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Review

A Review of Laboratory Biosafety and Infection Prevention and Control Guidelines on the Management of High-Risk Pathogens in Canada

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Abstract: The safety precautions required for certain pathogens are different in clinical laboratories and patient-facing healthcare settings, causing confusion for laboratorians and infection preventionists. The current review aims to summarize information from reputable Government of Canada guidance commonly used in clinical laboratories in Canada, including the Government of Canada Human Pathogens and Toxins Act and Regulations, the ePATHogen—Risk Group Database, biosafety directives and advisories, Transportation of Dangerous Goods Regulations, and the *Canadian Biosafety Standard* (2022). Guidelines from the Centers for Disease Control and Prevention's (CDC) *Biosafety in Microbiological and Biomedical Laboratories* (2020), Clinical and Laboratory Standard Institution's (CLSI) *M29 Protection of Laboratory Workers from Occupationally Acquired Infections* (2014), and Association of Public Health Laboratories's *Biothreat Agent Bench Cards for the Sentinel Laboratory* (2018) were also used to supplement specific details. In comparison, information regarding infection prevention and control practices in patient-facing healthcare settings was summarized: Public Health Agency of Canada: Routine Practices and Additional Precautions for Preventing the Transmission of Infection in Healthcare Settings (2017) and CDC Infection Control Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings (2007). Contrasting levels of precautions exist between laboratories and patient-facing settings, especially for endemic fungi and certain security-sensitive biological agents. Acknowledging this contrast may facilitate risk communication relative to the counterparts to minimize the threat and disease effects and ensure public confidence.

Keywords: biosafety; infection prevention and control (IPAC); pathogen risk group; laboratory acquired infection (LAI); occupational safety; transportation of dangerous goods; Public Health Agency of Canada (PHAC); isolation precaution; containment level; security-sensitive biological agents

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1. Introduction

Laboratorians constantly encounter infectious materials at clinical laboratories and are at heightened risk of occupationally acquired infections. Compared to the general population, microbiology laboratorians are more likely to acquire infections associated with the *Brucella* species, *Coccidioides* species, and *Neisseria meningitidis* [1,2]. In 2018, the Public Health Agency of Canada (PHAC) reported 89 laboratory exposure incidents to human pathogens that involved 235 people in the country [3]. These laboratory exposure incidents remained consistently high in 2023, with 207 incident reports that affected 85 individuals in Canada [4]. In this surveillance study in 2023, communication was deemed to be the root

cause of 23.8% of laboratory exposure incidents. These incident reporters commented that communication did not occur but should have, and communication was unclear and ambiguous. From 2016 to 2021, PHAC confirmed nine cases of laboratory-acquired infections (LAIs) in the country [5]. Although the number of incidents was small compared to the general population, this could be due to the strict implementation of biosafety practices in clinical laboratories, generally adapted from published guidance by the Government of Canada [6,7], Centers for Disease Control and Prevention (CDC) [8], and Clinical and Laboratory Standard Institution (CLSI) [1].

The Government of Canada recognizes the varying levels of the risk of human pathogens relative to the health and safety of the public and thereby assented to the Human Pathogens and Toxins Act (HPTA) [9] and Human Pathogens and Toxins Regulations (HPTR) [10], which not only categorized the risk group of certain human pathogens but also specified the controlled activities authorized in licensed facilities. The risk groups and descriptions are listed in Table 1.

Table 1. Risk groups and descriptions of human pathogens as per the Government of Canada Human Pathogens and Toxins Act (HPTA). Note that HPTA does not provide descriptions for Risk Group 1 pathogens [9].

Risk Group 2 are human pathogens that exhibit the following: • Pose a moderate risk to the health of individuals; • Pose a low risk to public health; • Are able to cause serious disease in a human but unlikely to do so; • Have effective treatment and preventive measures; • Pose a low risk of spreading the disease.
Risk Group 3 are human pathogens that exhibit the following: • Pose a high risk to the health of individuals; • Pose a low risk to public health; • Are likely to cause serious disease in a human; • Usually have effective treatment and preventive measures; • Pose a low risk of spreading the disease
Risk Group 4 are human pathogens that exhibit the following: • Pose a high risk to the health of individuals; • Pose a high risk to public health; • Are likely to cause serious disease in a human; • Usually have no effective treatment and preventive measures; • Pose a high risk of spreading the disease.

The Government of Canada also categorizes the containment levels (Levels 1 to 4) required for different pathogens [7]. Through the publication of the *Canadian Biosafety Standard*, the Government of Canada details the physical containment and operational practice requirements for each level [6]. These details are similar to the summary of containment level requirements published by CLSI (Table 2) [1]. Although the risk group and containment level numbers often match, there are some exceptions for certain pathogens depending on the activities involved, as detailed by the biosafety directives and advisories released by the Government of Canada [11]. For instance, endemic fungi, such as *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, and *Blastomyces dermatitidis*, are categorized as Risk Group 3 human pathogens, but Containment Level 2 with additional biosafety practices is the minimum requirement for non-propagative identification activities [12].

