

Laboratory-Acquired Infections

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Laboratory-acquired infections due to a wide variety of bacteria, viruses, fungi, and parasites have been described. Although the precise risk of infection after an exposure remains poorly defined, surveys of laboratory-acquired infections suggest that *Brucella* species, *Shigella* species, *Salmonella* species, *Mycobacterium tuberculosis*, and *Neisseria meningitidis* are the most common causes. Infections due to the bloodborne pathogens (hepatitis B virus, hepatitis C virus, and human immunodeficiency virus) remain the most common reported viral infections, whereas the dimorphic fungi are responsible for the greatest number of fungal infections. Because of the increasing attention on the role of the laboratory in bioterrorism preparation, I discuss the risk of laboratory-acquired infection with uncommon agents, such as *Francisella tularensis* and *Bacillus anthracis*. Physicians who care for a sick laboratory worker need to consider the likelihood of an occupationally acquired infection while advising exposed laboratory workers about postexposure prophylaxis. In addition, physicians should be aware of the importance of alerting the laboratory if infection with a high-risk agent is suspected.

An estimated 500,000 workers are employed in laboratories in the United States [1]. These workers are exposed to a variety of pathogenic microorganisms that may put them at risk of infection. However, the precise risk posed to individual laboratory workers after an exposure is difficult to determine, in part because of a lack of systematic reporting. Current available data are limited to retrospective and voluntary postal surveys, anecdotal case reports, and reports about selected outbreaks with specific microorganisms.

Laboratory workers frequently become unwittingly infected through hitherto unexpected modes of transmission. This was illustrated by the first laboratory-acquired case of severe acute respiratory syndrome (SARS) coronavirus, which occurred ~4 months after the end of the SARS epidemic [2]. A 27-year-old microbiology graduate student in Singapore, who was working with a nonattenuated strain of West Nile virus, was evaluated for flulike symptoms. The patient denied any exposure to SARS and had no travel history. He was discharged from the emergency department but returned 5 days later because of persistent fever. Because Singapore remained in a heightened state of alert for SARS, a polymerase chain reaction assay was per-

formed with a sputum specimen and returned a positive result for SARS coronavirus. Additional epidemiologic investigation revealed that the laboratory where he worked was also involved in research on SARS coronavirus and that one of the cell cultures of West Nile virus was contaminated with the same infecting strain of SARS coronavirus. Although this case represents an exceptional event, it serves to highlight the inherent risk posed to laboratory workers by virtue of their occupation.

Infectious diseases specialists may be asked to evaluate an ill laboratory worker. This article provides a framework for assessment of such patients by reviewing the published literature on infections acquired in the clinical diagnostic laboratory.

SURVEYS OF LABORATORY-ACQUIRED INFECTIONS

Laboratory infections due to a wide variety of bacteria, viruses, rickettsiae, fungi, and parasites have been described in the literature. The largest survey of infections was reported in 1976 by Pike [3], who found that 4079 laboratory-acquired infections were due to 159 agents, although 10 agents accounted for >50% of the cases (table 1) [3, 4]. At least 173 deaths have resulted from laboratory-acquired infection [5, 6]. However, care should be taken in the interpretation of historical surveys, because some infections (e.g., Q fever, Venezuelan equine encephalitis, and dermatomycoses) occurred predominantly in research and animal laboratories, and many of these infections (e.g., psittacosis and typhoid) were reported before 1955 [1, 3].

Received 26 September 2008; accepted 16 February 2009; electronically published 29 May 2009.

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Clinical Infectious Diseases 2009;49:142-7

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1058-4838/2009/4901-0016\$15.00

DOI: 10.1086/599104

Table 1. Ten most frequently reported laboratory-associated infections worldwide.

Disease	No. of cases	No. of deaths
Brucellosis	426	5
Q fever	280	1
Hepatitis	268	3
Typhoid fever	258	20
Tularemia	225	2
Tuberculosis	194	4
Dermatomycoses	162	0
Venezuelan equine encephalitis	146	1
Psittacosis	116	10
Coccidioidomycosis	93	2

NOTE. Data are for the years 1976 [3] and 1978 [4].

