8)	0	
Leptospirosis	43 (1.5)	87 (2.2)	0	3 (8.8)
Salmonellosis	54 (1.9)	48 (1.2)	11 (11.6)	1 (2.9)
Shigellosis	54 (1.9)	58 (1.5)	26 (27.4)	
All reported infections	2,912	3,921	95	34

[a] 1969 data adapted from reference 151.
[b] 1976 data adapted from reference 110.
[c] 1980 to 1989 data adapted from references 51 through 55.
[d] Includes possibly attributable and attributable cases.
[e] NADC, National Animal Disease Center; 1975 to 1985 data adapted from reference 93.

and require the safe disposal of biohazardous waste (14, 103). Subsequent data (30, 157) suggest that these guidelines produced a decrease in the occupational risk of exposure to infectious agents but have not eliminated laboratory-acquired infections. Because occupational risks associated with working in a clinical, research, or production laboratory remain, there is a continued need for a strong laboratory safety program in all facilities where potentially infectious material is handled. However, most safety guidelines should be evaluated for their effectiveness and cost before they are implemented nationally.

SURVEY OF LABORATORY-ASSOCIATED INFECTIONS

The accounts of laboratory infections are usually organism specific or represent general surveys of diagnostic, research, and industrial laboratories. The most extensive surveys which illustrate the historical importance of these infections were published by Sulkin and Pike from 1949 to 1979 (110, 111, 135). In 1976, Pike published the cumulative cases collected through 1974 (110). A total of 3,921 infections were reported, with an overall mortality rate of 4.2%. Bacterial infections predominated, with 1,669 (42.5%) being reported, followed by viral infections (1,049 [26.7%]), rickettsial infections (573 [14.6%]), fungal infections (353 [9.0%]), chlamydial infections (128 [3.3%]), parasitic infections (115 [2.9%]), and unspecified infections (34 [0.9%]). The highest mortality rate (7.8%) was associated with chlamydial infections; all these deaths were from cases of psittacosis that occurred prior to 1955.

The most frequently reported laboratory-acquired infections through 1989 are listed in Table 1. For surveys completed in 1969 (151) and 1976 (110), the three most frequently reported infections were brucellosis, Q fever, and typhoid fever. Of the bacterial infections in Pike's survey (110), 64% were caused by *Brucella* spp., *Salmonella typhi*, *Franciscella tularensis*, and *Mycobacterium tuberculosis*. Over 90 viral agents were associated with laboratory infections; 36% of the infections were caused by hepatitis virus and Venezuelan equine encephalitis virus. Half of the cases of Venezuelan equine encephalitis were reported by only four laboratories. Over half of the rickettsial infections were due to *Coxiella burnetii* (Q fever), and approximately half of the fungal infections were due to *Histoplasma capsulatum* and *Coccidioides immitis. Toxoplasma gondii* accounted for 24% of the parasitic laboratory-acquired infections. After 1955, the total number and relative frequency of bacterial, chlamydial, and rickettsial infections declined dramatically (88, 110) while the relative frequency of viral and fungal infections increased 60 and 20%, respectively. Laboratory-acquired parasite infections increased less than 10%.

A survey of approximately 22,000 medical laboratory workers in Great Britain by Harrington and Shannon (63) found 45 cases of shigellosis, 38 cases of hepatitis, 21 cases of tuberculosis, and 1 case of brucellosis. The authors did not attempt to determine whether these infections were laboratory or community acquired. Grist (45–51) and Grist and Emslie (52–55) surveyed medical laboratories in Great Britain from 1979 through 1989 to determine the incidence of laboratory-associated infections (Table 1). Their results were compiled from responses to surveys, and there was no attempt to determine how the infection was acquired. In these surveys, shigellosis, tuberculosis, and hepatitis were the three most frequently reported laboratory-acquired infections. In addition, their series of surveys attempted to identify the types of laboratories with the highest attack rate among the employees. The data clearly indicate that the most frequent laboratory-associated infections are enteric infections (shigellosis and salmonellosis) in microbiology laboratories, tuberculosis in morbid anatomy laboratories, and hepatitis in medical laboratories.

A 25-year (1960 to 1985) review of laboratory-acquired infections at the National Animal Disease Center summarizes the risks associated with working in an animal research facility (Table 1) (93). As reported in the other laboratory surveys, *Chlamydia* spp., *Brucella* spp., and *Mycobacterium* spp. were responsible for 76% of the total infections. *Brucella* spp. accounted for the majority of the cases identified at the National Animal Disease Center.

Two other surveys were conducted in the United States. Jacobson et al. (73) reviewed laboratory infections occurring in Utah from 1978 through 1982, and Vesley and Hartmann (145) surveyed 54 public and territorial health laboratories and 165 hospital clinical laboratories in Minnesota in 1986. The Utah survey found an annual incidence of 3 infections per 1,000 employees. Infections, in order of decreasing frequency, included hepatitis B, shigellosis, pharyngitis, cellulitis, tuberculosis, conjunctivitis, and non A, non B hepatitis. The number of each infection ranged from 1 to 5, which makes it difficult to recognize trends in types of agents causing laboratory-associated infections. The incidence of infections was three times greater in smaller laboratories (fewer than 25 employees) than in larger laboratories, and all cases of shigellosis occurred in microbiologists. The greater number of infections in smaller laboratories may reflect the greater number of generalists, who are presumed to have less experience working with infectious agents and may not realize the potential hazard. In the Vesley and Hartmann (145) survey, the annual incidence was 3.5 infections per 1,000 employees in hospital laboratories versus 1.4 infections per 1,000 employees in public health laboratories. The difference observed between the two types of laboratories was most probably related to the risks associated with performing phlebotomy in hospital laboratories.

Harding and Lieberman (62) reviewed 58 publications between 1980 and 1991 on laboratory-associated infections.

Three hundred seventy-five infections or seroconversions were reported. Most of the reported bacterial infections were caused by *Salmonella typhi*, *Brucella melitensis*, and *Chlamydia* spp.; approximately three-quarters of the 119 viral infections were caused by arboviruses and hantaviruses; and 95% of the 162 rickettsial infections were caused by *Coxiella burnetii*. Most of the 13 parasitic infections were caused by protozoans.

The individual reports of laboratory infection by a specific microbial agent are scattered throughout the medical literature of the last 100 years. Because of the paucity of current data on laboratory-acquired infections, this review relies heavily on the historical reports and the material presented in three excellent recent texts (19, 33, 142).

SPECIFIC LABORATORY-ASSOCIATED INFECTIONS

Bacteria

***Brucella* spp.** Over the years, brucellosis has been the most commonly reported laboratory-associated bacterial infection; it may be caused by *B. abortus*, *B. canis*, *B. melitensis*, or *B. suis* (19, 57, 87, 93, 106, 110, 130, 142, 158). The incidence of brucellosis has fallen in countries that have attempted to eradicate the disease in cattle, but sporadic cases still occur in the general population (87). The lack of recognition of an isolate as a *Brucella* sp. by laboratory workers (4) and failure to work with *Brucella* isolates in a biological safety cabinet often result in a laboratory-acquired infection (130). *Brucella* spp. are isolated from blood, tissue, cerebrospinal fluid, semen, and urine. In the early reports, most large outbreaks occurred in research facilities, among people working with liquid cultures. Transmission often occurs via production of infectious aerosols but can also occur from direct contact. Person-to-person transmission from an infected laboratory worker to a spouse has been documented, presumably through sexual intercourse (116).

***Burkholderia* (*Pseudomonas*) *pseudomallei*.** Cases of laboratory-associated melioidiosis have been reported sporadically since 1950 (19, 110). Of the most recent cases, one was associated with exposure to an aerosol and concomitant skin exposure (43) and one was associated with exposure to an aerosol (125). Ashdown (3) reported the serological conversion of three laboratory workers in one hospital following subclinical infections. Since the laboratory was located in an area where melioidosis was endemic, it also was proposed that the infections may have been environmentally acquired. The primary hazards for laboratory workers arise from direct contact with cultures and infectious samples and from exposure to infectious aerosols. The risk of infection is presumably greater for workers in areas where the disease is not endemic, because they lack experience working with *B. pseudomallei.*

***Chlamydia* spp.** *Chlamydia psittaci* , *C. trachomatis*, and *C. pneumoniae* are all potential hazards for laboratory workers. In Pike's review (110), chlamydial infections were common and were associated with the highest mortality rate. Most of the reported cases were psittacosis that occurred before 1955, but sporadic laboratory infections with *C. psittaci* and *C. trachomatis* have continued to occur (7, 93, 124). To date, there are no documented cases of laboratory-acquired infections by *C. pneumoniae*, but few researchers are working with the organism.

