Publications on laboratory-associated infections (LAIs) provide critical information for prevention strategies. The review of actual case studies illustrates the importance of adhering to biosafety protocols and may trigger changes in laboratory procedures. Singh has stated that it is time for a centralized system for reporting, analyzing, and communicating “lessons learned” about LAIs to be developed (1). Surveys on some subsets of laboratory workers, and case reports on individual LAIs, have been published; however, without a centralized system, it is impossible to assess the true incidence of LAIs. In addition, the underreporting of such infections is widely acknowledged due to fear of reprisal and the stigma associated with such events (2).

To address the need for collecting additional LAI data, experts have recommended that a “nonpunitive surveillance and reporting system with the potential for anonymity” be implemented in the United States for diagnostic laboratories (3) and high-containment research laboratories (4). This has not been implemented for all LAIs; however, mandatory reporting for infections with Select Agents, a class of infectious agents that pose a severe threat to human and animal health, has been instituted in the United States. Data are available on the LAIs that occurred with Select Agents in the United States for the years 2004–2012. Between 2004 and 2010, approximately 10,000 researchers had access to Select Agents; eight primary LAIs occurred, no secondary LAIs, and no fatalities. In addition, three clinical laboratories reported LAI with Brucella, a Select Agent (5).

Systematic reporting of LAI would support the assessment of containment practices and the development of evidence-based biosafety measures (6). Until more comprehensive data are available, a literature review such as this one provides updated information about the types of microorganisms and exposures responsible for LAIs and generates awareness that laboratory workers continue to be at risk of infection.

EPIDEMIOLOGIC STUDIES OF LAI

In this chapter, we review the LAIs reported in the literature since 1979, compare them to the data from the 1930–1978 Pike and Sulkin surveys, and present a summary of the agents, routes of exposure, and types of activities, as
well as the host and environmental factors available on LAIs. Incidence data, when available, are included. This summary was compiled to support the continued development of biosafety programs to minimize the occupational risk of infection from diagnostic, research, teaching, and production activities. Information on hazard assessment and prevention strategies is available in other chapters.

Epidemiology is defined as the study of the distribution and determinants of diseases and injuries in human populations. That is, epidemiology is concerned with the extent and types of illnesses and injuries in groups of people and with the factors that influence their distribution. In the context of this chapter, the illnesses are LAIs, and the factors analyzed include the infectious agent, the activities conducted when the exposure occurred (clinical, research, field, teaching, animal work), and the routes of transmission. Inherent in the definition of epidemiology is the necessity for measuring the amount of disease in a population or occupation by relating the number of cases to a population base. Cases or events that fit the case definition are identified and counted; the number of cases in a potentially exposed population (attack rates, or incidence) can then be calculated and compared to the rates of occurrence in other populations. Comparisons of the data from clinical, research, and production laboratories from published case studies may be misleading, because attack rates for a given population are rarely available.

Incidence

Estimates from the Pike data suggested that the risk for researchers was six to seven times greater than that for hospital and public health laboratory workers; the calculated attack rate for researchers was 4.1 per 1,000 (7). Reid, in 1957, reported that the incidence of tuberculosis among laboratory personnel working with Mycobacterium tuberculosis was three times higher than among those not working with the agent (8). Phillips, in 1965, estimated that the frequency of LAIs (using available U.S. and European data) resulted in the expected number of one to five infections per million working hours (9). A 1971 survey of laboratory-acquired cases of tuberculosis, shigellosis, brucellosis, and hepatitis in England and Wales reported an annual incidence rate of 43 infections per 1,000 medical laboratory employees (10).

Since these early studies, only a few surveys, primarily in clinical laboratories, have provided incidence data. Grist (11, 12) reported that the incidence for clinical microbiologists was 9.4 infections per 1,000 employees. Jacobson et al. surveyed supervisors of 1,191 clinical laboratory workers in Utah to determine the LAIs that occurred between 1978 and 1982. The annual incidence of LAIs in that population was 3 per 1,000 employees (13).

Further analysis of the data indicated that the annual incidence in small laboratories (less than 25 employees) was greater than that in large laboratories (5.0 versus 1.5 per 1,000) and that approximately 1% of all microbiologists reported an LAI. Vesley and Hartmann surveyed LAIs among 4,202 public health and 2,290 hospital clinical laboratory employees (14). The annual incidence rate for all full-time employees was calculated at 1.4 infections per 1,000 employees for public health laboratories and 3.5 infections per 1,000 employees in hospital laboratories. Incidence in microbiology laboratories was higher, at 2.7 per 1,000 staff in public health laboratories and 4.0 per 1,000 employees in hospital microbiology labs. The relatively low incidence in the Vesley and Hartman study was attributed to safety awareness and improvements in safety devices. A Japanese survey of clinical laboratory workers in 306 hospitals cited an annual incidence rate of 2.0 infections per 1,000 persons (15).

Baron and Miller conducted a voluntary online survey of clinical microbiology laboratory directors between 2002 and 2004 (16). Forty-five LAIs were reported by directors of 88 U.S. hospital laboratories of various sizes and three reference laboratories. The calculated incidence of LAIs was compared with incidence of infection in the general population aged 30–59. Clinical microbiologists were at high risk for Brucella infections, with calculated incidences of 641 cases per 100,000 laboratory technologists, compared to 0.08 cases per 100,000 in the general population. The incidence of Neisseria meningitidis was 25.1 per 100,000 for microbiologists compared to 0.6 per 100,000 for the general population; for Escherichia coli O157:H7, it was 83 versus 0.96. The risk of Shigella infection was the same in both populations (6 per 100,000) and nearly the same for Coccidioides (13.6 per 100,000 microbiologists versus 12 per 100,000 general population). The incidence of Salmonella and Clostridium difficile infections was lower in microbiologists than in the general population. For Salmonella, the incidence for clinical laboratory staff was 1.5, compared to the incidence in the general population of 17.9 per 100,000; for C. difficile the incidence was 0.2 compared to 8 per 100,000 in the general population (16).

Interventions Based on LAIs

Many reports also document responsible internal review of the factors contributing to the LAI. An example would be the report on a LAI that occurred when a technician was subculturing a collection of N. meningitidis isolates. In compliance with the existing laboratory protocols, the infected technician conducted the work on the open bench and used glass Pasteur pipettes to remove colonies
from the frozen agar surface. Analysis of the laboratory procedures after the LAI was confirmed resulted in protocol revisions to prevent recurrence. After the LAI, laboratory procedures were updated. Subculturing the N. meningitidis isolates is conducted in the biosafety cabinet, soft cotton swabs have replaced the glass Pasteur pipettes, and the vaccine against N. meningitidis is offered to staff (17). In another incident, a glass lyophilization vial punctured a researcher’s gloved hand, resulting in a buffalopox LAI. To prevent recurrence, the freezing temperature for the vials prior to lyophilization was reduced to −60°C and a better-quality glass vial is now used (18). The “lessons learned” from these incidents were published to prevent additional LAIs in staff conducting similar procedures.

In 2011, the Centers for Disease Control and Prevention (CDC) reported on 109 cases linked to clinical and teaching microbiology laboratories. The cases were identified through PulseNet, the electronic monitoring system for foodborne outbreaks in the United States. Twelve percent of the cases required hospitalization, and there was one fatality. Fifty-four cases responded to CDC surveys, and 65% reported association with a university/college/community college teaching laboratory (19). An investigation revealed that the facilities and safety policies in all of the teaching laboratories were essentially equivalent. However, students in laboratories without LAIs were more familiar with biosafety training and the symptoms of infection associated with the agents studied. This led to the design of a poster for the student population illustrating that objects such as pens, lab notebooks, and cell phones or personal music devices used in the lab can be a source of infection. The poster also promoted effective preventive measures such as hand washing to prevent transmission of LAI. In addition to advice for students, the CDC Salmonella outbreak website has a message for teachers and clinical supervisors on prevention of LAI. Another outbreak linked to clinical and teaching microbiology laboratories was reported in 2014, with 41 cases, 36% hospitalization, and no fatalities (20). The poster has provided supervisors with an excellent training tool; however, it is an ongoing challenge to reinforce appropriate work practices with each new class of inexperienced students.

**LAIs: THE CONTINUUM**

LAIs were not a new phenomenon in the 20th century, as historical accounts of typhoid, Brucella, and tetanus were recorded as early as 1885, 1887, and 1893, respectively (21, 22). Reports from the 1930s and 1940s demonstrate that microbial agents were potentially hazardous to individuals within the laboratory and posed some risk to those working in close proximity to the laboratories (23, 24).

LAIs are defined as all infections acquired through laboratory or laboratory-related activities regardless of whether they are symptomatic (over) or asymptomatic (subclinical) in nature. In 1950, Sulkin and Pike circulated a questionnaire to 5,000 laboratories in the United States, including those associated with state and local health departments, accredited hospitals, private schools of medicine and veterinary science, undergraduate teaching institutions, manufacturers of biologic products, and various government agencies. The questionnaire solicited information on unreported infections resulting from laboratory work and slightly more than half of those surveyed responded (23, 24). During the period 1930–1975, these authors published cumulative data describing 3,921 LAIs in the United States and other countries (25, 26). In 1978, Pike added 158 new infections, bringing the total to 4,079 documented LAIs, 168 of which were fatal (27).

As an apparent reflection of the work being performed in the responding laboratories at that time, bacteria accounted for 1,704 of the infections, viruses for 1,179, ricketsia for 398, fungi for 354, chlamydia for 128, and parasites for 116. Bacteria or viruses were associated with more than two-thirds of the lethal and nonlethal infections. Brucella, Coxiella burnetii, hepatitis B virus, Salmonella enterica serovar Typhi, Francisella tularensis, and M. tuberculosis, as shown in Table 1, were the infections reported most frequently (28). While the risk of infection with these agents remained, Pike noted that most (96%) Brucella and typhoid fever cases and 60% of hepatitis cases were reported before 1955. Unfortunately, between 1979 and 2015, Brucella spp., M. tuberculosis, C. burnetii, Salmonella spp., and hepatitis B virus have remained among the top 10 causes of reported LAIs (see Table 1).

In an attempt to extend the Sulkin and Pike LAI data, 475 references published between 1979 and 2015 were reviewed to determine the microorganisms associated with laboratory infections, the primary function of the facilities in which the infections occurred, and the type of work activity associated with the event. To be included in this survey, an infection had to result from laboratory work, and the infected individual had to be a laboratory worker or another person who inadvertently was exposed (by being in the area) as a result of work with the infectious agents or infected animals. Secondary infections were also noted in this literature survey and are defined here as LAIs transmitted by a laboratory worker to a person not associated with, or in the vicinity of, the laboratory, such as a family member or health care provider. These secondary infections were not included in the primary LAI count unless they were responsible for a fatality. A tertiary infection results from transmission from a secondary infection. During the period 1979–2015,
publications described 2,376–2,392 symptomatic infections with 42 deaths, 19 secondary infections, and 8 tertiary infections. The overt infections were caused by bacteria (51%), viruses (32%), rickettsiae (9%), parasites (7%), and fungi (<1%). This information is summarized in Table 2 by category of agent and available published information on asymptomatic, secondary, and tertiary LAIs is also included. If the rickettsial infections are included with bacteria, as is the case today, 60% of the LAIs are bacterial in origin.