Surveys of diagnostic laboratory workers in the United Kingdom conducted since 1971 have reported that tuberculosis and enteric infections (especially shigellosis) were the most common laboratory-acquired infections [7, 8]. A follow-up survey of UK laboratories from 1994–1995 reported that gastrointestinal infections predominated, particularly shigellosis [9]. Similar results were obtained from a survey of clinical microbiology laboratories in Utah from the period 1978–1992, with shigellosis reported to be the most common laboratory-acquired infection [10]. These results suggest a shift in the pattern of laboratory-acquired infections, with enteric infections predominating. However, no denominator data have been provided that would help determine the actual risk or incidence of infection for laboratory workers.

In a 2002–2004 survey of clinical laboratory directors who participate in ClinMicroNet, an online forum sponsored by the American Society of Microbiology, 33% of laboratories reported the occurrence of at least 1 laboratory-associated infection (table 2) [11]. The 3 most common laboratory-acquired infections were shigellosis, brucellosis, and salmonellosis. In contrast, the highest incidences of infection were associated with *Brucella* species (641 cases per 100,000 laboratory technologists, compared with 0.08 cases per 100,000 persons in the general population) and *Neisseria meningitidis* (25.3 cases per 100,000 laboratory technologists, compared with 0.62 cases per 100,000 persons in the general population).

Of note, the annual number of laboratory-acquired infections has steadily decreased since 1965 [3, 5]. For example, survey results from the United Kingdom from the period 1988–1989 found an infection incidence of 82.7 cases per 100,000 person-years, compared with an incidence of 16.2 cases per 100,000 person-years during the period 1994–1995 [8, 9]. This finding undoubtedly reflects an improved awareness of the hazards of working with infectious agents and placement of a

greater emphasis on laboratory safety, such as through the use of personal protective equipment. In addition, there have been improvements in laboratory design, such as the use of laminar-flow biological safety cabinets (BSCs), which provide unidirectional airflow that entraps any aerosolized particles in the airstream and subsequently into air filters [12].

SPECIFIC LABORATORY-ACQUIRED INFECTIONS

Bacterial Infections

Bacteria account for the largest proportion of infections (43%) in diagnostic laboratories, with over 37 different species reported [3]. Below, I highlight common causes of infection that are currently of most concern.

***Brucella* species.** Brucellosis continues to be the most frequently reported laboratory-associated bacterial infection [13–19]. In the United States, *Brucella* infection is one of the most common laboratory-acquired infections, accounting for 24% of laboratory-acquired bacterial infections and 11% of deaths due to laboratory infection [20]. Aerosolization is the major source of transmission, but the bacterium can also be transmitted via direct contact. However, in many reported cases, it has not been possible to accurately determine the mechanism for transmission. The disease has also affected janitors and persons who have made brief visits to the laboratory [21]. Person-to-person transmission is rare, although a case of *Brucella* infection transmitted from a laboratory worker to a spouse has been documented, presumably through sexual intercourse [22].

Although no controlled studies have been performed to assess the benefit of postexposure prophylaxis (PEP), it should be considered for laboratory workers who have high-risk exposure to *Brucella* species (e.g., because of direct manipulation

Table 2. Laboratory-associated infection and relative risk of infection, compared with the risk among the general population.

Organism	No. of cases of infection	Relative risk of infection
<i>Shigella</i> species	15	1
<i>Brucella</i> species	7	8012.5
<i>Salmonella</i> species	6	0.08
<i>Staphylococcus aureus</i>		
All	6	NA
MRSA	5	NA
<i>Neisseria meningitidis</i>	4	40.8
<i>Escherichia coli</i> O157:H7	2	8.6
<i>Coccidioides</i> species	2	1.1
<i>Clostridium difficile</i>	1	0.03

NOTE. Data are for the years 2002–2004 [11]. MRSA, methicillin-resistant *S. aureus*.

of *Brucella* cultures outside of laminar-flow BSCs). Doxycycline (or trimethoprim-sulfamethoxazole for pregnant women) and rifampin have been frequently used for PEP [13, 23]. In a report from Canada, 26 laboratory workers were exposed to *Brucella melitensis*, which had been isolated from a patient from India with a draining chest sinus. Six laboratory workers were offered PEP with doxycycline (100 mg twice daily) and rifampin (600 mg daily) for 3 weeks. Only 1 person declined PEP; 10 weeks after exposure, the technologist developed fever (temperature, $\leq 40^{\circ}\text{C}$), and 2 sets of blood cultures confirmed brucellosis. None of the other laboratory workers developed infection or evidence of seroconversion. Follow-up serologic tests should be performed for all exposed individuals, probably every fortnight for the first 3 months, then every month for an additional 6–9 months [13, 18].

