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Investigating innovative approaches and strategies for effective Ebola epidemic control: Case studies from Guinea and the Democratic Republic of the Congo

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**Doctoral Program (PhD) in Biomedical Sciences,
Global Health**

Mory KEITA

**Investigating innovative approaches
and strategies for effective Ebola
epidemic control: Case studies from
Guinea and the Democratic Republic
of the Congo**

Thesis for doctoral degree (PhD)

INSTITUTE OF GLOBAL HEALTH
FACULTY OF MEDICINE



**UNIVERSITÉ
DE GENÈVE**

I | Acknowledgements

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Figure 1: The candidate in the field. On the left, traveling to an area accessible by car but deemed unsafe, equipped with helmets and bulletproof vests; on the right, riding a motorbike with a social anthropologist colleague for over 60 km through forested terrain to reach a remote and insecure village inaccessible by car

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II | List of publications, manuscripts in preparation, submitted manuscripts, oral communications produced during the study period

II.I | Core articles of the thesis

Keita M, Lucaccioni H, Ilumbulumbu MK, et al. **Evaluation of Early Warning, Alert and Response System for Ebola Virus Disease, Democratic Republic of the Congo, 2018–2020.** *Emerg Infect Dis* 2021; 27: 2988–2998. <https://doi.org/10.3201/eid2712.210290>

Keita M, Polonsky J, Finci I, et al. **Investigation of and Strategies to Control the Final Cluster of the 2018–2020 Ebola Virus Disease Outbreak in the Eastern Democratic Republic of Congo.** *Open Forum Infect Dis* 2022; 9: ofac329. <https://doi.org/10.1093/ofid/ofac329>

Keita M, Polonsky JA, Ahuka-Mundeke S, et al. **A community-based contact isolation strategy to reduce the spread of Ebola virus disease: an analysis of the 2018–2020 outbreak in the Democratic Republic of the Congo.** *BMJ Glob Health*; 8. Epub ahead of print 1 June 2023. <https://doi.org/10.1136/bmjgh-2023-011907>

Keita M, Cherif IS, Polonsky JA, et al. **Factors Associated with Reliable Contact Tracing During the 2021 Ebola Virus Disease Outbreak in Guinea.** *J Epidemiol Glob Health* 2024; 14: 699–709. <https://doi.org/10.1007/s44197-024-00202-y>

Keita M, Cherif MS, Sivahera B, et al. **Case Report: COVID-19 and Lassa Fever Coinfection in an Ebola Suspected Patient in Guinea.** *Am J Trop Med Hyg* 2022; 106: 1094–1097. <https://doi.org/10.4269/ajtmh.21-0713>

Keita M, Talisuna A, Chamla D, et al. **Investing in preparedness for rapid detection and control of epidemics: analysis of health system reforms and their effect on 2021 Ebola virus disease epidemic response in Guinea.** *BMJ Glob Health*; 8. Epub ahead of print 4 January 2023. <https://doi.org/10.1136/bmjgh-2022-010984>

II.II | Related to the thesis topic

Ogi-Gittins I, Polonsky J, Keita M, Ahuka-Mundeke S, Hart WS, Plank MJ, Lambert B, Hill EM, Thompson RN. **Real-time inference of the end of an outbreak: Temporally**

- aggregated disease incidence data and under-reporting.** Infectious Disease Modelling. 2025 Apr 1. <https://doi.org/10.1016/j.idm.2025.03.009>
- Plank MJ, Hart WS, Polonsky J, Keita M, Ahuka-Mundeke S, Thompson RN. **Estimation of end-of-outbreak probabilities in the presence of delayed and incomplete case reporting.** Proceedings B. 2025 Jan 29;292(2039):20242825. <https://doi.org/10.1098/rspb.2024.2825>
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- Thompson R, Hart W, Keita M, Fall I, Gueye A, Chamla D, Mossoko M, Ahuka-Mundeke S, Nsio-Mbeta J, Jombart T, Polonsky J. **Using real-time modelling to inform the 2017 Ebola outbreak response in DR Congo.** Nat Commun. 2024 Jul 6;15(1):5667. <https://doi.org/10.1038/s41467-024-49888-5>
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Kapaya F, Keita M, Sodjinou VD, Nanyunja M, Mpairwe A, Daniel EO, Akpan G, Mlanda T, Shikanga O, Abianuru AT, Mamadu I. **An assessment of the progress made in the implementation of the regional framework for cholera prevention and control in the WHO African region.** *BMJ Global Health*. 2025 Jan 22;10(1). <https://doi.org/10.1136/bmjgh-2024-016168>