Exposure to infectious aerosols while working with *C. psittaci*-infected birds or their tissues in animal research facilities and with blood, tissue, and sputum from infected humans poses the greatest hazard to laboratory workers. The risk from *C. trachomatis* occurs from mucous membrane exposure to conjunctival and genital specimens and lymph node tissue from infected individuals.

***Francisella tularensis*.** Tularemia was the third most common bacterial infection reported by Pike (110) in 1976, but most of the cases occurred at research laboratories where *F. tularensis* was studied. Few cases were reported from clinical laboratories. This probably reflects the overall low incidence of tularemia in the U.S. population. The greatest hazard to laboratory workers is from exposure to infectious aerosols generated from cultures. Infection also has occurred following contact of the skin and mucous membranes with infectious material.

***Leptospira* spp.** *Leptospira* spp. are found in a variety of mammals, including livestock, dogs, wildlife, and laboratory animals, and they therefore pose a greater risk to laboratory workers in animal facilities (34, 93). Pike (110) reported 67 laboratory-associated cases of leptospirosis and 10 deaths. Infection related to occupational exposure usually is caused by accidental parenteral inoculation, direct or indirect contact with cultures or infected materials (especially urine), and animal bites (40, 142, 147).

***Mycobacterium tuberculosis*.** Because the rate of new cases of tuberculosis (especially infections from multidrug-resistant strains) began to rise in 1986 (138), federal agencies have instituted regulations to prevent the transmission of tuberculosis from patients to HCW. The documentation of a case of laboratory-acquired tuberculosis is difficult because the source of the infection is often unclear, as a result of the potential for exposure outside of the workplace and the long incubation period before the development of symptomatic disease (19). The incidence of tuberculosis in laboratory personnel is estimated to be three to nine times that in individuals in other occupations (63, 115, 122). The annual incidence of tuberculosis for laboratorians employed in Utah was 0.3 infection per 1,000 persons (73). The survey of British laboratory personnel by Grist (49, 51) and Grist and Emslie (52–55) from 1979 to 1989 reported an incidence that varied from 0.035 to 0.56 infection per 1,000 persons. Overall, the incidence of tuberculosis is declining in British laboratory workers and infection now occurs primarily in personnel associated with anatomic pathology. Muller (96) reported an incidence of 26.3 infections per 1,000 persons based on a survey of 77 tuberculosis laboratories in Germany, Austria, and Switzerland. This was approximately 100 times the frequency observed in the general population.

Most cases of laboratory-acquired tuberculosis arise from processing specimens obtained from infected humans. Naturally or experimentally infected nonhuman primates and other animals also are potential sources of tuberculosis for animal handlers and animal laboratory personnel (34, 93, 142).

M. tuberculosis is isolated from a variety of clinical specimens including sputum, urine, tissue, stool, and other body fluids. Manipulation of specimens or cultures that generate aerosols is the most important risk factor for acquiring tuberculosis in the laboratory. Aerosolization occurs frequently during autopsies, preparation of frozen sections of infected tissue, and procedures involving liquid cultures (13, 142). Aerosols present the greatest hazard, but infection also can occur from cutaneous injuries (93, 96). The high infectivity of *M. tuberculosis* is related to the low infective dose for humans (i.e., a 50% infectious dose of <10 bacilli) (119, 120).

Stool pathogens. Laboratory-associated cases of salmonellosis and shigellosis are well documented in all published reports and surveys (19, 53–55, 73, 93, 110, 111). The incidence of shigellosis in laboratory workers in Utah was 0.7 infection per 1,000 persons for all clinical laboratory workers and 5.4 infections per 1,000 workers for clinical microbiologists. In Great

Britain, the overall incidence of *Salmonella* and *Shigella* infections is 0.137 and 0.322 infection per 1,000 persons, respectively. As expected, most of the workers affected were microbiologists. The number of cases of infections with enteric pathogens is most probably grossly underreported. *Salmonella typhi* causes the most serious infections of all the enteric pathogens. Gastroenteritis due to *Vibrio* spp., *Campylobacter* spp., or *Escherichia coli* is rarely a laboratory-acquired infection.

The primary risk of infection for laboratory personnel is from the ingestion and less frequently from the parenteral inoculation of the organism or infectious material. Another problem associated with the laboratory acquisition of the agent is transmission from the infected laboratory worker to persons outside of the microbiology laboratory (9, 10). *Salmonella* spp. occur in a variety of domestic and wild animals, which therefore pose a risk to workers in research facilities. Humans appear to be the only significant reservoir for *Salmonella typhi* and *Shigella* spp., although nonhuman primates can acquire shigellosis from humans and then serve as a source of infection. *Salmonella* spp. can be isolated from feces, blood, urine, and bile (*Salmonella typhi*), while *Shigella* spp. are present primarily in feces (142). Numerous cases of laboratory-acquired salmonellosis and shigellosis have resulted from handling proficiency test strains or from working with isolates for educational purposes (9, 69, 132).

Treponema pallidum. Laboratory-acquired syphilis is rare in relation to the amount of diagnostic and research work that is performed with *T. pallidum*. Pike (110) listed 15 cases of infection by *T. pallidum*. For laboratory personnel, the primary risk is from direct contact with material collected from syphilitic lesions and possibly blood from an infected individual (142).

Rickettsial Agents

Coxiella burnetii. Q fever is a commonly reported laboratory-associated infection and often causes multiple infections in the same laboratory (19, 34, 59, 110). Many reports originate from animal research facilities, especially facilities involved with research on sheep, which are often asymptomatic carriers of the agent, or facilities which propagate *C. burnetii*. The most likely sources of infection of laboratory workers are exposure to infectious aerosols and parenteral inoculation. *C. burnetii* is found in nearly all specimens obtained from infected humans or animals (142).

Other rickettsial agents. Early work with the agents of epidemic and murine typhus, scrub typhus, and Rocky Mountain spotted fever caused numerous laboratory-acquired infections and significant mortality (19, 110). In Pike's survey (110), all but 3 of the 23 fatal rickettsial infections occurred prior to 1945. Oster et al. (107) reported nine cases of Rocky Mountain spotted fever that occurred over a 6-year period (1971 to 1976). The risk for laboratory personnel is from exposure to infectious aerosols, accidental inoculation, or exposure to bites by infected ectoparasites. The most effective approach to diminishing the severity of a laboratory-acquired infection is early antibiotic treatment of a febrile illness in the employee (142).

Viral Agents

Common blood-borne viruses: hepatitis viruses and HIV. Numerous infectious agents (other than hepatitis viruses and HIV) may cause infections in laboratory workers following exposure to contaminated blood, and they are discussed elsewhere in this manuscript. In an excellent discussion of blood-borne pathogens, Hunt (71) has categorized these agents into three transmission groups: (i) agents transmitted through percutaneous or mucous membrane exposure to blood, (ii) agents transmitted through blood transfusions or tattoos, and (iii) agents transmitted via highly concentrated material or infected animals. Viral agents transmitted through blood and body fluids currently cause most of the occupationally acquired infections in laboratory employees and HCW. Because the degree of risk correlates with the frequency and extent of blood or body fluid exposure, clinical laboratory workers are at high risk for occupational exposure through their daily contact with blood and blood products (60). Of the common blood-associated viruses (hepatitis B virus [HBV], hepatitis C virus [HCV], and HIV), HBV infection is the most frequent laboratory-acquired infection. In addition, individuals infected with HBV are at increased risk of infection with hepatitis D virus, which requires HBV for replication.

