Latest News on Occupational Health

Chapter 1

Occupational Exposure to Biological Agents

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1. Introduction

Since humans became agrarians and therefore started to harvest and store crops, the potential for exposure to biological agents in large quantities associated with agriculture began. Any stored organic material – grain and vegetables for food, hay and straw for animal bedding, wood for fuel – can potentially be colonised by biodegrading fungi and bacteria. A person handling such microbially contaminated material could be exposed to aerosols of biological origin (commonly referred to as bioaerosols) capable of triggering an allergic response. Repeated high level exposure can lead to diseases such as occupational asthma and allergic alveolitis (hypersensitivity pneumonitis) such as Farmer's Lung Disease (FLD). This was recognised as long ago as the 17th century when Ramazzini described symptoms experienced by farmers handling dusty grain [1], syndromes that would be recognised in the 20th and 21st centuries as occupational lung diseases requiring intervention to improve workers' lives.

With a move away from fossil fuel use to renewable energy sources including biomass, and large scale storage of such material, any microbial degradation during that storage can lead to workers' exposure to potential allergens. Using this same scenario, stored organic materials attract vermin leading to worker exposure to them, their by-products and their potential to harbour zoonoses, i.e., diseases carried by animals that can affect humans. The keeping of livestock for food further increases this potential.

In a civilised society, there is the need to care for those who are sick. However, if they are suffering from an infectious disease there is a risk for carers to contract that disease. In laboratory diagnostics to support such healthcare, or in laboratory research, there may be the necessity to propagate and work with pathogenic micro-organisms capable of infecting the laboratory worker unless suitable controls are put in place to prevent exposure.

Finally, as human society became more industrialised, large scale use of wastewaters, process waters and the development of the built environment provided ecological niches for the development of biological microcosms that could adversely affect dwellers. Prime examples include building-related allergic diseases often associated with damp housing, sick building syndrome, and Legionnaires' disease.

This chapter will aim to provide an overview of the above.

2. Allergic and Toxic Respiratory Hazards Associated with Occupational Exposure to Biological Agents

2.1. Background

By far the most common causes of occupational allergy are chemicals such as isocyanates used in paints and resins [2,3]. However, as described above, exposure to biological agents can trigger an allergic response, especially if that exposure is repeated and at high concentration over a long period. Some workplace activities can create conditions that lead to the proliferation of micro-organisms such that inadvertent exposure of workers to those micro-organisms can occur. This may be either through contaminated materials being handled or from introduction into the workplace, e.g., through contaminated air, while in other instances the work undertaken relies on the presence of micro-organisms (e.g., composting, anaerobic digestion, biotechnology) and thus leads to potential exposure. Examples in various workplaces are noted below.

2.2. In agriculture

As well as the potential for exposure to dust and bioaerosols during harvesting, in the classic example of FLD, fungi and bacteria that are naturally present in low levels on the harvested hay or grain begin to multiply if the crops are stored with too much moisture. The metabolic processes involved in that proliferation generates heat which encourages a succession of growth of different species culminating in growth in large numbers of thermotolerant fungi such as *Aspergillus fumigatus* and thermophilic actinomycete bacteria such as *Saccharopolyspora rectivirgula*. These are recognised as allergens and causes of FLD [1]. Any human disturbance of this contaminated material, such as manual movement of hay bales, shovelling of grain, movement of material by tractor, especially in an enclosed space, can result in bioaerosols in excess of 10^6 spores or culturable cells (colony forming units; CFU) per m^3 of air. Initial high level inhalation exposure to these spores can stimulate an immune response and, if followed by repeated exposure, can lead to occupational asthma or FLD with decreased lung function and debilitating disease [4].

In commercial mushroom production, the product is grown on compost which usually comprises a mixture of manure and straw. Preparation of this compost relies on the controlled

and purposeful encouragement of the same microbiological activity that occurs as described above inadvertently, to break down the raw materials and provide nutrients for mushroom growth. The mixing of the compost during preparation, and the seeding of the compost with mushroom spores (spawn), is likely to create bioaerosols and this is often done in an enclosed environment for quality control purposes. This therefore potentially exposes workers to these bioaerosols at high concentration. Unless suitable controls to limit exposure are in place, a respiratory syndrome similar to FLD, known as mushroom workers' lung, can occur [5]. Further bioaerosol exposure can occur during mushroom harvesting if done manually causing disturbance of the growing substrate, as well as during disposal of spent compost [6].

Other stored crops can be contaminated with micro-organisms in soil from the fields, or growth during storage. Examples include root vegetables such as potatoes, carrots and onions or legumes such as peas. Mechanical handling either to remove soil or to grade into sizes for the end market can create aerosols of organic dust and bioaerosols. This bioaerosol may comprise significant numbers of bacteria present in soil and associated endotoxin. Endotoxin is a cell wall component of Gram negative bacteria. Inhalation exposure to endotoxin is recognised to stimulate immunotoxicological response in the human lung, leading initially to 'flu-like symptoms often referred to as inhalation fever with potential long-term sequelae of reduced lung function following repeated exposure [7]. Other crop handling such as herbs, hops, grass and silage, and rice milling, also glasshouse crop production such as tomatoes and cucumbers, are all known sources of potential occupational exposure to bioaerosols including endotoxin as described by Spaan [8] and Duquenne [9]. Unlike fungi and bacteria for which there is no workplace exposure limit, a limit has been proposed by the Netherlands Standards Committee for endotoxin of 90 Endotoxin units (EU) per m^3 of air although this has yet to be ratified [10].