Table 2. Summary of Containment Level 1–4 requirement, adapted from the Clinical and Laboratory Standard Institute (CLSI) *M29 Protection of Laboratory Workers from Occupationally Acquired Infections* (2014) [1].

Containment Level 1 (CL1) • Practices: standard microbiological practices • Primary barriers: none required • Personal protective equipment: laboratory coats and gloves; eye and face protection, if needed • Secondary barriers (facilities): laboratory bench and sink
Containment Level 2 (CL2) • Practices: CL1 practice plus limited access, biohazard warning sings, and biosafety manual defining any needed waste decontamination or medical surveillance policies • Primary barriers: biosafety cabinets or other physical containment devices for all infectious splash or aerosol generating procedures • Personal protective equipment: same as CL1 • Secondary barriers (facilities): CL1 plus autoclave
Containment Level 3 (CL3) • Practices: CL2 practice, plus controlled access; decontamination of all waste; and decontamination of laboratory clothing before laundering • Primary barriers: biosafety cabinets or other physical containment devices for all open manipulation of agents • Personal protective equipment: protective laboratory clothing; gloves, face, eye, and respiratory protection, as needed • Secondary barriers (facilities): CL2, plus physical separation from access corridors; self-closing, double-door access; exhausted air not recirculated; negative airflow into laboratory; entry through airlock or anteroom; and handwashing sink near laboratory exit
Containment Level 4 (CL4) • Practices: CL3 practice, plus clothing change before entering; shower on exit; decontamination of all material upon exiting the facility • Primary barriers: all procedures conducted in Class III or Class II biosafety cabinets • Personal protective equipment: full-body, air-supplied positive pressure suit • Secondary barriers (facilities): CL3, plus separate building or isolated zone; dedicated supply and exhaust vacuum; and decontamination systems

The public and transport workers are at risk of acquiring infection if there is accidental spillage or loss of patient specimens with infectious substances during transport. The Government of Canada publishes the Transportation of Dangerous Goods Regulations (TDGR), which classifies whether primary specimens and culture isolates should be packaged in Category A or B: Category A substances can cause permanent disability or life-threatening or fatal disease to humans or animals, whereas Category B substances are unlikely to cause permanent disability and will not lead to fatality [13]. However, this becomes complicated when infectious substances are classified as Category A and contained as primary specimens (rather than cultures), as they may be shipped as Category B under certain conditions, as per TDGR Section 2.36(2) [14]. In addition, the Government of Canada lists certain infectious substances as security-sensitive biological agents (SSBAs); the misuse of SSBAs can pose a risk to Canada's national security. Therefore, workers are required to obtain HPTA clearance if they wish to conduct controlled activities with SSBAs or have access to facility areas with controlled activities with SSBAs.

Like laboratorians, other health care workers (HCWs) who handle specimens from infected patients are at heightened risk of occupationally acquired infections [1]. Patient-

facing HCWs are also at risk of acquiring infections directly from the source patients if the pathogens involved are easily communicable. Nevertheless, the safety precautions required for certain pathogens are different in clinical laboratories and patient-facing healthcare settings, causing confusion for laboratorians and infection preventionists. For instance, patients infected with endemic fungi, such as *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, and *Blastomyces dermatitidis*, generally require only routine infection prevention and control (IPAC) precautions during their inpatient stays [15,16]. In contrast, their specimens would require Containment Level 3 precautions if undergoing propagative activities with a high risk of infectious aerosols [12]. One must understand the context of encounters with these pathogens, which may influence biosafety and IPAC practices. For instance, when fungal microorganisms are growing in filamentous forms in culture, the communicable risk increases compared to collecting primary specimens directly from patients. *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, and *Blastomyces dermatitidis* were known to cause LAIs in the past, whereas there is little evidence of direct human-to-human transmission [17–19]. The historical evidence probably supports a higher level of biosafety precautions compared to IPAC practices. In contrast, some infections with high communicable risks in patient-facing healthcare settings may not receive the same recognition in clinical laboratories. For example, patients infected with measles and pulmonary tuberculosis require airborne IPAC precautions in hospitals [15,16]. However, when their primary specimens arrive in a laboratory for non-propagative diagnostic activities, only Containment Level 2 precautions are needed [20,21]. This lower level of biosafety precautions may be justifiable because these pathogens only grow in special culture media, and laboratorians have biosafety cabinets and immunization policies as additional layers of protection for certain procedures, such as plating the primary specimens on culture media.

Despite having Risk Group 3 and 4 pathogens in their differential diagnoses, clinicians may order multiple microbiology tests to help narrow down the differentials. To enhance biosafety, laboratorians may opt to withhold testing until Risk Group 3 and 4 pathogens are ruled out, but this is not always practical as some tests have long turnaround times. Clinicians and infection preventionists may not fully understand the different levels of risk of pathogens in laboratories versus patient-facing healthcare settings. The use of Category A and B for packaging infectious substances per the TDGR is complex and goes beyond simply knowing the risk group of pathogens. There is yet a published reference that helps differentiate the practices required for laboratorians versus patient-facing HCWs. As discussed earlier, communication errors were a root cause of laboratory exposure incidents; fortunately, corrective actions could be implemented 80% of the time [4]. Effective risk communication could have a significant life-or-death impact; it helps minimize the threat and disease effects and reassure the trust in the organization's ability to protect the public [22].