TABLE 2. Occupationally acquired AIDS cases or HIV infections reported to CDC through 1992[a]

Occupation	No. (%) of occupational transmissions[b]
Laboratory technician	25 (24.8)
Nurse	26 (25.7)
Physician	13 (12.8)
Medical technician/paramedic	7 (6.9)
Dentist/dental technician	6 (5.9)
Health aide/attendant	6 (5.9)
Housekeeper/maintenance worker	6 (5.9)
Morgue technician	3 (3.0)
Technician/therapist	3 (3.0)
Respiratory therapist	2 (2.0)
Surgical technician	2 (2.0)
Other HCW	2 (2.0)
Total	101

[a] Adapted from reference 15.
[b] HCW who had documented seroconversion after occupational exposure to HIV and HCW in whom occupational transmission was possible but HIV seroconversion was not documented.

Of the hepatitis viruses, HBV continues to cause significant morbidity and mortality in HCW (98, 118). The incidence of HBV infections in all HCW in the United States is estimated at 3.5 to 4.6 infections per 1,000 workers, two to four times that in the general population (26, 118, 154). The risk to laboratory workers is approximately 10 times that to the general public (58, 73) and almost 3 times that to other hospital employees (26). From 1974 to 1978, HCW in Denmark contracted viral hepatitis at a rate approximately five times that of the general population (129). In Great Britain, the attack rate of hepatitis infections declined from a high of 1.61 infections per 1,000 persons in 1971 to 0 to 0.035 infection per 1,000 persons from 1986 to 1989 (45, 54, 55).

Today, the greatest concern among HCW is that of becoming infected by HIV from exposure to contaminated blood and body fluids in the workplace. While it is difficult to assess the precise risk of occupationally acquiring HIV without a long-term prospective study, a number of reports have estimated the risk. Reports of HIV-infected research personnel, clinical laboratory workers, and other HCW submitted to Centers for Disease Control and Prevention (CDC) through September 1992 indicate that laboratory workers (25%) and nurses (26%) had the greatest number of documented or possible occupational transmissions (Table 2) (15). For 1,534 HCW enrolled in a prospective study on occupational exposure to HIV, most of the exposures to blood or body fluids occurred among nurses

(63%), laboratory workers and phlebotomists (17%), and physicians and medical students (15%) (90, 118). The most common exposure was from needlestick injuries (80%). Other exposures to blood or body fluids included cuts with sharp objects (8%), contamination of an open wound (6%), and contamination of mucous membranes. The infection rate in one report was calculated to be approximately 0.3% (3 infections per 1,000 HIV exposures), but the authors emphasized the difficulties inherent in estimating occupational risks for HIV infection (6). Hunt (71) estimated the relative risk for occupationally acquired infection after exposure to infected blood at 0.25% (2.5 infections per 1,000 HIV exposures). In 1989, the Occupational Safety and Health Administration (OSHA) estimated that the risk of seroconversion following a needlestick exposure to HIV-infected blood was between 3.5 and 4.7 infections per 1,000 exposures, with 95% upper confidence limits of 9 and 14 infections per 1,000 exposures, respectively (102). For research and production workers, the risk was estimated to be 4.8 infections per 1,000 person-years, with a 95% upper confidence limit of 24 per 1,000. Various reports have placed the rate of seroconversion following a needlestick injury at between 0 and 0.9%, with an average of 0.4% (36, 98). This compares with a risk of 6 to 30% for acquiring HBV infection (98). In general, the risk of infection increases as follows on the basis of the type of exposure incident: contamination of intact skin < mucous membranes < solid needle < hollow-core needle < massive parenteral exposure (98).

The occupational risk of HCV infection is unknown but is believed to be in the range of 2 to 10%. Currently, the prevalence of antibody to HCV in HCW is slightly higher than that in the general public (142).

The laboratory transmission of HIV, HBV, and presumably HCV occurs via direct contact of contaminated blood, blood products, and body fluids with nonintact skin and mucous membranes, and, most importantly, via percutaneous inoculation (needlesticks and cuts). The difference in the risk of a laboratory-associated infection by each virus is related to the concentration of virus in the blood sample. HBV can be present at concentrations of 10^8 to 10^9 infectious particles per ml, HCV can be present in the range of 10^2 to 10^3 infectious particles per ml, and HIV can be present at levels of 10^0 to 10^4 infectious particles per ml (93). It has been suggested that transmission may be related also to the freshness of the clinical specimen, the health of the exposed worker, the stage of the patient's illness, and the severity of the exposure (71, 118).

Numerous types of specimens may contain HBV, HCV, and HIV. HBV (and presumably HCV) has been recovered from blood and blood products, semen, saliva, urine, cerebrospinal fluid, and tissue. In addition to the specimens listed for HBV, HIV has been isolated from vaginal secretions, breast milk, and a variety of other body fluids.

Another route of HBV transmission involves indirect contact with contaminated items in the laboratory (e.g., bench surfaces, test tubes, and telephones), because the virus remains viable in dried blood for up to 7 days at 25°C (98, 142). Transmission of HIV via this route has not been documented, possibly because the viral inoculum in blood is lower than in HBV infection and because HIV appears less stable than HBV in the laboratory environment. Desiccation of the virus causes a rapid decline in the number of viable virions. Viability in other environments ranges from 1 to 7 days in cell-associated cultures (e.g., tissue and blood cultures), 6 days in cadavers, 15 days in cell-free medium, and extended periods at 4°C (98). HCV is not very stable to storage at room temperature (142).

Herpesvirus simiae (B virus). Herpesvirus simiae is common in the Old World monkeys of the *Macaca* genus and usually causes mild or inapparent infections in monkeys, however, infection of humans may result in a lethal encephalomyelitis. There have been 36 reported cases of B virus infection in humans through 1992. Thirty of these individuals suffered severe encephalomyelitis (23), and 23 of them died. The fatality rate has declined with the availability of antiviral therapy. The greatest risk of B virus infection is among monkey handlers and other persons having direct contact with macaques. Potentially, laboratory personnel may be exposed to the virus through parenteral, mucosal, or wound contact with infected rhesus monkey kidney cells or infected tissues (68, 77, 153).

Lymphocytic choriomeningitis virus. Lymphocytic choriomeningitis virus naturally infects rodents (e.g., mice, hamsters, and guinea pigs) and other laboratory animals, including nonhuman primates (19, 27, 75, 142). In addition, laboratory-associated infections may arise from work with contaminated cell lines (44). Lymphocytic choriomeningitis virus is present in nearly all body fluids, secretions, blood, and tissues of infected animals. Risks to laboratory workers arise from parenteral inoculation, infectious aerosols, and contamination of skin or mucous membranes with infectious material. Most laboratory-acquired infections have occurred in research laboratories.

Parvovirus B19. At least nine probable laboratory-associated infections by parvovirus B19 have been documented by different laboratories (18, 128). Infected individuals were working with material containing parvovirus B19. The mode of transmission was presumed to be an infectious aerosol.

Vesicular stomatis virus. Laboratory-associated infections with vesicular stomatitis virus occur in humans who work with infected livestock or tissue. Pike (110) reported 40 cases. Working with laboratory-adapted strains rarely results in infections (142). Vesicular stomatitis virus is present in vesicular fluid, tissues, and blood of infected animals, and laboratory infections are caused by parenteral inoculation, exposure to an infectious aerosol, and contamination of skin and mucous membranes.

Arboviruses, arenaviruses, and filoviruses. As of 1991, 535 arboviruses have been registered by the American Committee on Arthropod-Borne Viruses and are assigned to biosafety level 1 to 4 (BSL-1 to BSL-4) (142). Many of these viruses, arenaviruses, and filoviruses have caused laboratory-acquired infections, often associated with significant morbidity and mortality (19, 110, 142, 156). Each virus is assigned to a BSL on the basis of its mode of transmission (aerosol versus nonaerosol), the frequency and severity of laboratory-associated infections, and the availability of a vaccine. Viruses are classified as a BSL-3 risk if the laboratory experience necessary to assess the risk is inadequate. The viruses assigned to BSL-3 category may be present in blood, urine, cerebrospinal fluid, and other exudates. Risks are from exposure to infectious aerosols, accidental inoculation, and contact with skin or mucous membranes. More-virulent agents are assigned to the BSL-4 category; these include Congo-Crimean hemorrhagic fever, Ebola, Guanarite, Jurin, Lassa, Machupo, and Marburg viruses and the viruses associated with the tick-borne encephalitis virus complex. These BSL-4 viruses are present in blood, urine, respiratory and throat secretions, semen, and tissue of humans and animals (rodents and nonhuman primates), as well as arthropods. Clinical specimens from persons suspected of being infected with one of these agents should be submitted to a BSL-4 facility.

