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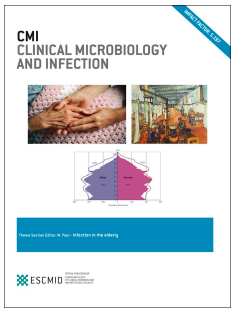

Delayed correct diagnoses in emerging disease outbreaks: Historical patterns and lessons for contemporary responses

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Delayed correct diagnoses in emerging disease outbreaks: Historical patterns and lessons for contemporary responses

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Abstract

Background: The gap between early diagnostic assumptions and final diagnoses in disease outbreaks represents a persistent challenge in global health despite advancements in diagnostic and response capabilities.

Objectives: To analyze the unfolding 2025 outbreak in the Democratic Republic of Congo (DRC) through the lens of historical cases where initial misattributions contributed to delayed recognition of novel or unexpected threats with varying public health consequences; identifying patterns from past outbreaks that can inform current diagnostic approaches and response strategies.

Sources: We selected illustrative examples from peer-reviewed publications, focusing on cases with initial diagnostic uncertainties that highlight specific diagnostic patterns relevant to the current DRC outbreak. For the ongoing DRC outbreak, we analyzed official World Health Organization Africa bulletins and communications from the DRC Ministry of Health through February and early March 2025.

Content: As of beginning of April 2025, health authorities continue investigating clusters of unexplained acute febrile illness in Équateur Province with clinical features that were initially being suggestive of a viral haemorrhagic fever. Primary VHF pathogens have now been excluded. From selected historical and recent outbreaks, it can be deduced that diagnostic challenges extend beyond individual cognition to include structural biases in global health systems, methodological limitations and sociocultural factors.

Implications: We identified five evidence-informed interventions to mitigate diagnostic delays: systematic consideration of multiple working hypotheses, development of sustainable local diagnostic capacity, enhancement of clinician-to-public-health

communication networks, implementation of cognitive debiasing strategies, and strengthening of One Health surveillance platforms. Historical ‘misdiagnoses’ offer crucial lessons for transforming outbreak response from reactive to anticipatory, potentially averting future epidemics through earlier, more accurate recognition of emerging pathogens within their complex ecological and social contexts.

Keywords

Emerging infectious diseases; outbreak; diagnosis; toxins; infectious agents; viral haemorrhagic fever (VHF); disease X

Word count: Abstract – 272 words; Main text body – 3966 words; references – 41; Tables – 4.

Introduction

When unusual clusters of illness emerge, particularly in remote regions with limited diagnostic infrastructure and challenging access, the conditions suspected to be at the top of the initial list of differential diagnoses may prove incorrect. This inaccuracy reflects the complexity of identification of novel or unexpected pathogens against the background noise of endemic diseases [1]. Despite the remarkable achievements in the field of diagnostic technology and surveillance systems over the past century, the gap between early hypotheses and final diagnoses persists and has significant implications for public health response, communication and patient outcomes [2,3].

This diagnostic conundrum stems from both biological and cognitive factors [4]. Novel pathogens may present with non-specific symptoms (fever, malaise, respiratory or gastrointestinal complaints) that mimic those seen in several endemic diseases. Faced with ambiguous symptoms, healthcare providers in general usually gravitate towards familiar diagnoses, a manifestation of availability bias. Healthcare providers are also influenced by limitations of their specific expertise that determines the angle of approach to reasoning. While this thought process is usually reliable, it can delay the recognition of rare or new emerging threats in a region, particularly when amplified by technological limitations in resource-constrained settings and sociopolitical factors, including reluctance to report unusual illnesses that might trigger economic and other disruptions [5,6]. Importantly, not all novel infectious agents develop into public health emergencies; many remain localized or cause self-limiting illness. This uncertainty, determining which unusual disease clusters warrant extraordinary response measures despite initial

resemblance to common conditions, creates a persistent challenge for public health systems globally [7,8].

Here, we examine a selection of historical outbreaks with particular attention to the disparity between early assumptions and final diagnoses. This is not intended as a comprehensive review; rather, we selected illustrative examples that highlight specific diagnostic patterns relevant to current challenges. Understanding these patterns is crucial for improving contemporary outbreak responses, including the current unfolding outbreak of an unknown disease in the Democratic Republic of the Congo (DRC) at the time of writing (early March 2025) [9]. By analyzing factors contributing to misdiagnosis, we aim to extract actionable insights that strengthen the early recognition and characterization of emerging health threats.