Aims

The primary aim of the current review is to summarize the laboratory biosafety and IPAC practices required for commonly encountered high-risk pathogens to help practitioners in the two areas acknowledge the risks encountered by their counterparts. The secondary aim is to include the test turnaround time to help laboratorians and clinicians decide whether to withhold testing or proceed with enhanced precautions when encountering potential high-risk pathogens.

2. Materials and Methods

A narrative review was conducted on 15 November 2024 to summarize information from reputable Government of Canada guidance commonly used in clinical laboratories in Canada, including the Human Pathogens and Toxins Act and Regulations [9,10], the ePATHogen—Risk Group Database [7], biosafety directives and advisories [11], Transportation of Dangerous Goods Regulations [13,14], and the *Canadian Biosafety Standard* (2022) [6]. When more information was needed, guidance from the Centers for Disease Control and Prevention's (CDC) *Biosafety in Microbiological and Biomedical Laboratories* (2020) [8], Clinical and Laboratory Standard Institution's (CLSI) *M29 Protection of Laboratory Workers from Occupationally Acquired Infections* (2014) [1], and Association of Public Health Laboratories's Biothreat Agent Bench Cards for the Sentinel Laboratory (2018) [23] was used to supplement specific details.

Information regarding IPAC practices in healthcare settings was summarized: Public Health Agency of Canada: *Routine Practices and Additional Precautions for Preventing the Transmission of Infection in Healthcare Settings* (2017) [15] and CDC Infection Control Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings (2007) [16]. Information regarding diagnostic test availability and turnaround time was from the British Columbia Centre for Disease Control's (BCCDC) eLab Handbook [24], the Public Health Ontario (PHO) Test Information Index [25], and the National Microbiology Laboratory's (NML) Guide to Services [26]. Guidance from other external sources, including non-North American resources, case reports, and observational studies, was not included in the current review.

The Scale for the Assessment of Narrative Review Articles (SANRA) checklist was followed [27]:

(1) The review's importance was explicitly justified to readers (there is yet a published reference that helps differentiate the practices required for laboratorians versus patient-facing HCWs; effective risk communication helps minimize the threat and disease effects).
(2) One or more concrete aims were formulated (the primary aim was to summarize laboratory biosafety and IPAC practices required for commonly encountered high-risk pathogens; the secondary aim was to include the test turnaround time).
(3) The literature search was described in detail (the included specific guidelines used were listed above).
(4) Key statements were supported by references (the key statements were all referenced below).
(5) Appropriate evidence was generally present (reputable guidelines were used as evidence for the current review).
(6) Relevant outcome data were generally presented appropriately (qualitative evidence was collected and presented in tables).

3. Results

The biosafety and IPAC precautions and test turnaround time for common high-risk bacteria, fungi, and viruses and prions are summarized in Table 3, Table 4, and Table 5, respectively. Information not available from the referenced literature is omitted from the tables.

Table 3. Biosafety and IPAC precautions and test turnaround time for selected high-risk bacteria.

Pathogens	Risk Group	Biosafety Containment Level #	TDGR Category for Ground Transport	Precautions in Patient-Facing Healthcare Settings	Culture Test Turnaround Time	Serology or Antigen Test Turnaround Time	Molecular Test Turnaround Time	SSBA
Bacillus anthracis	3	2+ for suspected cases 3 for confirmed cases	A for culture B for non-culture	Routine	7–14 days at BCCDC ≤3 days at PHO	N/A	1 day at BCCDC 3–5 days at PHO	Yes
Brucella species	2 or 3 depending on the species	2+ for suspected cases 3 for confirmed cases	A for culture B for non-culture	Routine; contact if draining lesions	≤10 days at BCCDC ≤3 days at PHO	5–7 days at BCCDC ≤10 days at PHO	24–48 h at BCCDC ≤3 days at NML	Yes for *B. melitensis* and *B. suis*
Burkholderia mallei	3	2+ for suspected cases 3 for confirmed cases	A for culture B for non-culture	N/A	N/A	N/A	(from pure culture) 14–28 days at NML	Yes
Burkholderia pseudomallei	3	2+ for suspected cases 3 for confirmed cases	A for culture B for non-culture	N/A	≤14 days at BCCDC	N/A	(from pure culture) 14–28 days at NML	Yes
Chlamydophila psittaci	3	2+ for diagnostic specimen 3 for propagation	A for culture B for non-culture	Routine	N/A	N/A	10 days at NML	Yes
Coxiella burnetii	3	2+ for diagnostic specimen 3 for propagation	A for culture B for non-culture	Routine	≤10 days at PHO	15 days at NML	15 days at NML	Yes
Francisella tularensis	3	2+ for suspected cases 3 for confirmed cases	A for culture B for non-culture	Routine	≤7 days at BCCDC ≤3 days at PHO	30 days at NML	N/A	Yes
Mycobacterium tuberculosis complex	3	2 for non-propagative activities 3 for propagative activities	A for culture B for non-culture	Airborne for respiratory and laryngeal infections; AGMP	Normally 7–14 days at BCCDC (could be up to 56 days) Up to 49 days at PHO	1–7 days at BCCDC	1–3 days a BCCDC 1–3 days at PHO	No
Orientia tsutsugamushi	3	2+ for diagnostic specimen 3 for propagation	B	N/A	N/A	≤15 days at NML	≤15 days at NML	No
Rickettsia species	2 or 3 depending on species	2+ for diagnostic specimen 3 for propagation	A for culture of *R. prowazekii* and *R. rickettsii* B for culture of *Rickettsia* species excluding prowazekii and rickettsii B for non-culture	Routine	N/A	≤10 days at PHO ≤15 days at NML	15 days at NML	No
Yersinia pestis	3	2+ for suspected cases 3 for confirmed cases	A for culture B for non-culture	Routine; droplet if pneumonic	≤10 days at BCCDC	≤21 days at PHO	24–48 h at BCCDC	Yes