Hantaviruses. Recently, in the southwestern United States, one or more newly identified hantaviruses were associated with the hantavirus pulmonary syndrome (16). Other viruses in this group include the Hantaan virus, Dobrava virus, Puumala virus, and Seoul virus, all of which cause a hemorrhagic fever

with renal syndrome and are found in various parts of the world. The aerosol transmission of hantaviruses from rodents to humans is well documented (78, 141). Other routes of infection include ingestion, contact of infectious materials with mucous membranes and skin, animal bites, and working with cell cultures or infected animal tumors (16, 78, 86). To date, hantaviruses that cause hemorrhagic fever with renal syndrome or hantavirus pulmonary syndrome have not been transmitted to laboratory workers via clinical laboratory specimens, but viral RNA has been detected in blood and plasma specimens (16). At this time, BSL-2 practices are recommended for handling clinical specimens and BSL-3 practices are recommended for handling infected tissue and viral cell culture.

Other viral agents. Laboratory workers are exposed to a variety of other viral agents such as hepatitis A virus, hepatitis E virus, influenza virus, respiratory syncytial virus, enteroviruses, adenovirus, mumps virus, measles virus, and herpesviruses. Although small numbers of laboratory workers have been infected, these viruses do not appear to pose a significant risk for occupational acquisition of the agent (19, 142, 156). Laboratory-acquired rabies is extremely rare. Two cases occurred following exposure to infectious aerosols in a research and vaccine production laboratory (142). Immunization is recommended for all individuals working with the rabies virus, because it is a potentially fatal infection.

Fungal Agents

Blastomyces dermatitidis. Both laboratory-acquired cutaneous blastomycoses following accidental parenteral inoculation and pulmonary infections following presumed inhalation of conidia have been reported (5, 19, 24, 84, 142). Few cases were reported after 1980. The risk to laboratory personnel is related to accidental inoculation and infectious aerosols.

Coccidioides immitis. Numerous reports of laboratory-associated coccidioidomycosis are documented in the literature published prior to 1980 (19, 110, 142). Although cutaneous infections from accidental inoculation are documented, most laboratory-associated infections are caused by inhalation of the infectious arthroconidia. As with other infections that are endemic to a geographic area, it is often difficult to determine whether the infection in a laboratory worker represents an occupational or environmental exposure.

Dermatophytes. Most dermatophyte infections have occurred in laboratory workers who have contact with an infected animal or its bedding; they are usually not associated with handling clinical specimens (19, 34, 93, 110, 142).

Histoplasma capsulatum. Most laboratory-associated cases of histoplasmosis occur through inhalation of conidia produced by the mold form (19, 97, 110, 142), although cutaneous infections have occurred following accidental inoculation (139, 140). Again, this is a geographically restricted fungus, and it is difficult to confirm laboratory versus environmental acquisition.

Sporothrix schenckii. Most of the reported cases of laboratory-acquired sporotrichosis occurred before 1960 and involved cutaneous lesions arising from accidental injections of infectious material or contamination of the skin or mucous membranes (19, 110, 142).

Other fungal agents. There are no reports of laboratory-acquired infections with other fungal agents except *Cryptococcus neoformans* (41) and *Penicillium marnefii* (126).

Parasitic Agents

The increased research interest in parasitic diseases, the availability of world travel, and the susceptibility of immunocompromised patients to parasites have combined to place more persons working in research and clinical laboratories at risk for acquiring a parasitic infection. Laboratory-acquired infections with *Ascaris* spp., *Strongyloides* spp., *Enterobius* spp., hookworm, *Fasciola* spp., *Schistosoma* spp., *Entamoeba* spp., *Giardia lamblia*, coccidia, and *Cryptosporidum parvum* have been reported infrequently in clinical laboratories (8, 20, 66, 85, 85a, 110, 142, 144). In animal research facilities, *G. lamblia* and *C. parvum* infections are common, especially among persons handling the infected animal (34, 67, 112, 142). *C. parvum* is resistant to most disinfectants and can remain viable for months in a cool, moist environment (85, 85a). No laboratory-associated infections with cestodes have been documented. The most common laboratory-acquired parasitic infections involve the protozoal agents that cause severe and potentially life-threatening disease: *Toxoplasma gondii*, *Plasmodium* spp., *Trypanosoma* spp., and *Leishmania* spp. Laboratory-acquired babesiosis has not been reported but is possible because of the high rate of parasitemia in erythrocytes (71, 85, 85a, 142).

Toxoplasma gondii. Toxoplasmosis is the most common laboratory-associated parasitic infection (19, 34, 65, 66, 71, 110, 142). The majority of laboratory infections occurred in research facilities from accidental ingestion, inoculation, or contamination of a mucous membrane by organisms, but a significant number of infected individuals do not recall a laboratory accident (31, 66, 94, 108, 113). The use of live organisms in the Sabin-Feldman dye test is presumed to be a significant hazard to laboratory workers, but Parker and Holliman (108) did not detect any significant serological difference between laboratory workers in a *Toxoplasma* reference unit, laboratory workers in a microbiology laboratory, and residents in the same geographical area.

***Plasmodium* spp.** Laboratory-acquired infections with *Plasmodium falciparum*, *Plasmodium vivax*, and *Plasmodium cynomolgi* have been reported (19, 22, 29, 65, 66, 76, 95, 110, 142, 155), as well as non-transfusion-related transmission from patients to HCW (85, 85a). The infections were caused by contact with infected blood (human or animal) or parasite culture through accidental needlestick or contamination of open wounds or were caused by an infected vector from a mosquito colony.

***Leishmania* spp.** Laboratory-acquired infections with *Leishmania tropica*, *Leishmania donovani*, and *Leishmania braziliensis* have been reported (19, 28, 35, 65, 66, 85, 85a, 110, 121, 123, 142). The infections were acquired from infected animals or from parasite cultures, by exposure through accidental needlesticks, and by contamination of mucosal membranes and preexisting skin abrasions.

***Trypanosoma* spp.** Over 50 cases of laboratory-associated *Trypanosoma cruzi* infections have been documented (11, 19, 65, 66, 81, 85, 85a, 142). Laboratory-associated infections with *Trypanosoma rhodensiense* and *Trypanosoma gambiense* are rarely documented (65, 114). Infections from trypanosomes are acquired by handling *Trypanosoma* cultures or blood specimens from infected humans or animals, and they also result from accidental parenteral inoculation, contamination of skin or mucous membranes, and possibly inhalation of infectious aerosols.

DISEASE TRANSMISSION AND INFECTION

The fact that laboratory workers, especially those in microbiology, are at greater risk of becoming infected than is the general population has focused attention on the factors associated with laboratory-acquired infections. These factors include the method of transmission, the development of infec-

TABLE 3. Routes of exposure associated with laboratory work

Route	Microbiological practice
Ingestion	Mouth pipetting Splashes of infectious material into mouth Contaminated articles or fingers placed in mouth Consumption of food in workplace
Inoculation	Needlestick accidents Cuts from sharp objects Animal and insect bites and scratches
Contamination of skin and mucous membranes	Spills or splashes into eyes, mouth, nose Spills or splashes on intact or nonintact skin Contaminated surfaces, equipment, articles
Inhalation	Numerous procedures that produce aerosols

TABLE 4. Zoonotic pathogens of laboratory animals[a]

