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Review

Laboratory-Acquired *Yersinia pestis* Infection: Occupational Exposure, Clinical Presentation and Microbiological Identification

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Abstract

Laboratory work with *Yersinia pestis* is governed by detailed containment provisions, and laboratory-acquired infection is rare: a scoping review covering 2000 to 2021 attributed two of 309 cases to *Y. pestis*. Preventing exposure and recognising infection after an unidentified exposure are, however, distinct problems, and the second has received less attention. This narrative review, supported by a documented search of PubMed, PubMed Central and major biosafety and public-health agency websites to October 2026, classified evidence into seven categories and analysed them without pooling. The record that can be reconstructed in detail comprises two cases: a fatal infection reported from Chicago in 2009, in which no exposure event was identified, occupation was absent from the clinical record and the organism was identified only after death; a survived infection from a United States laboratory in 1959, in which the exposure was likewise unrecognised but the occupational context was known at admission and the organism was identified within 18 h. Evidence from naturally acquired plague documents bidirectional misidentification of *Y. pestis* by commercial automated and mass-spectrometry systems, attributable to reference-library composition rather than instrument performance. Recognition therefore appears to depend on information held separately by the worker, the employing institution, the treating clinician and the clinical microbiology laboratory, while many containment and response measures become operative only once exposure or plague is suspected. Post-work health monitoring and symptom reporting are specified as requirements in Russian and Canadian national documents but appear only as recommendations in the United States guidance reviewed. These observations rest on a small case record and indicate areas for evaluation rather than an established pattern.

Keywords: *Yersinia pestis*; plague; laboratory-acquired infection; occupational exposure; biosafety; MALDI-TOF mass spectrometry

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Academic Editor: Maria King

Received: 13 October 2026
Revised: 11 November 2026
Accepted: 13 November 2026
Published: 18 November 2026

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1. Introduction

Yersinia pestis is handled under some of the most detailed containment provisions specified for any bacterial pathogen. The sixth edition of Biosafety in Microbiological and Biomedical Laboratories (BMBL) assigns biosafety level 2 practices for clinical material and diagnostic quantities, with biosafety level 3 practices for propagative work and for

procedures carrying a high potential for aerosol or droplet production, and notes a reported human infectious dose below 100 colony-forming units [1]. In the United States, *Y. pestis* is a select agent requiring registration. Sentinel-level clinical laboratory guidelines specify a rule-out algorithm and referral pathway for isolates that cannot be excluded as *Y. pestis* [2,3].

Against this background, laboratory-acquired infection is rare. A scoping review of laboratory-acquired infections and accidental pathogen escapes reported worldwide between 2000 and 2021 identified 309 individual cases, of which two were attributed to *Y. pestis* [4]. A subsequent systematic review of risk factors and mitigation strategies covering 2000 to 2024 identified 712 human cases across 250 reports, with *Yersinia* contributing one fatal case acquired in a research laboratory and one acquired during fieldwork [5]. Prior to 1970, at least ten laboratory-acquired *Y. pestis* infections with four deaths are reported in the Public Health Agency of Canada's pathogen safety data sheet, citing a 1976 survey of laboratory-associated infections [6,7]; the primary survey was not available to the authors of this review.

Preventing exposure and recognising infection after an exposure has not been identified are distinct problems. Containment provisions address the first. The second begins at the point where containment has already been unsuccessful and no incident has been recorded, and it proceeds through a series of settings—the worker, the employing institution, the treating clinician, the receiving clinical microbiology laboratory, and the public-health system—each of which may hold information that the others do not. These settings are ordinarily examined in the separate works of literature. The occupational biosafety literature addresses exposure and containment; the clinical microbiology literature addresses identification of *Y. pestis* in specimens from naturally infected patients. They are not routinely read together.

This review examines how laboratory-acquired *Y. pestis* infection may come to be recognised and brings those two bodies of evidence into a single analysis. The argument advanced is narrow: available evidence suggests that recognition of laboratory-acquired *Y. pestis* infection depends on information distributed across occupational, clinical and microbiological settings, while many established containment and response measures become operative only after occupational exposure or plague is suspected. No claim is made that a universal or quantified pattern of recognition failure has been demonstrated; the documented case record is too small to support such a claim, and this constraint is addressed explicitly throughout.

2. Scope, Definitions and Evidence Approach

This is a narrative review supported by a documented search. PubMed, PubMed Central and the websites of the Centers for Disease Control and Prevention, the Association of Public Health Laboratories, the American Society for Microbiology, the World Health Organization and the Public Health Agency of Canada were searched up to 5 October 2026, using combinations of the terms laboratory-acquired infection, laboratory-associated infection, *Yersinia pestis*, plague, biosafety, MALDI-TOF, misidentification and occupational exposure, together with citation tracking from retrieved articles. Targeted Russian-language web searches for laboratory-acquired plague (внутрилабораторное заражение чумой, лабораторное заражение чумой, аварии при работе с возбудителем чумы; i.e., "intralaboratory plague infection", "laboratory plague infection" and "accidents during work with the plague pathogen") were conducted on 11 November 2026. English, German and Russian sources were used. No formal systematic search protocol was registered and the review is not presented as systematic.

Because the terms used in this field are applied inconsistently, evidence was classified into seven categories before analysis, and the categories were not pooled at any point

(Table 1). A confirmed laboratory-acquired infection (C1) required microbiological identification of *Y. pestis* from the worker, a documented occupational relationship to laboratory work with the organism or infected material, and a published investigation or official report. A historically documented laboratory-acquired infection (C2) required contemporaneous clinical and bacteriological diagnosis by the methods of the period together with an unambiguous laboratory link, assessed by the diagnostic standards of its time rather than retrospectively. A laboratory-linked secondary infection (C3) is one acquired by person-to-person transmission from a C1 or C2 index case and is treated throughout as an outcome of a laboratory-acquired infection and never as a case of one. Clinical-laboratory exposure or infection arising from naturally acquired specimens (C4) covers personnel handling diagnostic material whose identity was unknown at the time. Fieldwork-associated infection (C5) is used only as comparator evidence. Aggregate historical reports lacking case-level detail (C6) are reported as counts with their chain of attribution and are never disaggregated or added to case totals. Unconfirmed or contested events (C7) are excluded from all analyses.

One source limitation requires a statement. The 1976 survey underlying the pre-1970 aggregate figure could not be obtained; claims deriving from it are reported here with the secondary attribution through which they were accessed [6,7]. The 1962 case report and review, which contains the most recent previously published review of laboratory-acquired plague, was obtained during revision and is reported here directly (Section 3.2) [8]. In addition, Russian-language regulatory documents and case reports have been included (Sections 3.4, 8 and 9), but the wider literature of the anti-plague institute network was not searched systematically, which is a limitation of this search rather than evidence of absence.

Table 1. Evidence categories and their role in the review.