Examples of early diagnostic assumptions and bias in historical outbreaks

The consequences of outbreak 'misdiagnoses' vary dramatically across the historical records, from minimal public health impact to catastrophic loss of life. Table 1 summarises some key aspects of the outbreaks mentioned here, including suggestions for potential individual main sources of bias. Table 2 provides some key terms definitions used throughout the manuscript, including the definitions of the various forms of biases.

Misdiagnosis of infectious disease outbreaks

The Great Influenza Pandemic (1918-1920), one of the biggest global outbreaks in the early 20th century, was initially mistakenly linked to the bacterium *Haemophilus*

influenzae, as this microorganism was visible under a microscope in patients primarily infected with underlying influenza A virus who incidentally had a secondary bacterial infection [10]. While this finding could be viewed as a manifestation of anchoring bias—researchers focusing on bacterial pathogens visible with available technology—the misattribution stemmed primarily from technological limitations of the era. The conceptual framework to understand viruses was still developing, as viruses were largely unknown entities and beyond the detection capabilities of available methods.

The West African Ebola virus disease epidemic (2013-2016) represents perhaps the most consequential misdiagnosis in recent history. In late 2013, a 'mysterious disease' began spreading in southeastern Guinea but was not recognized as Ebola virus disease for approximately three months.

The clinical presentation significantly contributed to this misdiagnosis. Lacking haemorrhagic manifestations, patients primarily presented with fever, vomiting, and watery (non-bloody) diarrhea—symptoms common in all of malaria, cholera, and typhoid fever—leading local officials to pursue these diagnoses with which they were most familiar [11]. Availability bias directed attention to common endemic diseases (West Africa had never experienced an Ebola disease outbreak before), while the absence of classic haemorrhagic features and positive tests for other infections reinforced these initial assumptions through confirmation bias.

Importantly, these diagnostic challenges occurred within a broader context of structural limitations. Limited laboratory capacity necessitated sending samples to international

facilities and surveillance systems designed to detect unusual disease patterns were insufficient in the affected regions.

Consequently, the virus smouldered undetected for over three months, establishing multiple transmission chains across Guinea's border region and adjacent countries. By the time international laboratories confirmed an orthoebolavirus outbreak in March 2014, the pathogen had already spread to Liberia and Sierra Leone [12]. The international response timing further complicated containment efforts. Despite early warning signs, global health mechanisms failed to activate promptly. International assistance and resources were mobilized only after the outbreak had established multiple transmission chains across national borders, rendering containment more difficult.

This delay partly contributed to what became the largest Ebola disease outbreak in history, ultimately causing over 11,000 deaths [13]. The delayed identification represents a multilevel systems challenge, where regional healthcare infrastructure, national coordination capabilities, and international alert mechanisms all faced significant constraints in rapidly identifying and responding to an unexpected pathogen in a resource-limited setting [14].

In contrast to the West African epidemic, the first recognized Ebola disease outbreak in Yambuku, Zaire (now DRC), in 1976 demonstrates how rapid diagnostic correction can contain consequences despite initial misattribution. The outbreak was believed to be yellow fever or typhoid at the beginning, and patients received treatment for these conditions as symptoms escalated [15]. However, the unusual severity, high mortality, and distinctive clinical presentation, fitting what can be termed a ‘classical’ viral

haemorrhagic fever pattern, enabled recognition by trained local nurses and prompted rapid investigation. Samples were quickly sent to international laboratories, that were equipped and prepared to analyze potential haemorrhagic fever specimens, leading to the identification of a novel filovirus (now species *Orthoebolavirus zairense*) within approximately five weeks from the onset of the first cases [16]. The relatively contained geography of the outbreak (centered around a mission hospital) and lower population mobility from remote rural areas at that time, combined with the rapid mobilization of containment measures once the unusual nature of the disease was recognized, helped limit its spread. While 280 deaths occurred (88% case fatality ratio), the outbreak remained geographically contained, and transmission was interrupted within approximately three months. In this case, recognizing an unusual disease pattern triggered effective containment measures even without knowing the specific pathogen initially. The critical variable was not the initial attribution to familiar diseases, which occurred in both the 1976 and 2013-2016 outbreaks (and was complicated by actual coinfections with endemic pathogens in some patients), but rather the presence of highly qualified Congolese colleagues, including professor Jean-Jacques Muyembe, and international health workers, who made the right decisions and identified quickly that something unusual was occurring and the rapid implementation of appropriate infection control measures.