Noufack G, Bissengue P, Zobanga JK, Malingao JS, Keita M, Razaiarimanga MC, Raguenaud ME. **Reaching Forest Workers with Yellow Fever Vaccine Through Engagement of the Private Sector in Central African Republic.** *Vaccines*. 2024 Dec 17;12(12):1424. <https://doi.org/10.3390/vaccines12121424>

John Otokoye Otshudiema, Patrick Otim Ramadan, Mory Keita, Brama Koné, Jeremiah Mushosho, Fiona Braka, Abdou Salam Gueye. **Rising Public Health Emergencies Associated with Climate Change in Africa: A Systematic Review.** (*Under review*)

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Fazaludeen Koya S, Abdalla SM, Kodama C, Keita M, Abubakar A. **Vector-Borne and Zoonotic Diseases in the Eastern Mediterranean Region: A Systematic Review.** Journal of Epidemiology and Global Health. 2023 Feb 9:1-0.
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Sodjinou VD, Keita M, Chamla D, Kimenyi JP, Braka F, Talisuna A, Lata H, Mbayo G, Kapaya F, Mlanda T, Conteh NI. **Assessment of the countries' readiness to detect and control cholera outbreaks in the WHO African Region.** Archives of Clinical and Biomedical Research. 2022;6(4):656-62. <https://www.doi.org/10.26502/acbr.50170277>

Sodjinou, Vincent Dossou, et al. "The 2021 cholera outbreak in West Africa: epidemiology and public health implications." *Archives of Clinical and Biomedical Research* 6.2 (2022): 296-307. <https://www.doi.org/10.26502/acbr.50170245>

II.IV | Oral presentations

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Keita M. Investigation of and Strategies to Control the Final Cluster of the 2018–2020 EVD outbreak in DRC. Paper presented at: The 2nd Guinean Public Health Days; 2022 Nov 25-26; Conakry, Guinea.

Keita M. A community-based contact isolation strategy to reduce the spread of Ebola Virus Disease: An analysis of the 2018-2020 outbreak in the Democratic Republic of Congo. Paper presented at: The The 2nd Guinean Public Health Days; 2022 Nov 25-26; Conakry, Guinea.

III | Abstract in English

The African region experiences a disproportionate burden of public health emergencies, with over 90% linked to infectious diseases. This thesis investigates innovative approaches to epidemic preparedness and response, focusing on Ebola Virus Disease (EVD) and leveraging real-world data from Guinea and the Democratic Republic of Congo (DRC). It evaluates early warning systems, community-driven interventions, and health system reforms to enhance outbreak containment. Key findings include the effectiveness of the Early Warning, Alert, and Response System (EWARS) during the 2018–2020 EVD outbreak in the DRC. This decentralised system demonstrated robust sensitivity, specificity, and rapid investigation capabilities, improving epidemic detection and response. The study further highlights the pivotal role of genomic sequencing and targeted interventions in controlling residual transmission clusters during the outbreak's final stages. Community-based strategies emerged as transformative tools for outbreak management. In Beni and Mabalako, community-led contact isolation achieved a significant reduction in transmission, fostering trust and collaboration through culturally sensitive approaches. These findings underscore the importance of integrating local engagement with technical interventions to achieve rapid epidemic control. The thesis also examines factors influencing the reliability of contact tracing, revealing that socio-demographic characteristics, resource allocation, and community trust are critical determinants. Lessons from Guinea's 2021 EVD outbreak emphasise the need for tailored strategies that address urban and rural dynamics. An examined case of Lassa fever and COVID-19 coinfection during an EVD outbreak in Guinea underscores the necessity of integrated diagnostic systems to manage overlapping health emergencies effectively. Finally, the thesis also explores the impact of investing in preparedness, with a focus on health system reforms in Guinea following the 2014-2016 EVD epidemic. Investments in decentralised early warning systems, workforce capacity-building, and community engagement yielded substantial improvements in outbreak responsiveness. These reforms enhanced the detection and containment of emerging health threats, highlighting the importance of sustained funding and strategic planning. Ultimately, this research advances the understanding of epidemic preparedness, offering practical insights to strengthen health systems and improve responses in resource-limited settings. The findings contribute to global health security efforts, particularly in regions facing recurrent zoonotic disease threats.