Animal	Pathogen	Prevalence in animal
Rodents (rats,[b] mice,[c] guinea pigs,[d] hamsters,[e] rabbits[f])	Lymphocytic choriomeningitis virus[b,c,d,e]	Rare[d]/low[b,c,e]
	Leptospira spp.[b,c,d,e,f]	Rare[e,f]/low[b,c,d]
	Salmonella spp.[b,c,d,e,f]	Low[b,c,d,e]/moderate[f]
	Dermatophytes[b,c,d,e,f]	Rare[e]/low[b,c,d,f]
	Campylobacter spp.[d,e,f]	Rare[f]/moderate[d]/high[e]
	Cryptosporidium spp.[c,d]	Low[c,d]
	Giardia spp.[c]	Low[c]
	Hantavirus[b]	Rare[b]
	Hymenolepis nana[c]	Low[c]
Dogs,[g] cats[h]	Cat scratch fever agents[h]	Low[h]
	Brucella spp.[g]	Low[g]/moderate[g]
	Campylobacter spp.[g,h]	Low[g]/moderate[g,h]
	Salmonella spp.[g,h]	Low[g]/moderate[h]
	Giardia spp.[g]	Moderate[g]
	Dermatophytes[g,h]	Low[g]/moderate[g,h]
	Toxoplasma spp.[h]	Moderate[h]/high[h]
	Coxiella spp.[h]	Moderate[h]
	Toxocara spp.[g,h]	Low[g,h]
	Capnocytophaga spp.[g]	Low[g]
	Pasteurella spp.[g,h]	Moderate[g,h]
	Leptospira spp.[g]	Low[g]
	Rabies virus[g,h]	Rare[g,h]
Sheep, goats	*Coxiella* spp.	Moderate
	Orf virus	Low/moderate
	Leptospira spp.	Low/moderate
	Salmonella spp.	Low/moderate
	Cryptosporidium spp.	Low
Nonhuman primates	Herpesvirus simiae	Moderate/high
	Hepatitis A virus	Low
	Measles virus	Moderate
	Cytomegalovirus	Low
	Rabies virus	Low
	Campylobacter spp.	Moderate
	Salmonella spp.	Moderate
	Shigella spp.	Moderate
	M. tuberculosis	Low
	Yersinia spp.	Low/moderate
	Giardia spp.	Low/moderate
	Cryptosporidium spp.	Low
	Dermatophytes	Low
	Marburg, Ebola, and monkeypox virus	Rare
	Simian immunodeficiency virus	Low

[a] Adapted from references 19 and 34.
[b–h] Identifies the animal associated with the pathogen and prevalence.

tion in the host, the route and source of infection, and the laboratory environment (e.g., ventilation, equipment, and procedures). Early investigators recognized that some microorganisms (e.g., *Brucella* spp. and *M. tuberculosis*) cause more infections than others (e.g., *E. coli*) and that some equipment, procedures, and tasks are associated with a higher incidence of infections in laboratory workers; they therefore explored measures to prevent infections associated with specific organisms and tasks. In industry, the identification and management of potential safety problems have been approached through job safety analysis and hazard analysis critical control point approaches, which are similar to the approach currently used to monitor quality assurance in the health care setting.

Routes of Exposure

The most common routes of exposure associated with laboratory work are listed in Table 3. Ingestion of microorganisms occurs through mouth pipetting, transfer of organisms to the mouth from contaminated items such as pencils or fingers, consumption of food and drink in the laboratory, and accidental splashes that fall into the mouth. Specimen collection, specimen processing, and manipulation of cultures during routine laboratory operations frequently contaminate containers, bench tops, equipment, laboratory requisitions, and fingers from spillage of infectious material and generation of aerosols. Eating, drinking, and applying cosmetics in the laboratory pose such a hazard that these activities are universally prohibited. Food should not be brought into a laboratory or stored in refrigerators designated for the storage of clinical specimens or cultures.

The accidental parenteral inoculation of infectious material is one of the leading causes of laboratory-associated infections (19, 33, 110). Nearly all microorganisms can produce an infection following penetration of the skin by contaminated needles, scalpels, or broken glass. Laboratory workers in animal research facilities are also exposed to infection following animal or insect bites and scratches. Infections are caused by naturally occurring zoonotic pathogens (Table 4) or by the infectious agents inoculated into animals for experimental purposes. The experimental use of nonhuman primates is especially hazardous to animal handlers, because animal bites and scratches may transmit herpesvirus simiae and simian immunodeficiency virus.

The intact skin is an excellent barrier to most pathogenic microorganisms, but most skin contains small cuts and abrasions that serve as portals of entry for organisms picked up from contaminated objects or from accidental spills and splashes. The mucous membranes of the eyes, mouth, and nasal cavity are especially vulnerable to splashes, sprays, hand-to-eye, hand-to-nose, and hand-to-mouth transmissions.

Numerous procedures in the laboratory generate aerosols that cause infection when inhaled (Table 5) (19, 39, 79, 133). Depending on their size, droplets will either settle out of the air quickly (>0.1 mm in diameter) or evaporate in 0.4 s (<0.05 mm in diameter) (19). The microorganisms in these latter droplets (droplet nuclei) will remain suspended and move

TABLE 5. Laboratory activities that generate aerosols

Laboratory activity	Microbiological practice
Inoculating-loop manipulation	Subculturing and streaking culture "Cooling" a loop in culture media Flaming a loop
Pipette	Mixing microbial suspensions Pipette spills on hard surfaces
Needle and syringe manipulation	Expelling air Withdrawing needle from stopper Injecting animals Spray created when needle separates from syringe
Others	Centrifugation Using blenders, shakers, sonicators, and mixing instruments Pouring or decanting fluids Opening culture containers Spillage of infectious material Lyophilization and filtration under vacuum Egg inoculation and harvesting

around rooms and buildings on air currents. Other materials that act as droplet nuclei include lyopholized cultures, dried material on benches and stoppers, and bacterial and fungal spores. Droplet nuclei of <5 μm in diameter are able to reach the alveoli of the lung, while particles of >5 μm in diameter are trapped on the mucous membranes of the airways (39, 64).

Aerosols can be removed from a room within 30 to 60 min with a ventilation system that produces an air exchange rate of 6 to 12 changes per hour (39). The major outbreaks of laboratory-acquired infections presumed to be caused by infectious aerosols have been associated with *Brucella* spp., *Coxiella burnetii* (Q fever), *Chlamydia psittaci* (psittacosis), and *M. tuberculosis*. Most organisms designated for handling in BSL-3 and BSL-4 exhibit the potential for respiratory transmission via aerosols.

Sources of Laboratory-Associated Infections

Pike (110) tabulated the most common sources of infections from published literature and survey data through 1976. Of the 3,921 laboratory infections reported, 59% occurred in research laboratories, compared with 17% in diagnostic laboratories. At that time, approximately 70% of laboratory infections resulted from work with the infectious agents (21%) or animals (17%), exposure to infectious aerosols (13%), and accidents (18%). Less frequent sources of infection included clinical specimens (7%), autopsies (2%), and contaminated glassware (1%). The source of the laboratory-associated infection was not apparent in 20% of the cases. It is reasonable to assume that many of these laboratory-acquired infections of unknown origin were caused by exposure to an infectious aerosol.

Laboratory accidents were the second greatest source of infections; nearly 70% were associated with needlesticks (25%), splashes or spills (27%), and cuts from sharp objects (16%) (Table 6). At the time of Pike's survey, 13.1% of accidents were still attributable to mouth pipetting. The National Animal Disease Center reported similar sources of infections, but in that study the total number of laboratory-associated infections was much smaller and the source was not apparent in 73.5% of the infections. Because the spectrum of natural zoonotic pathogens in laboratory animals is large (Table 4), researchers who work with animals are at greater risk for acquiring an infection (19, 93, 110).

TABLE 6. Types of accidents associated with laboratory-acquired infections[a]

Accident	No. (%) of infections reported by:	
	Pike[a]	NADC[b]
Splashes and sprays	188 (26.7)	2 (5.9)
Needlesticks	177 (25.2)	3 (8.8)
Sharp objects	112 (15.9)	2 (5.9)
Animal or ectoparasite bite/scratch	95 (13.5)	2 (5.9)
Mouth pipetting	92 (13.1)	0
Other, unknown	39 (5.5)	25 (73.5)
Total	703	34

[a] Adapted from reference 110.
[b] NADC, National Animal Disease Center; adapted from reference 93.

Proficiency test samples, stock cultures, and quality control samples are not usually identified in the published tables as a source of infections (9, 19, 52, 55, 69, 73). However, this material has been identified as a common source of infection over the years, especially infections associated with the handling of *Salmonella* and *Shigella* spp. All stock cultures should be labeled by the user as to the appropriate BSL risk category, so that laboratory personnel who handle the organisms will use the appropriate containment practices.