These recommended biosafety containment levels generally apply to propagative activities of the selected Risk Group 3 pathogens. Specific recommendations for the precautions required for other routine diagnostic workups are provided if available: 2+: biosafety Containment Level 2 with enhanced precautions (e.g., taping the culture plates, workup in biosafety cabinets, biosafety level 3 practices with biosafety level 2 engineer control). See the abbreviation list on the first page if needed.

Table 4. Biosafety and IPAC precautions and test turnaround time for selected high-risk fungi.

Pathogens	Risk Group	Biosafety Containment Level #	TDGR Category for Ground Transport	Precautions in Patient-Facing Healthcare Settings	Culture Test Turnaround Time	Serology or Antigen Test Turnaround Time	SSBA
Blastomyces dermatitidis *Blastomyces gilchristii* *Blastomyces helicus* *Blastomyces percursus*	2 or 3 depending on species	2+ if low risk of infectious aerosols * 3 if high risk of infectious aerosols *	B	Routine	≤42 days at BCCDC ≤28 days for negative culture but could be longer for positive culture at PHO	≤10 days at PHO	No
Cladophialophora bantiana	3	3	B	N/A	≤42 days at BCCDC ≤28 days for negative culture but could be longer for positive culture at PHO	N/A	No
Coccidioides species	3	2+ for diagnostic specimen 3 for propagation	A for culture B for non-culture	Routine	≤42 days at BCCDC ≤28 days for negative culture but could be longer for positive culture at PHO	7 days at BCCDC ≤10 days at PHO	Yes
Cryptococcus gattii complex	3	2 if low risk of infectious aerosols * 2+ if high risk of infectious aerosols *	B	Routine	≤42 days at BCCDC ≤28 days for negative culture but could be longer for positive culture at PHO	3–5 days at BCCDC	Yes
Cryptococcus species other than *C. gattii* complex	2	2	B	Routine	≤42 days at BCCDC ≤28 days for negative culture but could be longer for positive culture at PHO	3–5 days at BCCDC	No
Histoplasma capsulatum	3	2+ if low risk of infectious aerosols * 3 if high risk of infectious aerosols *	B	Routine	≤42 days at BCCDC ≤28 days for negative culture but could be longer for positive culture at PHO	≤10 days at PHO	No
Paracoccidioides brasiliensis *Paracoccidioides lutzii*	3	2+ if low risk of infectious aerosols * 3 if high risk of infectious aerosols *	B	Routine	≤42 days at BCCDC ≤28 days for negative culture but could be longer for positive culture at PHO	N/A	No

Table 4. *Cont.*

Pathogens	Risk Group	Biosafety Containment Level #	TDGR Category for Ground Transport	Precautions in Patient-Facing Healthcare Settings	Culture Test Turnaround Time	Serology or Antigen Test Turnaround Time	SSBA
Rhinocladiella mackenziei	3	3	B	N/A	≤42 days at BCCDC ≤28 days for negative culture but could be longer for positive culture at PHO	N/A	No
Sporothrix brasiliensis	2	2	B	Routine	≤42 days at BCCDC ≤28 days for negative culture but could be longer for positive culture at PHO	N/A	No
Talaromyces marneffei	2	2	B	Routine	≤42 days at BCCDC ≤28 days for negative culture but could be longer for positive culture at PHO	N/A	No

These recommended biosafety containment levels generally apply to the propagative activities of selected Risk Group 3 pathogens. Specific recommendations for the precautions required for other routine diagnostic workups are provided if available: 2+: biosafety Containment Level 2 with enhanced precautions (e.g., taping the culture plates, workup in biosafety cabinets, biosafety level 3 practices with biosafety level 2 engineer control). * As per Government of Canada Public Health Agency of Canada (PHAC) [12], activities with low risk of infectious aerosols are activities that only involve non-readily aerosolized material, such as yeasts, spherules, and yeast-like cells in a state unlikely of becoming readily aerosolized material (e.g., when incubation conditions are kept above 37 degrees Celsius) and that only include procedures with a low potential of generating infectious aerosolized particles or liquid droplets. Activities with a high risk of infectious aerosols include laboratory procedures with a high potential of generating infectious aerosolized particles or liquid droplets and/or activities that involve a material that is or may produce a readily aerosolized material (e.g., spores, filamentous forms) based on the source (e.g., environmental sample), the incubation conditions (e.g., below 37 degrees Celsius), and the laboratory procedures. See the abbreviation list on the first page if needed.