**Laboratory Function**

The distribution of the symptomatic infections according to type of work performed in a facility is shown in Table 3. Clinical (diagnostic) and research laboratories account for (17% and 59%, respectively) of the symptomatic infections reported in the earlier Sulkin and Pike surveys and (42% and 36%, respectively) in the 1979–2015 survey. It appears that more LAIs from clinical laboratories are being reported in recent years. The increases in reported clinical infections may be due in part to a more active employee health program. Another explanation is that, during the early stages of culture identification, personnel are working with unknowns and may not be using adequate containment procedures. Clinical microbiology staff rely on physician notification that a sample is suspected of containing a pathogen transmitted by the aerosol route to avoid working on the open bench; unfortunately, the presence of a Risk Group 3 pathogen is not always suspected or the notification does not always occur. For example, despite a hospital policy requiring

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**TABLE 1.** Comparison of 10 most commonly reported LAIs 1930–1978 and 1979–2015

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. LAIs</td>
<td>No. deaths</td>
</tr>
<tr>
<td>1</td>
<td><em>Brucella</em> spp.</td>
<td>426</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td><em>Coxiella burnetii</em></td>
<td>280</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Hepatitis B</td>
<td>268</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td><em>Salmonella enterica serovar Typhi</em></td>
<td>258</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td><em>Francisella tularensis</em></td>
<td>225</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>194</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td><em>Blastomyces dermatitidis</em></td>
<td>162</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Venezuelan equine encephalitis virus</td>
<td>146</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td><em>Chlamydia psittaci</em></td>
<td>116</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td><em>Coccidioides immitis</em></td>
<td>93</td>
<td>10</td>
</tr>
</tbody>
</table>

*Adapted from reference 27.
*Not included are 113 cases of hemorrhagic fever contracted from wild rodents in one laboratory in Russia in 1962 (486).
*All deaths are aborted fetuses.
*Typical arboviruses and orbiviruses, rhabdoviruses, and arenaviruses that are associated with arthropods or have zoonotic cycles (233), with additional arboviral reports added.
*One death was a secondary exposure case (47).

---

**TABLE 2.** Total LAIs 1979–2015

<table>
<thead>
<tr>
<th>Category of agent</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
<th>Total primary LAIs</th>
<th>Deaths</th>
<th>Secondary infections</th>
<th>Tertiary infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td>1,212–1,226</td>
<td>142</td>
<td>1,354–1,368</td>
<td>21</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td><strong>Rickettsiae</strong></td>
<td>205</td>
<td>269</td>
<td>474</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td>764–766</td>
<td>439</td>
<td>1,203–1,205</td>
<td>19</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td><strong>Parasites</strong></td>
<td>170</td>
<td>4</td>
<td>174</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td>25–26</td>
<td>0</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2,376–2,392</td>
<td>854</td>
<td>3,230–3,246</td>
<td>41</td>
<td>19</td>
<td>8</td>
</tr>
</tbody>
</table>
notification, no precautionary statements accompanied the samples submitted from a suspected *F. tularensis* infection. As a result of the missing notification, 12 microbiology staff and two autopsy staff received antibiotic postexposure prophylaxis (PEP) (29). In addition, because notifications advising the need for biosafety level 3 (BSL3) practices are infrequent, clinical laboratory personnel may be unaware of the procedural changes required to safely handle atypical specimens (30).

### Underreporting

Table 3 provides data on the accumulated reports of LAIs over the past 85 years and the setting in which the LAIs occurred. It is widely accepted (24, 31) that the numbers represent a substantial underestimation of the extent of LAIs. Many scientists (32) and safety professionals can recount numerous unrecorded cases. With improvements in containment practices and equipment, and occupational health programs providing immunization and postprophylaxis therapy, one would expect that the number of infections due to bacterial, rickettsial, and fungal agents would be decreasing. This appears to have occurred in the clinical laboratories of the United Kingdom, where the incidence of LAI was 62.7 cases per 100,000 person-years in 1988–1989 surveys (11) compared to 16.2 cases per 100,000 person-years reported in the 1994–1995 surveys (33).

### RECENT INFORMATION ON WORKPLACE EXPOSURES

### Bacterial LAIs

Table 4 summarizes information on the bacterial infections published in the literature during the period 1979–2015. During the past 36 years, 1,212 symptomatic LAIs, 142 asymptomatic infections, 12 secondary infections, and 3 tertiary infections due to bacteria were reported. The most frequently reported bacterial infections were *Brucella* spp. (389–393 LAIs), *M. tuberculosis* (243–246 LAIs), *Salmonella* (133–137 LAIs), *Shigella* (90 LAIs), *N. meningitidis* (43 LAIs), and *Chlamydia* (20 LAIs). A range is reported for a few species to include the data consolidated from two surveys conducted in Belgium for the period 2007–2012 (34).

Twenty-two fatalities due to bacterial LAIs occurred; 13 fatal LAIs were due to *N. meningitidis* (33, 35–41); 4 involved pregnancies that resulted in aborted fetuses as a consequence of LAIs with *Brucella melitensis* (42–45); 3 were due to *Salmonella* spp., one of which was a secondary infection (19, 46, 47); and one each for the attenuated (48) and wild-type strain of *Yersinia pestis* (49).

Secondary infections, the transmission of a LAI to another person outside the work environment, are rare. Between 1979 and 2015, 12 secondary bacterial infections and three tertiary bacterial infections occurred. A primary LAI with *Shigella sonnei* in a clinical laboratory resulted in the secondary transmission to a grandchild, with tertiary infections in three additional relatives (50). Four secondary infections in children under age 4 occurred with *Salmonella Typhimurium* in a 2011 outbreak associated with teaching or clinical laboratories (19). Two separate incidents of secondary *Brucella* infections were attributed to sexual transmission (51, 52). A microbiologist prepared dinner and transmitted *Salmonella* to his wife and son (47). A lactating mother with an LAI transmitted *Leptospira interrogans* to her infant through breast milk (53). Two secondary transmissions of *Bordetella pertussis* occurred (54).

### Table 3

<table>
<thead>
<tr>
<th>Number of LAIs associated with indicated primary work purpose</th>
<th>Clinical</th>
<th>Research</th>
<th>Production</th>
<th>Teaching</th>
<th>Site not listed</th>
<th>Field</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>396</td>
<td>783</td>
<td>914</td>
<td>122</td>
<td>40</td>
<td>81</td>
<td>69</td>
</tr>
<tr>
<td>Rickettsiae</td>
<td>27</td>
<td>1</td>
<td>455</td>
<td>204</td>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Viruses</td>
<td>173</td>
<td>215</td>
<td>706</td>
<td>497</td>
<td>73</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Parasites</td>
<td>18</td>
<td>5</td>
<td>70</td>
<td>77</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Fungi</td>
<td>43</td>
<td>4</td>
<td>155</td>
<td>16</td>
<td>2</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Unspecified</td>
<td>20</td>
<td>—</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>677</td>
<td>1,008</td>
<td>2,307</td>
<td>916</td>
<td>134</td>
<td>90</td>
<td>106</td>
</tr>
</tbody>
</table>

*Adapted from reference 26.*
### TABLE 4

Bacterial LAI references 1979–2015

<table>
<thead>
<tr>
<th>Agent</th>
<th>Number of LAI</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacillus anthracis</td>
<td>1</td>
<td>88, 155</td>
</tr>
<tr>
<td>Bacillus Calmette-Guérin</td>
<td>2</td>
<td>34, 147</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>1</td>
<td>325</td>
</tr>
<tr>
<td>Bacteroides asaccharolyticus</td>
<td>1</td>
<td>326</td>
</tr>
<tr>
<td>Bartonella henselae</td>
<td>3</td>
<td>34, 158</td>
</tr>
<tr>
<td>Bordetella pertussis</td>
<td>12</td>
<td>54, 327</td>
</tr>
<tr>
<td>Burkholderia pseudomallei and B. mallei</td>
<td>3</td>
<td>78, 318, 342</td>
</tr>
<tr>
<td>Campylobacter spp.</td>
<td>5–6</td>
<td>12, 15, 34, 343, 344</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>3</td>
<td>16, 89</td>
</tr>
<tr>
<td>Corynebacterium diphtheriae</td>
<td>2</td>
<td>67, 68</td>
</tr>
<tr>
<td>Corynebacterium equi</td>
<td>1</td>
<td>348</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>1</td>
<td>349</td>
</tr>
<tr>
<td>Escherichia coli O157 and SP88, Klebsiella</td>
<td>22</td>
<td>16, 33, 64–66, 148, 151, 152, 332, 350–356</td>
</tr>
<tr>
<td>Francisella tularensis</td>
<td>11</td>
<td>5, 86, 87, 357–361</td>
</tr>
<tr>
<td>Gastrospirillum hominis</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>Haemophilus ducreyi</td>
<td>2</td>
<td>13, 362</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>4</td>
<td>363–365</td>
</tr>
<tr>
<td>Leptospira interrogans</td>
<td>8</td>
<td>53, 93, 366–368</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>2</td>
<td>6, 34</td>
</tr>
<tr>
<td>Mycobacterium bovis</td>
<td>1</td>
<td>369</td>
</tr>
<tr>
<td>Mycobacterium kansasii</td>
<td>1</td>
<td>370</td>
</tr>
<tr>
<td>Mycobacterium leprae</td>
<td>1</td>
<td>156</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>4</td>
<td>15, 34</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>43</td>
<td>16, 17, 35–41, 63, 80–84, 351, 384–388</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>2</td>
<td>146</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>212</td>
<td>11, 12, 15–17, 19, 34, 46, 47, 70–73, 77, 93, 131, 132, 149, 332, 389–395</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>18</td>
<td>13, 16, 33, 55, 332, 400, 401; D. Vesley, 30th Biol. Safety Conf.,a 1987</td>
</tr>
<tr>
<td>Streptobacillus moniliformis</td>
<td>2</td>
<td>74, 402</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>12</td>
<td>12, 13, 131, 403–406</td>
</tr>
<tr>
<td>Vibrio cholerae and V. parahaemolyticus</td>
<td>4</td>
<td>91, 131, 407, 408</td>
</tr>
<tr>
<td>Yersinia pestis</td>
<td>2</td>
<td>49, 85</td>
</tr>
<tr>
<td><strong>Total bacteria</strong></td>
<td><strong>1,212–1,226</strong></td>
<td><strong>142</strong></td>
</tr>
</tbody>
</table>
The asymptomatic infections included serological evidence without clinical symptoms for organisms such as *Brucella* and *Chlamydia* as well as six incidences of nasal carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) without clinical symptoms. In one case, the same strain of MRSA worked with in the laboratory was isolated from the nasal passages of both a laboratory worker and the worker’s cat (55).

