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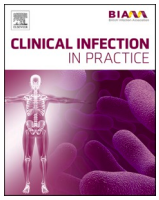

Disease X: Unraveling a mysterious outbreak in the Democratic Republic of the Congo

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Introduction

The recent emergence of an undiagnosed febrile-respiratory illness in the Panzi Health Zone of Kwango Province, Democratic Republic of the Congo (DRC) reflects a scenario that global health agencies have long anticipated: a "Disease X" event (Undiagnosed Disease, 2024). The term "Disease X" is frequently used by the World Health Organization (WHO) and other public health bodies as a placeholder for a new, potentially severe pathogen that could cause significant morbidity and mortality before its etiology is clearly understood (Bardhan et al., 2024). This conceptual framework acknowledges that the next major infectious threat may not match that of previously known pathogens. Instead, it could present as a hybrid clinical syndrome and challenge the diagnostic, surveillance, and response capacities of healthcare systems, particularly in low-resource settings (Anjum et al., 2024; Christofferson and Cormier, 2022).

Between October 24 and December 5, 2024, a surge in cases presenting with fever, headache, cough, runny nose, and body aches was observed in the Panzi Health Zone of Kwango Province, DRC. By early December, 406 cases and 31 deaths had been recorded, the majority of which affected young children. A substantial subset of severe cases exhibited malnutrition, suggesting underlying vulnerabilities that may exacerbate the disease severity. The epicenter lies in a region distant from major urban centers, with a more than forty-eight-hour journey by road from Kinshasa. Seasonal rains, infrastructural constraints, and minimal laboratory capacity have delayed diagnostic confirmation. This outbreak initially appeared unexplained, but further data indicate severe malaria in most samples (25/29 by quantitative polymerase chain reaction and 55/88 by rapid tests) along with malnutrition (Cases, 2024). As of December 20, 2024, at least 592 cases have been identified with a fatality rate of 6.2 % per official statement, although unverified community deaths may raise this figure to 62 %, and on the same date, one fatal case presenting with hemorrhagic symptoms was reported, prompting further testing. (Cases, 2024; Malaria, 2024; Rise, 2024). Ongoing diagnostic challenges, compounded by poor sample quality, highlight the urgent need for expanded surveillance and robust health interventions in this resource-limited setting (Rise, 2024; Ondoa et al., 2020).

Epidemiological and clinical overview

According to official notifications, the Panzi Health Zone documented a sudden increase in pediatric respiratory illnesses starting in late October 2024 (Democratic Republic of the Congo Ministry of Health Press, 2024). A peak in the reported cases occurred in early November, with the outbreak persisting in December. Nine out of thirty health areas in Panzi have been affected, but nearly all cases cluster in three health areas: Tsakala Panzi, Makitapanzi, and Kanzangi. The overwhelming burden on children, particularly those under five, is alarming. Children represent approximately 64 % of all cases, and over half of all reported deaths have occurred in this youngest age bracket. Females account for approximately 60 % of the cases, although the significance of this gender distribution remains unclear. Clinically, the disease presents as a febrile illness accompanied by respiratory symptoms, notably cough, a runny nose, and generalized malaise. Severe cases frequently exhibit respiratory distress, anemia, and evidence of acute malnutrition. Malnutrition, a known risk factor for severe outcomes in many infectious diseases, likely amplifies the severity and mortality risk (Trollebø et al., 2024). Given that most deaths have occurred in the community rather than in formal healthcare settings, there is concern about delayed care-seeking and the limited capacity of health facilities to provide timely, quality treatment.

Differential diagnosis and potential causative agents

The non-specific symptom profile coupled with high pediatric mortality warrants a broad differential diagnosis. Measles, a critical consideration in settings with low immunization coverage, typically presents with fever, cough, coryza, conjunctivitis, and a characteristic rash (Amankwa et al., 2023). The absence of a reported rash does not exclude measles as incomplete clinical information or atypical presentations can occur. Influenza and COVID-19 remain plausible pathogens in this scenario. Influenza viruses can cause fever, cough, and body aches, with severe complications in malnourished children (Gwela et al., 2019). Similarly, SARS-CoV-2 can present non-specifically and may overlap with other infections (Midha et al., 2020). Pneumonia, whether bacterial or viral, can cause severe respiratory symptoms and anemia