Large scale animal farming can create the potential for bioaerosol exposure from the animals themselves or from their waste. Poultry housed indoors create bacterial bioaerosols from their waste, together with fungal spores associated with bedding [11,12]. Indoor confinement of pigs and cows can generate mainly bacterial bioaerosol from deposited, collected and stored waste [13-17]. Animal handling and especially mucking out and cleaning down of animal pens (often involving jet washing) can create splash, spray and bioaerosol and is likely to rely heavily on manual input thus potentially exposing workers. Table 1 provides a summary of typical exposures to bioaerosols in a range of agricultural environments.

Table 1: Typical exposure to bioaerosols (airborne fungi, bacteria and endotoxins) associated with agricultural work activities

Work activity	Fungi (CFU/m^3)	Bacteria (CFU/m^3)	Endotoxin (EU/m^3)	Predominant organisms	References
Grain harvesting	10^7 - 10^8	10^5 - 10^7	10^4	Fungi including *Aspergillus,* Gram positive bacteria	9, 20
Stored grain handling	10^5	10^4	10^4	Fungi including *Aspergillus*	9, 20,21
Stored hay handling	10^8	10^8	Not measured	*Aspergillus fumigatus*, actinomycetes	1
Animal feed mills	10^3 – 10^4	10^3	10^2 -10^3	Fungi including *Aspergillus*	21
Greenhouse crops	10^4	10^4	10^3	Fungi including *Cladosporium, Botrytis*	8, 22, 23
Handling harvested vegetables	10^4	10^4 - 10^5	10^2	Fungi including *Penicillium*, Gram positive soil bacteria	24, 25
Handling harvested herbs & grasses	10^4 - 10^5	10^4 - 10^5	10^5 – 10^6	Gram positive soil bacteria	9, 26,27
Handling harvested hops	10^3 - 10^5	10^3 - 10^5	10^3	Fungi including *Penicillium*, *Alternaria*	28
Handling harvested hemp	10^5	10^6	10^3 – 10^4	Gram negative bacteria	29
Cattle sheds	10^3 - 10^5	10^4 - 10^5	10^4 - 10^5	Fungi including *Aspergillus*	16,17
Indoor poultry rearing	10^5	10^3	10^3	Fungi including *Aspergillus*	11,12
Indoor swine rearing	10^4 - 10^6	10^4 - 10^5	10^3 -10^5	Gram positive and negative bacteria	9, 13, 23
Horse stables	10^5	10^3 - 10^4	10^2 – 10^4	Fungi including *Aspergillus*	9, 30
Handling mushroom compost	10^7	10^5	10^3	Actinomycetes, fungi including *Aspergillus*	5, 6
Picking mushrooms	10^3	10^5	Not measured	Fungi (*Trichoderma*), Actinomycetes	5

An indirect hazard associated with biological agents can occur from bulk storage of animal waste in slurry tanks, pits and lagoons. Subsequent handling such as stirring and transfer into tankers for spreading onto land can lead to exposure to by-products of the bacteria degrading the slurry. This can include volatile gases which, if not dissipated, can rapidly create an asphyxiation hazard in enclosed spaces. Most significant of these is hydrogen sulphide that not only leads to oxygen depletion under these circumstances but also, because of its extreme toxicity, can cause rapid loss of consciousness to those exposed. Several cases have occurred in which multiple fatalities have resulted from one person initially being overcome by hydrogen sulphide, with others succumbing as rescue attempts fail [18,19].

2.3. In industrial settings

Moving away from agriculture does not remove the potential for large scale exposure to biological agents that can cause respiratory sensitisation and ill health. In industrialised countries, mass production of goods can also lead to inadvertent microbiological contamination.

One example is the machining of metal to produce, e.g., engine components. Oil in water emulsions, or synthetic emulsions, collectively termed metalworking fluids (MWF) are used to cool and lubricate machine parts and to remove excess metal (swarf). Usually MWF are recirculated and re-used over a long period, delivered to the drilling or cutting machines either from individual sumps or larger reservoirs supplying many machines. The MWF however is susceptible to colonisation mainly by bacteria but also sometimes by fungi if not well maintained and dosed with sufficient biocide to deter growth [31,32]. The MWF is delivered as a jet onto moving machinery and as a result spray, splash and aerosols (also referred to as MWF mist) are created with the potential to expose operators to bioaerosol [33]. The contaminating bacteria are predominantly Gram negative (*Pseudomonas* species and related genera) and therefore endotoxin is likely to be a significant component. Outbreaks of occupational asthma and allergic alveolitis have been reported in several countries associated with these exposures [34]. In a major investigation in the UK, over 100 cases of occupational asthma and allergic alveolitis occurred at a car component factory. Although some MWF reservoirs were well maintained and yielded few bacteria, some were heavily colonised with bacteria and associated endotoxin and were likely to have created bioaerosols that spread around the factory. Blood samples from exposed workers showed immunological response to extracts prepared from bacteria isolated from the MWF, prompting interventions to reduce contamination and worker exposure [35,36]. Another potential coloniser of MWF is non-tuberculous *Mycobacterium* species, likely to originate from the water used to make up the MWF emulsion. These have been isolated in some investigations of respiratory ill health in factories using MWF and although their role is not yet fully understood it is likely that they contribute to the immunological response via inhalation in exposed workers [37,38].