### Infections in clinical laboratories

A majority of the bacterial LAIs occurred in clinical laboratories, and four of these occurred in veterinary diagnostic laboratories. A survey of 88 hospital microbiology laboratories and three national reference laboratories was conducted for the years 2002–2004 (16). In that 2-year period, the bacterial LAIs reported were *Shigella* (15 LAIs), *Brucella* (7 LAIs), *Salmonella* spp. (7 LAIs), *S. aureus* (6 LAIs, with 5 of these being methicillin-resistant), *N. meningitidis* (4 LAIs), *E. coli* O157:H7 (2 LAIs), and *C. difficile* (1 LAI).

It should be noted that a single unexplained isolation of *Brucella* can result in multiple exposures. Analysis of two cases of *Brucella* in clinical microbiologists revealed that 146 staff were potentially exposed to the same samples; antibiotic PEP was offered to those at high risk of exposure, and serology indicated that no one other than the two previously identified LAIs had been infected (56). Sufficient data have been collected from *Brucella* LAIs to define criteria for staff at high risk of infection and a strategy for offering antibiotics for PEP (56). This was important for the proper follow-up to the clinical efficiency test of 2007 that involved sending an “unknown” sample to 1,317 laboratories in the United States and Canada. The laboratories were informed that the samples should be handled in a Class II biosafety cabinet using BSL3 practices to identify the sample. Unfortunately, 916 laboratory workers were exposed to the sample, identified as *Brucella* RB51, including 679 staff (74%) with high-risk exposures and 237 (26%) with low-risk exposures. PEP was offered, and no cases of brucellosis were reported (30).

### Infections in teaching laboratories

Teaching laboratories were the setting for a number of bacterial infections. Twenty-seven students and their teacher were infected with *Brucella* in a veterinary teaching laboratory in China (69). Twenty-four students in college laboratories studying clinical microbiology in the United States were infected with *S. Typhimurium* (19); some of the students were also working in a clinical laboratory (Gaines, personal communication). Two of the LAIs in this cluster occurred at a university that, 3 years...
earlier, had removed S. Typhimurium from the curriculum due to safety concerns. During the outbreak investigation, it was determined that the stock culture of Citrobacter freundii used for student identification of “unknown specimens” was actually a mislabeled S. Typhimurium culture (70). Two additional cases were reported in 2013 (71). Another student contracted S. Typhimurium enteritis associated with erythema nodosum and reactive arthritis caused by the strain used in her microbiology class (72). Typhoid fever with serious complications developed 3 weeks after a student participated in a classroom identification exercise involving S. enterica serovar Typhi (73). A single case of Streptobacillus moniliformis occurred when a psychology undergraduate student was bitten by a rat (74).

**Infections in production laboratories**

A total of 73 LAIs were associated with production of vaccines against B. pertussis (R. McKinney et al., 28th Biol. Safety Conf., 1985) (54), Brucella (60, 75, 76), and Salmonella (77). The materials from a spill cleanup in a Salmonella poultry vaccine plant infected 21 staff (77). Fifteen workers at a Brucella S19 plant had active brucellosis, and 6 had asymptomatic infections (76). Twenty-two workers at a Brucella rev-1 vaccine plant developed brucellosis, and 6 had asymptomatic infections (60). One Burkholderia pseudomallei infection occurred when a culture mistakenly believed to be Pseudomonas cepacia was sonicated on the open bench for enzyme preparation (78).

An outbreak occurred from the wind-borne spread of anthrax from a military microbiology plant in Russia. The 77 individuals, 68 of whom died as a result of exposure to Bacillus anthracis, were not included in this survey (79).

**Infections in research laboratories**

A total of 116 bacterial infections were reported from research facilities. Six cases of N. meningitidis infection occurred in research laboratories (39, 80–84). Fatalities resulted from an LAI with N. meningitidis serotype B (39) and from an LAI with an attenuated strain of Y. pestis (85). The U.S. Select Agent program reported three B. melitensis LAIs and four F. tularensis LAIs. Three researchers in the same laboratory were infected by handling F. tularensis incorrectly assumed to be the avirulent strain (86). In another case, video surveillance tapes of work in the biosafety cabinet were analyzed after diagnosis of an LAI with F. tularensis; the unvaccinated researcher wore insufficient respiratory protection and disposed of contaminated waste materials outside the biosafety cabinet (87). A researcher did not notice that a paper towel was contaminated with spores before disposing of it outside the biosafety cabinet; the follow-up nasal culture was positive for B. anthracis (88).

Case studies of graduate students infected while conducting research activities include a Ph.D. student infected with C. difficile (89). An infection with Gastrospirillum hominis was attributed to ingestion (90). The infected researcher did not wear gloves during the dissection of a cat stomach and also was splattered on the face and glasses with material from the tissue bath (90). Another student was infected during the supervised cleanup of a spilled shaker flask of Vibrio cholerae; this was the first case of indigenous cholera reported in Austria in 50 years (91).

**Means of exposure for bacterial LAIs**

Sniffing plates for identification purposes is frequently cited as a route of aerosol exposure. An experimental evaluation of this risk was conducted using overnight cultures and an air sampler (92). The highest number of organisms from a 4-minute air sample was from S. aureus (12.5 CFU/ml). Bacillus spp., B. pseudomallei, Pseudomonas aeruginosa, and nonpathogenic E. coli produced 6.25 CFU/ml. The authors conclude that the risk is low, because a sniff is estimated to inhale 50 to 200 ml of air; however, the recommendation is avoidance if a pathogen transmitted by the airborne route is suspected (3). Baron and Miller (16) state that the attribution of sniffing plates as a cause of LAI may be historical; subculturing, preparing smears, and performing catalase assays are more likely sources of aerosol transmission.

**Brucella infections**

Aerosol exposures to Brucella occurred in clinical, production, and research laboratories, with infections documented in staff that were not working directly with the organism. Although mucous membrane exposures from splashed cultures (42, 44, 45) and parenteral exposures (42, 93) were reported, these cause less than 20% of the exposure incidents (94).

**Brucella infections in clinical laboratories.** In addition to Brucella exposure incidents described previously in this chapter (56, 95), 31% of the staff in a large U.S. clinical laboratory were infected when one slant was subcultured on the open bench (61). Brucella is an endemic zoonotic in many countries, which increases the risk of infection in the general population and in clinical laboratory staff. For example, 2.5% of the positive aerobic blood culture results from 2002–2009 in an area of southern Israel were positive for B. melitensis. Because a significant amount of handling occurs prior to isolate identification, it is recommended that, in countries where Brucella is endemic, all positive blood cultures be manipulated in the biosafety cabinet to prevent exposures (96). Routine identification procedures conducted on the open bench resulted in 7 LAIs in Saudi Arabia (97), 12 LAIs in Turkey (98), 7 LAIs in Israel (94), and 38 LAIs in Iran (99). An LAI in Australia resulted from a Brucella suis isolation; the samples were...
from a hunter of feral pigs (100). In Beijing, a nonendemic area of China, a laboratory technician was infected by an isolate from an acute case of brucellosis; the index case was a fur-maker from Inner Mongolia (101). Travel-associated infections in tourists were the source of seven LAIs in clinical laboratory staff in Germany (102). LAIs with *B. melitensis* in clinical laboratories in France, Turkey, Canada, and Saudi Arabia (98, 103–109) were attributed to sniffing plates.

There are several reports of misidentification of *Brucella* from commercial bacterial identification kits; this resulted in exposures when antibiotic sensitivity testing procedures were conducted on the open bench (57, 109–112). According to two reports, the clinical laboratory worker was infected while culturing the blood of a lab worker with a LAI (110, 113). A similar event occurred when, following misidentification, index patient cultures were forwarded to reference laboratories where two staff members were exposed and developed brucellosis (114, 115). Bouza et al., in a retrospective study of *Brucella* infections in clinical laboratory staff in Spain, analyzed 75 LAIs; 62 occurred between 1980 and 1999 and were included in this survey (116). These investigators found that the number of LAIs correlated with the number of *Brucella* isolations in the laboratory. Attack rates were: 6.4% in labs with less than five isolations of *Brucella* per year, 13.9% for labs with 5–10 isolates per year, 21.4% for labs with 11–20 isolates per year, and 46% for labs with more than 20 isolations of *Brucella* spp. per year. The route of exposure was airborne in 68 cases, contact with skin in 1 case, and unknown in 6 cases (116). A veterinarian became infected while isolating *Brucella* from dromedary camel milk (117). One of the nine technicians isolating *Brucella* from goats in a veterinary microbiology laboratory in Malaysia was infected (118).

A literature review and analysis of English-language reports of *Brucella* LAIs provided information on exposure risk and PEP (119). Routine identification activities resulted in 88% of the infections. Staff identified as having had high-risk exposures were 9.3 times more likely to develop an LAI as staff in the low-risk exposure group. The CDC has revised the risk classifications for *Brucella* exposures as follows: “High—All persons manipulating a *Brucella* isolation in a class II biosafety cabinet without using biosafety level 3 precautions or on an open bench and any person present within a 5-ft. radius of these activities; all persons present in a laboratory room during widespread aerosol-generating procedures. Low—All persons present in a laboratory room at a distance greater than 5 ft. from manipulation of a *Brucella* isolate but without high-risk exposures as defined above. None—if all handling and testing of a *Brucella* isolate was done in a Class II biosafety cabinet using biosafety level 3 precautions” (120).

### Brucella Infections in Production Laboratories

Analysis of 22 symptomatic and 6 asymptomatic LAIs from the production of live *B. melitensis* Rev-1 vaccine virus revealed a 17.1% attack rate for all staff and a 39.5% attack rate for staff working in areas with open windows above the exhaust from a production area (60). Fifteen symptomatic and 5 asymptomatic infections resulted from working in a *Brucella* S19 plant; aerosol is assumed to be the major route of exposure because only 5 individuals recalled exposure incidents (76).

### Brucella infections in research laboratories

When one polystyrene centrifuge tube containing *Brucella abortus* shattered during transport, 11 researchers and 1 administrative staff member were infected (58). In the United States, research with *Brucella* is conducted under strict regulations because it is a potential agent for bioterrorism; three of the reported six infections with *Brucella* occurred in research laboratories. One LAI resulted from conjunctival exposure while decontaminating an aerosol chamber used for rodent experiments with aerosolized *Brucella* (121). *Brucella* isolated from a marine mammal caused an LAI despite appropriate use of BSL3 procedures (122). Antigen production from the M-strain of *Brucella canis*, which is avirulent in dogs, also caused an LAI (123). A postgraduate student became infected from cultures collected for study of bovine miscarriage (124).