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(from chronic illness), and is more lethal in malnourished populations (Chowdhury et al., 2020). Malaria is endemic in many parts of the DRC and can present with fever, anemia, and general malaise. Coinfections, such as viral-bacterial respiratory pathogens superimposed on malaria, might explain the complexity and severity. Recent investigations strongly suggest that malaria alone may be driving many cases, but malnutrition and possible viral coinfections (including hemorrhagic fever–type viruses) cannot be ruled out. Moreover, the presence of hemorrhagic symptoms in at least one fatal case highlights the need to test for emerging or reemerging pathogens that could clinically overlap with malaria. Table 1 presents a comparative analysis of potential pathogen characteristics and diagnostic approaches, considering the clinical presentation and epidemiological context of "Disease X".

Contextual challenges: Malnutrition, food insecurity, and remote terrain

Kwango Province has faced increasing food insecurity in recent months, pushing many children into severe or moderate malnutrition (Democratic Republic of the Congo, 2024). Malnutrition impairs immune responses, increasing susceptibility to infections and the severity of illness (Morales et al., 2023). The remoteness of the Panzi Health Zone hinders rapid intervention. Access to health services, diagnostic testing, and stockpiles of essential medications is severely constrained by poor road conditions and ongoing rains. Travel to the area from Kinshasa takes nearly two days by road, delaying the arrival of the response teams and laboratory samples. With no functional laboratory in the immediate vicinity, all samples must be transported to the national reference laboratory in Kinshasa.

Public health response efforts

National and provincial health authorities, supported by WHO and other partners, have intensified coordination and implemented rapid response activities. Daily coordination meetings at the national level guide interventions, while field teams conduct active case findings in health facilities and communities. Data collection efforts focused on building a detailed line list and characterizing the epidemiology of the outbreak. Investigations into community deaths are ongoing, as these may provide clues to transmission dynamics and the reasons for high mortality. Case-management efforts strive to improve patient outcomes through prompt treatment. Deployed teams bring essential medications, including antimalarials and symptomatic relief, while also introducing basic diagnostic tools, such as rapid diagnostic tests (RDTs) for malaria and COVID-19. The response emphasizes training healthcare workers in infection prevention and control (IPC) measures (Verma et al., 2024). The use of masks, proper hand hygiene, gloves, and isolation of suspected cases are reinforced to limit further transmission. Risk communication strategies aim to engage the community, dispel rumors, and encourage timely care-seeking. Messages emphasize preventive behaviors, such as handwashing, avoiding crowded gatherings when ill, and seeking early medical attention for respiratory symptoms.

Laboratory investigations

Identifying the etiological agent remains a priority, and the initial data point to widespread malaria positivity and concurrent malnutrition. While the primary suspicion now leans toward severe malaria, further evaluations continue at the National Institute of Biomedical Research (INRB) in Kinshasa to detect any additional pathogens. Response teams have collected multiple sample types—blood, sera, nasopharyngeal swabs, and stool—to rule out co-infections such as hemorrhagic viruses or bacterial agents. The combination of poor sample quality, minimal on-site testing capacity, and logistical obstacles impedes rapid and definitive diagnosis (Rise, 2024).

Risk assessment and broader implications

Current outbreak poses a high local risk. Pediatric populations, already compromised by malnutrition, bear the disease burden. Gaps in baseline data on respiratory illness rates in the Panzi Health Zone challenge efforts to contextualize the current surge. Low vaccination coverage for common childhood diseases such as measles increases vulnerability. Potential household transmission clusters are being investigated, raising concerns about person-to-person spread. Without definitive pathogen identification, the development of effective countermeasures remains challenging. At the national level, the risk is considered moderate. The outbreak is presently localized, but given the DRC's porous borders, the potential for spread into neighboring Health Zones or even across frontiers is real. Surveillance and preparedness of the adjacent areas should be increased. Regionally, risk remains low for now, but the possibility of cross-border transmission to Angola or other countries in the region, especially given the seasonal movements of populations and trade, cannot be ignored. This evolving field situation highlights the dynamic nature of the outbreak. Updated data confirm a significant malaria burden, and officials from the Africa Centres for

Table 1
Potential pathogen characteristics of disease X – A differential approach.