Table 5. Biosafety and IPAC precautions and test turnaround time for selected high-risk viruses and prions.

Pathogens	Risk Group	Biosafety Containment Level #	TDGR Category for Ground Transport	Precautions in Patient-Facing Healthcare Settings	Molecular Test Turnaround Time	Serology Test Turnaround Time	SSBA
Avian influenza A (H5N1)	3	2+ for diagnostic specimens 3 for concentration, propagation, and isolation	A for culture B for non-culture	Contact; droplet	1–3 days at BCCDC ≤2 days at PHO	N/A	Yes
Chikungunya virus	3	3	B	Routine	≤5 days at PHO 21 days at NML	≤8 days at PHO 14 days at NML	Yes

Table 5. *Cont.*

Pathogens	Risk Group	Biosafety Containment Level #	TDGR Category for Ground Transport	Precautions in Patient-Facing Healthcare Settings	Molecular Test Turnaround Time	Serology Test Turnaround Time	SSBA
Crimean-Congo Hemorrhagic fever virus	4	4	A	Contact; droplet; AGMP	2 days at NML	N/A	Yes
Dengue virus	2	2	A for culture B for non-culture	Routine	≤5 days at PHO 21 days at NML	≤8 days at PHO 14 days at NML	No
Eastern equine encephalitis virus (Alphavirus eastern)	3	3	A for culture B for non-culture	Routine	21 days at NML	≤8 days at PHO 14 days at NML	Yes
Ebola virus	4	4	A	Contact; droplet; AGMP	2 days at NML	N/A	Yes
Flexal virus	3	3	A	N/A	N/A	N/A	No
Guanarito virus	4	4	A	N/A	2 days at NML	14 days at NML	Yes
Hantavirus	3	2+ for diagnostic specimen 3 for propagation	A	Routine	14 days at NML	14 days at NML	Yes
Hendra virus	4	4	A	N/A	2 days at NML	14 days at NML	Yes
Herpes B virus (Cercopithecine Herpesvirus-1)	4	4	A	N/A	2 days at NML	14 days at NML	No
Human immunodeficiency virus	3	2+	A for culture B for non-culture	Routine	1–5 days at BCCDC ≤5 days at PHO	Screening enzyme immunoassay: 1–3 days at BCCDC Confirmation of immunoblot: 3–5 days at BCCDC ≤3 days for non-reactive specimens and ≤6 days for reactive specimens at PHO	No
Human T-lymphotropic virus	3	2+	B	Routine	14–28 days at BCCDC	1–3 days at BCCDC ≤5 days for negative results and ≤14 days for positive results at PHO	No

Table 5. *Cont.*

Pathogens	Risk Group	Biosafety Containment Level #	TDGR Category for Ground Transport	Precautions in Patient-Facing Healthcare Settings	Molecular Test Turnaround Time	Serology Test Turnaround Time	SSBA
Japanese encephalitis virus (Orthoflavivirus japonicum)	3	3	A for culture B for non-culture	Routine	21 days at NML	14 days at NML	Yes
Junin virus	4	4	A	N/A	2 days at NML	14 days at NML	Yes
Kyasanur Forest virus	4	4	A	N/A	2 days at NML	N/A	Yes
Lassa virus	4	4	A	Contact; droplet; AGMP	2 days at NML	14 days at NML	Yes
Lymphocytic choriomeningitis	3	3	B	Routine	14 days at NML	14 days at NML	No
Machupo virus	4	4	A	N/A	2 days at NML	14 days at NML	Yes
Marburg virus	4	4	A	Contact; droplet; AGMP	2 days at NML	14 days at NML	Yes
Measles virus (Rubeola virus)	2	2	B	Airborne	1–2 days at BCCDC 7 days at NML	3–5 days at BCCDC 5 days at PHO 3–21 days at NML	No
Middle East Respiratory Syndrome Coronavirus	3	2+ for non-propagation 3 for propagation	A for culture B for non-culture	Contact; droplet; AGMP	1 day at BCCDC 1 day at PHO	N/A	Yes
Monkeypox virus	3	2+ for diagnostic specimen 3 for concentration, propagation, and isolation	B (temporary as of 2024)	Contact; Droplet; Airborne (or an isolated room as per provincial guidance)	36 h at BCCDC ≤2 days at PHO	N/A	Yes
Nipah virus	4	4	A	N/A	2 days at NML	14 days at NML	Yes
Omsk hemorrhagic fever virus	4	4	A	N/A	2 days at NML	N/A	Yes