### Mycobacterium tuberculosis infections

*Mycobacterium tuberculosis* infections

*Mycobacterium tuberculosis* infections in clinical settings. Twenty-three percent of the bacterial infections were due to *M. tuberculosis*. Workers were exposed to infectious aerosols from defective or improperly certified biosafety cabinets (125–127), the absence of biosafety cabinets (128), a defective ventilation system (11), autopsies, and preparing tissue sections (11, 12, 129–135). Analysis of 28 LAIs with *M. tuberculosis* in Japan indicated that 25 occurred in laboratories that did not have a biosafety cabinet (128). One laboratory reported that locating commonly used laboratory equipment in a mycobacteriology laboratory also resulted in exposure of personnel not working with *M. tuberculosis* (136); this was also a factor in some clinical laboratories in Japan (128). The aerosols generated in postmortem analysis of a dog (134) and by the use of pressurized refrigerant for cryosectioning human specimens (129) resulted in LAIs for staff involved in those procedures, but not for staff involved in clinical care of the unsuspected canine or human case of tuberculosis. One LAI was traced to the inadequacy of the heat-inactivation step (20 minutes at 80°C) for the large inoculum required for phenol-chloroform extraction used for IS6110 restriction fragment length polymorphism (RFLP) typing analysis of samples (137). Three workers in a medical waste processing facility were...
infected with *M. tuberculosis*; in one case, the strain was matched to a patient in a hospital that sent waste to the facility (138).

A study of seroconversion rates in 17 Canadian hospitals reported an overall annual risk of tuberculin conversion at 1% per year for laboratory technicians. Included in this study were measurements of room air-exchange rates for the microbiology and pathology laboratories, as well as the length of time required for diagnosis of tuberculosis. Menzies found that the risk of seroconversion was higher for staff working in laboratories with low air-exchange rates and in hospitals with delayed diagnosis of tuberculosis in admitted patients (133). Parenteral exposures to *M. tuberculosis* have also been documented (136, 139). While transferring a sample of *M. tuberculosis* for drug susceptibility testing, a microbiology laboratory technician sustained a needlestick and developed a cutaneous infection at the site (140).

**Mycobacterium tuberculosis infections in research.** A leaking pressure valve on an aerosol exposure chamber for infecting rodents with *M. tuberculosis* resulted in three subclinical infections (141). In another incident, two of the three researchers working with drug-resistant *M. tuberculosis* became infected; the third became tuberculin purified protein derivative (PPD) positive. This was considered an aerosol exposure because respirators were removed within the animal room after cage changing (D. Robbins, 40th Biol. Safety Conf., 1997).

**Neisseria meningitidis infections**

**Neisseria meningitidis infections in clinical laboratories.** Sejvar et al. reviewed 16 infections with *N. meningitidis* that occurred in clinical microbiology laboratories; 9 were serogroup B, and 7 were serogroup C (41). Fourteen of the staff had made suspensions of the organisms on the open bench; 2 had done the procedure behind a splash shield. In contrast to most of the *Brucella* exposures, only the staff member who worked with the specimen became infected. The microbiologists who became infected with *N. meningitidis* had all conducted routine procedures, such as making a suspension or doing a catalase test. This indicates transmission by droplet, not aerosol. Unfortunately, eight cases, or 50%, were fatal (41). One technician in a bacteriology laboratory had *N. meningitidis* group C cultured from her right elbow and *Salmonella enterica* serovar Enteritidis cultured from her right knee (17).

**Neisseria meningitidis in research laboratories.** Work on the open bench resulted in a fatality to a researcher working with serogroup B (39). An unvaccinated undergraduate student conducting a summer research project handled cultures on the open bench and became infected (81). Treatment of an LAI required that a researcher undergo amputation of her legs, left arm, and the digits of her right hand. Initially, the infection was considered to be community acquired by the Department of Labor, but subsequent analysis confirmed the workplace origin of the infection (63, 82). The Sejvar et al. article (41) was the basis for the successful appeal to the Department of Labor (63). A researcher became infected with Z5463, *N. meningitidis* group A strain, as a result of work in a defective biosafety cabinet (83).

**Aerosol exposures to Chlamydia**

Sonication of *Chlamydia trachomatis* cultures on the open bench caused seven LAIs (142; K. Peterson, 25th Biol. Safety Conf., 1982). Aerosolized *C. trachomatis* L34/bu serovar caused atypical pneumonia in two members of the same laboratory; one handled the organism directly, but the other did not (143). In a teaching laboratory, the aerosols from the contaminated plumage of a flying pigeon infected the instructor with *C. psittaci* (144). In preparation for an avian influenza study in 3-week-old turkeys, 1-day-old turkeys were placed in a negative-pressure chamber and cared for by a veterinary scientist. At 2 weeks of age, the turkeys developed a respiratory infection, and, simultaneously, the researcher was infected with *C. psittaci* genotypes D, F and E/B (145).

**Other routes of transmission for bacterial LAIs**

**Parenteral exposures.** A needle used to aliquot *Pasteurella multocida* isolated from a fowl cholera epidemic caused a severe inflammation infection of hand and arm; a needlestick from the Clemson strain of *P. multocida* produced only a mild local infection (146). A puncture from a Pasteur pipette contaminated with bacillus Calmette-Guérin (BCG) resulted in a carpal tunnel syndrome in a laboratory technician (147).

**Ingestion.** Contamination of the hands resulting in subsequent ingestion is the probable mode of transmission for enteric pathogens. LAIs associated with this route of transmission were *Salmonella* (124 LAIs), *Shigella* (85 LAIs), pathogenic *E. coli* (18 LAIs), *Vibrio* spp. (6 LAIs), *C. difficile* (3 LAIs), and *Listeria monocytogenes* (1 LAI). *Shigella* was the most commonly reported LAI in surveys of clinical laboratories in the United States and the United Kingdom (13, 16, 33). Many enteric pathogens have a low infectious dose, and hand-washing procedures may not remove all pathogens. In one incident, a child visiting the laboratory touched a culture of *E. coli* O157. The child’s hands were immediately washed by her parent; however, a serious infection occurred (148). A food-borne outbreak can result in a large number of cultures submitted to a laboratory, which increases the risk of infection for staff. This was a factor in an LAI with *E. coli* O157 (66) and three *Shigella* infections (33). Strict compliance with laboratory
policies for wearing and removing gloves, as well as hand washing after glove removal, must be required of all staff to prevent contamination of phones, computer keyboards, etc. (66).

The distribution of S. Typhi as a proficiency testing exercise resulted in a number of S. Typhi LAIs associated with poor work practices, such as mouth pipetting, smoking, and eating in the lab (46, 149). The importance of automatic faucets or foot pedals is illustrated by the 19 S. Typhi LAIs that occurred when a student in a clinical laboratory contaminated the hand-washing sink faucets (150) and by an outbreak of three simultaneous S. sonnei infections when only one staff member had handled the culture (16). Cleaning a biosafety cabinet was the only potential exposure to S. sonnei for one LAI (16). Twelve infections occurred when a disgruntled employee contaminated pastries in the staff break room using a stock strain of Shigella (16). E. coli O157 exposures caused 17 LAIs; 13 were in clinical laboratories settings. Five E. coli O157 LAIs occurred in research settings (151–153). Needlesticks resulted in cutaneous infections with M. tuberculosis (140) and Neisseria gonorrhoea (154). A cutaneous case of B. anthracis resulted from transport of contaminated vials without wearing gloves (155). A cutaneous infection with Bacillus cereus (325) and a possible Mycobacterium leprae cutaneous infection were also reported (156).

**Rickettsial LAIs**

For the sake of consistency with the Sulkin and Pike LAI surveys, rickettsia is considered as a separate category of agents rather than being included with bacteria as is current practice. Between 1979 and 2015, there were literature reports of 205 symptomatic rickettsial infections with one death. During this period, C. burnetii, the etiologic agent of Q fever, was the fifth most common cause of all LAIs and accounted for 195 symptomatic rickettsial infections and one fatality (see Table 4 for references). When asymptomatic infections are added, the total becomes 405. Eleven rickettsial infections were identified as belonging to the Typhus Group—Rickettsia typhi (8 LAIs), Rickettsia conorii (2 LAIs), and Rickettsiatsutsugamushi (1 LAI). No secondary infections were noted from rickettsial infections.

Research involving the use of sheep in hospitals and medical school laboratories continues to expose laboratory and nonlaboratory personnel to C. burnetii. Antibody titers against C. burnetii in three research staff were reported in 2009 and are recorded in Table 4; however, the interpretation of the titers is in dispute (121).

**Means of exposure for rickettsial LAIs**

When publications identify the mode of transmission, Q fever infections were attributed to inhalation. A total of 189 C. burnetii LAIs were associated with zoonotic transmission from naturally infected asymptomatic sheep. The infected personnel either worked with the sheep or were in some proximity to sheep during their workday. Sheep may carry the organism in their blood, urine, feces, tissue, and milk. It has been estimated that the placenta of infected sheep may contain 10⁶ organisms per gram of tissue and 10⁴ organisms per gram of milk (157). Wedum et al. (22) noted that the infectious dose for 25–50% of human volunteers for C. burnetii by inhalation is only 10 organisms (22). This knowledge may have positively impacted husbandry practices for sheep used in research in the United States. A survey of U.S. members of the Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC) who worked with research animals between 1999 and 2004 indicated only one confirmed case of Q fever (158). One case of Q fever resulted from necropsy of aborted fetuses of cattle, sheep, goats, pigs, and horses (T. Graham, Am. Biol. Safety Conf., 2014). The two nonzoonotic C. burnetii infections were attributed to exposure to a human placenta (159) and a leaking biosafety cabinet filter (160). The remaining rickettsial infections were associated with parenteral (161, 162), mucous membrane (163), and inhalation or unknown transmissions. The known sources of the exposures were an eye and lip splash from opening a microcentrifuge tube (163), sonication of infected cells on the open bench (164), and needlesticks. Other sources were not identified except that the agent was being worked with (165).

**Viral LAIs**

A total of 764 overt viral infections with 19 fatalities were reported between 1979 and 2015; references are listed in Table 5. The fatalities resulted from arboviruses (3 LAIs), hantavirus (2 LAIs), filovirus (1 LAI), Marburg virus (2 LAIs), severe acute respiratory syndrome coronavirus (SARS-CoV) (1 LAI), and one fetal abortion caused by a maternal parvovirus infection. The fatal hantavirus infections resulted from field studies with bank voles in Finland (166) and with rodents in West Virginia (167).

A groundbreaking genomic mapping study of Ebola virus contains a statement honoring the contribution of five authors who succumbed to the disease prior to the publication (168). In addition to sample collection, these authors were actively involved in Ebola patient care, and the fifth was also caring for an infected family member (169). Due to the difficulty of assessing exposure during the challenging field conditions of the 2014 Ebola epidemic, these infections are noted here but not included in the final total of viral LAI.
The seven secondary infections were due to a novel adenovirus titi monkey adenovirus (TMAdV) (1 LAI), *Macacine herpesvirus 1* (1 LAI), Marburg virus (1 LAI), a vaccine strain of poliovirus (1 LAI), SARS (2 LAIs), and Zika virus (1 LAI). Two of the 19 LAI fatalities listed were secondary infections resulting from the autopsy of a Marburg virus LAI and a mother providing care for a SARS LAI. The secondary polio infection occurred in the immunized child of a worker accidentally exposed to Mahoney prototype vaccine of poliovirus in a vaccine production facility. The stool isolate from the infected child demonstrated complete nucleotide sequence identity with the virus strain used for vaccine production (170). The Zika virus secondary infection occurred in the wife of a field virologist who collected mosquitoes in Senegal and developed symptoms after return to the United States. This case, and the infections of the two field virologists on this study, were the first identification of Zika virus in the Western world (171). An outbreak of a novel adenovirus (TMAdV) in a titi monkey colony caused a respiratory illness in a researcher and a secondary infection in a household member (172). It is notable that one primary SARS LAI led to two secondary infections (mother and nurse); this led to five tertiary infections that resulted from contact with a nurse who became a secondary case while caring for a primary LAI (173).