Two more recent examples demonstrate the challenge of correctly identifying novel or unexpected pathogens, with both availability bias and confirmation bias playing significant roles. In 2004-2005, an outbreak in Uige province, Angola, began with cases initially diagnosed as malaria. When patients failed to respond to antimalarial treatment and the illness spread to healthcare workers, further microbiologic investigation revealed the Marburg virus, species *Orthomarburgvirus marburgense*—marking Angola's first

recorded outbreak of this hemorrhagic disease and its first occurrence thousands of kilometers away from the East African region where its emergence is attributed. Local clinicians were unfamiliar with Marburg virus disease clinical features. With limited diagnostic capacity, the initial misdiagnosis allowed the virus to spread unchecked for several weeks, ultimately resulting in over 200 deaths before effective containment measures were implemented [17].

Similarly, when patients in northeastern Brazil presented with mild fever, rash, and joint pain in early 2015, cases were initially labelled as dengue fever or chikungunya due to symptom overlap. While Zika virus was a known pathogen, it had previously been associated mostly with mild illness. The critical turning point came when physicians noted an unusual increase in microcephaly cases among newborns, revealing implications far more serious than anticipated. By the time the connection between Zika virus and congenital abnormalities was established, the virus had already spread widely throughout Latin America [18].

Infectious diseases misattributed as non-infectious

A different scenario involves infectious diseases with epidemic or endemic patterns initially misdiagnosed as non-infectious conditions. Lyme disease was first mistaken for juvenile rheumatoid arthritis in the 1970s due to its presentation of joint pain and inflammation, without clear signs of infection [19]. It was only after epidemiologists linked cases to geographic clustering and outdoor exposure that *Borrelia burgdorferi*, a tick-borne spirochete, was identified as the true infectious cause.

In contrast, kuru, an endemic disease among the Fore people of Papua New Guinea, was long believed to be a hereditary neurodegenerative disorder due to its progressive neurological decline resembling conditions like amyotrophic lateral sclerosis. However, research in the 1950s by Carleton Gajdusek connected it to ritualistic cannibalism, leading to the discovery that prions were responsible [20]. When diseases like Lyme and kuru do not fit expected infection patterns, pattern recognition bias leads clinicians to categorize them within familiar non-infectious frameworks, which can delay proper identification for years or even decades.

Immune-mediated disease misdiagnosis

A compelling addition to our discussion of diagnostic complexity involves nodding syndrome, a debilitating neurological condition affecting children in parts of East Africa [21]. For years, this 'mysterious illness'—characterized by distinctive head nodding, seizures, and progressive cognitive decline—evaded clear etiological classification. Initial investigations pursued various hypotheses ranging from novel infectious agents to environmental toxins and nutritional deficiencies. After decades of uncertainty, recent research by professor Robert Colebunders and colleagues (2023) suggests the syndrome represents an autoimmune response to onchocerciasis (river blindness), a parasitic infection caused by *Onchocerca volvulu*s [22]. The complex interplay between infection and immune response can create distinctive clinical syndromes that defy straightforward classification, requiring sustained cross-disciplinary investigation to unravel.

Non-infectious agents mimicking infectious outbreaks

Not all initially ill-understood outbreaks involve infectious agents. Some notable disease clusters initially investigated as infectious were ultimately traced to environmental toxins or product contamination. In Minamata, Japan (1950s), a neurological disorder suspected to be encephalitis was eventually identified—after four years of investigation—as methylmercury poisoning from industrial waste in seafood, affecting over 2,000 people [23]. Similarly, the 1989 Eosinophilia-Myalgia Syndrome outbreak in the United States, first thought to be a novel infection, was traced to contaminants in L-tryptophan supplements, causing 1,500 cases and 37 deaths [24]. The 2019 outbreak of acute encephalitis syndrome in children from Bihar, India, was initially thought to be of viral origin. However, later investigation revealed that the primary cause was methylene cyclopropyl-glycine (MCPG), a naturally occurring toxin in unripe litchi fruit, which disrupts glucose metabolism and leads to severe hypoglycaemia, particularly in malnourished children [25]. Among environmental toxins that can mimic infectious outbreaks, cyanotoxins deserve special mentioning in the differential diagnosis of haemorrhagic syndromes. In 1996, an outbreak of acute liver failure in Caruaru, Brazil resulted in 52 deaths among hemodialysis patients. Some patients presented with haemorrhagic manifestations due to severe liver damage and coagulopathy, initially raising suspicions of a viral haemorrhagic fever. However, the cause was ultimately identified as microcystin contamination in the water used for dialysis treatment [26]. These misclassifications delayed appropriate interventions and, in the case of Minamata disease, allowed continued exposure to the toxic source. Framing bias and premature closure have repeatedly delayed the identification of environmental toxins and product contamination when disease clusters were initially—and incorrectly—investigated

through an exclusively infectious disease lens. Such examples highlight the importance of maintaining a broad differential diagnosis that includes non-infectious etiologies when investigating unusual disease clusters.