N. meningitidis. Sejvar et al. [24] examined the risk of laboratory-acquired *N. meningitidis* infection using postings on listservs, to obtain reports of laboratory-acquired meningococcal disease occurring worldwide during the period 1985–2001. Sixteen cases of probable laboratory-acquired meningococcal disease were identified, including 6 cases in the United States. Nine cases (56%) were due to serogroup B, and 7 (44%) were due to serogroup C. Overall, 8 cases (50%) were fatal. All cases occurred among clinical microbiologists and were likely due to exposure to aerosols containing *N. meningitidis*. The calculated attack rate was 13 cases per 100,000 microbiologists, compared with an attack rate of 0.3 cases per 100,000 persons among the general population. The results of this analysis suggest that laboratory-acquired meningococcal disease represents a significant occupational hazard to clinical microbiologists.

Although primary prevention of laboratory-acquired meningococcal disease should focus on appropriate handling and manipulation of cultures in a laminar-flow BSC, all laboratory microbiologists should be offered the tetravalent vaccine [25]. It will decrease—but not eliminate—the risk of infection, because it is less than 100% effective and does not provide protection against serogroup B [26]. Microbiologists who inadvertently manipulate invasive *N. meningitidis* isolates on an open bench-top in a manner that could result in aerosolization should consider PEP with either a single 500-mg dose of ciprofloxacin or 600 mg of rifampin given twice daily for 2 days [24].

Mycobacterium tuberculosis. Early surveys of laboratory-acquired tuberculosis found an incidence of tuberculosis among laboratory personnel 3–9 times greater than that in the general population [7, 27]. However, unless there is some accident to which the infection can be traced, it is difficult to state with certainty that tuberculosis was laboratory acquired, because of the potential for exposure outside of the workplace and the long incubation period before symptomatic disease develops.

M. tuberculosis can be isolated from a variety of clinical spec-

imens, and manipulation of specimens or cultures that generate aerosols is the most important risk factor for acquiring tuberculosis in the laboratory. The high infectivity of *M. tuberculosis* is related to the low infective dose for humans (50% infective dose, <10 bacilli) [28]. The use of laminar-flow BSCs for aerosol-generating manipulations with biosafety level ≥ 2 practices and fit-tested respirators with N-95 rating should be routinely used [12, 29]. Laboratory personnel should undergo an annual Mantoux purified protein derivative skin test or an interferon- γ release assay to demonstrate conversion. Persons with positive test results should be evaluated for active tuberculosis by chest radiography. In the event of accidental exposure, laboratory workers should be tested 3 and 6 months after the accident, and persons with new conversion should be offered prophylaxis [29].

Francisella tularensis. *F. tularensis* is a fastidious, gram-negative coccobacillus that is infrequently encountered in the clinical microbiology laboratory, but it has gained increased importance because of its possible use as a bioterrorism agent [30]. The greatest hazard to laboratory workers is from exposure to infectious aerosols from manipulation of cultures. Clinicians should be aware that, although patients with tularemia, brucellosis, or endemic mycoses do not pose a communicable disease risk to health care workers, specimens obtained from these patients pose a significant threat to laboratory workers.

Shapiro et al. [31] described 12 laboratory workers who were exposed to *F. tularensis* after clinicians failed to notify the laboratory about a suspected case of pneumonic tularemia in a 43-year-old man who eventually died. Blood cultures, sputum cultures, and autopsy pleural fluid were all positive for gram-negative coccobacilli, which failed to grow on sheep blood agar and MacConkey agar and were initially misidentified as *Haemophilus* species. Eleven laboratory workers and 2 autopsy personnel with high-risk exposure to *F. tularensis* received PEP with doxycycline (100 mg twice daily for 14 days), with no resulting infections. To minimize the risk of exposure of laboratory workers, any suspicion about infection with a high-risk pathogen should be immediately communicated to the laboratory. This practice not only protects the staff but also benefits the patient, because a faster and more directed laboratory evaluation can be initiated.

Bacillus anthracis. Before the 2001 outbreak of bioterrorism-related anthrax in the United States, anthrax was an uncommon illness in the United States [32]. In March 2002, the Centers for Disease Control and Prevention were alerted about a laboratory worker who had received a diagnosis of cutaneous anthrax [33]. One day after he had cut himself over the right jaw while shaving, the patient assisted a coworker in moving vials of *B. anthracis* from the laminar-flow BSC in the main laboratory to a freezer. The patient had handled the vials with-

Table 3. Laboratory-acquired parasitic infections.