Of the 759 viral LAIs, 497 (65%) occurred in research laboratories, 215 (28%) in clinical laboratories, 16 (2%) in field work, and 9 (1%) in production laboratories. A total of 460 asymptomatic infections were also reported between 1979 and 2015. Refer to Table 5 for citations for these viral infections. It should be noted that “research” activities include laboratory studies with animal models and field studies.

**Retroviruses**

LAIs with retroviruses were first described in 1988. Retroviral infections associated with human immunodeficiency virus (HIV), simian immunodeficiency virus (SIV), simian foamy virus (SFV), and simian D retrovirus (SDR) have been reported since then. In the United States, between 1985 and 2015, there were 17 confirmed occupationally acquired cases of HIV in clinical laboratory technicians and 21 possible cases; in addition, 4 researchers were infected handling HIV cultures (174). The Ippolito review provides details on occupationally acquired cases through 1997 (175). An HIV LAI is listed in the Belgian survey (34), and a seroconversion to HIV in a clinical laboratory worker was also reported in the literature (176).

Two technicians seroconverted to SIV while handling samples from nonhuman primates (NHPs), and one of the SIV-infected individuals may have been persistently infected (177). Seroconversions to spumavirus have been documented in staff occupationally exposed to NHPs. Details are provided in the discussion of zoonotic infections associated with NHP studies.

**Poxviruses**

Twenty-seven LAIs resulted from research activities with poxviruses between 1986 and 2015, and 23 were due to vaccinia virus. Recombinant viruses constructed from the Western Reserve strain of vaccinia virus caused nine LAIs (178–182); one LAI was caused by recombinant New York City Board of Health (NYCBOH) strain (183) and one by recombinant raccoonpox virus (184). Immune responses to the insert in the vaccinia virus construct were demonstrated in three of the LAIs (180, 184, 185). Although thymidine kinase deletion mutants are less pathogenic in mice than the parent vaccinia virus strain, nine LAIs were caused by these deletion mutants (180–183, 186, 187).

Sixteen exposures to vaccinia virus were reported to the CDC Poxvirus Team in a 3-year period (183). Five of the exposures reported to the CDC were from eye splash, seven were from needlesticks, two occurred in an animal care facility, one occurred as a result of tube leakage, and one was unknown. Ten exposures did not result in infection; however, 5 LAIs occurred and 4 of these required hospitalization. All of the infected staff members had not complied with the requirement of smallpox vaccination within 10 years (183). A case report that provides more detail on one of the needlestick exposures listed in the CDC report is available (188). Two individuals were working on immunizing mice in the small space of a 1.2-meter biosafety cabinet. After placing an immunized mouse in its cage, the hand of one individual was scratched by the needle being held by the other individual. The scrape went through the glove and skin, and, although the plunger of the syringe was not depressed, the individual developed an LAI that required hospitalization. Procedures were revised, and now, when sharps are used, only one person may work in a biosafety cabinet. Double gloves are also required, and Occupational Health requires vaccination or a signed declination form (188). In 2015, a needlestick with wild-type Western Reserve strain resulted in an LAI in a recently immunized individual (179). In addition, two LAIs from cowpox virus (189, 190) and one each from raccoonpox virus (184) and buffalopox virus (18) were reported.

**Zoonotic viral infections**

Analysis of the viral LAIs associated with animal activities demonstrates how critical it is for laboratory staff to understand the potential for zoonotic infections in animal models. Between 1979 and 2015, there were 219 overt infections, 2 fatalities, and 180 seroconversions associated with zoonotic viral infections that were not experimentally introduced to the research model. The overt zoonotic LAIs were caused by hantavirus (188 LAIs), *Macacine herp...
### TABLE 5.
Viral LAI references 1979–2015

<table>
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<tr>
<th>Microorganism</th>
<th>Number of LAIs</th>
<th>References</th>
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<tr>
<td></td>
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<td>Subclinical</td>
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<td>Adenovirus, novel TMAAdV</td>
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<td>Machupo virus&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Marburg virus</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Mayaro virus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mimivirus</td>
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<td>0</td>
</tr>
<tr>
<td>Newcastle disease virus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Norwalk virus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Orf virus</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Orungo virus</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>10–11</td>
<td>1</td>
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<tr>
<td>Poliovirus</td>
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</table>

(continued)
herpesvirus 1 (10 LAIs), lymphocchoriomeningitis virus (LCMV) (6 LAIs), influenza A virus (5 LAIs), West Nile virus (5 LAIs), orf virus (2 LAIs), Ebola virus (1 LAI), and a novel adenovirus in titi monkeys, TMAdV (1 LAI). The fatalities were caused by hantavirus in a graduate student doing field research in West Virginia (167) and West Nile virus in a veterinary student doing a postmortem on a horse (191).

Zoonotic infections from rodents in animal colonies
The 189 hantavirus transmissions and 36 subclinical infections occurred among researchers who thought they were working with uninfected rodents. Rodent colonies may be infected by feral animals, and this may explain hantavirus infections in Argentina (192), Belgium (193), China (194–196), France (197), Japan (198, 199), Korea (200), the United Kingdom (201, 202), and Singapore (203). This association was confirmed when Seoul virus was identified in the wild rat population of Yunnan, China, and identified as the cause of a hemorrhagic fever with renal syndrome (HFRS) outbreak in students using rats for research (195). One lot of rats produced by a commercial vendor and supplied to three colleges in Yunnan, China, infected a researcher with a reasortant of Hantaan virus that had not been previously described; subclinical infections with the same reasortant were also detected in 5 students who had been bitten and 11 animal care staff (196). Another example of zoonotic infection involved eight animal handlers and junior scientists who were exposed to LCMV while working with nude mice (204). In this incident, the mice were inadvertently infected by an LCMV-contaminated tumor cell line. The serological monitoring program for sentinel animals in the facility had lapsed for 6 months. An animal care technician was diagnosed with LCMV 3 months after he became ill, when the sentinel mice in the animal room seroconverted. The source of infection was traced to an LCMV-contaminated cell line (A. Braun, 47th Biol. Safety Conf., 2004).

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Number of LAIs</th>
<th>Overt</th>
<th>Subclinical</th>
<th>References</th>
</tr>
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<tr>
<td>Rabies virus</td>
<td>1</td>
<td>0</td>
<td>34</td>
<td></td>
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<tr>
<td>Rabbitpox virus</td>
<td>1</td>
<td>0</td>
<td>183</td>
<td></td>
</tr>
<tr>
<td>Raccoon pox virus (recombinant)</td>
<td>1</td>
<td>0</td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>Rift Valley fever virus&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0</td>
<td>2</td>
<td>234</td>
<td></td>
</tr>
<tr>
<td>Rocio virus&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>0</td>
<td></td>
<td>R. Gershon, 27th Biol. Safety Conf., 1984</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>6</td>
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<td>15</td>
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<tr>
<td>Sabia virus</td>
<td>2</td>
<td>0</td>
<td>235, 446</td>
<td></td>
</tr>
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<td>SARS-CoV</td>
<td>6</td>
<td>0</td>
<td>173, 227–229</td>
<td></td>
</tr>
<tr>
<td>Semliki Forest virus&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1</td>
<td>0</td>
<td>447</td>
<td></td>
</tr>
<tr>
<td>Simian foamy virus</td>
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<td>20</td>
<td>210–213, 448–450</td>
<td></td>
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<tr>
<td>Simian immunodeficiency virus</td>
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<td>177, 251, 258, 451</td>
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<td>Simian type D retrovirus</td>
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<td></td>
</tr>
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<td>SPH114202</td>
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<td>0</td>
<td>452</td>
<td></td>
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<tr>
<td>Swine influenza virus</td>
<td>2</td>
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<td>239</td>
<td></td>
</tr>
<tr>
<td>Tacaribe virus</td>
<td>1</td>
<td>0</td>
<td>453</td>
<td></td>
</tr>
<tr>
<td>Tick-borne meningonecephalitis virus&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1</td>
<td>0</td>
<td>454</td>
<td></td>
</tr>
<tr>
<td>Vaccinia virus</td>
<td>23</td>
<td>2</td>
<td>160, 178, 183, 185–188, 254, 262–264, 455</td>
<td></td>
</tr>
<tr>
<td>Varicella virus</td>
<td>1</td>
<td>0</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Venezuelan equine encephalitis virus&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4</td>
<td>0</td>
<td>160, 234, 456</td>
<td></td>
</tr>
<tr>
<td>Vesicular stomatitis virus</td>
<td>1</td>
<td>0</td>
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<td></td>
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<tr>
<td>Vesivirus</td>
<td>2</td>
<td>0</td>
<td>219</td>
<td></td>
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<tr>
<td>Wesselsbron virus&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3</td>
<td>0</td>
<td>234</td>
<td></td>
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<tr>
<td>West Nile virus&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>0</td>
<td>191, 218, 253, 458</td>
<td></td>
</tr>
<tr>
<td>Zika virus</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Total viral LAIs</td>
<td>759–760</td>
<td>460</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> References for Biological Safety Conference are meetings sponsored by the American Biological Safety Association, Mundelien, IL.

<sup>b</sup> Typical arboviruses, orbiviruses, rhabdoviruses, and arenaviruses associated with arthropods or that have zoonotic cycles.

<sup>c</sup> Additional infections with this virus listed in the SALS report (233).
Zoonotic infections associated with non-human primate studies

Macacine herpesvirus 1, formerly CHV-1 or herpes B virus, was transmitted from NHPs to 11 caretakers or researchers, resulting in a fatality and a secondary infection (see Table 5 for references). One fatality resulted from an eyelash exposure to urine and feces from a caged NHP; eye protection was not worn and rinsing the eye was not attempted for 45 minutes because observation was considered a low-risk activity (205). A researcher dissecting optic nerve from a sample of NHP tissue was hospitalized to receive treatment with intravenous, high-dose ganciclovir and then discharged with a life-long prescription for oral valacyclovir to keep the latent virus in check (K. Johnson and T. Winters, Harvard School of Public Health Grand Rounds, 2012).