Psychosocial factors in outbreak diagnosis

Social and psychological dynamics can sometimes create outbreaks without infectious causes. Several historical instances of suspected infectious outbreaks have ultimately been attributed to mass psychogenic illness. For example, the 'June Bug' incident at a textile factory in the United States (1962) initially raised concerns about a possible infectious agent or toxic exposure when dozens of workers developed symptoms, including numbness, nausea, and weakness [27]. After a thorough investigation, no organic cause was found, and the outbreak was finally attributed to psychological factors. In mass psychogenic illness, two key mechanisms often work together: symptoms spread through social networks (social contagion), and more people experience symptoms as they see others affected (bandwagon effect) [28]. The initial cases triggered anxiety that cascaded throughout the workplace, producing real physiological symptoms without an organic cause, though it remains challenging to definitively exclude subtle environmental or toxic triggers even with retrospective analysis.

Multifactorial aetiologies and syndemic presentations

Finally, in resource-limited settings, the confluence of multiple endemic health problems can create a clinical presentation that mimics emerging pathogens. More recently, a suspected outbreak of viral haemorrhagic fever (VHF) in the DRC at the end of 2024

prompted initial concern about possible Ebola or Marburg virus disease [29]. After international investigation, the cluster of severe illness with bleeding manifestations was reported to be a combination of severe malaria, anaemia and underlying malnutrition rather than a novel pathogen or VHF. In this case, multiple concurrent health problems in vulnerable populations created a syndemic effect, presenting a cumulative clinical picture arising from a mixture of multiple endemic health problems that altogether mimics a novel infectious threat. While Occam's razor—the principle of favoring simpler explanations over complex ones—is often valuable in clinical reasoning, this case demonstrates how multifactorial causes can manifest as what appears to be a single disease entity (instead of a collision of endemic disease with socioeconomic factors).

Diagnostic challenges in bioterrorism events

While our focus has been on naturally occurring outbreaks, intentional pathogen releases present a categorically different diagnostic challenge. Unlike natural outbreaks where misdiagnosis stems from cognitive biases or technological limitations, bioterrorism events involve deliberate deception that exploits these same vulnerabilities. The 2001 anthrax letters in the United States provide an instructive example of how bioterrorism can present diagnostic challenges [30]. The initial cases were misdiagnosed as influenza or conventional pneumonia, with the first patient receiving a correct diagnosis only after severe deterioration prompted additional testing. This delayed recognition occurred not only because of availability bias and pattern recognition bias affecting clinicians, but also because the perpetrator intentionally created conditions to delay detection. The unusual route of exposure and targeted distribution created a presentation pattern designed to confuse surveillance systems. As Jansen et al. (2014) and Broertjes et al. (2023) note;

while the bioweapon potential of many pathogens may be limited, unfamiliarity with rare agents can lead to missed diagnoses even in sophisticated healthcare systems [31,32]. Therefore, maintaining knowledge about uncommon pathogens, including those eliminated from natural circulation like smallpox, remains important for comprehensive outbreak investigation, though such scenarios should not overshadow more probable explanations in routine practice.

Analysis of the current DRC unknown disease situation

The ongoing unknown disease outbreak in Équateur Province, DRC, reported in February 2025, provides a real-time case study of the diagnostic challenges discussed throughout this paper [33]. As of mid-February, health authorities are documenting two distinct clusters most likely, at the time of writing, representing two separate aetiologies: one in Bolomba Health Zone (12 cases, 8 deaths, CFR 66.7%) and another in Basankusu Health Zone (943 cases, 52 deaths, CFR 5.5%). Cumulatively, 955 cases with 60 deaths (CFR 6.3%) have been reported across the two health zones and children under five years old constitute 18.0% of cases. The clinical presentations include fever (93.6%), chills (79.8%), vomiting (76.6%), abdominal pain (76.6%) and dyspnoea (73.4%). Laboratory testing has been performed in a tiered diagnostic approach: locally using rapid diagnostic tests for malaria (with 54.1% of samples testing positive), and nationally by PCR at the National Institute of Biomedical Research (INRB) in Kinshasa, which has swiftly ruled out orthoebolaviruses and orthomarburgviruses. This coordinated testing process was facilitated by the WHO and partners providing technical and operational support to provincial authorities. While these priority pathogen investigations yielded rapid results,

further laboratory investigations including metagenomic sequencing are ongoing at INRB, and the exact cause remains undetermined to date [9].