In other industries, process water is used to move material or as part of the manufacturing process. The primary example is in papermaking, where pulp from virgin wood or recycled paper is suspended in water before being concentrated, squeezed, rolled into sheets and dried to form the final paper product. The process water is largely recycled to reduce cost and environmental impact of discharge to water courses. However, not surprisingly the water can become heavily colonised mainly by bacteria (and associated endotoxin) utilising nutrients from the pulp to form slimes on machinery as well as free-living bacteria in the water. Splash and aerosol generated during the processing, or from slime removal, can expose workers to significant bioaerosol [39,40]. While slimes on machinery can affect paper quality as they slough off and become incorporated in the product, biocide addition to limit growth of these and free-living bacteria requires a careful balance so as not to affect paper quality. Therefore a certain level of bacterial contamination may be tolerated from a production viewpoint although this could create a potential for worker exposure.

Indirect exposure to bioaerosols derived from water and introduced into the workplace

may result from the use of humidifiers. Controlling humidity is important in printing to prevent paper shrinkage affecting product quality and in textile production to prevent yarn breaking. However, if this humidification is provided via poorly maintained water reservoirs there is the potential for microbial growth occurring which may be further fuelled by organic dusts from the process material. Delivery of this water as a mist into the workplace can thus expose workers to bioaerosol, leading potentially to an allergic respiratory syndrome referred to as 'humidifier fever' [41].

Also in textile production, microbial contaminants on the raw products can lead to significant exposure of workers to bioaerosols including endotoxin during processing. Examples include cotton and wool [42,43,44]. In sawmills, cutting and handling wood can expose workers to bioaerosols of fungal spores and endotoxin from the microbial contaminants naturally present on the raw material or where proliferation occurs during storage [45,46].

Table 2: Typical exposure to bioaerosols (airborne fungi, bacteria and endotoxins) associated with industrial work activities

Work activity	Fungi (CFU/m^3)	Bacteria (CFU/m^3)	Endotoxin (EU/m^3)	Predominant organisms	References
MWF	10^2	10^2-10^5	10^2-10^3	Gram negative bacteria	[9, 31]
Papermill	10^2	10^4-10^6	10^4	Gram negative bacteria	[9, 39]
Cotton mill	10^2	10^5	10^4	Gram negative bacteria	[9, 43, 44]
Wool mill	10^2	10^4	10^4	Gram negative bacteria	[9, 42]
Sawmills	10^4-10^6	10^2	10^3	Fungi including Rhizopus	[9, 45, 46]

Table 2 summarises typical bioaerosol levels in industrial workplaces.

2.4. In waste and recycling

Handling and disposal of municipal waste can expose workers to biological agents derived from the degradative process occurring in the organic content of the waste. While some disposal processes are increasingly automated, there is still significant manual handling input thus placing the worker in close proximity to any bioaerosols generated [47,48]. This can start with doorstep collection of household waste, although bioaerosols are likely to be dissipated in the open air. However, waste collection vehicles are emptied at depots referred to as transfer stations, usually enclosed buildings, and the material is further handled for example to feed incinerators or to transfer into bulk containers to send to landfill sites. Therefore there is the potential for exposure to large concentrations of a cocktail of fungal spores, bacteria

and endotoxin as well as organic dust, chemicals and volatiles [49,50,51]. While much of this is done remotely using grab cranes and bulldozers, maintenance workers and drivers may be exposed [52].

Similarly, handling and burying waste at landfill sites creates significant dust and associated bioaerosols, the latter exacerbated by the longer storage period before the material reaches landfill allowing further degradation leading to increased microbial numbers [53]. However, a combination of remote handling by diggers and bulldozers in the open air will reduce the potential for exposure unless there is a need for direct contact with the waste. One potential future area for significant, although unknown, exposure is landfill mining. It is feasible for completed landfill sites to be re-opened to recover materials previously discarded but now deemed recyclable [54,55].

With the increased impetus toward recycling, the circular economy and the economical and environmental advantage of this over disposal, there is a possible downside of the potential for worker exposure to biological materials. As also described above, any microbial proliferation that occurs prior to materials handling can create bioaerosol. Materials Recycling Facilities (MRFs) are premises where disposed municipal waste materials – paper, card, plastics, glass and metals - are separated ready for recycling. While some can be done by automated means there is a heavy reliance on hand sorting and with it the potential for worker exposure to dust and significant levels of fungal spores, bacteria and endotoxin [56,57,58]. This is further exacerbated during manual maintenance and cleaning of such premises.