Category	Definition	Role in This Review
C1 Confirmed laboratory-acquired infection	Microbiological identification of *Y. pestis* from the worker, a documented occupational relationship to laboratory work with the organism or infected material, and a published investigation or official report. Route of exposure need not be identified	Primary evidence
C2 Historically documented laboratory-acquired infection	Clinical and bacteriological diagnosis made contemporaneously by the methods of the period, with an unambiguous laboratory link, documented in the primary literature of the time or in modern scholarship working from primary records	Primary evidence, reported separately from C1 and assessed by the diagnostic standards of its period
C3 Laboratory-linked secondary infection	Infection acquired by person-to-person transmission from a C1 or C2 index case	Reported as an outcome of laboratory-acquired infection; never counted as a laboratory-acquired infection
C4 Clinical-laboratory exposure or infection from naturally acquired specimens	Exposure or infection in personnel handling diagnostic specimens or isolates from a naturally infected patient or animal, where the identity of the organism was not known at the time of handling	Evidence of microbiological recognition; identified as naturally acquired at each use

Table 1. *Cont.*

Category	Definition	Role in This Review
C5 Fieldwork-associated occupational infection	Infection acquired during field investigation, trapping, necropsy or specimen collection outside a laboratory facility	Comparator only
C6 Aggregate report without case-level detail	A count of infections or deaths reported in a survey, review or safety data sheet where constituent cases cannot be identified	Reported as a count with its chain of attribution; not disaggregated; not added to case totals
C7 Unconfirmed or contested event	A reported event in which the aetiology has not been established by an authoritative body, or in which authoritative accounts conflict	Excluded from all analyses

3. Documented Laboratory-Acquired *Yersinia pestis* Infection

The documented record is summarised in Table 2. Two cases can now be reconstructed in detail, one fatal and one survived, and the historical record supports a narrower inference than is sometimes drawn from it.

Table 2. Documented laboratory-acquired and laboratory-linked *Y. pestis* cases.

Case, Year and Country	Category	Setting, Role and Exposure Recognition	Organism and Strain	Clinical Course and Outcome	Source
Researcher, aged 60 years; 2009, USA	C1	University research laboratory; researcher. Exposure not recognised at the time; route not determined	*Y. pestis* KIM D27, pigmentation-negative, attenuated, excluded from the National Select Agent Registry	Septicaemic plague with septic shock; no pneumonic pathology at autopsy. Died 13 September 2009	[9,10]
Chemist, aged 22 years; 1959, USA	C1	United States Army Medical Unit, Fort Detrick; chemist analysing cultures. Exposure not recognised at the time; probable exposure (centrifugation of viable organisms) identified retrospectively from the work log	Virulent strain; isolate comparable in virulence to the Alexander strain	Primary pneumonic plague; diagnosed by sputum microscopy 18 h after onset. Tetracycline and streptomycin; recovered, discharged 11 days after onset. No secondary cases	[8,9]
Franz Barisch; 1898, Austria-Hungary	C2	Pathological-anatomical institute; laboratory attendant. Exposure not recognised; infection described as unnoticed	Plague bacillus; no strain characterisation available	Pneumonic; initially attributed to influenza or pneumonia. Died 18 October 1898	[11,12]

Table 2. *Cont.*

Case, Year and Country	Category	Setting, Role and Exposure Recognition	Organism and Strain	Clinical Course and Outcome	Source
Hermann Franz Müller; 1898, Austria-Hungary	C2 or C3; not resolvable from available sources	Same institute; physician and investigator, also attended the index case. Recognition not reported	As above	Plague pneumonia. Died 23 October 1898	[11,12]
Albine Pecha; 1898, Austria-Hungary	C3	Hospital; trainee nurse assigned to the index case	As above	Pneumonic. Died 30 October 1898	[11,12]
Second nurse; 1898, Austria-Hungary	C3; infection not established	Hospital; nurse assigned to the index case	As above	Mild illness; survived	[12]
Pre-1970 aggregate; to 1970, various	C6	Not specified	Not specified	At least 10 infections, 4 deaths	[6,7]
2000–2021 aggregate; various	C6	Research laboratories	Not specified	2 cases among 309 laboratory-acquired infections	[4]
2000–2024 aggregate; various	C6	Research and fieldwork	Not specified	1 fatal research case; 1 fatal fieldwork case	[5]

Note. C1–C6 categories are defined in Table 1. The 1959 case is reported in the 1962 primary case report [8] and is also cited by CDC [9]; the pre-1970 aggregate is reported by the Public Health Agency of Canada citing a 1976 survey [6,7].

3.1. Chicago, 2009

The principal modern case (C1) was investigated jointly by the Chicago Department of Public Health, the Illinois Department of Public Health, the Centers for Disease Control and Prevention and the employing university and was reported in 2011 [9]; an account by clinicians and investigators at the institution was published separately in the same year [10].

The patient was a researcher aged 60 years with insulin-dependent diabetes mellitus who worked with a pigmentation-negative (*pgm*−) attenuated strain, *Y. pestis* KIM D27. A virulent strain, CO92, was in use by a separate group on another floor of the same building. He last worked in the laboratory on 4 September 2009. On 10 September he was assessed at an outpatient clinic for fever, body aches and cough of approximately three days' duration, was referred to an emergency department for further evaluation, and did not attend at that time. The account published in the New England Journal of Medicine describes a one-week history of worsening shortness of breath with dry cough, fevers, chills and weakness at emergency department presentation [10]; the two accounts use different reference points and are reported here separately rather than combined.

He was brought by ambulance to an emergency department on 13 September with fever, cough and worsening dyspnoea. On arrival he was alert, with a temperature of 38.3 °C, a respiratory rate of 42 breaths per minute, and a chest radiograph described as showing normal lung fields. Investigations showed renal failure, incipient acidosis, raised transaminases and a white cell count of 79.2×10^9/L with 22% band forms; extracellular bacteria were noted on a peripheral blood smear. He was initially treated with diuretics for suspected congestive heart failure, and subsequently with vancomycin and piperacillin–tazobactam once infection was suspected. Neither agent is a recommended regimen for

plague [13]. He was intubated approximately 12 h after presentation and died of cardiac arrest about an hour later, on 13 September [9].

Blood cultures drawn on 13 September yielded Gram-negative bacilli in four of four bottles, reported on 14 September, together with Gram-positive cocci subsequently identified as nutritionally variant streptococci. Efforts to identify the slow-growing Gram-negative organism were in progress when, on 16 September, an emergency department physician learned that the patient had worked in a laboratory conducting research on select agents and notified the hospital clinical laboratory. On 18 September, 16S ribosomal DNA sequencing performed by that laboratory narrowed the identification to *Y. pestis* or *Y. pseudotuberculosis*, and the public health department was notified the same day. Polymerase chain reaction identified the clinical isolate as a *pgm*− strain; state and federal laboratories confirmed *Y. pestis*, and immunohistochemistry demonstrated the organism in blood vessels of multiple organs, consistent with septicaemic rather than pneumonic plague [9].

The route of exposure was not determined. No needlestick, splash or other incident was reported by family members or coworkers, no recent work-related injury or illness appeared in the relevant occupational safety records, and assessment of the laboratory environment identified no major deficiency in engineering controls. Review of training records identified deficiencies in attendance at required biosafety courses, including by the patient, and coworkers reported that he had complied inconsistently with the laboratory policy requiring gloves when handling KIM D27 cultures [9]. The patient's occupation was not documented in the records of either the outpatient clinic or the emergency department [9].