It is important to note that, as of the time of writing, some early media reports about potential exposures, including unconfirmed accounts of children having had contact with bats, have not been verified in official WHO updates [34]. This uncertainty brings another challenge in outbreak investigation: the need to carefully evaluate preliminary reports while awaiting confirmation through official channels and thorough epidemiological investigation. As of early March 2025, the precise etiology and transmission events remain under investigation.

This outbreak demonstrates key advances in response protocols such as rapid diagnostics, with high-priority pathogen testing completed within days; preemptive containment measures implemented before diagnosis confirmation; and coordinated multi-level communication established from outbreak onset. However, persistent challenges mirror historical patterns. The geographic separation between field sites and reference laboratories recalls obstacles faced in previous outbreaks and difficulty to provide laboratory diagnosis due to degraded samples. Moreover, response efforts face significant challenges due to remote locations and fragile healthcare infrastructure in the affected areas. The possibility of separate etiologies in the two clusters also introduces additional complexity to the investigation.

As investigations continue, metagenomic sequencing offers potential identification of novel or unexpected pathogens. Accessing this potential diagnostic methodology requires close local collaboration between researchers and public health stakeholders. Could this

outbreak be caused by a novel virus? In theory, yes. The very fact it was initially unexplained put health authorities on high alert for a 'Disease X' scenario [35]. However, history also shows that most mystery outbreaks turn out to be known diseases in disguise. The possibility of two unrelated but timely overlapping events in geographical proximity is not to be dismissed. In DRC, the scale and demographics (hundreds of patients, mainly children) fit a pattern seen in severe malaria seasons. By contrast, Ebola virus disease or a novel VHF-causative organism would likely spread differently (affecting more adults, causing person-to-person transmission chains).

The contemporary context of outbreak investigations presents new challenges for accurate assessment. While acceleration of drivers for emergence of novel, or previously rare, diseases (climate change, land use changes, biodiversity decline, increased global mobility) has potentially increased the frequency of novel pathogen spillover events, we must also consider the measurement bias introduced by today's perpetual alert surveillance systems. Social media and unofficial websites rapidly disseminate unvalidated information, creating visibility for outbreaks that might previously have gone unnoticed externally. This increased sensitivity may lead to more frequent 'Disease X' alerts, even as the proportion of such alerts ultimately attributed to known pathogens or non-infectious causes remains high. As investigators, we should weigh these factors, recognizing that common diseases can present in uncommon ways under certain conditions, while maintaining appropriate vigilance for truly novel threats.

Lessons from past outbreaks' early diagnostic assumptions

This – subjective, not comprehensive - journey through historical initial misdiagnoses highlights well how understandable cognitive heuristics might affect outbreak investigations. When faced with the unfamiliar, we reach for what we know—malaria instead of Marburg virus disease, arthritis instead of Lyme disease. We can get anchored to early theories, struggle to recognize unusual patterns, and sometimes frame problems too narrowly. This reflects the traditional medical maxime 'when you hear hoofbeats, think horses not zebras'—yet outbreak investigation demands the flexibility to recognize when those hoofbeats might indeed signal zebras, or perhaps horses presenting in unusual ways. These mental shortcuts appear across history, geography, and healthcare settings, they are fundamentally human, and we are not immune. Perhaps, the art lies in developing an ear that distinguishes the subtle music of each hoofbeat—recognizing when familiar rhythms shift toward the unexpected, without hearing zebras in every echo.

However, diagnostic challenges extend beyond individual cognition. Structural biases in global health systems can delay recognition of outbreaks in certain regions due to surveillance inequality. Social and cultural biases affect how symptoms are reported and interpreted across different communities. Methodological biases in testing and case definitions can skew our understanding of emerging threats. These non-cognitive factors often amplify the cognitive biases we experience as individual clinicians and investigators. To systematize our understanding of these challenges, we have compiled a comprehensive framework of factors that can contribute to outbreak misdiagnoses (Table 3).

The West African Ebola virus disease epidemic in 2013-2016 illustrates how these factors interact. It was not solely a diagnostic delay but exposed broader systemic vulnerabilities

across local, national and international response systems. Resource constraints, healthcare infrastructure, population mobility, political will, coordination challenges, and community trust all profoundly influenced outcomes. Similarly, in the current DRC situation investigators are dealing with geographic isolation, limited laboratory capacity, and complex socioeconomic factors. While investigations continue, we must remain vigilant about our own susceptibility to the same biases we have identified throughout history.