IV | Résumé en français

La région Africaine subit une charge disproportionnée d'urgences de santé publique, dont plus de 90 % sont liées à des maladies infectieuses. Cette thèse étudie des approches innovantes en matière de préparation et de réponse aux épidémies, en se concentrant sur la maladie à virus Ebola (MVE) et en s'appuyant sur des données factuelles provenant de la Guinée et de la République démocratique du Congo (RDC). Elle évalue les systèmes d'alerte précoce, les interventions communautaires et les réformes du système de santé afin d'améliorer le contrôle des épidémies. Les principales conclusions incluent l'efficacité du système d'alerte précoce et de réponse (EWARS) pendant l'épidémie de MVE de 2018-2020 en RDC. Ce système décentralisé s'est révélé très sensible, spécifique et a permis de mener des investigations dans les meilleurs délais, améliorant ainsi la détection et la réponse à l'épidémie. Les résultats de cette thèse mettent également en évidence le rôle central du séquençage génomique et des interventions ciblées dans le contrôle des clusters de transmission résiduels au cours des dernières phases de l'épidémie. Des stratégies communautaires se sont révélées aussi être des outils de transformation pour la gestion des épidémies. À Beni et à Mabalako, l'isolement des contacts au niveau communautaire a considérablement réduit la transmission, tout en favorisant la confiance et la collaboration grâce à des approches empreintes de tact et de respect de la réalité culturelle. Ces résultats soulignent l'importance d'intégrer l'engagement communautaire aux interventions techniques pour parvenir à un contrôle rapide de l'épidémie. Cette thèse examine également les facteurs influençant la fiabilité du suivi des contacts, en démontrant que les caractéristiques sociodémographiques, l'allocation des ressources et la confiance de la communauté sont des facteurs déterminants. Les leçons tirées de l'épidémie de MVE de 2021 en Guinée soulignent la nécessité d'élaborer des stratégies sur mesure qui tiennent compte des dynamiques urbaines et rurales. Une étude de cas de co-infection par la fièvre de Lassa et le COVID-19 au cours d'une épidémie de MVE en Guinée souligne la nécessité de systèmes de diagnostic intégrés pour gérer efficacement les urgences sanitaires qui se chevauchent. Enfin, la thèse explore également l'impact de l'investissement dans la préparation, en mettant l'accent sur les réformes du système de santé en Guinée à la suite de l'épidémie de MVE de 2014-2016. Les investissements dans les systèmes d'alerte précoce décentralisés, dans le renforcement des capacités du personnel et dans l'engagement des communautés ont permis d'améliorer considérablement la réponse aux épidémies. Ces réformes ont permis d'améliorer la détection et le contrôle des menaces sanitaires émergentes, mettant en évidence l'importance d'un financement durable et d'une planification stratégique. Somme toute, cette thèse fait progresser

la compréhension de la préparation aux épidémies, en offrant des idées pratiques pour renforcer les systèmes de santé et améliorer les réponses dans les environnements à ressources limitées. Les résultats contribuent ainsi aux efforts de sécurité sanitaire mondiale, en particulier dans les régions confrontées à des menaces récurrentes de zoonoses.