Following recognition, antimicrobial prophylaxis was offered to all 30 staff of the research laboratory and to close contacts, defined as persons within six feet (approximately 2 m) of the patient or handling his blood or tissue between 7 and 18 September. All 30 coworkers were prescribed a seven-day course of doxycycline on 19–20 September; of one household and 64 other close contacts, including medical, laboratory and pathology personnel, 61 of 65 (94%) accepted prophylaxis between 18 and 20 September. No additional infections were identified [9].

3.2. United States, 1959

The most recent laboratory-acquired *Y. pestis* infection in the United States before 2009 is reported to have occurred in 1959 and to have followed inhalation of a virulent strain, as stated by CDC citing a 1962 case report and review [8,9]. That primary report has been obtained during revision, and the case is described below from it [8]. The patient, identified as R. L. P., was a chemist aged 22 years who had worked for seven months analysing cultures of *Y. pestis* (then *Pasteurella pestis*) for nucleic acid content at the United States Army Medical Unit, Walter Reed Army Medical Center, Fort Detrick, Maryland. He had received an initial series of Cutter plague vaccines in March 1959 and a booster on 10 August 1959. No exposure incident was recognised at the time; subsequent analysis of his work log identified centrifugation of viable organisms on 27 August 1959 as the probable exposure, an interval consistent with the usual incubation period of pneumonic plague [8].

Illness began on 1 September 1959 with a shaking chill, fever, a dry hacking cough with severe pleuritic chest pain, occipital headache, and neck stiffness with lower back pain; he was admitted the same day. He was placed in isolation shortly after admission because of the meningeal signs and the possible occupational exposure, before any diagnosis had been established. Recognition followed from direct microscopy of the first sputum produced, 18 h after onset, which showed numerous Gram-negative bipolar safety-pin forms as the predominant organism; a diagnosis of pneumonic plague was made and complete isolation was instituted. The organism was subsequently isolated by culture and by guinea pig

inoculation from sputum, the isolate being comparable in virulence to the Alexander strain, but was not recovered from later sputum specimens or from blood [8].

Tetracycline was given orally 13 h after the onset of symptoms and continued intravenously, and intramuscular streptomycin was added the following morning because the drug sensitivity of the infecting strain was uncertain; a total of 19 g of streptomycin over seven days and 30 g of tetracycline over 10 days was administered. A self-limited secondary rise in temperature occurred on the fifth day of illness without evidence of superimposed infection. The patient was removed from isolation on the third hospital day and was discharged 11 days after onset, with complete radiographic clearing and no residua. All close contacts were observed for 10 days with temperatures recorded twice daily, hospital personnel caring for the patient received sulfadiazine for six days, and no secondary cases occurred [8].

This case is set out in full because it provides a second course of recognition that can be reconstructed, and because that course differs from the Chicago case in a respect that bears directly on the argument advanced here. In both, the exposure itself was unrecognised and was reconstructed only afterwards. In 1959, however, the nature of the patient's work was known to the institution that admitted him; isolation was instituted on that basis before a diagnosis existed, and the organism was identified within 18 h of the first sputum. The occupational information that reached the clinical setting only after death in 2009 was present at the point of admission in 1959. The same report also reviews four earlier laboratory-acquired pneumonic cases, occurring in Michigan in 1901, San Francisco in 1944, Nanking in 1947 and Johannesburg in 1947, the last fatal and followed by a secondary infection in a close contact; these are summarised from the reports of their time and are not added to the case totals in Table 2 [8].

3.3. Vienna, 1898

The best-documented historical episode (C2) followed investigations in Vienna using *Y. pestis* strains brought from Bombay by an Austrian plague commission. A laboratory attendant, Franz Barisch, became infected during animal infection experiments without the exposure being noticed and died on 18 October 1898. Two further deaths followed: a physician who had worked in the laboratory and had also attended Barisch, and a trainee nurse assigned to his care; a second nurse experienced a mild illness and survived. A contemporaneous report described four cases, three of them fatal, of pneumonic form, and noted that the laboratory was closed and its cultures and animals destroyed [11,12].

Two features merit emphasis, because they distinguish this episode from the Chicago case rather than aligning it. First, the death of the trainee nurse was a laboratory-linked secondary infection (C3) and is not counted as a laboratory-acquired infection. The physician both worked in the laboratory and attended the index case, and the available sources do not resolve whether his infection was laboratory-acquired (C2) or secondary (C3); he is reported here under both categories rather than assigned to one. The episode nonetheless documents that a laboratory-acquired *Y. pestis* infection can give rise to a lethal transmission chain, which is the single inference drawn from it here. Second, institutional recognition occurred: although the index illness was initially attributed to influenza or pneumonia, isolation was instituted on the insistence of a colleague before the diagnosis was established [12]. The 1898 and 2009 episodes are accordingly not presented as instances of the same recognition problem, and the lethality of the 1898 episode is at least as plausibly attributable to the absence of effective antimicrobial therapy.

3.4. Irkutsk, 2026 (Contested Event, C7)

In late September 2026, a 28-year-old laboratory technician at the Irkutsk Anti-Plague Research Institute of Siberia and the Far East was hospitalised with severe pneumonia and died in early October; media reports described suspected pneumonic plague following a laboratory accident, and close to 200 persons were reportedly placed under medical observation [14,15]. The federal health authority, Rospotrebnadzor, reported the diagnosis as pneumonia of unknown aetiology and stated that extended testing of material from the patient had not detected microorganisms associated with her professional activity [16]. At the time of writing, no authoritative account establishing the aetiology has been published, and the event is therefore classified as C7 and excluded from all analyses. It is noted here because it illustrates, in a facility specialising in plague, several of the constraints identified in this review: the clinical presentation did not itself establish the diagnosis, the aetiology remained contested after laboratory investigation, and the information on which independent assessment would depend is not available in the published record.

4. Recognition Checkpoints for the Exposed Laboratory Worker

An unrecognised occupational exposure may come to be identified as plague at any of several distinct points: the worker, the employing institution, the treating clinician, the clinical microbiology laboratory, and the public-health system. These are set out here as independent checkpoints rather than as a sequence. Each is a locus at which information bearing on recognition may reside and at which recognition may therefore occur or fail; none depends on any other having functioned. These checkpoints are a way of organising heterogeneous evidence, not a validated causal model, and no claim is made that they describe every case. They are not derived from the Chicago investigation. Each corresponds to a locus already addressed separately in the guidance reviewed for this article—worker reporting obligations and institutional biosafety oversight in BMBL and select-agent registration [1], clinical assessment and treatment in the plague treatment recommendations [13], isolate handling and referral in the sentinel-level laboratory guidance [2,3], and contact management in the public-health response provisions [11]—as set out in Section 8. The checkpoints therefore reflect a division of responsibility already present in the guidance reviewed, and the case record is used to examine how that division operated, not to construct it.

Setting the checkpoints out this way makes explicit where the relevant information resides and therefore where recognition is possible at all. The worker knows what organism was handled and may know of a procedural deviation. The employing institution holds the strain, the containment conditions and the training record. The treating clinician holds the clinical presentation and, if elicited, the occupational history. The clinical microbiology laboratory holds the isolate and the identification result. The public-health system holds the reporting and contact-management apparatus. Information held at one checkpoint is not necessarily available at any other, and the guidance reviewed for this article did not identify a general requirement governing transmission of this information across these settings.