Moving forward to improving outbreak response

The ongoing 2025 acute febrile syndrome outbreak in DRC represents a typical conundrum for modern outbreak science. Public health officials must balance rapid intervention with diagnostic thoroughness, weigh familiar explanations against novel threats and integrate field realities with laboratory findings. Though current approaches show marked improvements over historical precedents, as exemplified by the rapid control gained by local authorities and their partners during recent outbreaks of Ebola and Marburg virus diseases in Uganda, Rwanda, and Tanzania, significant challenges persist in many outbreak scenarios [36,37]. The scientific and financial communities should maintain momentum and financial resources like the Pandemic Fund must be strengthened as we go along [38].

In this manuscript, neither easy nor uniform solutions that have not been suggested before are presented. We must acknowledge the difficulty in identifying patterns that add up to an outbreak signal and the swift and correct recognition of deviations from the usual occurrence in the local context.

From theoretical understanding to actionable change, this is the bridge we must build. Drawing on both historical 'misdiagnoses' and the current DRC situation, we propose five interventions that balance ideal practices with real-world constraints. Table 4 offers some more detail on the suggestions summarized below.

1. Encourage multiple working hypotheses. Develop approaches that systematically consider both prevalent and unusual causes simultaneously. Prioritizing likely endemic causes while remaining alert to unusual possibilities. This approach does not necessarily require additional resources, but rather a shift in diagnostic thinking that maintains openness to multiple etiologies while initiating empirical treatment for common conditions.
2. Build sustainable local diagnostic capacity. Rather than relying solely on external mobile laboratories, focus on strengthening sustainable regional diagnostic hubs with appropriate technology transfer and training. Point-of-care testing, particularly syndromic panels that can detect multiple pathogens simultaneously, should be prioritized for strategic deployment.
3. Enhance communication networks. Establish or strengthen clear channels for clinicians to report unusual presentations or treatment failures to regional and national health authorities. These networks should bridge clinical settings with public health systems and leverage existing communication infrastructure while minimizing reporting burden.
4. Implement cognitive debiasing strategies. Develop simple clinical decision support tools that prompt consideration of alternative diagnoses when particular

red flags appear. These prompts could include treatment failure, unusual demographic patterns, or healthcare worker infections.

5. Strengthen One Health surveillance. Promote integration of human, animal, and environmental health monitoring in particular in high-risk settings for spillover events. This approach should build upon existing systems rather than creating parallel structures.

To measure progress in outbreak response, the 7-1-7 framework is currently gaining international momentum [39]. This approach, adopted by the WHO Regional Office for Africa and The Pandemic Fund, creates concrete targets: seven days to identify outbreaks; one day to report and begin investigation; and seven days to mount an effective response [40]. Though challenging to implement in resource-constrained environments, these timeline goals provide clear metrics needed to advance and reduce diagnostic delays.

Overall, historical outbreak misdiagnoses have been important lessons to build forward global capacity for response. By integrating these learnings, we can preemptively diminish the risk of early misinterpretation of future outbreaks. The transition from reactive to proactive response to outbreaks, from rumor-based to evidence-based action, and from compartmentalized to global coordinated action is a major global health security breakthrough.

Declaration of potential conflicts of interest

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Authors contributions

MPG conceived the paper. GPG drafted the first version of the manuscript, with input from all authors. All authors contributed further to the final version of the manuscript, and endorsed its submission for publication.

Disclaimers

Pikka Jokelainen is part of EU-co-funded consortia. Views and opinions expressed do not necessarily reflect those of the EU or European Health and Digital Executive Agency. Neither the EU nor the granting authority can be held responsible for them. Effrossyni Gkrania-Klotsas is supported by the NIHR Cambridge Biomedical Research Centre (NIHR203312). The views expressed are those of the authors and not necessarily those of the NIHR nor of the UK Department of Health and Social Care.

Role of the ESCMID Emerging Infections Subcommittee (EIS) [41]

As the EIS, we recognize our responsibility to provide balanced expertise without overstepping our role or adding burden to frontline responders. We propose to:

- Provide timely, evidence-based technical assessments through ESCMID's established communication channels, focusing on distinguishing verified information from speculation during emerging outbreaks.

- Leverage our international network to synthesize relevant expertise while respecting the authority of local health officials and WHO in outbreak response.
- Develop and disseminate educational resources on outbreak investigation and diagnosis, with practical debiasing strategies for clinicians.
- Support knowledge exchange between settings with different resource levels, avoiding one-size-fits-all recommendations.