Parasite	No. of cases (n = 313)
Blood and tissue protozoa	
<i>Trypanosoma cruzi</i>	65
<i>Toxoplasma gondii</i>	75
<i>Plasmodium</i> species	52
<i>Leishmania</i> species	16
<i>Trypanosoma brucei</i>	6
<i>Trypanosoma</i> species	17
<i>Leukocytozoon</i> species	1
Intestinal protozoa	
<i>Cryptosporidium parvum</i>	16
<i>Isospora belli</i>	8
<i>Giardia lamblia</i>	4
<i>Entamoeba histolytica</i>	23
Helminths	
<i>Schistosoma</i> species	9
<i>Strongyloides</i> species	6
<i>Ancylostoma</i> species	1
<i>Ascaris lumbricoides</i>	8
<i>Enterobius vermicularis</i>	1
<i>Fasciola hepatica</i>	2
<i>Sarcocystis</i> species	1
Hookworm	2

NOTE. Data are for the years 1976 [3] and 2001 [45].

out gloves but washed his hands with soap and water. Over the next 3 days, the cut over the laboratory worker's jaw increased in size, and he developed low-grade fever, cervical lymphadenopathy, and cellulitis around the scab. Cultures of specimens from beneath the scab were positive for *B. anthracis*, and the patient was treated with intravenous ciprofloxacin and doxycycline and discharged while receiving ciprofloxacin.

Epidemiologic investigation of this case revealed that the tops of the vials tested positive for *B. anthracis*. Although all specimen processing surfaces were decontaminated with 10% bleach solution, storage vials were sprayed with 70% isopropyl, because bleach caused labels to become dislodged. This case brings the number of cases of bioterrorism-related anthrax identified since 3 October 2001 to 23 and is the first laboratory-acquired case of bioterrorism-related anthrax.

Enteric pathogens. Salmonellosis is one of the most common reported infections in published surveys [3, 5, 6, 8, 11]. Blaser et al. [34] reported 32 cases of laboratory-acquired typhoid fever in the United States over a 42-month period from 1977 to 1980, representing 11.2% of the sporadic cases of typhoid fever reported in the United States. Of particular concern was that a number of cases occurred in individuals who had not directly worked in the microbiology laboratory, including cases in 2 family members of a microbiologist who worked with *Salmonella* culture, 1 of which proved to be fatal. In fact, ty-

phoid fever has accounted for more reported fatalities than any other laboratory-acquired infection [5]. Of note, many earlier reported cases of typhoid fever were associated with mouth pipetting and handling of proficiency test strains—practices which are now avoided [1, 35, 36].

In recent surveys, *Shigella* species was the most frequently identified agent of laboratory-acquired infection [9–11]. One explanation for the large number of reported cases of laboratory-acquired shigellosis is that *Shigella* species are more virulent and require a much lower inoculum to cause illness. However, it is also probably true that microbiology laboratory staff who develop diarrhea are more likely to attempt to establish a cause for their illness, compared with the general population. A number of other enteric pathogens have also been identified as less common causes of laboratory-acquired infection, including *Clostridium difficile* and *Escherichia coli* O157:H7 [11, 37].

Viral Infections

Viral agents transmitted through blood and bodily fluids cause most of the laboratory-acquired infections in diagnostic laboratories and among health care workers [1]. Although the viral hemorrhagic fevers incite the most fear and dominate the imagination of the media and public, the viruses responsible are rare causes of laboratory infection [3, 4]. However, there is always the possibility that an agent not previously seen may be encountered. This occurred in 1967, when 31 workers were infected while handling tissue specimens from African green monkeys, with 7 deaths resulting [38]. The causative agent was named Marburg virus, after the town in Germany where most cases occurred.

Of the common blood-associated viruses, hepatitis B virus (HBV) is the most common cause of laboratory-acquired infection [1]. The incidence of HBV infection among all health care workers in the United States is estimated to be 3.5–4.6 infections per 1000 workers, which is 2–4 times than the level for the general population [39]. It is encouraging that, in the 2 most recent surveys of laboratory-acquired infections in the United Kingdom, there were no reported cases of HBV infection among laboratory workers [8, 9]. This finding is probably related to the use of universal precautions when handling blood specimens, improvements in needleless devices, and the availability of immunization.