The Chicago investigation illustrates these checkpoints rather than validating them. The exposure was not perceived and no incident was recorded; the illness was communicated to a supervisor as an explanation for absence from work, although laboratory policy required workers with illness consistent with plague to report to occupational health or an emergency department; the clinical assessments did not record the patient's occupation; and the organism remained unidentified until the occupational history reached the hospital laboratory from a clinician, three days after the patient's death [9]. The route by which recognition was finally achieved supports treating these points as independent. The decisive information did not pass from worker to institution to clinician in turn; it entered at the

clinical stage and was conveyed from there to the laboratory. Recognition was reached by a single checkpoint functioning in isolation, after the others had not.

The checkpoints also indicate where the evidence base for this review is strongest and weakest, and the asymmetry is substantial. The clinical and microbiological checkpoints are supported by multiple independent reports, the latter by seven documented identification events in both error directions and by quantified method performance from three independent studies (Section 6). The worker and institutional checkpoints are supported by one detailed modern investigation, with partial corroboration from the 1959 report, in which the exposure was likewise reconstructed only retrospectively but institutional knowledge of the work prompted isolation on admission. Claims about the first two are therefore offered as findings; claims about the latter two are offered as one detailed instance with partial corroboration and are framed throughout as such. The public-health checkpoint is addressed only where the case record documents it, and no general claim about its operation is made.

5. Clinical Recognition and Occupational Exposure History

The early clinical presentation of plague is non-specific. Primary pneumonic plague typically begins one to six days after exposure with fever, headache, weakness and cough, progressing to rapidly developing pneumonia; septicaemic plague may present with fever and shock without localising features [13]. None of these features discriminates reliably from influenza or community-acquired pneumonia at first presentation.

The converse also applies. Because these features are shared by many other conditions, a diagnosis of plague in a laboratory worker should be reached through differential diagnosis rather than inferred from occupational exposure or from a single pathogen-specific result. Detection of *Y. pestis* nucleic acid by polymerase chain reaction establishes the presence of genetic material, not active infection or causation; case definitions differ on this point, since the United States surveillance definition requires isolation of the organism or a fourfold change in antibody titre to the F1 antigen for confirmation, whereas current World Health Organization definitions accept detection of *Y. pestis* DNA by species-specific polymerase chain reaction as confirmatory in a suspected case [17,18]. Under the latter, the confirmatory weight of a molecular result rests on the clinical and epidemiological criteria that define a suspected case. Where the search for other causes is curtailed once such a result is obtained, a co-existing or alternative cause of illness may be overlooked. The cases reviewed here illustrate the point: the Chicago patient had concurrent nutritionally variant streptococcal bacteraemia and insulin-dependent diabetes mellitus, which the investigation could not exclude as contributory [9], and in the 2020 Arizona case a presumptive identification by polymerase chain reaction preceded confirmation by three days [19]. The contested Irkutsk event shows the reverse difficulty: a suspected laboratory exposure in a plague facility did not, on the information published, establish the cause of illness (Section 3.4) [16].

The Chicago case illustrates the resulting difficulty. The initial outpatient assessment attributed the illness to influenza or another acute respiratory infection. At emergency department presentation three days later, with a respiratory rate of 42 breaths per minute and a chest radiograph reported as showing normal lung fields, the patient was treated initially for suspected congestive heart failure, and subsequently with vancomycin and piperacillin–tazobactam, neither of which is recommended for plague [9,13]. The clinical features alone did not generate a suspicion of plague at any point before the patient's death.

The information that did generate that suspicion was the patient's occupation, which was not documented in the records of either the outpatient clinic or the emergency department [9]. Identification proceeded only after a clinician learned that the patient had worked in a laboratory conducting research on select agents and conveyed this to the hos-

pital laboratory; 16S ribosomal DNA sequencing narrowing the organism to *Y. pestis* or *Y. pseudotuberculosis* followed two days later [9]. In this case, therefore, the occupational history functioned as the trigger for the diagnostic pathway that produced the identification, and it entered that pathway from outside it. The published investigation's recommendation that health-care providers routinely enquire about occupational exposures when evaluating patients follows from this [9].

Two constraints on interpretation should be stated. First, this observation derives from a single case, and no evidence identified for this review quantifies how often occupational history is recorded or elicited in the assessment of acute febrile illness; no claim about the frequency of its omission is made here. Second, the patient presented in established shock with renal failure, acidosis and marked leucocytosis, and died approximately 13 h later [9]. Whether earlier recognition and earlier initiation of an active antimicrobial regimen would have altered that course is not determinable from the record and is not asserted.

A naturally acquired case reported from Coconino County, Arizona, in July 2025 (C4 context) provides a comparator in which contextual exposure information operated in the opposite direction. Matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) of growth from a blood culture identified *Y. pseudotuberculosis*, and bipolar-staining Gram-negative bacilli were seen. The published account states that the combination of Gram stain results, the MALDI-TOF result, the patient's clinical signs and symptoms, and the known endemicity of *Y. pestis* in northern Arizona raised sufficient suspicion for pneumonic plague; the patient had had occupational exposure to two domestic cats with illness consistent with pneumonic plague in the days before onset [20]. Contextual exposure information, weighed alongside microscopy and clinical findings, was sufficient to override a confident contrary automated identification and to initiate the public-health response, although the patient had already died and laboratory confirmation followed only afterwards. The analogy to the laboratory setting is partial, since regional endemicity is a cue available in Arizona and not available to a clinician assessing a laboratory worker in a non-endemic city.

6. Microbiological Recognition and Identification of *Yersinia pestis*

The evidence in this section derives almost entirely from naturally acquired plague, and each case is identified as such. It is used here on the basis that identification of an isolate by a clinical microbiology laboratory proceeds by the same mechanisms irrespective of how the patient acquired the organism. That extrapolation rests on the organism and the identification method, not on direct evidence from laboratory-acquired cases, of which there is none in the published record examined. The case-level evidence is summarised in Table 3 and the reported diagnostic performance in Table 4.

Table 3. Documented *Y. pestis* identification and misidentification evidence.