Declaration of Generative AI and AI-assisted technologies in the writing process Statement

During the preparation of this work, GPS used Claude 3.7 Sonnet to improve readability and language in specific sections of the manuscript. All AI-generated content was carefully reviewed, edited, and verified by all authors, who take full responsibility and accountability for the entire contents of the work.

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Tables

Table 1: Summary of historical outbreak misdiagnoses

Outbreak / Disease	Initial Diagnosis	Actual Cause	Key cognitive biases	Consequences
1918 Influenza Pandemic	*Haemophilus influenzae* infection	Influenza A virus	Availability bias (lack of viral understanding)	Misattribution of primary pathogen
West Africa Ebola (2013-2016)	Malaria, cholera, typhoid	Zaire Ebola virus	Availability bias, confirmation bias	11,000+ deaths, multinational spread
Angola (2004-2005)	Malaria	Marburg virus	Availability bias	200+ deaths, delayed containment
Brazil (2015)	Dengue, chikungunya	Zika virus	Confirmation bias	Widespread outbreak
Lyme disease (1970s)	Juvenile rheumatoid arthritis	*Borrelia burgdorferi*	Pattern recognition bias	Delayed identification of infectious cause
Kuru (1950s)	Hereditary neurodegenerative disorder	Prion disease from ritualistic cannibalism	Pattern recognition bias	Decades-long delay in identifying infectious cause
Nodding syndrome	Various neurological conditions	Likely autoimmune response to onchocerciasis	Multifactorial causation bias	Years of ineffective interventions, ongoing research
Minamata disease (1950s)	Encephalitis	Methylmercury poisoning	Framing bias	2,000+ affected, continued exposure
Eosinophilia-Myalgia Syndrome (1989)	Novel infection	Contaminants in L-tryptophan supplements	Framing bias	1,500 cases, 37 deaths, delayed product recall
Bihar encephalitis (2019)	Viral infection	Litchi toxin (MCPG)	Framing bias	Seasonal outbreaks among malnourished children
Caruaru, Brazil (1996)	Viral haemorrhagic fever	Cyanotoxin (microcystin) contamination	Framing bias	52 deaths, liver failure in haemodialysis patients

		in dialysis water		
"June Bug" incident (1962)	Infectious/toxic agent	Mass psychogenic illness	Social contagion Bandwagon effect	Unnecessary medical interventions
DRC hemorrhagic cases (2024)	Viral hemorrhagic fever	Combination of malaria, anemia, malnutrition	Occam's razor heuristic	Appropriate non-VHF interventions
US Anthrax (2001)	Influenza, pneumonia	Deliberate anthrax release	Availability bias Pattern recognition bias	Delayed recognition of bioterrorism

Table 2: Key terms and definitions

Term	Definition
Availability bias	Tendency to overestimate likelihood of diagnoses that come readily to mind due to recent exposure or familiarity
Confirmation bias	Tendency to search for and interpret information that confirms pre-existing beliefs or hypotheses
Pattern recognition bias	Tendency to categorize new situations based on how well they match patterns previously encountered
Framing bias	Tendency to approach problem-solving differently based on how information is presented
Anchoring bias	Over-reliance on first piece of information encountered (the 'anchor')
Syndemic	Synergistic interaction of two or more coexistent diseases that exacerbates the burden of disease
Public health emergency	Occurrence or imminent threat of illness with high potential for rapid spread requiring immediate public health action
Index case	First identified case in an outbreak or epidemic
Sentinel event	Unexpected occurrence involving death or serious injury requiring immediate investigation
Zoonotic spillover	Transmission of a pathogen from a vertebrate animal to a human

Table 3. Multi-level factors contributing to delays in outbreak diagnosis

Factor Category	Specific Factor	Description
Cognitive Biases	Availability bias	Tendency to overestimate likelihood of diagnoses that come readily to mind due to recent exposure or familiarity
	Anchoring bias	Over-reliance on first piece of information encountered (the "anchor")
	Confirmation bias	Tendency to search for and interpret information that confirms pre-existing beliefs or hypotheses
	Pattern recognition bias	Tendency to categorize new situations based on how well they match patterns previously encountered
	Framing bias	Tendency to approach problem-solving differently based on how information is presented
	Occam's razor heuristic	Preference for simplest explanation that fits the facts
	Social contagion effect	Spread of behaviors, attitudes, or symptoms through social networks
Clinical	Symptom overlap	Similar clinical presentation with endemic diseases
	Atypical manifestations	Unusual or incomplete symptom presentation
	Syndemic effect	Synergistic interaction of two or more coexistent diseases that exacerbates the burden of disease
	Coinfections	Presence of multiple pathogens complicating diagnosis
	Disease severity spectrum	Variable presentations from mild to severe
Structural	Limited diagnostic capacity	Insufficient laboratory resources for testing
	Geographic isolation	Remote locations hampering sample transport
	Health system fragmentation	Poor coordination between levels of care
	Surveillance gaps	Insufficient systems to detect unusual patterns
	Resource constraints	Limited staff, equipment, or supplies
Technological	Diagnostic technology limitations	Technical constraints of available existing tests
	Sequencing availability	Access to genomic technologies
	Test sensitivity/specificity	Performance characteristics of diagnostic tests
	Data management systems	Capacity to process and analyze surveillance data