Table 5. *Cont.*

Pathogens	Risk Group	Biosafety Containment Level #	TDGR Category for Ground Transport	Precautions in Patient-Facing Healthcare Settings	Molecular Test Turnaround Time	Serology Test Turnaround Time	SSBA
Oropouche virus	3	3	B	Routine	N/A	N/A	Yes
Powassan virus	3	3	B	Routine	N/A	≤8 days at PHO 14 days at NML	Yes
Prion (Creutzfeldt–Jakob Disease)	3	2+	B	Routine and additional precautions for surgery and medical procedures	N/A	15 days at NML	No
Rabies virus	3	3	A for culture B for non-culture	Routine	7–21 days at CFIA	30 days at NML	No
Rift Valley Fever virus (Phlebovirus riftense)	3	3	A	N/A	2 days at NML	14 days at NML	Yes
Russian Spring—Summer encephalitis virus	4	4	A	N/A	14 days at NML	14 days at NML	Yes
Sabia virus	4	4	A	N/A	2 days at NML	14 days at NML	Yes
Severe acute respiratory syndrome (SARS) associated coronavirus	3	2+ for diagnostic specimen 3 for propagation	A for culture B for non-culture	Contact; droplet; AGMP	14 days at NML	N/A	Yes
Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)	3 2 for Full length SARS-CoV-2 RNA	2 for activities that are unlikely to result in entry of SARS-CoV-2 RNA into a cell 3 for propagation, isolation, and concentration	A for culture B for non-culture	Contact; droplet; AGMP	1–2 days at BCCDC 1–2 days at PHO	N/A	No
Varicella zoster virus	2	2	B	Contact; airborne	1–4 days at BCCDC ≤4 days at PHO	3–5 days at BCCDC ≤5 days at PHO	No

Table 5. *Cont.*

Pathogens	Risk Group	Biosafety Containment Level #	TDGR Category for Ground Transport	Precautions in Patient-Facing Healthcare Settings	Molecular Test Turnaround Time	Serology Test Turnaround Time	SSBA
Variola (smallpox virus)	4	4	A	Contact; droplet; airborne	2 days at NML	N/A	N/A
Venezuelan equine encephalitis virus (Alphavirus venezuelan)	3	3	A for culture B for non-culture	Routine	N/A	N/A	Yes
West Nile Virus (Orthoflavivirus nilense)	3	2+ for diagnostic specimen 3 for propagation	A for culture B for non-culture	Routine	1–3 days at BCCDC	7 days at BCCDC 2–5 days at PHO	No
Western Equine Encephalitis	3	3	N/A	Routine	N/A	≤8 days at PHO	Yes
Yellow fever virus (Orthoflavivirus flavi)	3	3	A for culture B for non-culture	Routine	N/A	14 days at NML	Yes
Zika virus	2	2	B	Routine	3–4 days at BCCDC ≤5 days at PHO	3–7 days at BCCDC ≤5 days at PHO	No

These recommended biosafety containment levels generally apply to the propagative activities of the selected Risk Group 3 and 4 pathogens. Specific recommendations for the precautions required for other routine diagnostic workups are provided if available. Viral hemorrhagic fever in general requires contact, droplet, and aerosol-generating medical procedure (AGMP) precautions in patient-facing healthcare settings, as per Public Health Agency of Canada (PHAC): *Routine Practices and Additional Precautions for Preventing the Transmission of Infection in Healthcare Settings* (2017) (https://www.canada.ca/en/public-health/services/publications/diseases-conditions/routine-practices-precautions-healthcare-associated-infections.html) (accessed on 2 December 2024). Level 2+: biosafety Containment Level 2 with enhanced precautions (e.g., taping the culture plates, workup in biosafety cabinets, biosafety level 3 practices with biosafety level 2 engineer control). See the abbreviation list on the first page if needed.

4. Discussion

4.1. Summary of Precautions Required for High-Risk Bacteria

In general, Risk Group 3 bacteria that belong to the SSBA, such as *Brucella* species, *Burkholderia mallei*, *Burkholderia pseudomallei*, and *Francisella tularensis*, can be cultured in clinical laboratories using Containment Level 2 precautions with enhancements until the identification of the microorganisms is confirmed [23]. It is not recommended to use matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) because this method could be considered as an infectious aerosol-generating procedure if proper inactivation is not performed [28]; moreover, the MALDI-TOF MS libraries may not have sufficient databases to identify these rarely encountered Risk Group 3 bacteria [29].

Some of these Risk Group 3 bacteria, such as *Chlamydophila psittaci* and *Coxiella burnetii*, can be safely worked up in a Containment Level 2 laboratory despite belonging to SSBAs. This is because they do not typically grow in routine culture media used in clinical laboratories; they require molecular or serological methods for laboratory diagnosis that are not considered to be high-risk propagative activities [8,30]. *Mycobacterium tuberculosis* complex, *Orientia tsutsugamushi*, and certain *Rickettsia* species also belong to Risk Group 3 bacteria but not the SSBA. They can be safely worked up in Containment Level 2 laboratories with enhanced practice precautions. In general, Category A packaging is required for culture isolates, whereas Category B packaging is suitable for primary specimens.