BIOSAFETY IN THE MICROBIOLOGY LABORATORY

The most hazardous agent in the laboratory is a microorganism that is frequently associated with laboratory infections, can be transmitted by a variety of routes (especially by aerosols), and produces a fatal infection with a low infectious dose. As the trend toward decentralization of the laboratory continues, the laboratory work performed in clinics, offices, and at the bedside by less experienced personnel will expose more people to potentially infectious biological specimens. In the last decade, the number of guidelines and regulations that affect the safe operation of clinical, research, and industrial laboratories where infectious agents are handled has increased dramatically. These guidelines and regulations affect all aspects of the laboratory operation from the licensure of clinical laboratories to work with various infectious agents, packaging and shipment of infectious material, disposal of biohazardous waste, and prevention of employee exposure to blood-borne pathogens (92).

The federal agencies that regulate safety-related issues in microbiology laboratories are the OSHA, the National Institute for Occupational Safety and Health (the research arm of OSHA), and the Environmental Protection Agency. Compliance with the standards produced by these agencies is mandatory, and failure to comply results in fines and other penalties. The standards with the greatest impact on microbiology laboratories and health care facilities are the blood-borne pathogens standard (103), the policy on exposure to tuberculosis (104, 105), and the handling of biohazardous waste (143). In addition to the federal agencies, states and local jurisdictions often regulate exposure to infectious agents, licensure of laboratories, and disposal of biohazardous material.

Other agencies and associations that set standards that pertain to safety in the workplace include the Joint Commission on Accreditation of Healthcare Organizations, the College of American Pathologists, the National Committee on Clinical

Laboratory Standards, CDC, and the National Institutes of Health (NIH). Although the recommendations proposed by these groups are not mandated by law, they do represent a consensus of opinions by peers and therefore define a "standard of practice" that laboratories should follow. Current information on the effectiveness of universal precautions for reducing risk suggests that adherence to the guidelines promulgated by the various regulatory agencies decreases the risk of occupational exposure to infectious agents and therefore contributes to a safer work environment (30, 142, 157). Additional studies are needed to evaluate the effectiveness of other safety measures implemented or mandated in the laboratory.

With the implementation of the OSHA regulations, the facility administration is responsible for the development and institution of safety procedures and employee training programs that minimize the occupational risk from a laboratory-associated infection on the basis of present or anticipated infectious hazards. The strategy for minimizing the occupational exposure of laboratory workers, other facility employees, and the surrounding environment to infectious agents is based on the concept of microorganism containment, which includes physical factors (e.g., facility design and safety equipment), standard microbiological practices, and administrative controls (33, 37, 39, 100, 142). The microorganisms encountered and procedures performed in laboratories are stratified by risk into BSL-1 to BSL-4. Each increasing BSL number implies increased occupational risk from exposure to an agent or performance of a procedure and therefore is associated with more stringent control and containment practices. Primary containment provides physical separation of the infectious agent from the laboratory worker. Primary barriers include strict adherence to microbiological practices and techniques and use of safety equipment such as biological safety cabinets (BSCs), safety centrifuge containers, and personal protective equipment (PPE) (e.g., gloves, masks, face shields and glasses, coats, and gowns). Secondary containment refers to the facility design and acts as a secondary barrier to protect all workers within the facility and to protect the outside environment.

Each facility should have a safety manual that is understood by the employees and an educated safety officer who is knowledgeable about the risks associated with different work practices. Management must provide a safe work environment, promote safety awareness through training programs, and demand adherence to safety procedures. Ultimately, the prevention of infection in the laboratory and the health care facility requires that management ensure that the occupational risks and consequences of infection are understood by all employees, that proven safety and microbiological practices are consistently observed by all workers, and that the employees use common sense when working with infectious material or infected patients on a daily basis.

Personal Risk Factors

Risk factors related to the individual employee must be considered when developing an overall safety program. These risk variables are of two general types: factors related to the immunocompetency of the individual, and factors related to behavior patterns and attitudes of employees, especially perceptions of safety and risk.

Employees with reduced immunocompetence are at increased risk of infection. The decreased immunocompetence may be hereditary, from the presence of disease (neoplastic or infectious), or from immunosuppressive therapy. Other factors that seem to decrease host resistance to infectious agents include age, race, sex, pregnancy, surgery (e.g., splenectomy or gastrectomy), diabetes, and lupus erythematosis. Prophylactic immunizations should be required for all at-risk laboratory workers when the benefits of vaccination outweigh the risks (e.g., hepatitis B, yellow fever, rabies, and poliomyelitis) (19, 98, 100, 103, 142). The vaccine administered to a worker or the refusal of vaccination by the employee should be documented. OSHA requires that employers provide HBV vaccination to all employees who are at risk for occupational exposure to bloodborne pathogens. A complete list of available vaccines and recommendations for vaccination is available (19, 136).

A safety program also provides medical surveillance to laboratory employees for infections that may result from exposure to agents encountered in the performance of routine duties (e.g., HIV and HBV serological tests, tuberculosis skin testing) and when early diagnosis reduces the risk of serious consequences of the infection (e.g., rickettsial infections) (142). Usually, the facility provides these services through an employee health service or contract with an outside organization.

The behavior patterns and attitudes of individuals toward safety programs influence their involvement in laboratory accidents that put themselves and fellow workers at risk (62, 109). Characteristics of persons who have few accidents include adherence to safety regulations, a respect for infectious agents, "defensive" work habits, and the ability to recognize a potentially hazardous situation. In contrast, persons involved in laboratory accidents tend to have low opinions of safety programs, to take excessive risks, to work too fast, and to be less aware of the infectious risks of the agents they are handling. Also, men and younger employees (17 to 24 years old) are involved in more accidents than women and older employees (45 to 64 years old). Gershon and Zirkin (38) provide an excellent discussion of the need to address behavioral factors in the development of an effective safety program. OSHA requires that all occupational injuries, illnesses, and incidents of potential exposure be recorded and reported (103). Any fatality or injury that hospitalizes five or more employees must be reported to OSHA within 48 h. Most safety programs require that all potential exposures or accidents be reported to the supervisor, who in turn reports to the appropriate individual in the organization. Personnel who display risk-prone behavior or are pregnant, immunocompromised, or immunosuppressed should be restricted from performing work with highly infectious microorganisms and, in some situations, be restricted to a low-risk laboratory.

Risk Assessment and Management

The quantitation of the occupational risk associated with working with an infectious agent or performing a specific task is difficult, because these data are not collected and analyzed in a consistent manner. Therefore, each task, procedure, or activity performed in the laboratory must be analyzed for its potential risk to the employee who performs the task. The job safety analysis or hazard analysis critical control point approach to risk assessment involves identifying the task, describing the individual steps of the task, assessing the potential hazards of each step, and implementing safety solutions for each hazard (72, 117, 131). Risk assessment should not focus on specific infectious agents but on developed standard practices for handling infectious material that will prevent the transmission of all pathogens.

Occupational risk assessment criteria are influenced by the type of manipulations or activities performed with the agent, the experience of the laboratory worker, and the infectious agent. The risk associated with the performance of procedures by the worker is related to the frequency of infection associ-

TABLE 7. Infectious dose of specific agents for humans[a]

Agent or disease	Inoculation route	Dose[b]
Anthrax	Inhalation	≥1,300
Campylobacter jejuni	Ingestion	10^2–10^6
Entamoeba histolytica	Ingestion	10–100 cysts
Escherichia coli	Ingestion	10^8
Giardia lamblia	Ingestion	10–100 cysts
Measles	Intranasal spray	0.2[c]
Plasmodium vivax	Intravenous	10
Q fever	Inhalation	10
Scrub typhus	Intradermal	3
Shigella flexneri	Ingestion	180
Shigellosis	Ingestion	10^9
Syphilis	Intradermal	57
Tuberculosis	Inhalation	<10
Tularemia	Inhalation	10
Salmonella spp.	Ingestion	10^5
Venezuelan equine encephalitis virus	Subcutaneous	1[d]
Vibrio cholerae	Ingestion	10^8

[a] Adapted from references 88, 119, 120, 149, and 150.
[b] Number of microorganisms that cause disease in 25 to 50% of volunteers.
[c] Median cell culture infectious dose.
[d] Animal infectious unit.