Other forms of waste recycling include mechanical-biological treatment (MBT), for example to generate methane as a microbial by-product and a source of power, or waste-to-energy such as incineration of municipal waste, wood waste or purpose-grown biomass. MBT and municipal waste incineration will involve handling facilities similar to the transfer station previously described. This will include the same potential for exposure to biological agents, while storage of wood waste or biomass can result in the potential for stored material degradation described previously for agricultural products, and worker exposure to dust and bioaerosols [59,60,61]. Also in this instance exposure to microbially derived volatiles and oxygen depleting conditions in enclosed storage could occur [62,63,64].

Commercial scale composting of organic municipal waste is an increasingly important component of the waste recycling process. As described previously, the composting process actively encourages and manages microbial proliferation, while the high temperatures achieved kill off weed species and, if animal waste is included in the compost, eliminates food-borne animal pathogens. In the UK, this pasteurisation process is an industry standard requirement for waste-derived composts to be offered for sale [65]. Workers could be exposed to bioaerosols of compost-derived bacteria and fungi at various stages in the process, from initial handling of

waste, to turning of the composting material to encourage aeration, to movement of the material with tractors during final maturation and screening into different size fractions. Increasingly, as an alternative to traditional open 'windrow' composting (long heaps of material), commercial composting is carried out 'in-vessel' in enclosed containers that allow greater control of the composting process. However there is still the potential for worker exposure to bioaerosols during post-vessel processing [66]. There is also the potential for downwind dispersal and spread of bioaerosols that could affect nearby neighbours, although studies have shown that airborne concentrations are usually reduced to near background levels within 100 m of activities [66]. Composting is also undertaken indoors which limits potential spread of bioaerosols off site, but could increase the potential for workers' exposure [67].

Workers at wastewater treatment plants (WWTP) are at risk of exposure to bioaerosols including potentially pathogenic coliform bacteria. Although performed on an industrial scale much of the work at WWTP is automated, some manual input is required, such as cleaning screens and maintenance work, which may involve pressure washing causing aerosolisation of deposited materials [68].

Table 3: Typical exposure to bioaerosols (airborne fungi, bacteria and endotoxins) associated with waste and recycling work activities

Work activity	Fungi (CFU/m^3)	Bacteria (CFU/m^3)	Endotoxin (EU/m^3)	Predominant organisms	References
Municipal waste collection	10^2-10^4	10^2-10^4	10^2	Gram negative bacteria	[47, 52]
Waste transfer stations	10^2-10^5	10^2-10^5	10^3-10^4	Fungi including *Aspergillus,* Gram negative bacteria, Gram positive soil bacteria	[48, 49]
MRF	10^4-10^5	10^4-10^5	10^3-10^4	Fungi including *Aspergillus*, Gram negative bacteria, Gram positive soil bacteria	[56, 57]
Landfill sites	10^2-10^4	10^2-10^4	10^3	Gram positive soil bacteria	[10, 53
Green waste composting	10^4-10^6	10^4-10^5	10^6	Actinomycetes, fungi including *Aspergillus*	[9, 66]
Wastewater treatment plants	10^4	10^4	10^3	Gram negative bacteria	[68]

Table 3 summarises typical bioaerosol levels associated with waste and recycling.

2.4. Building related disease

A move away from manufacturing industry to office-based occupation potentially exposes workers to a different range of biological hazards associated with the built environment. Aside from infections such as legionellosis (noted below) two recognised health-related syndromes

include sick building syndrome (SBS) and building-related disease. Aetiology of SBS is multifactorial with symptoms including those affecting mucous membranes of the eyes, nose and throat, dry skin, and general symptoms of headache and lethargy. While these are common in the general population, what attributes them to SBS is a temporal relation with work in, or occupation of, a particular building [69,70]. Therefore, with SBS most of the above symptoms should improve within hours of leaving the problem building. Contributors to SBS in the indoor office environment can be divided into personal and building factors. Personal factors leading to greater reporting of SBS include lower status in the organisation and working on more routine tasks. Building factors include raised levels of paper dust or office dust, extensive use of computers, high indoor temperature, little or no outdoor air ventilation, poor individual control of temperature and lighting, air conditioning and especially its poor maintenance, poor office cleaning regimes and water damage. While mould exposure may also be a factor, there is no strong evidence of a contribution [71].

There is a clearer link between mould exposure and respiratory allergic symptoms in the indoor (mainly office) working environment where there has been obvious mould growth, or where heating, ventilation and air conditioning (HVAC) systems have become contaminated [72,73]. The main factors influencing mould growth in buildings are the fundamentals of mould growth in any circumstances. Construction materials and furnishings can provide nutritional requirements that promote colonisation. Many moulds can utilise cellulose in wallpaper, or starch in wallpaper paste, and the toxigenic mould *Stachybotrys sp*. can grow on the paper covering on gypsum plaster boards and timber used in construction [74,75]. Wooden furnishings and fabrics can be colonised, augmented by organic soiling, dust and food debris. The right conditions of water availability are required, usually relative humidity greater than 60% throughout a building or in localised areas, together with sufficient warmth to allow mould spore germination and growth. This can be exacerbated by inadequate ventilation, poor maintenance, water intrusion and poorly maintained HVAC systems [76]. Investigations of mould in buildings where users have reported respiratory and other ill health complaints have identified major factors as being ingress of rainwater, such as from a roof or drainage system leak, especially an insidious and undiscovered roof leak. The result could be visible mould growth on surfaces which is removable, but less obvious mould colonisation could remain, such as on a wall behind wallpaper or under floor coverings. Localised damp areas can occur in the space between a wall and a large item of furniture such as a cupboard. Water damage and resulting mould growth may not be apparent on the room side of suspended ceiling panels, but may be extensive behind the panels in the ceiling void. Similarly, mould growth may develop in cavity wall spaces [72,77].