It is not always practical to wait for the workup of Risk Group 3 bacteria to be ruled out at reference laboratories (BCCDC, PHO, and NML) in order to determine whether a Containment Level 2 laboratory should work up the patient specimens. This is because some test turnaround times take weeks to complete. During the waiting period, microorganisms in the specimens may no longer be viable; patients could also be in a critical state while waiting for a clear laboratory diagnosis. Therefore, while reference laboratories work up the potential Risk Group 3 bacteria, Containment Level 2 laboratories should consider continuing the workup of other pathogens with enhanced precautions to help with differential diagnoses.

Notably, *Mycobacterium tuberculosis* complexes are slow growers that could take up to 56 days for the culture results to complete. Although the *Mycobacterium tuberculosis* complex is commonly known to require airborne precautions in patient-facing healthcare settings, this requirement is mainly for patients with active pulmonary and laryngeal tuberculosis and may be discontinued when the source patient has a minimum of 2 weeks of effective therapy and 3 consecutive negative acid-fast bacilli sputum smears [31]. The other Risk Group 3 bacteria generally require only routine IPAC precautions in patient-facing healthcare settings. These precaution requirements should be considered when risk assessments are needed to evaluate laboratorians exposed to only the primary specimens rather than culture isolates. In addition, a biosafety cabinet might have been used when they plate primary specimens on culture plates. In these instances, laboratorians can be reassured that their risks of developing infections should not be any more than patient-facing HCW.

4.2. Summary of Precautions Required for High-Risk Fungi

Only *Coccidioides* species and *Cryptococcus gattii* complex belong to SSBAs. Many of the Risk Group 3 fungi, such as *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Paracoccidioides brasiliensis*, belong to the dimorphic fungi group, which exists as yeasts above 37 degrees Celsius and molds below this temperature [12]. Compared to yeasts, the molds are filamentous forms that can be easily dislodged and aerosolized, leading to LAIs [12]. Therefore, these dimorphic fungi can be safely worked up in a Containment Level 2 labora-

tory when their incubation temperature is kept above 37 degrees Celsius, with enhanced practice precautions and minimized activities with a high risk of infectious aerosols.

Not all dimorphic fungi are Risk Group 3 pathogens. For instance, *Sporothrix brasiliensis* and *Talaromyces marneffei* are Risk Group 2 pathogens that require Containment Level 2 precautions only. The *Cryptococcus* species are unique, and only the *Cryptococcus gattii* complex belongs to Risk Group 3. However, a Containment Level 2 laboratory is sufficient to work up *Cryptococcus* species. There is no guidance on whether some Risk Group 3 fungi like *Cladophialophora bantiana* and *Rhinocladiella mackenziei* could be worked up in a Containment Level 2 laboratory with enhanced practice precautions to mitigate the risk of LAIs. Except for the *Coccidioides* species, Category B packaging is sufficient regardless of culture or primary specimens.

The culture workup turnaround time for fungi takes even longer than for bacteria; therefore, it is likely impractical to hold the workup in a Containment Level 2 laboratory while waiting for the culture results at a reference laboratory. Although fungal serology results may guide the diagnosis with a quicker turnaround time, the tested analytical sensitivity is notoriously bad. For instance, *Histoplasma*, *Blastomyces*, *Paracoccidioides*, and *Coccidioides* serology test sensitivities could be as low as 21%, 33%, 65%, and 65%, respectively [32].

The drastic differences between biosafety and IPAC precautions in patient-facing healthcare settings may surprise laboratorians and infection preventionists alike. In patient-facing healthcare settings, only routine IPAC precautions are generally recommended for patients infected with Risk Group 3 fungi. One must understand that in patient-facing healthcare settings, these dimorphic fungi are in yeast forms at 37 degrees Celsius, which are not as easily dislodged and aerosolized compared to laboratory settings [12]. The propagative activities involved in microbiology culture also put laboratorians at a higher risk of infections compared to other HCWs [12]. The risk perception of high-risk fungi may be different for clinicians and laboratorians, which could impact effective risk communication.

4.3. Summary of Precautions Required for High-Risk Viruses and Prions

Many high-risk viruses and prions belong to SSBAs. Unlike bacterial and fungal culture testing, the diagnostic workups of viruses and prions are very much reliant on molecular and serological methods, which are non-propagative activities with fewer risks of LAIs. Therefore, Containment Level 2 practices with enhanced precautions may be considered if a laboratory is not intended to isolate, concentrate, or propagate these Risk Group 3 and 4 pathogens. If these molecular and serological test results have a quick turnaround time, laboratorians may have the option to hold other tests until the requested Risk Group 3 and 4 viruses or prions are ruled out. Except for the dengue virus, viruses with the potential to cause viral hemorrhagic fever generally require Containment Level 3 practice precautions in clinical laboratories. Similarly, patients infected with these viruses require routine, droplet, and aerosol-generating medical procedure precautions in patient-facing healthcare settings. Some Risk Group 4 viruses (such as Crimean–Congo Hemorrhagic fever virus, Ebola virus, Guanarito virus, Hendra virus, Junin virus, Kyasanur Forest virus, Lassa virus, Machupo virus, Marburg virus, Nipah virus, Russian Spring–Summer encephalitis virus, and Sabia virus) are not only SSBAs but also always require Category A packaging for transport regardless of culture isolates or primary specimens. Interestingly, patients with measles virus and varicella zoster virus generally require airborne precautions in patient-facing healthcare settings but only Containment Level 2 precautions in laboratories. This could be owing to the use of biosafety cabinets and the availability of immunizations that protect laboratorians.