TABLE 8. Route of laboratory-associated infection with microorganisms[a]

Organism	Route of infection			
	Nonintact skin or mucosa contact	Inhalation	Ingestion	Animal contact
Bacteria				
Bacillus anthracis	X	X		X
Bordetella pertussis	X	X		
Borrelia spp.	X			X
Brucella spp.	X	X		X
Campylobacter spp.	X		X	X
Chlamydia spp.	X	X		
Coxiella burnetii	X	X		X
Francisella tularensis	X	X	X	X
Leptospira spp.	X	X	X	
Mycobacterium tuberculosis	X	X		
Burkholderia (*Pseudomonas*) *pseudomallei*		X		
Rickettsia spp.	X	X		X
Salmonella typhi	X		X	
Other *Salmonella* spp.	X		X	X
Treponema pallidum	X	X		
Vibrio cholerae	X		X	
Other *Vibrio* spp.	X		X	X
Yersinia pestis	X	X	X	X
Fungi				
Blastomyces dermatitidis	X	?		
Coccidioides immitis	X	X		
Cryptococcus neoformans	X	?		X
Histoplasma capsulatum	X	X		
Sporothrix schenckii	X			X
Dermatophytes				X
Viruses				
Hantavirus	X	X	X	X
Hepatitis viruses (HBV, HCV)	X			
Herpes simplex virus	X			
Herpesvirus simiae	X			X
HIV	X			
Lassa virus	X	X	X	X
Lymphocytic choriomeningitis virus	X	X	X	X
Marburg and Ebola viruses	X			X
Parvovirus		X		
Rabies virus	X	X		X
Venezuelan equine encephalitis virus	X	X		X
Vesicular stomatitis virus	X	X		X
Parasites				
Leishmania spp.	X			X
Plasmodium spp.	X			
Toxoplasma gondii	X		X	X
Trypanosoma spp.	X	X		

[a] Adapted from references 56, 142, and 152.

ated with a specific procedure (e.g., aerosol-generating activities) and with the type of laboratory (e.g., clinical, research, or industrial) where the procedures are performed. The risk of exposure tends to be greater in facilities (usually research or industrial) that handle large, highly concentrated quantities of infectious material.

The host susceptibility varies with immune status, age, pregnancy, race, and sex. The occupational risk to the individual can be decreased through provision of safety equipment, vaccination, availability of effective antimicrobial therapy, training in the handling of infectious material, and restriction of duties for highly susceptible individuals.

The most important determinant in risk assessment is the pathogenicity of the microorganism. The infectious agent is assigned to a specific risk class (BSL) by assessing its virulence (history of laboratory-acquired infections and incidence in the community), the consequence of infection (associated morbidity and mortality), its epidemic potential, the dose required to initiate infection (infectious dose), the route of infection or mode of transmission in both the laboratory and the community setting, the host spectrum including animal reservoirs and vectors, and the viability of the infectious agent in the laboratory environment. The most frequently reported laboratory-acquired infections prior to 1989 are listed in Table 1, the infectious dose for a limited number of pathogens is shown in Table 7, and the route of infection for some microorganisms is shown in Table 8. Additional information is available in the designated references.

Management of the risk associated with working with infectious agents is accomplished by administrative efforts, implementation of standard microbiological practices and safety equipment, engineering and facility design, and employee health programs (118). The facility administration has a legal responsibility to provide a safe work site for its employees by establishing a comprehensive safety program consisting of written policies, record keeping of exposures and infections, and employee training that provides laboratory workers with an understanding of the proper safety and infection control practices. The standard microbiological practices and safety equipment required by a laboratory are described in the guidelines established by CDC and NIH (33, 142). The design of a laboratory should protect the laboratory worker, the other individuals in the facility, and the external environment from an accidental release of microorganisms (21, 142). The barriers required to ensure protection depend on the potential hazard associated with working with a particular microorganism. In general, laboratories should be easily cleaned and should contain hand-washing sinks, an autoclave or other decontamination equipment, bench tops that are impervious to liquids and

TABLE 9. Summary of recommended BSLs for infectious agents[a]

BSL	Practices and techniques	Safety equipment	Facilities
1	Standard microbiological practices	None	Basic
2	BSL-1 plus biohazard warning signs, limited access, "sharps" precautions, and decontamination of identified wastes	Class I or II BSC and PPEs	Basic
3	BSL-2 plus controlled access, decontamination of all waste, protective clothing, and a baseline serum specimen	BSC or other containment device used for all manipulations of infectious agents; all necessary PPEs	BSL-2 plus negative air flow, double doors, air exhaust to outside
4	BSL-3 plus decontamination of all waste on exit, change to protective clothing before entering, and shower on exit	Class III BSC or other BSC in combination with a full-body, air-supplied positive-pressure suit for all procedures	BSL-3 plus separate building or dedicated systems

[a] Adapted from reference 142.

resistant to chemicals, and eyewash stations. Access is limited to authorized personnel only. As the risk for aerosol transmission increases, the laboratory ventilation system should produce a negative pressure with respect to outside corridors (i.e., air flows from corridors into the laboratory), should have approximately 10 to 15 air changes per hour, and should be exhausted to the outside (118).

All microbiology laboratories should contain a BSC. BSCs are the single most useful piece of equipment for the prevention of laboratory-acquired infections (148). The types of BSCs and their use have been described elsewhere (19, 82, 83, 89, 118, 142). In brief, a BSC protects the laboratory worker and the external environment from the infectious agent. To effectively use a BSC as a containment device, the worker must understand the principle of operation and limitations of the BSC.

All laboratory workers should have a preemployment medical examination that identifies prior exposure of the individual to infectious agents (e.g., *M. tuberculosis*) and underlying conditions (e.g., immunosuppression) that require special employment placement. The recommendation that the facility collect and store a baseline serum sample from all at-risk employees is not consistently followed in many laboratories (118).

Biosafety Principles and Practices

Biosafety levels. The four levels of biosafety for working with infectious agents and experimental animals are described in the CDC-NIH guidelines (142). Each BSL consists of combinations of equipment, procedures and techniques, and laboratory design that are appropriate for the type of laboratory (e.g., clinical, research, or industrial) and infectious agent handled. A concise summary of the recommended BSLs is presented in Table 9.

BSL-1 is recommended for teaching activities with agents that are not associated with infections. BSL-2 practices are used in clinical laboratories that manipulate agents that are not transmitted via aerosols (e.g., HBV, HIV, enteric pathogens, and staphylococci). BSL-3 is recommended when working with agents that are highly infectious and are transmitted via aerosols (e.g., *M. tuberculosis*, *Brucella* spp., and *Coccidioides immitis*) and for large-scale work with BSL-2 agents. BSL-4 practices are required when working with unusual agents that cause life-threatening infections. BSL-4 is available only in a limited number of facilities. A more detailed discussion of the BSLs can be found in other publications (33, 37, 142).

Microbiological procedures and techniques. Awareness of the risk of occupational exposure to infectious agents in laboratories and the common routes of infection (e.g., inhalation, ingestion, mucous membrane contact, direct inoculation, and contact with animals and insect vectors) has led to the development, modification, and use of equipment and procedures that minimize the risk associated with working with infectious microorganisms (32).

Exposure to blood-borne pathogens is a common microbiological hazard facing workers in all areas of the clinical laboratory. The use of a syringe and needle is the most hazardous laboratory procedure (100). Infections associated with needles and syringes occur through three routes: (i) inhalation of aerosols, (ii) contamination of fingers and the environment, and (iii) direct inoculation (19). Aerosols are generated when the user adjusts the volume in the syringe by expelling the contents into the air, when the needle is withdrawn from a rubber stopper, and when the needle separates from the syringe under pressure. The environment or operator's fingers can be contaminated from leaking syringes or from the injection site on animals inoculated with infectious agents. Many of these hazards are avoided by covering the needle and rubber stopper with a disinfectant-soaked pledget and cleansing the inoculation site, which reduces contamination of the injection site by 70% (82). Needle-locking syringes eliminate the accidental separation of the needle under pressure. Direct inoculation of the worker from an accidental needlestick is a leading cause of infections by the blood-borne pathogens. The use of needleless systems in hospitals for drawing blood samples and the mandatory disposal of needles and syringes in labeled, leak- and puncture-resistant containers have decreased the number of needlestick exposures of HCW.