3. Infection Hazards Associated With Occupational Exposure to Biological Agents

3.1. Laboratory acquired infections

Working with biological agents in the laboratory environment may involve handling biological agents, including those that have been genetically modified, that have the potential to cause infection, allergy or toxicity. This might be in pure culture, and often in very high titre, for research purposes or biotechnology, or samples for diagnostic purposes that may contain known or unknown biological agents. Consequently, there a requirement to protect the laboratory workers directly working with such materials, to protect others such as those in the nearby vicinity, those providing support such as handling laboratory waste, as well as protection of the wider environment and community from release of pathogens. Protection is generally applied proportionate to the hazard and based on the inherent characteristics of the pathogen, i.e., the ability to cause disease, severity of disease, likelihood of spreading to the wider community and availability of prophylaxis or treatment. This results in four risk or hazard groups and four Biological Safety Levels (BSL, also known as Containment Level). Each BSL, ranging from BSL1 being the lowest hazard level, to BSL4, has a specific set of facility and operational requirements. Guidance from Centers for Disease Control and Prevention (CDC) in USA [78], the European Biological Agents Directive in Europe [79] and Health and Safety Executive (HSE) in the UK [80] provide more detail. Most routine microbiological analytical work is undertaken in laboratories operated at BSL2. Examples of bacteria handled at this level include food poisoning organisms (e.g., *Campylobacter*, most *Salmonella* species), also *Staphylococcus aureus*. Although these bacteria can cause disease in humans, typically following exposure they usually present a low-to-moderate risk to employees. More hazardous pathogens that are handled in higher containment at BSL-3 include bacteria such as *Mycobacterium tuberculosis, Bacillus anthracis*, *Brucella* and *Rickettsia* species, and viruses such as rabies, Middle East Respiratory Syndrome coronavirus (MERS), HIV and Hepatitis. Agents that are handled at BSL-4 are exclusively viruses, including Ebolavirus, Marburg virus and some of the tick-borne encephalitis viruses.

While work in laboratories undertaken in a controlled environment should not lead to exposure, in some instances measures that are needed to eliminate or control risk are not implemented, or are implemented incorrectly. This can result from errors, or through failures in competency of the staff to undertake the work safely. Individual case reports and some surveys provide examples of laboratory acquired infections (LAIs) and the underlying factors that led to them. Willemarck *et al* [81] sourced 57 surveys and reports and selected 47 for further review, with a total of 309 LAIs included. These are summarised in **Table 4**, showing the pathogens most associated with LAI.

Table 4: Summary of recent LAIs worldwide, agent responsible and number of cases

Infectious agent	Biosafety level	Number of LAI cases (%)
Salmonella	2	130 (42%)
Brucella	3	123 (40%)
Neisseria meningitidis	2	11 (4%)
Vaccinia virus	2	11 (4%)
Francisella tularensis	3	6 (2%)
Filovirus (Ebola, Marburg)	4	5 (2%)
E coli O157:H7	3	4 (1%)
Mycobacterium	2-3	4 (1%)
Staphylococcus aureus	2	3 (1%)
Bacillus anthracis and *B. cereus*	2-3	2 (1%)
Burkholderia pseudomallei and *B mallei*	3	2 (1%)
Clostridium difficile	2	2 (1%)
Chlamydophila psittaci	3	1 (<1%)
Cowpox virus	2	1 (<1%)
Dengue virus	3	1 (<1%)
Leptospira	2	1 (<1%)
SARS	3	1 (<1%)
Shigella sonnei	2	1 (<1%)

A review of 28 case reports between 1982 and 2007 of *Brucella* species LAIs showed 167 potential exposures and 71 LAI. Of these, 18 (11%) were attributed to laboratory accidents but 147 (88%) to aerosolisation during routine identification work, presumably due to failure in the use of engineered protection such as a Biological Safety Cabinet [82].

Another survey was conducted which reviewed laboratory exposures to genetically modified organisms (GMOs) leading to LAI [83]. Out of 139 reported exposures, 14 LAIs were reported. The most frequent agents associated with these incidents are summarised in Table 5. This largely reflects the most frequently used GMOs and of these, vaccinia virus was responsible for 10 of the 14 LAIs, most often associated with needlestick injuries.

Table 5: Summary of genetically modified biological agents most frequently reported in association with occupational exposures (from Campbell, 2015 [83]).