Asymptomatic infections with an Ebola-related filovirus were reported in 42 animal handlers (206–208). Two seroconversions to the zoonotic SDV have also been reported in animal handlers; one of the individuals was also infected with spumavirus from a bite in a separate incident (209). Seroconversions to the zoonotic spumavirus, or SFV, were documented in 20 animal handlers or persons working with NHPs (210). The significance of these seroconversions to simian retroviruses is not well understood. The virus causes a latent infection, and seropositivity has been documented 10 years after a bite from a mandrill and 22 years after a macaque bite (211). In one case, SFV was isolated from a culture of peripheral blood monocytes obtained from a healthy animal caretaker who seroconverted to SFV 20 years prior to the virus isolation (212). Switzer et al. commented “although SFV is nonpathogenic in naturally infected NHPs, the significance of SFV infection in humans is poorly defined. The introduction of SFV infections is of concern because changes in the pathogenicity of simian retroviruses following cross-species infection are well documented, since both HIV-1 and HIV-2 emerged from benign SIV infections in the natural primate hosts.” To date information on this subject is inadequate to come to any conclusions; however, the importance of long term follow-up on these exposures has been recognized and has been initiated by the Centers for Disease Control and Prevention” (213). Novel zoonotic adenoviruses have also been identified in titi monkey (TMAdV) and baboon colonies (BaAdV-1 and BaAdV-2). TMAdV caused a primary infection and a secondary in a household member (172). Eleven seroconversions to BaAdV-1 and BaAdV-2 occurred in staff who worked with a baboon colony (214).

Experimentally infected animals

In comparison, there were reports of only 20 symptomatic infections, and no asymptomatic infections, from work with experimentally infected animals. The LAIs from experimentally infected animals were caused by cowpox virus (1 LAI), Ebola virus (1 LAI), LCMV (3 LAIs), Marburg virus (1 LAI), swine influenza (2 LAIs), vaccinia virus (7 LAIs), Venezuelan equine encephalitis virus (3 LAIs), and West Nile virus (2 LAIs). The inoculation of guinea pigs with Marburg virus and Ebola virus each resulted in a fatal LAI (215, 216).

Viral LAIs in field work

One overt infection with a new strain of Ebola virus was reported in a researcher who autopsied a wild chimpanzee to determine the cause of death (217). Fortunately, that infection did not result in the fatal hemorrhagic disease associated with other filovirus infections (Marburg virus and Ebola virus) in Europe and Africa. Transmission of West Nile virus occurred during field collection of blue jays (218) and horse autopsy (191); five investigators were infected with influenza A virus during an investigation of seal deaths (219). A field researcher examining seals (220) and one examining sea lions were painfully infected with marine calciviruses that cause lesions (220). Two cases of hantaviral infection occurred in field studies. A graduate student evaluating the impact of forestry practices on small mammals was fatally infected in West Virginia; a technician working on a similar study in California was also infected (221). In effort to evaluate the occupational risk for field studies, 995 mammalogy conference attendees who had exposure to rodents in North America provided samples for a survey of antibody levels. Antibodies against Sin Nombre virus were found in four persons, and two had antibodies to Arroyo or Guanarito virus (221). None of the seropositive individuals had worn any personal protective equipment prior to the U.S. hantavirus outbreak.

Viral LAIs in research and clinical activities

Sixty-seven percent of the viral LAIs occurred in research facilities. Arboviruses and other vector-borne viruses in both research and field settings accounted for 223 of the LAIs with three fatalities (see Table 5 for arbovirus references). A total of 215 viral infections occurred in clinical laboratories between 1979 and 2015. The 114 hepatitis B virus LAIs reported in the scientific literature are undoubtedly the tip of the iceberg, because one study calculated the attack rates for clinical laboratory technicians at 70% prior to the systematic introduction of hepatitis B virus vaccine (222). Following the implementation of the Occupational Safety and Health Administration (OSHA) Bloodborne Pathogen Standard in the United States (223), significant reductions in workplace transmission of hepatitis B virus have resulted from the availability of hepatitis B virus immunization, the use of “universal precautions,” or consistent BSL2 containment practices, needles with safety devices, and improved sharps disposal (224). This experience is mirrored in the report from the Wroclaw region of Poland, where 323 health care workers
were infected with hepatitis B virus between 1990 and 2002; 30 of the 323 cases were clinical laboratory staff. Since 2002, the number of cases reported annually in that region decreased due to the increasing number of vaccinated staff. However, the number of hepatitis C virus infections was increasing (225). In the absence of a hepatitis C virus vaccine or a recommended PEP regimen, strict adherence to safety practices is the most effective defense against infection with hepatitis C virus.

Means of exposure for viral LAIs
It is often not possible to determine the exact cause of a LAI; only that it has occurred and the information available is that the individual “worked with” the agent. One example would be a researcher in a nonendemic area who performed the initial infection of a mosquito colony by feeding dengue-infected blood under an artificial membrane. The researcher was bitten by an escaped, but unengorged, mosquito. The virus later isolated from the infected researcher was 98.9% homologous with the laboratory strain. The authors of the case study did not rule out percutaneous infection with infectious blood droplets. If the researchers had not been vaccinated for dengue, the researchers would have been infected, as they were bitten by mosquitoes that were not infected. However, if the researchers had been vaccinated, they would not have been infected, as dengue is a viral disease and does not cause infection via percutaneous exposure to infectious blood droplets. The researchers did not rule out percutaneous exposure to infectious blood droplets, but they did rule out percutaneous exposure to infectious blood droplets.

Aerosol exposures
Many of the viral LAIs resulted from inhalation of infectious virus. SARS was transmitted to four researchers in China when incompletely inactivated infectious materials were removed from the BSL3 laboratory for further analysis at BSL2 (173, 227). In Singapore, another SARS infection occurred due to cross-contamination of a culture of West Nile virus with SARS, and subsequent handling of the SARS-infected West Nile preparation at BSL2 (228). One SARS LAI occurred in Taiwan when liquid waste leaking from a biohazard bag in a BSL4 lab was cleaned up; the researcher wore inadequate personal protective equipment and did not use a disinfectant effective against the virus (229). Exposure to aerosolized Mayarovirus occurred during a sucrose-acetone extraction procedure that involved dehydration of the product with a vacuum pump (230). A technician performing Western blots with patient samples from a pneumonia outbreak unfortunately became the first documented infection with Mimivirus, which is a virus isolated from amoebae in a cooling tower (231).

Four serious LAIs and five seroconversions to African horsesickness virus were the first indication that this virus could infect humans. In this case, individuals were exposed to a aerosol from a dried powder vaccine that were released when vials broke as they were being filled (232). Historically, about 20% of arbovirus infections are attributed to inhalation exposures (233). Some of the inhalation transmissions from arboviruses included infections due to the spread of Wesseliern virus from work in another room, to opening a blender containing Dugbe virus-infected mouse brains without precautions (234), and to a centrifuge bottle containing Sabin virus cracking during a run (235). Five infections with Dohri virus resulted from inhalation of aerosols generated when opening flasks (236). Enteropathica endemica was transmitted, presumably by aerosol, from close contact with bank voles (237). The hantavirus LAIs were attributed to aerosol exposure from handling mice and preparing tumor samples from mice that may have been infected by feral animals. The LCMV infections occurred when personnel handled mice that had been inadvertently infected by a contaminated cell line (204). A clinical laboratory worker was exposed to Machupo virus aerosols when a blood tube broke in the centrifuge (238); that technician developed Bolivian hemorrhagic fever. The wearing of dust masks instead of respirators resulted in two LAIs with swine influenza in staff collecting nasal cultures from infected pigs (239).

Parenteral exposures
Laboratory and wild animals were the source of many of the viral LAIs, with parenteral exposures due to bites, scratches, and accidents with sharps resulting in infections. Monkey bites and/or scratches transmitted Spumavirus (SFV) to 23 NHP handlers; that route of exposure was transmitted Mokola virus (234). During a procedure to insert gavage tubes, two researchers were bitten by sheep and infected with orf virus (249). Six NHP animal handlers developed antibodies to filovirus antigens; four had evidence of recent infection, and one of these sustained a scalp cut during the autopsy of an infected NHP (208).

In addition to phlebotomy, parenteral exposures to HIV in clinical settings were associated with handling broken blood tubes and a broken capillary tube (175). A parenteral exposure in a laboratory producing large quantities of concentrated HIV occurred when a blunt cannula was used to clean a centrifuge rotor (250). An HIV researcher was infected with the virus by needlestick (174). The first
report of SIV infection in a human being resulted from a deep puncture wound (251). West Nile virus LAIs were caused by needlestick (252); parenteral exposures were received during necropsy of an infected bird and preparation of an infected mouse brain (253). A needlestick during a viral purification procedure (254) or animal inoculation (182, 188) each caused a vaccinia LAI; a needlestick also caused the raccoonpox virus infection (184). A puncture from a glass lyophilization vial transmitted buffalopox virus (18). Hepatitis C virus was transmitted when a sample tube containing infected blood broke and cut two fingers (255). The bite of a rat infected with cowpox virus transmitted the virus (189). LCMV infection was confirmed by serology on blood drawn 5–7 years after exposure to Armstrong clone 53b (1 case) and clone 13 (3 cases) (256).

**Mucocutaneous exposures**

Mucocutaneous exposures to HIV in clinical settings were the result of splatter from an apheresis machine, sink disposal of blood samples (175), a blood analyzer apparatus (257), and opening a Vacutainer tube (176). In production laboratories, mucocutaneous exposures to HIV occurred when concentrated virus splashed a worker in the face or seeped through gloves in contact with leakage from a centrifuge (250). A nonintact skin exposure to SIV was also reported (258). One worker contracted conjunctivitis due to an eye splash while pipetting dilutions of coxsackie virus (259). Despite immediate lavage, conjunctivitis occurred in a researcher who sustained splatter in the eye while injecting mice with influenza B virus (260). A conjunctival infection with influenza A virus occurred when a seal sneezed in the face of a researcher; four other field workers were also infected with influenza A virus while doing autopsies to investigate seal deaths (261). A veterinary student who removed the brain and spinal cord of a pony infected with West Nile virus neuroinvasive strain 2 became infected; mucous membrane infection by droplet is suspected (191). The secondary case of *Macacine herpesvirus 1* occurred when the wife of an infected worker applied his contaminated cortisone cream to her nonintact skin (244). Three of the vaccinia LAIs were the result of failure to wear gloves (160, 180, 262). An investigator was infected with a strain of vaccinia virus that was a contaminant of the viral stock he was working with (178). Two vaccinia virus LAIs were caused by inadvertent contact with contaminated surfaces (181, 263). The exact cause of an eye infection could not be determined; however, plates were opened for analysis on the bench, eye protection was not worn, and glove use may not have been consistent (264). Similarly, an infection with cowpox was attributed to handling contaminated reagents or touching contaminated surfaces; cowpox virus DNA was found on many lab surfaces and as a contaminant in other viral stocks. The infected person was not working directly with the virus and, for this reason, had not chosen to become vaccinated (190). In four instances, staff members seeking medical attention for infections did not initially disclose the fact that their research may have resulted in exposure to them with vaccinia (186, 187, 262, 263). Fortunately, there were no nosocomial transmissions.