Finding/Event	Identification Reported	Correct Identification	Reported Consequence	Source
Oregon and New Mexico, 2010–2011	Misidentification by automated systems	*Y. pestis*	Delayed diagnoses of human plague infections	[21]
Colorado, June–July 2014	*Pseudomonas luteola*, automated system, hospital laboratory	*Y. pestis*, state public health laboratory, 8 July 2014	Pneumonic plague outbreak with dog-to-human and possible human-to-human transmission; prophylaxis recommended for 88 persons	[22]

Table 3. *Cont.*

Finding/Event	Identification Reported	Correct Identification	Reported Consequence	Source
Veterinary hospital, United States, reported 2019 (canine)	*Y. pseudotuberculosis*, Vitek-MS (bioMérieux, Marcy-l'Étoile, France), 91.1% confidence, with 5 *Y. pestis* spectra in the instrument database	*Y. pestis*	Potential exposure of more than 116 persons and 46 hospitalised animals	[23]
Navajo County, Arizona, 2020	*Y. pseudotuberculosis*, MALDI-TOF MS, commercial reference laboratory, reported 30 June	*Y. pestis*, presumptive by PCR 12 July; confirmed 15 July	Isolate reported 24 June; presumptive identification 12 July. Patient discharged on an agent with limited activity against *Y. pestis*; delay attributed to misidentification and reporting lag	[19]
Coconino County, Arizona, July 2025	*Y. pseudotuberculosis*, MALDI-TOF MS	*Y. pestis*, PCR-confirmed 6 days after death	Identification overridden on Gram stain, clinical and endemicity grounds; diagnosis of pneumonic plague reached	[20]
France, reported 2014	*Y. pestis*, MALDI Biotyper (Bruker Daltonics, Bremen, Germany), score 2.388; Vitek 2 GN (bioMérieux) returned *Y. pseudotuberculosis* at 99%	*Y. pseudotuberculosis* ST42 (O:1), by genotyping	False-positive identification of a select agent	[24]
Australia, reported 2022	*Y. pestis*, MALDI-TOF MS, score 2.25	*Y. pseudotuberculosis*, by sequencing and biochemistry	False-positive identification of a select agent	[25]

Note. All events involved naturally acquired infection. Intervals are given only where reported in the source. Abbreviations: GN, Gram-negative identification card (Vitek 2); MALDI-TOF MS, matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry; MS, mass spectrometry (Vitek-MS); O:1, serotype O:1; PCR, polymerase chain reaction; ST, sequence type.

Table 4. Reported diagnostic performance of automated and mass-spectrometry identification for *Yersinia pestis*.

Finding	Reported Value	Study Basis	Source
MALDI-TOF MS sensitivity for *Y. pestis*, standard commercial database	41.9%	National reference laboratory verification; 272 target and 160 near-neighbor isolates	[26]
MALDI-TOF MS sensitivity for *Y. pestis*, custom in-house library	70.6%	Same study	[26]
Corresponding specificity, standard commercial database vs. custom in-house library	93.1% vs. 86.9%	Same study	[26]

Table 4. *Cont.*

Finding	Reported Value	Study Basis	Source
Species discrimination within genus *Yersinia*	Not achieved, except for *Y. enterocolitica*	Diagnostic method verification	[27]
Attributed cause	Standard commercial taxonomy database contains *Y. pseudotuberculosis* main spectra but not adequate *Y. pestis* spectra	Same study	[27]
Performance with purpose-built database	Accurate species-level identification and biotype discrimination	Database construction and blind validation	[28]

Note. All values are as reported in the cited studies. Sensitivity and specificity figures derive from a single national reference laboratory verification and are not pooled with any other source. Abbreviations: MALDI-TOF MS, matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry.

6.1. The Basis of the Limitation

Y. pestis is a recently emerged clone of *Y. pseudotuberculosis*, and the two species are closely related at the level of the protein profiles on which MALDI-TOF MS identification depends. A verification study of a MALDI-TOF MS method for diagnostic identification of high-consequence bacterial pathogens reported that, with the exception of *Yersinia enterocolitica*, the method could not discriminate between species within the genus *Yersinia* and attributed this in part to the inclusion of *Y. pseudotuberculosis* main spectra but not adequate *Y. pestis* spectra in the standard commercial taxonomy database; the method was accordingly accredited only as a confirmatory method for identifying or ruling out security-sensitive bacterial agents at genus level [27]. A verification of MALDI-TOF MS performance for security-sensitive agents at a national reference laboratory reported sensitivity for *Y. pestis* of 41.9% using the standard commercial database, rising to 70.6% using a custom in-house library, with corresponding specificities of 93.1% and 86.9%, against a panel of 272 target and 160 near-neighbour isolates [26]. An earlier study constructing a purpose-built *Yersinia* database reported accurate species-level identification and biotype discrimination and noted that identification using the original commercial database had been incorrect [28].

These findings are consistent with one another and point to reference-library composition rather than instrument performance as the operative limitation. The practical consequence is that an analyser functioning as designed may return a confident species-level identification that is wrong, and that the error is remediable by database curation.

6.2. Documented Under-Identification

Misidentification of *Y. pestis* by automated systems has been reported as the cause of delayed diagnoses of human plague infections in Oregon and New Mexico during 2010–2011 [21]. In a naturally acquired pneumonic plague outbreak in Colorado in 2014, the organism had been misidentified as *Pseudomonas luteola* by an automated system in a hospital laboratory before referral; it was correctly identified at the state public health laboratory, after which antimicrobial prophylaxis was recommended for 88 persons [22]. In a naturally acquired case of septicaemic plague in Navajo County, Arizona, in 2020, an atypical Gram-negative blood culture isolate reported on 24 June was sent to a commercial reference laboratory and identified by MALDI-TOF MS as *Y. pseudotuberculosis*, reported on 30 June; the isolate reached the state public health laboratory on 10 July, where *Y. pestis* was presumptively identified by polymerase chain reaction on 12 July and confirmed on 15 July. The published account attributes the delay to initial misidentification of the pathogen and

to delays in laboratory reporting and notes that the patient had been discharged on an agent with limited activity against *Y. pestis* [19]. In the naturally acquired Arizona case of July 2025 described in Section 5, MALDI-TOF MS again returned *Y. pseudotuberculosis*; here the identification was overridden on clinical and contextual grounds [20].

6.3. Documented Identification in the Opposite Direction

The error is not unidirectional. A strain recovered from a human patient in France was identified as *Y. pestis* by MALDI Biotyper at a score of 2.388, above the threshold conventionally regarded as a species-level identification, while the Vitek 2 GN system returned *Y. pseudotuberculosis* as its best match with a probability of 99%; genotyping assigned the isolate to *Y. pseudotuberculosis* sequence type 42 [24]. A blood culture isolate reported from Australia was likewise assigned by MALDI-TOF MS as *Y. pestis* at a score of 2.25 and reclassified as *Y. pseudotuberculosis* by rapid sequencing and biochemical confirmation [25]. These reports complicate any simple account of automated identification as a source of under-recognition alone; they also strengthen the attribution of the problem to the reference library, since a library gap would be expected to produce error in both directions.

6.4. Consequences for Exposure and Containment

Sentinel-level guidance is explicit that, as soon as *Y. pestis* is suspected, further work should be performed within a Class II biological safety cabinet using biosafety level 3 practices, and that commercial automated or kit identification systems should not be used for further identification where *Y. pestis* cannot be ruled out; the isolate is referred to a Laboratory Response Network reference laboratory [2,3]. Published bench guidance identifies preparing samples for, and using, automated identification systems among the procedures that may result in exposure [3].

These provisions are conditioned on suspicion. Where an isolate is not suspected of being *Y. pestis*, it may be manipulated at the open bench and processed through automated systems before any heightened practice is adopted. A naturally acquired episode involving pneumonic plague in a dog at a veterinary hospital illustrates the potential scale: a swab of lung parenchyma yielded growth identified by MALDI-TOF MS as *Y. pseudotuberculosis* with 91.1% confidence, although the instrument database contained mass spectra for five *Y. pestis* strains, and the published investigation reports that delayed diagnosis resulted in potential exposure of more than 116 persons and 46 concurrently hospitalised animals [23].