Agent	Occupational exposures	LAI reported
Lentivirus	21	0
Vaccinia virus	19	10
Adenovirus	15	1
Toxoplasma gondii	9	0
E coli	7	1
HIV-1	6	0

Specific case studies highlight potential failures leading to LAIs. A classic example of multiple failures is of Sabia virus infection [84]. A researcher unfamiliar with their laboratory facility was working alone in a BSL-3 facility. They had an accident which led to leakage from a bottle into a centrifuge which they cleaned up. However, the researcher underestimated the infectious potential and route, had worn inadequate PPE and did not report the incident until symptoms occurred. In another example, a LAI of tularaemia occurred while working with the bacterium *Francisella tularensis*. Although working in a BSL-3 facility, the laboratory staff thought they were working with an attenuated strain and did so on the open bench instead of in a Biological Safety Cabinet. Due to mislabelling of stored cultures they were actually working with a virulent strain which led to infection via inhalation [85]. There is one reported case of an incident, though no infection, with Ebolavirus where a virologist acquired a needlestick injury while inoculating a mouse [86].

3.2. Infection risk in healthcare

While caring for patients with infectious diseases, not surprisingly the healthcare workers (HCW) are at significant risk of infection if not adequately protected. While infection control practices in hospitals focus on patient protection, it is equally important to consider the requirements of the HCW. It is also important to consider the infection risk for HCW outside the more controlled environment of a hospital, such as in emergency response and pastoral care.

The potential for significant impact from pandemic influenza has led to preparedness for infection control on a global scale [87]. The outbreak of Ebola Virus Disease (EVD) in West Africa in 2014-15 not only claimed in excess of eleven thousand lives, it also emphasised the potential infection risk for health workers (i.e., HCW and carers) HCW coming into contact with contaminated body fluids. In the early stages of the outbreak many health workers, with limited access to infection control measures including adequate personal protective equipment (PPE), were infected with the virus at a high rate (60-70%) of fatality [88]. As of mid-April 2019, an outbreak of EVD in the Democratic Republic of Congo had resulted in 1220 cases and 772 deaths, of which 88 health workers had been infected (7.2% of all cases) with 31 deaths [89]. By contrast, HCW deployed to West Africa in 2014-15 from European countries and USA to run the Ebola Treatment Centres set up as part of the outbreak response, were kept safe by being thoroughly trained and provided with effective PPE [90].

In the UK in 2015, in response to the possibility of travellers returning from affected countries with EVD infection, patient care contingencies were put in place. This was primarily focused on facilities where patients could be cared for in ‘Trexler’ isolation beds which provide a physical barrier between the patient and the HCW. These were used successfully on the occasions they were required. However, if patients could not be treated in such facilities, or

if patient numbers exceeded capacity at this facility, specialist infectious disease units were established at a network of hospitals. These units however did not have Trexler facilities, and as such HCW had to rely on PPE to provide protection from infection risk both during initial assessment and during continued care. More recently, three cases of monkeypox disease in the UK have resulted in one infection of a HCW during the initial assessment and treatment stage, emphasising the importance of adequate PPE and its safe use [91]. In recent studies, those PPE ensembles used for initial assessment of a patient suspected to have a high consequence infection have been evaluated, including safe removal (doffing) of PPE components potentially contaminated with infective body fluids. Objective tests were devised around a simulation of clinical procedures and using Ultraviolet (UV) fluorochromes in simulated infectious body fluids to expose HCW and evaluate the potential for contamination during doffing [92,93]. This led to the development of a unified PPE ensemble for HCW protection during initial assessment of a patient with possible infection of a high consequence disease [94].

At a less life-threatening level, but nevertheless with major impact on healthcare, is norovirus infection, sometimes referred to as winter vomiting disease. Due to its highly infectious nature at extremely low dose, possibly as low as 10 virus particles, an outbreak of infection can spread rapidly and lead to the closure of wards and illness in HCW subsequently requiring absence from work. Work to study the nature of transmission and simulate its spread through projectile vomiting from an infected patient has led to improvements in procedures to facilitate clean-up of infected body fluids without the HCW becoming contaminated leading to potential infection [95,96].

3.3. Infection risk from zoonotic infection

Zoonoses are diseases that can be transmitted from animals to humans and between animals, and as such a variety of occupations exist where workers are at risk of exposure. This may be as a result of working with infected animals, or through handling of contaminated by-products. The following provides a summary of some of the more common zoonoses, the agents that cause them, modes of transmission and the occupations potentially at risk. CDC in the USA [97], Public Health Agency in Canada [98], ECDC in Europe [99], OIE globally [100] and Public Health England and HSE in the UK [101,102] provide valuable data sources of more detailed information.

Anthrax is a rare but potentially life threatening bacterial disease caused by the spore-forming *Bacillus anthracis*. It affects cattle, sheep, pigs, and goats and can be transmitted to humans through contact with infected animals or animal products such as animal hair or wool, causing serious respiratory infection, a more self-limiting cutaneous infection or, more rarely, intestinal infection through consuming infected meat. Historically in northern UK it was referred to as ‘wool sorter’s disease’ with significant numbers of workers in woollen

mills affected when handling animal hair imported from countries where anthrax infection in animals was endemic [103]. Improvements in hygiene controls and working practices have all but eradicated the disease in factories and, while occasional cases occur in animals, human infections are rare. Others theoretically at risk include farmers and demolition workers, the latter because in the past the practice was to use animal hair to strengthen plaster in building work. Because the spores can survive for many decades, there is a possibility for spores to survive in old plaster and workers to be exposed to dust created during demolition or renovation.