**Parasitic LAIs**

A total of 170 symptomatic, 4 asymptomatic, and 2 secondary parasitic infections representing 6 different genera and 20 species were reported during this period. The activities resulting in LAI were research (76 LAIs) veterinary teaching (81 LAIs), diagnostic in a clinical laboratory (3 LAIs), field studies (1 LAI), and not specified (9 LAIs). The agents responsible for the infections were *Cryptosporidium* (96 LAIs), *Leishmania* (15 LAIs), *Trypanosoma* (26 LAIs), *Toxoplasma* (15 LAIs), *Plasmodium* (17 LAIs), and *Schistosoma* (1 LAI) (see Table 6 for specific references). In addition, Brener reported personal knowledge of 50 cases of laboratory-associated *Trypanosoma cruzi*, with one fatality; however, details on dates and types of exposure were not available so these were not included in this survey (32).

**TABLE 6.**

Parasitic LAI references 1979–2015

<table>
<thead>
<tr>
<th>Agent</th>
<th>LAI overt</th>
<th>LAI subclinical</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Cryptosporidium</em> spp.</td>
<td>96</td>
<td>2</td>
<td>266–269, 287, 459–465</td>
</tr>
<tr>
<td><em>Leishmania</em> spp.</td>
<td>15</td>
<td>0</td>
<td>270, 276, 284–286, 289, 292, 294, 466, 467</td>
</tr>
<tr>
<td><em>Plasmodium</em> cynomolgi</td>
<td>4</td>
<td>0</td>
<td>280, 468</td>
</tr>
<tr>
<td><em>Plasmodium</em> falciparum</td>
<td>9</td>
<td>0</td>
<td>270–273, 288, 293, 469, 470</td>
</tr>
<tr>
<td><em>Plasmodium</em> vivax</td>
<td>4</td>
<td>0</td>
<td>272, 280</td>
</tr>
<tr>
<td><em>Schistosoma</em> mansoni</td>
<td>1</td>
<td>0</td>
<td>277</td>
</tr>
<tr>
<td><em>Toxoplasma</em> gondii</td>
<td>15</td>
<td>2</td>
<td>34, 279–283, 291, 471–475</td>
</tr>
<tr>
<td><em>Trypanosoma</em> spp.</td>
<td>26</td>
<td>0</td>
<td>34, 270, 275, 280, 290, 476–479</td>
</tr>
<tr>
<td>Total</td>
<td>170</td>
<td>4</td>
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</tr>
</tbody>
</table>
Means of exposure to parasitic infections

The most common means of acquiring the reported parasitic LAIs were ingestion and parenteral exposure, generally needles associated with animal inoculation. With one exception, an airborne infection (265), all of the Cryptosporidium infections were associated with ingestion of the infectious microorganisms. The Cryptosporidium infections occurred in veterinary students and were zoonotic transmissions through contact with infected calves. Two secondary infections occurred in spouses who washed the veterinary student’s contaminated clothing (266, 267). Two separate outbreaks were from veterinary laboratory exercises involving the removal of calves from artificial wombs (268, 269). The veterinary medical schools where the outbreaks occurred adopted preventive measures such as requiring testing of calves used for teaching, on-site doffing of personal protective equipment, and providing facilities for hand washing and changing clothing (268).

Until the LAIs were diagnosed, researchers had assumed that Plasmodium cynomolgi only infected monkeys; however, mosquito bites in the infected monkey colony transmitted the parasite to humans (270). Mosquito bites in insectories also transmitted Plasmodium falciparum and Plasmodium vivax (271–274).

The most common source of the exposure to parasitic agents was working with infected animals, insects, or ectoparasites, and accidents related to sharps and spills or splashes accounted for the remainder. Some of the activities associated with the transmission of parasitic infection include working without gloves (275–278) or eye protection (279–283), injecting animals (284, 285), recapping needles (286), smelling or being sprayed with stomach contents (265, 287), being bitten by infected mosquitoes (271–274, 288; H. Mathews, 42nd Biol. Safety Conf., 1999), and numerous needlesticks (283, 289, 290). Unique exposures were associated with assuming that the strain being handled was avirulent (291), being on immunosuppressive therapy while working with infectious materials (292), and puncturing a thumb while pressing a glass hematocrit tube into clay sealant (293). One infection was contracted during an unrelated field study of birds (294).

Fungal LAIs

Only 25 fungal LAIs were found in the literature review; the references are listed in Table 7. There were seven cases of Trichophyton mentagrophytes, and four to five additional dermatophyte infections, including Trichophyton verrucosum and Microsporum canis, were reported (34). Three cases each of Blastomyces dermatitidis (295, 296) and Coccioidioides immitis (5, 16) (H. Mathews, 42nd Biol. Safety Conf., 1999) were reported. Sporothrix schenckii caused two LAIs (297, 298); one LAI each were caused by Arthroderma benhamiae (299), Encephalitozoon cuniculi (300), Penicillium marneffei (301), and Trichophyton simii (302). Three infections occurred in clinical or public health laboratories (16, 295), while 18 occurred during research activities and 4 to 5 cases in an unspecified location.

Means of exposure to fungal infections

Fungal LAIs resulted from cutaneous, parenteral, inhalation, and mucous membrane exposures. Handling lab rats

<table>
<thead>
<tr>
<th>Fungus</th>
<th>Overt</th>
<th>Subclinical</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthroderma benhamiae</td>
<td>1</td>
<td>0</td>
<td>299</td>
</tr>
<tr>
<td>Blastomyces dermatitidis</td>
<td>3</td>
<td>0</td>
<td>295, 296</td>
</tr>
<tr>
<td>Coccioidioides immitis</td>
<td>3</td>
<td>0</td>
<td>5, 16 H. Mathews, 42nd Biol. Safety Conf., 1999</td>
</tr>
<tr>
<td>Dermatophytes, including</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichophyton verrucosum, Microsporum canis</td>
<td>4–5</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>Encephalitozoon cuniculi</td>
<td>1</td>
<td>0</td>
<td>300</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>1</td>
<td>0</td>
<td>480</td>
</tr>
<tr>
<td>Paracoccidioides brasiliensis</td>
<td>1</td>
<td>0</td>
<td>481</td>
</tr>
<tr>
<td>Penicillium marneffei</td>
<td>1</td>
<td>0</td>
<td>301</td>
</tr>
<tr>
<td>Sporothrix schenckii</td>
<td>2</td>
<td>0</td>
<td>297, 298</td>
</tr>
<tr>
<td>Trichophyton mentagrophytes</td>
<td>7</td>
<td>0</td>
<td>303, 304</td>
</tr>
<tr>
<td>Trichophyton simii</td>
<td>1</td>
<td>0</td>
<td>302</td>
</tr>
<tr>
<td>Total</td>
<td>25–26</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*aReferences for Biol. Safety Conf. are abstracts of meetings sponsored by the American Biological Safety Association International, Mundelein, IL.*
or guinea pigs that were not experimentally infected resulted in seven zoonotic LAIs (303, 304). Cutaneous infections occurred when two drops of liquid culture spilled on the bandage over a cut (298) and when one drop of culture fell on the skin while filtering a fungal mat (302). Two LAIs resulted from cuts acquired during tissue sectioning in pathology (295). An immunosuppressed student visited a mycology laboratory where the agent was handled (301) and became infected with *P. marneffei*. Failure to wear gloves or use correct work practices (297; H. Mathews, 42nd Biol. Safety Conf., 1999) resulted in LAI. Contaminated hands rubbing the eye probably inoculated the mucous membrane of the lower eyelid (299). Culture supernatant containing spores of *E. cuniculi* splashed into the eyes of a laboratory worker; this incident resulted in a severe eye disease with one cornea still clouded a year later (300).

Allergic reactions should also be an occupational concern for those working with fungal agents. Aerosol exposure during release of a pressurized canister used in the isolation of lysosomal enzymes from slime mold resulted in rhinoconjunctivitis and asthma in a research microbiologist (487). Ten staff required medical attention for allergic responses to *Penicillium citrinum* after working for 1 day on production of adenosine triphosphate (ATP) (305).

### Role of Infectious Aerosols in LAIs

Laboratory studies on potential sources of infection have focused on hazards produced from routine microbiological techniques. Table 8 lists data from several studies on the number of viable particles recovered within 2 feet of a work area, on the basis of an extensive series of air sampling determinations. Aerosols present two means of worker exposure—through minute respirable airborne particles and by the disposition of larger heavy droplets onto surfaces, equipment, and personnel. The data in Table 9 indicate that standard laboratory procedures can generate aerosolized particles that are respirable and, therefore, potentially hazardous to the laboratory workers and to others in the vicinity. However, the mere presence of organisms in the air is insufficient to cause disease. For infection to be initiated, the infectious dose, a means of exposure, and a susceptible host are all required. The FDA cautions that published infectious doses do not take into account the wide variability in the virulence of the strain and host susceptibility. For example, the published infectious dose for *E. coli* O157 is as low as 10 organisms (306); however, other strains of *E. coli* require an infectious dose of $10^8$ (22) to initiate infection.

### Occupational Health Programs

The continued development of occupational health programs will result in a minimization or reduction of LAIs through increased access to preemployment counseling on host factors, immunization, and timely PEP. In the United States, occupational health programs provide vaccination against hepatitis B virus and PEP for hepatitis B virus and human immunodeficiency virus (HIV); this is required for compliance with the OSHA Bloodborne Pathogen Standard.

### TABLE 8

<table>
<thead>
<tr>
<th>Operation</th>
<th>No. of viable colonies</th>
<th>Particle size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixing culture with: Pipette</td>
<td>6.6</td>
<td>2.3 ± 1.0</td>
</tr>
<tr>
<td>Vortex mixer used with 5 ml of culture in capped tube for 15 seconds</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Vortex mixer used with 10 ml of culture in capped tube until culture overflow hit rotating head</td>
<td>9.4</td>
<td>4.8 ± 1.9</td>
</tr>
<tr>
<td>Use of blender: Top on</td>
<td>119.6</td>
<td>1.9 ± 0.7</td>
</tr>
<tr>
<td>Top off</td>
<td>1,500.0</td>
<td>1.7 ± 0.5</td>
</tr>
<tr>
<td>Use of a sonicator:</td>
<td>6.3</td>
<td>4.8 ± 1.6</td>
</tr>
<tr>
<td>Lyophilized cultures:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opened carefully</td>
<td>134.0</td>
<td>10.0 ± 4.3</td>
</tr>
<tr>
<td>Dropped and broken</td>
<td>4,838.0</td>
<td>10.0 ± 4.8</td>
</tr>
</tbody>
</table>

*Adapted from reference 482.

*Mean number of viable colonies per cubic foot of air sampled.