The relationship between prior suspicion and laboratory biosafety response is therefore reciprocal in a way that is relevant to the occupational setting. The suspicion that activates the rule-out algorithm ordinarily originates in clinical or epidemiological information—endemicity, animal contact, or occupational exposure—rather than in the laboratory itself. Where that information has not been recorded or transmitted, as in the Chicago case, both the identification pathway and the associated containment practices operate without it.

7. Attenuated Strains and Recognition

Strain designation is relevant to this review because it influences the threshold at which plague is considered, both in the laboratory and in the clinic.

The Chicago patient worked with *Y. pestis* KIM D27, a pigmentation-negative strain attenuated through defects in iron acquisition and excluded from the National Select Agent Registry; the strain had not previously been associated with laboratory-acquired infection or human fatality [9]. Comparative virulence testing undertaken during the investigation found no median lethal dose for either the infecting isolate or the parental stock at subcutaneous doses up to 10^8 colony-forming units, against a median lethal dose of 100 colony-forming units or fewer for the virulent strain CO92, and identified no acquired

or engineered virulence mechanism; a chloramphenicol resistance marker absent from the original stock was consistent with routine laboratory modification [9]. Post-mortem investigation established hereditary haemochromatosis, with homozygosity for the C282Y mutation of the *HFE* gene and marked iron overload; investigators found no evidence that the patient knew of this condition or was symptomatic from it [9].

The published investigation advanced hereditary haemochromatosis as one possible explanation for the unexpected outcome, noting experimental evidence that iron enhances the virulence of non-pigmented strains [9]. Subsequent experimental work reported that haemojuvelin-knockout mice, used as a model of human hereditary haemochromatosis, developed lethal plague on challenge with pigmentation-negative strains, whereas wild-type mice did not, and concluded that individuals with hereditary haemochromatosis should not be exposed to live-attenuated plague vaccines [29]. The patient also had insulin-dependent diabetes mellitus and concurrent nutritionally variant streptococcal bacteraemia, which the investigation could not exclude as contributory [9]. Haemochromatosis is therefore best described as a plausible and experimentally supported contributor to the outcome; no causal attribution is made here.

The implication relevant to recognition is narrower than the virulence literature it draws on. The Chicago case and the subsequent experimental evidence indicate that attenuation produced through impaired nutrient acquisition may be conditional on host phenotype rather than absolute. Where an attenuated designation is interpreted as implying negligible human risk, it could lower the index of suspicion when illness occurs. No claim is made that regulatory classification itself contributed to delayed recognition in this or any other case. The sixth edition of BMBL records this case in its agent summary statement for *Y. pestis* while continuing to indicate that attenuated strains such as A1122 may be handled using biosafety level 2 practices, containment equipment and facilities [1]. The same convention is reflected in the wider research literature, in which strains lacking the *pgm* locus are described as suitable for handling under biosafety level 2 conditions while work with wild-type strains is conducted under biosafety level 3 [30].

8. Biosafety Guidance and Recognition

The guidance reviewed for this article is compared in Table 5. Table 5 is confined to the United States documents; recognition-related provisions in Russian, Canadian and World Health Organization documents are compared in Table 6.

Table 5. Comparison of containment and recognition-related provisions in the guidance reviewed.

Provision	BMBL 6th Edition [1]	Federal Select Agent Program [9]	Sentinel-Level Clinical Laboratory Guidance [2,3]	Plague Treatment and Prophylaxis Recommendations [13]
Containment-related				
Containment by activity	BSL-2 practices; BSL-3 practices for propagative work and high aerosol or droplet potential	Not a containment specifier	BSL-2 for patient specimens; Class II BSC with BSL-3 practices once *Y. pestis* is suspected	Not addressed
Infectious dose	Reported as fewer than 100 CFU	Not addressed	Not addressed	Not addressed
Aerosol-generating procedures	Trigger for BSL-3 practices	Not addressed	Named procedures listed, including preparation for automated identification	Not addressed

Table 5. *Cont.*

Provision	BMBL 6th Edition [1]	Federal Select Agent Program [9]	Sentinel-Level Clinical Laboratory Guidance [2,3]	Plague Treatment and Prophylaxis Recommendations [13]
Attenuated strains	A1122 may be handled at BSL-2; the KIM D27 fatality recorded in the agent summary	Pigmentation-negative KIM D27 excluded from the registry	Not addressed	Not addressed
Diagnostic identification	Not the subject of the agent summary	Not addressed	Commercial automated or kit systems not to be used where *Y. pestis* cannot be ruled out; referral to an LRN reference laboratory	Not addressed
Post-exposure prophylaxis after recognised exposure	Not the subject of the agent summary	Not addressed	Not addressed	Single agent for 7 days; indications specified; laboratory workers following standard procedures and not otherwise exposed need not take prophylaxis, and may be placed on fever watch
Recognition-related				
Worker illness surveillance	No requirement identified in the guidance reviewed; recommended in the Chicago investigation [9]	No requirement identified	No requirement identified	No requirement identified
Clinician enquiry about occupational exposure	No requirement identified; recommended in the Chicago investigation [9]	No requirement identified	No requirement identified	No requirement identified
Occupation recorded in the clinical record	No requirement identified	No requirement identified	No requirement identified	No requirement identified
Institution-to-clinical-service notification before diagnosis	No requirement identified	No requirement identified	No requirement identified	No requirement identified
Validation of reference libraries for high-consequence organisms	No requirement identified	No requirement identified	No requirement identified; addressed by institutional decision in two reported instances [26,27]	Not addressed
Public-health escalation after identification	Not the subject of the agent summary	Registration and reporting obligations apply	Immediate notification and LRN referral specified	Contact definitions and prophylaxis specified

"No requirement identified" denotes that no such requirement was found in the documents reviewed for this article. It does not establish that no requirement exists in other jurisdictions, institutions or documents. Abbreviations: BMBL, Biosafety in Microbiological and Biomedical Laboratories; BSC, biological safety cabinet; BSL, biosafety level; CFU, colony-forming units; LRN, Laboratory Response Network.

Table 6. Recognition-related provisions in Russian, Canadian and World Health Organization documents.

Provision	SanPiN 3.3686-21, Russian Federation [31]	Canadian Biosafety Standard, 3rd Edition [32]	WHO Laboratory Biosafety Manual, 4th Edition [33]
Health monitoring of workers handling the agent	Medical observation for 6 days with daily temperature measurement after work with the plague pathogen	Medical surveillance programme required, designed to prevent and detect illness related to exposure	Addressed within biosafety programme management; risk-based rather than agent-specific
Reporting of symptoms or incidents by the worker	Symptoms characteristic of the infection to be reported to the laboratory head or institutional administration	Incidents to be reported immediately to the appropriate internal authority	Incident reporting addressed within biosafety programme management
Information for the treating clinician	Treating clinician in the general health network to be informed	Emergency medical contact card for personnel handling regulated materials that cause uncommon diseases in Canada	Emergency contact cards included in the programme-management checklist
Escalation on suspicion of infection	Isolation of the affected individual and contacts	Public Health Agency of Canada to be notified without delay after an exposure or recognition of disease that may have been caused by one	Referred to national oversight arrangements

Provisions are summarised from the documents cited and are not exhaustive. Abbreviations: SanPiN, Sanitary Rules and Norms; WHO, World Health Organization.