Avian influenza is a disease of birds but some strains are capable of causing human infection of varying severity dependent on the strain, further exacerbated by the potential for the virus to rapidly re-assort to generate new virulent strains. Exposure may occur in those in close contact with infected birds, especially for example in Asian livestock markets [104], or who work with materials or products from infected birds.

Bovine tuberculosis (bovine TB) is a bacterial disease caused by *Mycobacterium bovis* and affects animals including cattle, deer, and camelids (alpacas, llamas). In humans, clinical symptoms are similar to other forms of TB and can result from direct contact with infected animals but more likely through handling infected by-products such as in abattoir workers, meat processing plant workers and butchers. Others potentially at risk of exposure are cattle and dairy farmers or dairy workers; deer, alpaca or llama farmers; zookeepers; veterinary surgeons; and HCW treating persons affected.

Escherichia coli is a bacterium that lives in the gut of animals including cattle, sheep, deer and goats. It can be transmitted via contact with infected animals or their faeces, and especially the verocytotoxigenic strains, exacerbated by a very low infectious dose (possibly as low as 10 cells), can cause illness ranging from diarrhoea to kidney failure in humans. In some cases the illness can be fatal. Young children and the elderly are more susceptible, therefore as well as general farming practices, open farms or petting zoos are at significant risk [105].

Hantavirus infections are caused by a group of viruses carried by rodents. Infection is generally spread via contact with urine, faeces or saliva from infected rodents. Workers thus affected can include those in farming, sewage and waste water processing, water sports instructors, pest control, street cleaners and waste disposal, forestry and nature conservation.

Leptospirosis is a bacterial infection found worldwide, of which there are two forms. Weil's disease (*Leptospira icterohaemorrhagiae*) is most commonly acquired from water contaminated with rat urine and infection can cause kidney failure. *Leptospira hardjo* is similar to Weil's disease but is generally caught from infected cattle and is less serious. Workers thus affected can include those in farming, sewage and waste water processing or pest control, also water sports instructors and others working in outdoor leisure industries, particularly if

in contact with water. Others in contact with water include divers, construction/demolition/ building renovation workers where there are rodents and stagnant water.

Lyme disease is a potentially serious bacterial infection caused by *Borrelia burgdorferi* and transmitted via tick bites. Symptoms can include a rash which spreads from the site of the tick bite often with accompanying flu-like symptoms. In more serious cases infection of the nervous system can occur with longer term symptoms including viral-like meningitis, facial palsy or nerve damage. Ticks are common in forested areas, heathland, moorland and suburban parks and workers thus affected can include farmers (sheep and deer), game keepers, veterinary surgeons, agricultural workers, forestry and nature conservancy workers and rural outdoor pursuits instructors.

MERS is a viral disease mainly centred around the Arabian Gulf States and transmitted via tick bites from camels to humans, but also potentially from contact with infected animal by-products. Workers thus affected can include camel handlers or butchers.

Psittacosis (also known as ornithosis or parrot fever) is primarily an infection of birds caused by *Chlamydophila psittaci*. It can be transmitted to humans by breathing in infected material or occasionally by oral infection. Symptoms can include flu-like illness, with fever, headache, muscle ache and respiratory tract symptoms. Workers affected can include poultry farmers, bird keepers, pet shop workers, zoo and bird park keepers, street cleaners, demolition/ building renovation/building conservation workers active where birds have been nesting, veterinary surgeons and poultry processing plant workers, particularly during evisceration.

Q fever is a bacterial disease caused by *Coxiella burnettii*. In most people it only causes a mild flu-like illness, but it can lead to more severe disease. It may occur in workers who are in contact with infected animals (sheep, goats, cattle) in particular during delivery of lambs, kids and calves, or those who work with materials or products from infected animals, particularly the afterbirth from infected sheep, goats and cattle, or handling contaminated bedding. Workers thus at risk include farmers, abattoir workers, meat processing plant workers and butchers, and veterinary surgeons.

Rabies virus is endemic in animal populations in many countries worldwide, but is rare as a human infection. However, it is an acute disease, with initial symptoms that include fever and headache usually with pain, tingling or burning sensation at the site of infection. As the virus is neurotropic, it spreads to the brain and spinal cord and causes encephalitis leading to convulsions and eventually death unless vaccine and immunoglobulin treatment is given immediately. The virus is transmitted via an animal bite, scratch or lick, generally from a dog or foxes in the case of classical rabies and from a bat in the case of bat rabies. There is no evidence of person to person spread, although this is a theoretical possibility. Workers at risk include dog wardens, those working in dog pounds or quarantine kennels; veterinary surgeons;

outdoor workers at risk of contact with foxes. Occupations where bat rabies may present a risk include those who are in contact with saliva from infected bats, or who are in close contact with roosting bats, for example bat handlers, and demolition/building renovation/building conservation workers who may disturb a bat roost.

Salmonella bacteria usually cause a mild, self-limiting diarrhoeal disease, although it can occasionally be severe , such as infection with *S typhi*. The bacteria are found in the gut of many wild and domestic animals, especially poultry, swine and reptiles. It is most commonly transmitted via food, such as undercooked chicken, eggs or meat, but it can also be found in faecally contaminated soil or water. Outside of public health-related exposure, workers at risk can include farmers, especially poultry farmers, abattoir workers, meat processing plant workers and butchers handling chickens and pigs, zookeepers, reptile breeders or veterinary surgeons. From exposure to faecally contaminated soil or water, occupations at risk include sewage and waste water workers, also vegetable pickers and handlers. Healthcare and care workers can be at risk from looking after infected patients.