Prions are extremely difficult to destroy and require soaking contaminated items in 1 N sodium hydroxide (NaOH) or 1 N sodium hydroxide (NaOH) for 1 h, followed by autoclaving [1,33]. Furthermore, the anatomical sites, with which the items have been in contact, determine the infectivity of prions and, subsequently, whether the items should be quarantined, decontaminated, and reused or discarded. For the latest information regarding biosafety and IPAC precautions required for suspected prion cases, readers are encouraged to refer to the latest guidance applicable to their regional settings.

4.4. Strength and Limitations

A major strength of this review is its broad coverage of biosafety precautions against multiple high-risk pathogens. The review was based on reputable guidance commonly used in Canada and North America. Although other authors have also created similar reviews to summarize different biosafety precautions for propagative versus non-propagative activities for emerging viruses [34,35], the current review not only covers bacteria and fungi but also tests turnaround times and IPAC precautions in patient-facing healthcare settings. However, the test turnaround time is dependent on the regions and provinces of clinical laboratories. Laboratorians and infection preventionists who practice outside of British Columbia and Ontario, Canada, should be encouraged to create their own reviews to ensure the relevance of the information to their intended readers. Other laboratories may have various scopes regarding the common high-risk pathogens they encounter in their settings.

Another strength of this review is its coverage of precautions required in patient-facing healthcare settings in Canada. This information is beneficial to laboratorians who need to perform the risk assessment of exposure to high-risk pathogens. Laboratorians who perform the setup of primary specimens but not culture isolates can be reassured: Generally, their risk of LAIs is not any higher than the risk of occupationally acquired infections in healthcare settings. In addition, laboratorians have biosafety cabinets that act as extra layers of protection.

The current review does not cover parasites because they are Risk Group 2 pathogens that are not included in HPTA and TDGR [9,14]. The current review is sufficient in helping to create a job aid for laboratorians and infection preventionists. However, it is important to note that this review provides guidance for the minimum safety requirements in general situations. Local risk assessments and point-of-care risk assessments are recommended to determine whether further upgrading of precautions is needed [6,15].

One may argue that a systematic review of randomized controlled trials would be superior to a narrative review of expert opinions like the current review [36]. However, one must also realize that guidance for biosafety and IPAC practices is mainly based on expert opinions and extrapolations rather than randomized controlled trials [6,8,15]. It could be considered unethical to conduct trials to mainly assess harm to the subjects [37,38]. Although there are many relevant published case reports and retrospective observational studies, they are prone to bias and confounders and, therefore, are not included in the current study. It is important to acknowledge that expert opinions and extrapolations could also be biased due to different risk perceptions and historical evidence in specific work settings. For instance, the current review is mainly based on Canadian guidance and may not be applicable to other countries. As more evidence becomes available, we should anticipate amendments in the precautions required, as released by the *Canada Gazette* and the Government of Canada's biosafety directives and advisories [11,39].

5. Conclusions

There are differences in safety precautions required for laboratorians and patient-facing HCWs. Specifically, contrasting levels of precautions exist for endemic fungi and certain SSBAs. The contrast is justifiable due to the nature of the work involved in these two different areas, such as the propagative activities in laboratories that increase the risk of LAIs. Acknowledging the differences may help laboratorians and clinicians recognize the critical pathogens in their counterpart settings and thereby promptly warn their counterparts to apply additional precautions, as communication has been listed as a root cause of many laboratory exposure incidents. The current review serves as a beginner's guide to help infection preventionists understand why some tests need to be held until Risk Group 3 and 4 pathogens are ruled out; it also helps laboratorians appreciate why some microbiology tests still need to be performed with enhanced precautions because the test turnaround times of certain Risk Group 3 and 4 pathogens can be long.

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Abbreviations

AGMP	Aerosol-generating medical procedures
BCCDC	British Columbia Centre for Disease Control, Vancouver, British Columbia
CDC	Centers for Disease Control and Prevention
CFIA	Canadian Food Inspection Agency, Ottawa, Ontario
CL	Containment Level
CLSI	Clinical and Laboratory Standard Institution
HCW	Healthcare workers
HPTA	Human Pathogens and Toxins Act
HPTR	Human Pathogens and Toxins Regulations
IPAC	Infection prevention and control
LAI	Laboratory-acquired infection
MALDI TOF MS	Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
N/A	Information is not available from the references
NML	National Microbiology Laboratory, Winnipeg, Manitoba
PHAC	Public Health Agency of Canada
PHO	Public Health Ontario
Prion	Proteinaceous infectious particle
SSBA	Security-sensitive biological agent
TDGR	Transportation of Dangerous Goods Regulation

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