Numerous laboratory procedures and equipment are considered a potential aerosol source (Table 5) (17). The use of a microbiologist's loop is a common source of aerosol generation and subsequent contamination of laboratory surfaces. Procedures that generate aerosols and contaminate surfaces include the spontaneous discharge of liquid from a loop, the streaking of media (particularly media with a rough surface), spreading material on a microscopic slide, "cooling" a loop in culture media, and heating a loop in an open flame. Alternative procedures to decrease this risk include the use of well-formed

loops on a short shaft, disposable plastic loops, glass spreaders, and electric incinerators and the use of a BSC when working with hazardous organisms.

Pipetting is another time-honored laboratory technique that is a potential hazard (19, 61). The risks associated with pipetting include ingestion via mouth pipetting, inhalation via aerosols produced by mixing a microbial suspension or spilling drops on hard surfaces, contamination of bench tops and fingers, and injuries from broken glass pipettes. These risks are diminished by using disposable plastic pipettes; banning mouth pipetting, "blowing" out the last drop, and mixing with a pipette (use a tube mixer); and working over a disinfectant-wetted mat. Numerous micro- and macropipetting devices are available from commercial sources and should be required in the laboratory.

Centrifuge accidents cause relatively few laboratory-associated infections, but a single incident often exposes a large number of individuals (19, 82). Unrecognized releases of aerosols during centrifugation may be responsible for laboratory-acquired infections without an identifiable source. The usual cause of a release of microorganisms by a standard laboratory centrifuge is a broken or leaking centrifuge tube. This type of accident is prevented by using nonflawed centrifuge tubes, by ensuring proper use of the centrifuge (e.g., balanced tubes), and by enclosing the centrifuge tube in a safety cup which contains the aerosol when a tube breaks. The centrifuge safety cup must be opened in a BSC after centrifugation. Placing a bench top centrifuge in a BSC is not recommended, because the air turbulence within the cabinet allows aerosols to escape into the room (19).

The use of blenders, homogenizers, shakers, sonicators, and mixers also generates infectious aerosols and contaminates the environment. Infectious material should be manipulated in a BSC. An alternative method for clinical and research laboratories is the use of an instrument that compresses material inside a sealed plastic bag (19).

Additional hazardous procedures are routinely performed in the microbiological laboratory. If a film of liquid exists between two surfaces that are separated (e.g., when removing a petri plate cover or test tube cap), an aerosol results. Liquids hitting a hard surface (breakage or spillage) create large aerosols and contaminate of the environment. Opening lyopholized cultures aerosolizes the dried material. Laboratory request forms and specimen containers are often contaminated with blood or other potentially infectious material (19). Blood and clinical material spread over a microscopic slide may be a potential biohazard. Two studies have documented that *M. tuberculosis* survives in heat-fixed sputum smears but is killed during the staining procedure (2, 127). However, the actual risk of handling microscopic slides containing blood or other material has not been documented. Most of these hazards are minimized by enclosing the opening of the container with a disinfectant-soaked pledget or placing containers in a BSC before opening them. The other problems can be avoided through training, experience, and common sense.

Personal protective equipment and procedures. The basic approach to the management of risk associated with bloodborne pathogens and other infectious agents is to practice universal precautions, which presuppose that all blood, body fluids, and other specimens collected from patients are potentially infectious and are handled by using appropriate personal protective equipment (PPE) and techniques designed to minimize exposure of the HCW. The laboratory is required by OSHA regulations (103) to provide PPE for its employees. PPE generally includes gowns, laboratory coats, disposable gloves, face shields and goggles, splatter shields, and masks and respirators. In a laboratory where specimens are handled and tested, many of the tubes, containers, and equipment are contaminated (19, 118). In one study, 6% of the serum or plasma specimens received by the laboratory were HBV contaminated and 3% were HIV contaminated (141).

Protective gloves must be worn whenever a laboratory worker may have contact with blood, other potentially infectious material, or potentially contaminated surfaces and equipment. These activities include phlebotomy and the direct testing of clinical specimens. Gloves are changed when torn, punctured, or visibly soiled. Hands should be washed after removal of the gloves. Gloves are the most important protective barrier, because contamination of the hands is a frequent cause of exposure to HIV, HBV, and other pathogens (118).

Eye and mouth protection is used when there is a potential for accidental splashes and sprays from manipulation of infectious material during specimen collection or processing. The protective devices include goggles, face shields, and masks, and they should be used when injecting infectious material through a rubber septum or inoculating animals with a syringe and needle. These types of procedures should be performed behind a barrier protective shield whenever possible.

Protective clothing such as laboratory coats, gowns, and aprons that are impervious to liquids must be worn to protect the laboratory worker's skin from contamination by infectious material (74). Ideally, the clothing should reduce the penetration of blood and body fluids and cover the area from the hand to the elbow, which is most often contaminated. The garment should provide a snug fit around the wrists. Most conventional laboratory coats provide minimal fluid barrier protection and coverage for the wrists and forearms.

Respiratory protection must be used in areas where there is aerosol risk for infection by a highly infectious agent such as *M. tuberculosis*. Controversial OSHA regulations mandate that high-efficiency particulate respirators are required for HCW (including phlebotomists) entering the rooms of patients with tuberculosis (1, 101). In the laboratory, the use of these respirators is not normally required (39). However, the worker must use a high-efficiency particulate mask when aerosols may be generated.

Spills and disposal of biohazardous materials. Each laboratory must develop and implement a plan to handle accidental spills of infectious material or releases of infectious microorganisms into the laboratory or facility environment. The details of the management of the accident will depend on the infectious agent, the quantity of the spill, and whether an aerosol was generated. Minor spills or accidents can be handled immediately by cleaning up with a suitable disinfectant, while massive spills or aerosols may require disconnection of the ventilation system and decontamination of the entire room or laboratory. In general, tuberculocidal disinfectants are suitable for the decontamination of equipment, laboratory surfaces, and minor spills. Guidelines and protocols for handling accidents and spills, lists of effective disinfectants, and other safety-related information are available in a number of references (19, 25, 33, 91, 98, 100, 134, 146).

Laboratories also must have a comprehensive plan for waste management and disposal (19, 33, 42, 91, 98, 99, 134). Wastes that require special attention include microbiology infectious wastes, pathology laboratory waste, blood and blood products, and sharps (e.g., needles). The waste management plan identifies potentially infectious material and provides guidelines for the proper handling, transportation, storage, and disposal of the waste. Infectious material should be separated from other waste at the point or source of origin by being placed into leakproof red bags or bags with a universal biohazard symbol.

Sharps must be stored in leakproof, puncture-resistant containers. The infectious waste should be autoclaved prior to disposal in a landfill or should be incinerated. Blood, serum, urine, feces, and other patient secretions and excretions may be carefully poured into a sanitary sewer. The laboratory worker should have appropriate PPE, because this disposal method creates a splash and aerosol hazard. Alternative methods of sterilization include chemical treatments (e.g., hypochlorite, chorine dioxide, peracetic acid), microwaves, dry heat, radiowaves, and infrared radiation.

MANAGEMENT OF LABORATORY ACCIDENTS

The most prudent approach to the management of laboratory accidents and exposures to infectious agents is a safety plan that identifies potential hazards (risk assessment) and minimizes or controls the potential for exposure or accident (39). The management of an exposure to an infectious agent is based on the particular microorganism and an assessment of the potential risk of infection (98). All accidents and potential exposures are reported immediately to the appropriate individuals in the organization, usually the supervisor and safety officer. Follow-up to the incident should include immediate medical care directed toward removal of the infectious material and institution of first aid; accident investigation (identification of the source patient and risk factors in the case of blood-borne pathogens); confidential medical consultation with the employee to answer his or her questions regarding risk of infection, need of prophylaxis, potential transmission to family members, and future treatment and surveillance; and corrective action to prevent future accidents or exposures. Following exposure to a blood-borne pathogen (hepatitis viruses or HIV), the action plan is dependent on determination of the infection status of the source patient. The management of accidents and exposures should be explained in the employee health manual and should cover anticipated exposures based on the prevalence of infectious diseases in the patient population being served and the types of organisms used in research or industrial projects.

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