Streptococcus suis is a bacterium that causes disease in pigs, occasionally other animals, including horses and cows. It is generally spread to humans by direct contact, with the bacteria entering the body through cuts or abrasions in the skin. *Streptococcus suis* infection in humans is very rare, with those most at risk having suppressed immune systems. Initially symptoms are flu-like but progress to meningitis, septicaemia or endocarditis (infection of heart valves) and in extreme cases can progress to potentially fatal toxic shock syndrome through multiple organ failure. Workers at risk include pig farmers, abattoir workers, meat processing plant workers and butchers, and veterinary surgeons.

West Nile virus is an arbovirus that infects birds via a bite from an infected mosquito (*Culex* species). The mosquito becomes infected with WNV and then transmits the virus to humans and horses when they bite. The disease tends to be seasonal, with most cases occurring during the summer, and associated with bird migration. There is no known spread from person to person or from horse to person. While most infected people show no symptoms, some have mild flu-like illness with fever and headache. In a small number of people encephalitis or meningitis can develop with symptoms of stiff neck, sore eyes, disorientation, muscle weakness, convulsions and sometimes coma. Workers at risk can include nature conservancy workers, poultry farmers, bird keepers, zoo and bird park keepers and veterinary surgeons.

3.4. Legionellosis

Legionella bacteria are naturally present in low concentrations in water sources such as rivers, lakes and reservoirs where there is minimal likelihood of causing human infection. However, the built environment provides ideal growing conditions for rapid colonisation

and proliferation in water systems where water is stored and/or re-circulated at temperatures between 20–45°C, and if there is a source of nutrients, for example the presence of sludge, scale or fouling, as well as soluble iron from rusty metal. The bacteria grow in biofilm, usually associated with protozoa, before being released into moving water from which they can be spread by aerosol generation, leading to outbreaks of respiratory illness. Respiratory syndromes are the potentially fatal pneumonia-like Legionnaires' Disease (LD), or the generally milder Pontiac Fever (PF) and Lochgoilhead fever [106,107].

Niches for colonisation include hot and cold water systems, especially in larger premises where it is possible for hot water temperatures to drop to the optimum *Legionella* growth range (20-45^{0}C) in pipes with restricted flow, or remote from the water heating source, or where hot water temperatures may be reduced for safety reasons. Examples include hotels [108], leisure centres [109], apartment blocks with central hot water supply [110], hospitals [111] or care homes [112]. Other niches include recreational spa pools, which incorporate water recirculation and lengthy pipework that is difficult to maintain [113], ornamental fountains [114] or food bar misting systems [115]. Industrial sources include process water used to dissipate excessive heat, or for freezing/chilling [116]. In the latter, evaporative cooling systems such as cooling towers or evaporative condensers interface a warm air current with colder water, resulting in heat transfer creating warm water conditions, and often this will create an aerosol. If physical barriers to control or trap this aerosol are not effective it may be dispersed over a wide area. If the cooling water becomes contaminated by *Legionella* there is the potential for workers on site, neighbouring workplaces or nearby members of the public to be exposed.

While more cases of LD and PF are associated with hot and cold water systems, any sporadic outbreaks of LD associated with evaporative cooling systems are more likely to affect larger numbers of people. For example, 38 outbreaks in USA investigated by CDC over a 14 year period to 2014 resulted in 415 reported cases of LD and 65 deaths [117]. Although only six of these outbreaks were associated with cooling towers, cumulatively they accounted for more cases (184 out of 415 reported; 44%), and more deaths (33 out of the 65; 51%) than any other source. A review of outbreaks of LD and PF occurring globally between 2006 and 2017 identified 136, of which 115 were LD, 4 were PF and 17 were mixed outbreaks of LD and PF. Cooling towers were implicated or suspected in 30% of total outbreaks, 50% of confirmed outbreak-associated cases, and 60% of outbreak-associated deaths [118]. While these case numbers will include both workers and nearby members of the public exposed to infectious aerosols, occupational risk from LD was emphasised in a review of occupational legionellosis between 1978 and 2016 [119]. Examining factors such as aetiology, infection sources and work activities, it was concluded that workplaces most frequently associated with occupational legionellosis were industrial settings (62.0%), office buildings (27.3%) and healthcare facilities (6.3%).

3.5. Bioterrorism

The highest profile instance of bioterrorism occurred in USA in 2001 when letters containing *Bacillus anthracis* spores were sent to Senate offices and newspaper headquarters [120], creating a major public health emergency. However, it also became a significant occupational issue, as the cases of infection were mainly in postal workers exposed to spores that leaked from the letters as they were being handled in the mail sorting offices. This led to the necessity for treatment and mass vaccination of workers and the closure of sorting offices for clean-up and fumigation at significant cost [121].

4. Summary

In summary, this has demonstrated the significant impact that exposure to biological agents can have in almost any working environment. Awareness of the potential for xposure and the consequences, together with implementation of suitable and proportionate controls, can manage exposure and subsequent ill health.

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