On the containment side, the provisions are detailed and mutually consistent. BMBL assigns containment by activity and notes the low reported infectious dose [1]. *Y. pestis* is a select agent requiring registration, with pigmentation-negative KIM D27 among the excluded strains [9]. Sentinel-level guidance specifies when to move work into a Class II biological safety cabinet under biosafety level 3 practices, which procedures carry aerosol risk, when automated identification should be discontinued, and how isolates are referred [2,3]. Recommendations for the treatment and prophylaxis of plague specify agents, durations and the circumstances in which post-exposure prophylaxis is indicated [13]. These provisions are appropriate to their purpose and are not presented here as deficiencies.

One provision warrants specific comment because it directly addresses laboratory personnel. Current recommendations state that laboratory workers who followed standard procedures while handling specimens from patients with plague, and who were not exposed by other means, need not take post-exposure prophylaxis, and that exposed persons may be placed on fever watch if desired [13]. This is a considered position rather than an omission. Its scope, however, concerns workers whose handling of plague material is known; it does not address the situation in which neither the worker nor the institution is aware that an exposure has occurred.

On the recognition side, the picture in the United States documents differs in a specific respect: several relevant measures appear as recommendations rather than as requirements, and for others no provision was identified in the documents reviewed. The investigation of the Chicago case recommended that institutional safety committees implement and maintain effective surveillance programmes to identify and monitor acute illness among laboratory workers, and that health-care providers routinely enquire about occupational exposures when evaluating patients [9]. Both are recommendations within a case report

rather than requirements within a standard, and the guidance reviewed did not identify a requirement for either. Similarly, the guidance reviewed did not identify a requirement that occupation be recorded as an element of acute clinical assessment, that a research institution notify receiving clinical services of work with high-consequence agents in advance of a diagnosis, or that reference libraries used for automated identification be validated for high-consequence organisms—the two laboratories whose database performance is described in Section 6 appear to have addressed this by institutional decision [26,27].

The Russian, Canadian and World Health Organization documents show that such measures can be specified as requirements (Table 6). In the Russian Federation, SanPiN 3.3686-21 requires medical observation with daily temperature measurement for 6 days after work with the plague pathogen (paragraph 160), notification of the laboratory head or institutional administration (paragraph 342) if fever or characteristic symptoms develop, and notification of the clinician who begins treatment, with isolation of the affected individual and contacts where infection is suspected [31]. These provisions reflect the long operational experience of the Russian anti-plague system. The Canadian Biosafety Standard requires a medical surveillance programme, immediate reporting of incidents to an internal authority, and notification of the Public Health Agency of Canada following an exposure or recognition of disease that may have been caused by one; personnel handling regulated materials that cause uncommon diseases in Canada are issued an emergency medical contact card [32]. World Health Organization guidance on biosafety programme management includes emergency contact cards that alert a treating physician to the possibility of laboratory-acquired infection [33]. Each of these measures addresses one of the recognition checkpoints described in Section 4—the worker, the employing institution or the treating clinician. The absence of such requirements in Table 5 is therefore specific to the United States documents reviewed rather than general, and the existence of these frameworks indicates that the measures discussed in Section 10 are operationally feasible.

These observations are limited to the documents examined. They establish that no such requirement was identified in the guidance reviewed, not that no mechanism exists in any jurisdiction or institution. Local and jurisdictional provisions vary: Arizona administrative requirements for submission of *Yersinia* isolates, for example, formed part of the response to the 2020 case [19].

9. Boundaries of the Recognition Checkpoints

Several findings constrain the account set out above and are stated here without qualification.

The public-health response in the Chicago case operated rapidly and effectively once the organism had been identified. Ninety-five contacts were identified across laboratory, household, medical and pathology settings; all 30 research laboratory staff were prescribed prophylaxis, 61 of 65 other close contacts (94%) accepted it within three days of notification, and no additional infections were identified [9]. Recognition occurred three days after the patient's death, and no secondary transmission followed. Delay in recognition was therefore not sufficient, in this instance, to produce the transmission outcome that a focus on recognition delay might suggest.

Whether earlier recognition would have altered the outcome for the patient is not established. He presented with multi-organ dysfunction and died within approximately 13 h, and the available record does not support an inference either way.

In the Vienna episode, institutional recognition occurred: isolation was instituted while the index illness was still being attributed to influenza or pneumonia [12]. The subsequent deaths are at least as plausibly explained by the absence of effective antimicrobial therapy as by delayed suspicion, and the episode should not be read as an early instance of the same problem described in the Chicago case.

The published record also contains few accounts of instances in which a worker, laboratory head or institution acted appropriately after a possible exposure, and few case-level accounts of this kind were identified: the Vienna episode and the 1959 United States case, in which the employing institution's knowledge of the work prompted isolation on admission before a diagnosis existed, contacts were observed and staff given prophylaxis, and no secondary infections followed [8]. This reflects the selection described below rather than evidence that such action is uncommon. Where prior suspicion is established, recognition has operated effectively. In the Kosh-Agach district of the Republic of Altai in 2015, infection followed the dressing of a grey marmot during an epizootic; bubonic plague was confirmed serologically, and coordinated action by Rospotrebnadzor institutions, medical facilities and municipal authorities prevented further transmission [34]. In November 2019, two residents of Inner Mongolia were diagnosed with pneumonic plague in Beijing by real-time PCR and immunological methods, two further bubonic cases followed in Inner Mongolia, and genomic source tracking attributed all four cases to local rodent epizootics; *Y. pestis* was cultured from only one patient [35]. In both settings, recognition was supported by known endemicity and established surveillance—the contextual information that is absent when a laboratory worker presents outside an endemic area and occupation is not disclosed.

The Chicago exposure is substantially explained by individual non-compliance. Review of training records identified deficiencies in attendance at required biosafety courses, including by the patient, and coworkers reported inconsistent compliance with the glove policy [9]. A reading in which the applicable controls were adequate and were not followed is available on the published evidence.

The microbiological checkpoint can be corrected without occupational information, though not necessarily in time to alter the clinical course. In the naturally acquired Arizona case of July 2025, an erroneous automated identification was overridden on the basis of Gram stain morphology, clinical findings and known regional endemicity, but suspicion was raised only two days after the patient's death and the organism was confirmed later still [20]. Identification error is also bidirectional, and false-positive identification of *Y. pestis* carries its own operational consequences [24,25].

Finally, the available evidence is subject to selection. Exposures that are recognised, followed by prophylaxis, and not followed by illness do not ordinarily generate published reports. The evidence base for this review therefore consists largely of instances in which recognition was delayed, and the apparent consistency across those instances is to an unknown degree a product of what is published.

10. Implications and Research Priorities

The evidence reviewed here supports areas for evaluation rather than changes to practice, and the following are framed accordingly.