*Count median diameter of particle.
Vaccination programs

When available for the agents studied, vaccination programs are very effective in preventing or minimizing the severity of LAIs. An analysis of 16 vaccinia virus exposure incidents reported to the CDC between 2005 and 2008 revealed that only four individuals had received the recommended smallpox vaccination within the previous 10 years (183). Prior to an LAI with vaccinia virus, the occupational health service at an academic institution offered counseling only to individuals seeking vaccination. After an LAI occurred, the policy was amended. Now all staff working with vaccinia virus are required to receive vaccination counseling, the vaccine is offered to all staff without contraindications, and declinations must be documented (178).

Vaccination is also recommended for microbiologists at risk of exposure to N. meningitidis (307). Previously, vaccinations against serogroup B were not available in the United States. However, as of August 15, 2015, the CDC recommends an additional vaccination against serogroup B for microbiologists handling N. meningitidis cultures (see http://www.cdc.gov/vaccines/hcp/vis/vis-statements/mening-serogroup.html). To provide appropriate immunizations, staff with potential laboratory exposure must be referred to an occupational health service. The immunization status of an undergraduate summer student was not confirmed prior to work with N. meningitidis; the student assured the principal investigator, and admitting hospital physicians when he became ill, that he had been immunized. However, the student was misinformed; he had not been vaccinated and PCR results on cerebrospinal fluid were positive for N. meningitidis serogroup A (81). Vaccination is also recommended for laboratory staff routinely exposed to S. Typhi.

Vaccination is an important tool in the prevention of infectious agents with a low infectious dose by the aerosol route. A historical review of LAI at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) between 1943 and 1969 indicates that the introduction of biosafety cabinets reduced the risk of infection with anthrax, glanders, and plague. However, even after the introduction of biosafety cabinets, infections with F. tularensis continued at the average rate of 15 per year, for Venezuelan equine encephalitis at 1.9 per year, and Q fever at 3.4 per year. In contrast, between 1989 and 2002, only 5 LAIs resulted from 289 reported exposures. The LAIs were glanders, Q fever, vaccinia, chikungunya, and Venezuelan equine encephalitis. The Venezuelan equine encephalitis, vaccinia, and Q fever LAIs were instances where infection occurred in vaccinated staff; however, the Q fever symptoms were mild. Also, vaccination status was considered in the evaluation for PEP for low-risk exposures (159).

Specialized programs are required for high-containment laboratories and include physical and mental fitness for duty, as well as the capacity to quarantine exposed staff. Guidance is available on management of exposures to some Ebola virus (308).

Postexposure prophylaxis

Guidelines for PEP after occupational exposures to hepatitis B and C viruses and HIV are available and emphasize that such exposures should be considered medical emergencies requiring prompt evaluation and response (309, 310). Several publications reported incidents where PEP probably minimized or eliminated acute laboratory infections with B. abortus (58, 75), B. melitensis (109, 311), B. pseudomallei (312, 313), F. tularensis (29), and M. tuberculosis (488). However, prevention of exposures should be emphasized; side effects that inhibit completion of the prophylactic antibiotic treatment for B. melitensis (311, 314) and for B. pseudomallei (313) have been reported. In 2013, CDC published revised guidelines for PEP after Brucella exposures (120). All potentially exposed staff should receive serological monitoring, symptom surveillance, and daily temperature self-checks; staff with high-risk exposures should receive PEP (120). The CDC

<table>
<thead>
<tr>
<th>Disease or Agent</th>
<th>Dose</th>
<th>Route of Inoculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coxsackie A21 virus</td>
<td>≤18</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>10⁶</td>
<td>Ingestion</td>
</tr>
<tr>
<td>Francisella tularensis</td>
<td>10</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>10–100 cysts</td>
<td>Ingestion</td>
</tr>
<tr>
<td>Influenza A2 virus</td>
<td>≤790</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Malaria</td>
<td>10</td>
<td>Intra venous</td>
</tr>
<tr>
<td>Measles</td>
<td>0.2–0.5</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>&lt;10⁶</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Poliovirus 1</td>
<td>2–4⁶</td>
<td>Ingestion</td>
</tr>
<tr>
<td>Q fever</td>
<td>10</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Salmonella Typhi</td>
<td>10⁵</td>
<td>Ingestion</td>
</tr>
<tr>
<td>Scrub typhus</td>
<td>3</td>
<td>Intradermal</td>
</tr>
<tr>
<td>Shigella flexneri</td>
<td>180</td>
<td>Ingestion</td>
</tr>
<tr>
<td>Shigellosis</td>
<td>10³</td>
<td>Ingestion</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>57</td>
<td>Intradermal</td>
</tr>
<tr>
<td>Venezuelan encephalitis virus</td>
<td>1–10⁶</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>1–10⁹</td>
<td>Ingestion</td>
</tr>
</tbody>
</table>

*Adapted from reference 22.

*Dose in number of organisms unless otherwise indicated.

*Median infectious tissue dose.

*Adapted from reference 483.

*In children.

*Adapted from references 484 and 485.

*Plaque-forming units.

*Guinea pig infective unit.
reviewed 153 incidents that resulted in 1,724 exposures to *Brucella* between 2008 and 2011; 839 were high-risk exposures (see risk classification in section on *Brucella* in Clinical Laboratories). Only five LAIs occurred; four of the infected microbiologists had not taken PEP and the fifth worker started the antibiotic 21 days after the exposure incident (120).

Rusnak et al. describe a proactive occupational health response to an incident that was considered a low risk of exposure to *B. anthracis* spores in immunized staff (88). A staff member removed a rack of anthrax cultures from the incubator and transported it on a cart to a co-worker seated at the biosafety cabinet. The paper towel covering the top of flasks was contaminated with spores; this was noted only after the towel had been discarded outside of the biosafety cabinet. The occupational health service obtained nose and throat swabs from both potentially exposed staff members and initiated a short course of antibiotic therapy. The next day, 6 CFU of *B. anthracis* grew from the nasal passage sample from one researcher, so both were prescribed the full 1-month course of antibiotic therapy for PEP (88).

Guidance on PEP for many agents is available on the CDC website (www.cdc.gov). References on PEP for high-consequence exposures include advice for *B. pseudomallei* (160, 308, 315, 316).

**Host factors**

Another critical function of occupational health programs involves advising staff of preexisting medical conditions that may put them at greater risk for serious consequences from exposure to an infectious agent. The risk and severity of infection may be influenced by concurrent diseases, medical conditions, drugs that alter the host defense, allergic hypersensitivity, inability to receive a certain vaccine, and reproductive issues. These risk factors need to be recognized and addressed before initiating work with infectious agents (317).

Some workers may face increased risks for certain infections that alter or impair normal host defense mechanisms. For example, host defenses provided by healthy intact skin can be disrupted by diseases such as chronic dermatitis, eczema, and psoriasis, thus providing a portal of entry in the absence of personal protective clothing. Achlorhydric individuals are more susceptible to *Vibrio* infections (306), and individuals with heart valve problems should not be exposed to *C. burnetii*. Antibiotic therapy may suppress gastrointestinal flora, increasing the possibility of colonization by a foreign or resistant population of microorganisms. Deficiencies in the immune system function can place workers at a higher risk of occupational infection. Immunodeficiency may result from certain connective tissue diseases, cancer chemotherapy, or HIV infection (317). Other causes of immunodeficiency include steroid treatment for medical conditions such as asthma, inflammatory bowel disease, and acute viral infection. Pregnancy brings the potential for mild immunodeficiency, especially for the developing fetus. The risk of infection is also increased with diabetes; this was considered a factor in the first glanders infection in the United States since 1945, an LAI with *B. mallei* (318). Diabetes may also have been a factor in the unexpected fatality due to an attenuated, pigment-negative strain of *Y. pestis*, KIMD27, as well as undiagnosed hereditary hemochromatosis. The attenuation of KIMD27 is based on the strain’s inability to acquire iron; it is thought that the iron overload in the scientist’s blood may have provided the strain with the sufficient iron to recover virulence (85). It is known that individuals with hemochromatosis are more susceptible to infection with at least 32 organisms, including Gram-negative organisms, Gram-positive, or acid-fast bacteria, fungi, and parasites (319). Occupational risks associated with the reproductive system may involve exposures during pregnancy that result in adverse outcomes such as spontaneous abortion and birth defects. Infertility can occur in either sex. Male exposures can cause damage to sperm, transmission of toxic agents in seminal fluid, or infection of the pregnant woman from her partner’s contaminated clothing. Breast-feeding may also be a source of infection. More commonly, concerns are directed to the potential congenital infection of a fetus, in utero or during delivery, as a result of a pregnant woman acquiring a work-related infection. Exposure to microorganisms known to cause congenital or neonatal infections, such as *Brucella*, *Cytomegalovirus*, hepatitis B virus, herpes simplex virus, HIV, LCMV, parvovirus, *L. monocytogenes*, rubella virus, *Treponema pallidum*, and toxoplasmas, is a distinct possibility in laboratory work (320). There is also a link between Zika virus and microcephaly (http://wwwnc.cdc.gov/travel/notices/alert/zika-virus-central-america).

In microbiological and biomedical laboratories, workers can also develop allergies to proteins (biological products derived from raw materials, fermentation products, or enzymes), chemicals, and the dander or aerosolized urine products of animals (321, 322).

**Behavioral factors**

Regarding occupational exposures to pathogenic microorganisms, the worker is key in controlling the safe outcome of any operation. He or she handles the agent, performs experiments, operates equipment, handles animals, disposes of infectious waste, and, when necessary, cleans up spills. The worker must come to the workplace prepared to function successfully. This means having adequate education, technical experience, and safety training to understand a task or project and perform it safely; being able to focus on the work so that inattention...
or random distractions do not lead to accidents; and being motivated to adhere to safe work practices. Philips (323) and Martin (324) both discussed behavioral factors associated with laboratory safety. In a study conducted at Fort Detrick in a large microbiological research laboratory, Phillips described various characteristics associated with accident-prone and accident-free individuals. The study found that individuals in the 20- to 29-year age group had an abnormally high accident rate and that women had slightly fewer accidents than men. Unfortunately, the biomedical workforce is usually young and innovative and falls into the higher accident group. Sixty-five percent of all accidents in Phillips’ study were due to human error, and 20% were due to equipment problems. The remaining 15% were ultimately attributed to “unsafe acts,” which could also be considered human error. Although not always acknowledged as having a role in LAIs, behavioral factors need to be taken into consideration.

CONCLUSION

This review was written to support biosafety programs by heightening awareness that LAIs continue to occur and by providing data for reinforcement of biosafety practices in daily operations. The authors of publications cited in this chapter have made an important contribution to the objective risk assessment and the development of improved biosafety practices. The safety culture in a workplace must encourage the reporting of exposure incidents to determine whether steps can be taken to prevent recurrence. The risk of LAIs can be minimized if laboratory staff are aware of the potential for exposure to infectious agents and work continuously with biosafety and occupational health professionals to accomplish this goal.

References

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212. Public Health Service Laboratory. 1991. Microbiological test strip (API20NE) identifies Brucella melitensis as Moraxella phe- nylpyruvica. CDR (Land Engl Wkly) 1:165.


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