Characteristic	Possible Pathogens	Diagnostic Test Required	Rationale for Inclusion	Reference
High pediatric mortality	Measles, Influenza, Respiratory Syncytial Virus (RSV)	PCR for respiratory viruses; measles-specific IgM	Common in malnourished children with low immunization coverage.	(Jennings et al., 2004; Nosova et al., 2023)
Respiratory symptoms	SARS-CoV-2, Influenza, Adenovirus	Multiplex PCR for respiratory panel	Overlap of fever and respiratory distress suggests viral etiology.	(Matic et al., 2024; Chung et al., 2021)
Severe anemia	Malaria, Hookworm co-infection	Blood smear for malaria; stool test for ova/parasites	Co-infections with malaria or parasitic diseases can explain anemia, especially in endemic regions.	(Genanew et al., 2024; Mahittikorn et al., 2022)
Prolonged febrile course	Typhoid, Leptospirosis, Rickettsial infections	Blood cultures; serological tests for leptospirosis and rickettsia	Persistent fever beyond typical viral course warrants bacterial consideration.	(Aina et al., 2023; Cadavid González et al., 2018)
Malnutrition exacerbation	Opportunistic bacterial infections (e.g., Streptococcus pneumoniae), tuberculosis (TB)	Chest X-ray, TB-specific tests (GeneXpert, sputum smear)	Chronic diseases like TB often exacerbate malnutrition, creating a vicious cycle in children.	(Takele et al., 2016; Pates et al., 2023)
Potential co-infections	Viral (Measles) and bacterial (Staphylococcus aureus, Haemophilus influenzae) co-infection	Dual testing with bacterial cultures and viral PCR	Co-infections can increase severity and mortality.	(Patton et al., 2024; Sreenath et al., 2021; Boia et al., 2023)
Regional endemic diseases	Lassa fever, Yellow fever	ELISA for viral hemorrhagic fevers	Endemic diseases with overlapping symptoms must be excluded in certain hotspots.	(Opara et al., 2022; Francis, 2023)
Coinfection markers	Elevated CRP, anemia, neutrophilic leukocytosis	Full blood count (FBC), inflammatory markers	Indicative of bacterial superinfection on a viral or parasitic baseline.	(Rai et al., 2023; Radkhah et al., 2023)

Disease Control and Prevention are now weighing two hypotheses: either malaria is occurring alongside a viral infection against a backdrop of malnutrition, or a novel pathogen is being masked by widespread malaria. Regardless, the potential for further geographical spread, high pediatric susceptibility, and ongoing diagnostic gaps highlight the necessity for robust multi-pathogen testing and cross-border vigilance.

Recommendations for strengthening the response

Enhanced surveillance is of paramount importance. Field teams should continue active case detection, refine case definitions as more clinical data emerge, and involve community health workers in identifying cases early. Improving nutritional support and ensuring the availability of essential medicines, such as antipyretics, antibiotics for suspected bacterial pneumonia, antimalarials, and supportive therapies, are critical. Laboratory efforts should be escalated with prompt shipment of samples and, if feasible, deployment of mobile laboratories to the field. Infection prevention and control activities must be continued to protect healthcare workers and patients. Training, provision of personal protective equipment, and reinforcement of hygiene protocols reduce the risk of nosocomial transmission. Community engagement strategies that build trust, inform preventive measures, and encourage prompt healthcare utilization will support the overall response. Cross-border coordination between Angola and regional health bodies will help monitor any signs of outbreak spread.

Conclusion

The outbreak in the Panzi Health Zone illustrates the intricate interplay between infectious diseases, malnutrition, and limited access to healthcare in challenging environments. Although severe malaria is now strongly indicated by follow-up testing, at least one hemorrhagic febrile fatality raises the possibility of coexisting pathogens. In the absence of a fully confirmed single etiology, current responses emphasize broad-spectrum public health strategies, improved case management, and intensified surveillance. This crisis highlights the urgent need for sustainable investments in surveillance, nutrition, immunization, healthcare infrastructure, and a One Health approach, ensuring timely detection and effective control measures to prevent future outbreaks in vulnerable communities (Agarwal et al., 2023; Manna et al., 2024; Ayush Sharma et al., 2024; Bushi et al., 2024).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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