Because hepatitis B is a vaccine-preventable disease, all laboratory workers should be offered the hepatitis B vaccine without charge. Nonimmunized laboratory workers who have percutaneous, ocular, or mucous membrane exposure to contaminated blood should receive PEP with hepatitis B immunoglobulin and vaccine [39].

During 2005–2006, there were 802 confirmed cases of acute hepatitis C reported to the Centers for Disease Control and

Prevention, with 5 occupational exposures (1.5%) to blood [40]. However, there are few data on the incidence of hepatitis C among laboratory workers, and only single case reports in surveys have been performed in the United States and the United Kingdom [8–10].

Human immunodeficiency virus (HIV) infection associated with exposure to contaminated blood or body fluids probably causes the greatest concern. The risk of HIV transmission after a percutaneous exposure to HIV-infected blood has been estimated to be ~0.3%, and the risk has been estimated to be ~0.09% after exposure to a mucous membrane [41, 42]. Data on occupational transmission of HIV from the period 1981–1992 revealed a total of 32 health care workers in the United States with occupationally acquired HIV infection; 25% of these health care workers were laboratory workers [43]. In the event of laboratory-based exposure from a source person with HIV infection, or if information suggests the likelihood that the source person is HIV infected, immediate referral to employee health for HIV PEP should be sought [44].

Fungi

The dimorphic fungi *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Histoplasma capsulatum* are responsible for the majority of laboratory-acquired fungal infections in the United States (table 1) [1, 3, 4]. Although cutaneous infections due to accidental inoculation are documented, most laboratory-acquired infections are caused by inhalation of infectious conidia from the mold form, resulting in pulmonary infection. The mere lifting of a culture plate lid often suffices to cause the release of large numbers of conidia, and should a sporulating culture be dropped, millions of conidia would be dispersed.

The risk of infection in the mycology laboratory probably is low, because handling of specimens is done in laminar-flow BSCs, and culture plates are secured with shrink seal to prevent accidental opening. However, a greater risk of infection is likely on the aerobic culture bench, because colonies of *B. dermatitidis* and *C. immitis* can grow on routine media and may be visible within 2–3 days. It cannot be overemphasized that clinicians who suspect a dimorphic fungal infection should immediately alert the microbiology laboratory.

Parasites

Laboratory-acquired parasitic infections are uncommon in the diagnostic microbiology laboratory [1, 3, 6]. Approximately 313 cases of laboratory-acquired infection, with a variety of blood and intestinal protozoa, have been reported (table 3) [3, 45]. Most of these cases occurred in research and reference laboratories. Readers are referred to the review by Herwaldt [45].

Fifty-two cases of malaria among laboratory workers and health care workers have been reported, with 34 cases reviewed by Herwaldt [45]; 10 cases were due to *Plasmodium cynomolgi*,

9 cases were due to *Plasmodium vivax*, and 15 cases were due to *Plasmodium falciparum* [3, 45]. Most of the cases of *P. vivax* and *P. falciparum* infection occurred among health care workers and laboratory workers rather than among researchers and resulted from needlestick injuries that occurred while obtaining blood or preparing blood smears from patients [45]. Infection due to intestinal protozoa are uncommon in clinical diagnostic laboratories [45]. One case of giardiasis was reported in a clinical laboratory technologist who processed specimens, many of which were in leaky containers. One case of *Isospora belli* infection occurred in a technologist who examined numerous stool specimens from a patient infected with *I. belli*.

CONCLUSIONS

Laboratory-acquired infection represents an occupational hazard unique to laboratory workers, especially those in the microbiology laboratory. Exposures may occur inadvertently, may not even be recalled, or may result from lapses in technique leading to accidental inoculation. However, not every exposure results in infection. A risk assessment for infection based on the host's immune system, mechanism of the exposure, infectious dose of the exposure, virulence of the agent, use of personal protective equipment, and immunization status needs to be performed. The accurate quantification of such risk is unfortunately difficult, because there is no systematic reporting system that monitors the number of laboratory-related exposures and infections. The Centers for Disease Control and Prevention has recently convened a committee to address these issues that will, I hope, provide evidence-based guidelines on exposure risk and use of PEP.

Acknowledgments

Potential conflicts of interest. K.S. has served on the speakers' bureau for Wyeth.

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