Environmental	Ecological changes	Shifts in vector distribution or reservoir hosts
	Seasonal patterns	Timing coinciding with endemic disease seasons
	Environmental contamination	Exposure to toxins or environmental hazards
Social	Cultural practices	Traditions affecting disease transmission
	Healthcare seeking behavior	Patterns of when and where people seek care
	Trust in health systems	Willingness to engage with formal healthcare
	Stigma	Fear of diagnosis leading to concealment
	Mass psychogenic illness	Social transmission of symptoms
Political	Information restrictions	Censorship or limited transparency
	International relations	Geopolitical considerations affecting response
	Governance challenges	Weak institutional coordination
	Political priorities	Competing government interests
	Regulatory barriers	Legal obstacles to data sharing or response
	Funding constraints	Reduction in support for global health organizations
Economic	Resource allocation	Distribution of limited response resources
	Market incentives	Limited commercial interest for certain diagnostics
	Economic disruption fears	Concern about impact of outbreak declaration
	Cost-benefit considerations	Financial factors in testing strategies
Communication	Data sharing challenges	Barriers to information exchange
	Scientific communication	Delays in publishing or disseminating findings
	Risk communication	Ineffective public messaging
	Information overload	Excess data obscuring key signals
Temporal	Incubation periods	Time between infection and symptoms
	Reporting delays	Time lags in surveillance systems
	Investigation timing	Seasonal or logistical constraints
	Historical context	Prior experience affecting current approach
Organizational	Institutional memory	Retention of knowledge from past events
	Bureaucratic processes	Administrative delays
	Agency coordination	Collaboration between relevant entities
	Competing priorities	Resource division between multiple health concerns

Epidemiological	Novel transmission patterns	Unexpected modes of spread
	Index case identification	Recognition of first cases
	Case definition challenges	Difficulty establishing consistent criteria
	Surveillance biases	Systematic gaps in who gets detected
Intentional	Deliberate deception	Bioterrorism or intentional spread
	Misinformation	False information affecting response
	Security concerns	Classified information limiting sharing

Table 4: Proposed interventions to improve outbreak recognition and response

Intervention	Key Components	Implementation Considerations	Expected Impact
Encourage multiple working hypotheses	• Systematic consideration of both **common** and unusual causes • Empirical treatment for likely conditions while investigating alternatives	• Requires shift in diagnostic thinking, not necessarily additional resources • Can be incorporated into existing clinical workflows	• Earlier detection of unusual pathogens • Reduced diagnostic delay • Improved patient outcomes
Build sustainable local diagnostic capacity	• Regional diagnostic hubs with appropriate technology • Training and technology transfer • Syndromic panels and point-of-care testing	• Investment in infrastructure and human resources • Strategic deployment of limited testing resources • Sustainable funding mechanisms	• Faster local confirmation • Reduced dependence on distant reference labs • Enhanced regional preparedness
Enhance communication networks	• Clear reporting channels for unusual cases • Bridge between clinical and public health systems • Leverage existing infrastructure	• Minimize reporting burden • Integrate with existing communication systems • Establish standardized criteria for reporting	• Improved signal detection • Faster alerting of authorities • Better cross-border coordination
Implement cognitive debiasing strategies	• Clinical decision support tools • Recognition of red flags (treatment failure, unusual patterns, healthcare worker infections)	• Simple, accessible tools • Integration into clinical training • Regular updates based on emerging knowledge	• Reduced impact of cognitive biases • More consistent consideration of alternatives • Systematic approach to unusual presentations

Strengthen One Health surveillance	• Integration of human, animal, and environmental health monitoring • Focus on high-risk settings for spillover events	• Build upon existing systems • Avoid creating parallel structures • Cross-sectoral collaboration	• Earlier detection of zoonotic threats • Better understanding of emergence patterns • More comprehensive response capabilities