Occupational illness reporting. Where a reporting policy is conditioned on a recognised exposure event, it will not be activated by an exposure that is not perceived. Whether reporting criteria defined by symptom rather than by incident—for instance, febrile or respiratory illness in a worker handling *Y. pestis*—would improve ascertainment has not been evaluated and could be examined within existing institutional biosafety programmes.

Communication of occupational exposure information. In the one investigation that documents the case in detail, the information that initiated identification reached the clinical laboratory from a clinician rather than from the employing institution [9]. Mechanisms by which workers handling high-consequence agents might carry or convey that information at the point of clinical presentation merit evaluation; the existing recommendation that providers enquire about occupational exposures addresses the same problem from the clinical side [9].

Occupational history in acute clinical assessment. Its documented absence in the Chicago case is a single observation, and the frequency with which occupation is recorded in the assessment of acute febrile illness is not established by any source identified here. That frequency is itself a reasonable subject for study and would determine whether this merits further attention.

Validation of reference libraries. The performance difference reported between standard commercial and custom libraries for *Y. pestis* identification is substantial, and at least two laboratories have addressed it by institutional decision [26,27]. Whether broader curation or validation of reference libraries for high-consequence organisms is warranted, and at what level of the laboratory network, is an evaluable question with a measurable endpoint. At present, expansion of reference libraries for high-consequence organisms is ordinarily undertaken at institutional or departmental level, so that the performance of a given instrument depends on local decisions rather than on a network-wide standard.

Interpretation of genus-level *Yersinia* identification. Given the reported inability of the method to discriminate within the genus [27], the operational handling of a genus-level *Yersinia* result—and whether it should prompt referral independently of prior clinical suspicion—merits examination against existing sentinel-level algorithms [2,3].

Host assumptions in attenuation designations. Whether risk assessments for strains attenuated through nutrient-acquisition defects should state the host assumptions on which the designation rests, and how such information should be conveyed to workers, is a question for institutional biosafety committees and regulators rather than one this review can settle. Screening workers for host genotype is not proposed.

One study would materially improve the evidence base: an analysis of institutional exposure-incident records together with the associated prophylaxis, illness and outcome data. Such an analysis would address the selection bias described in Section 9 directly, because it would include exposures that were recognised and did not result in illness—the category of event that the published literature does not capture, and the absence of which constrains every inference drawn here. It was not attempted for this review and could not have been: incident records of this kind are held institutionally rather than published, are not aggregated in any registry identified here, and would require data-sharing agreements with individual facilities registered to work with the organism. The constraint is therefore one of data access rather than of method, and it applies to the published literature as a whole and not only to this review.

11. Limitations

The laboratory-acquired case record examined here is very small. Only two cases can be reconstructed in sufficient detail to trace how recognition was reached from exposure to identification, and the analysis of worker and institutional recognition therefore rests on those two reports. What so small a number of documented instances can establish is that a given failure of recognition is possible and has occurred; what it cannot establish is how often it occurs, or whether it is characteristic. The claims advanced here are of the former kind throughout, and the checkpoint structure set out in Section 4 is grounded in the division of responsibility across the guidance reviewed rather than in the cases themselves.

The evidence base is subject to publication and selection bias. Recognised exposures followed by prophylaxis and no illness are unlikely to be reported, so the available record consists disproportionately of instances in which recognition was delayed.

No denominator is available. The number of persons handling live *Y. pestis* worldwide, and the number of facilities in which such work is undertaken, is not established by any source identified here. The rarity of reported laboratory-acquired infection therefore cannot be interpreted as a rate.

The non-English literature is under-represented. Russian-language regulatory documents and case reports have been included [16,31,34], but the wider literature of the anti-plague institute network was searched only through targeted Russian-language web searches (Section 2), and further relevant reports are likely to exist. These searches identified one further record: current federal guidance notes a laboratory-acquired infection in the Tuva mountain plague focus in 1984, without case-level detail [36]; it is classified as C6 and not added to case totals.

One primary source could not be obtained: the 1976 survey of laboratory-associated infections [7], which has no DOI, is not available in digitised form and was not supplied through interlibrary request by the time of revision. Claims deriving from it are presented with their chain of secondary attribution, and the corresponding fields in Table 2 are marked as "source not retrieved" rather than "not reported".

The aggregate figures reported by two recent reviews [4,5] may overlap with cases named individually in this article; the constituent case lists were not available, and the figures are therefore reported as each review's figure and are not combined with the named cases.

Finally, the diagnostic evidence in Section 6 derives from naturally acquired infection. Its application to the occupational setting rests on the identity of the organism and of the identification method and not on direct evidence from laboratory-acquired cases. The extrapolation is also asymmetric: in several of the naturally acquired cases, regional endemicity or animal contact provided contextual information that would not be available to a clinician or laboratory assessing a laboratory worker outside an endemic area.

12. Conclusions

Laboratory-acquired *Yersinia pestis* infection is rare, and the containment provisions governing work with the organism are detailed and specific. The small documented record, considered alongside evidence on microbiological identification drawn from naturally acquired plague, is consistent with recognition depending on information held separately by the worker, the employing institution, the treating clinician and the clinical microbiology laboratory, and with many established containment and response measures becoming operative only once occupational exposure or plague is suspected. Requirements that address recognition directly—post-work health monitoring, symptom reporting and information for the treating clinician—are specified in Russian and Canadian national documents but were not identified as requirements in the United States guidance reviewed. Two cases allow the course of recognition to be reconstructed, and they differ in where the occupational information sat. In the 2009 case the organism was identified after the patient's death, and the information that initiated identification entered the diagnostic process from outside it; the subsequent public-health response was prompt and no secondary infections occurred. In the 1959 case the exposure was likewise unrecognised at the time, but the employing institution's knowledge of the work was available at admission, isolation preceded diagnosis, and the organism was identified within 18 h of the first sputum; the patient survived and no secondary infections occurred.

These observations rest on two fully documented laboratory-acquired cases, separated by fifty years, and on diagnostic evidence from a different acquisition route, and they describe a possibility that merits evaluation rather than an established pattern. The questions they raise—how occupational illness is reported, how exposure information reaches clinical services, and how automated identification of *Y. pestis* performs in routine use—are tractable and are amenable to study within existing institutional and laboratory systems.

Author Contributions: Conceptualisation, S.E.R.M. and S.M.A.; methodology, S.E.R.M. and S.M.A.; data curation, S.E.R.M. and S.M.A.; formal analysis, S.E.R.M. and S.M.A.; validation, S.R. and S.M.O.;

writing—original draft preparation, S.E.R.M.; writing—review and editing, S.E.R.M., S.M.A., S.R. and S.M.O. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analysed in this study. All sources supporting the findings of this review are cited in the reference list and are publicly available, with the exception of the one primary source noted in Section 11, which could not be obtained.

Acknowledgments: During the preparation of this manuscript, the authors used Claude (Anthropic; 2026) for the purposes of proofreading and language editing. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSC	biological safety cabinet
BSL	biosafety level
CFU	colony-forming units
LRN	Laboratory Response Network
MALDI-TOF MS	matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry
PCR	polymerase chain reaction

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