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VI.I | List of figures

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VII | Acronyms, and abbreviations

AAR	After Action Review
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
ANSS	National Health Security Agency (Guinea)
ASAT	Aspartate aminotransferase
BDBV	Bundibugyo virus
CA	California
CDC	Centers for Disease Control and Prevention (USA)
CFR	Case Fatality Rate
CHW	Community health workers
CI	Confidence interval
COVID	Coronavirus disease
CT	Contact tracing
DRC	Democratic Republic of the Congo
ED	Ebola disease
EOC	Emergency Operations Center
EPARE	Prefectural Epidemic Alert and Response Teams (Guinea)
ERARE	Regional Epidemic Alert and Response Teams (Guinea)
ETC	Ebola Treatment Center
ETU	Ebola Treatment Unit
EVD	Ebola virus disease
EWAR	Early Warning Alert System
EWARS	Early Warning Alert and Response System
FETP	Field Epidemiology Training Program
GP	Glycoprotein
GPS	Global Positioning System
HCW	Healthcare worker
HIV	Human Immunodeficiency Virus
HRH	Human resources for health
HZ	Health Zone (Democratic Republic of the Congo)
IASC	Inter-Agency Standing Committee
IDP	Internally Displaced Person

IDSR	Integrated Disease Surveillance and Response
IHR	International Health Regulations
INRB	Institut National de Recherche Biomédicale (Democratic Republic of the Congo)
IPC	Infection Prevention and Control
IQR	Interquartile range
JEE	Joint External Evaluation
MA	Massachusetts
MERS	Middle East respiratory syndrome
MHPSS	Mental health and psychosocial support
MVD	Marburg virus disease
NAPHS	National Action Plan for Health Security
NP	Nucleoprotein
NPV	Negative predictive value
OR	Odds ratio
PCR	Polymerase chain reaction
PHEIC	Public Health Emergency of International Concern
PHEOC	Public Health Emergency Operations Center
PPE	Personal Protective Equipment
PPV	Positive predictive value
RCCE	Risk communication and community engagement
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDB	Safe and dignified burial
SIMEX	Simulation Exercises
SRP	Strategic Response Plan
STAR	Strategic Tools for Assessing Risk
SUDV	Sudan virus
SVD	Sudan virus disease
TTX	Tabletop exercises
US	United States
USA	United States of America

USD	United States Dollar
VHF	Viral Hemorrhagic Fever
VRAM	Vulnerability Risk Assessment and Mapping
WGS	Whole Genome Sequencing
WHO	World Health Organization

1 | General introduction

1.1 | Background

With over 100 major public health events annually, the African region experiences the highest number of public health emergencies globally, the majority (92%) of which are attributable to infectious diseases(1). In recent decades, zoonotic events—instances where a pathogen transitions from animals to humans—have occurred with increasing frequency and scale(2). For example, Africa has witnessed a dramatic 87% increase in zoonotic disease outbreaks over the past two decades(1). Time and again, these (re)emerging pathogens have demonstrated the capacity to sustain human-to-human transmission following zoonotic spillover events. Examples include Ebola virus disease (EVD), severe acute respiratory syndrome (SARS), pandemic influenza, Middle East respiratory syndrome (MERS), and the recently emerged coronavirus disease 2019 (COVID-19)(3,4). While these viral epidemics differ in their basic reproduction number (R_0)—partly influenced by the mode of transmission (e.g., oral-fecal vs. droplet transmission)—the core strategies for containment remain consistent: testing, isolation, contact tracing, and treatment where possible(2).

Ebola disease (EBOD) is a severe disease with high case fatality caused by infection with Ebola virus or a closely related virus, such as Sudan virus (SUDV), and Bundibugyo virus (BDBV)(5). Among these, *Ebolavirus* is the most lethal, with a case-fatality rate of 60–100%, followed by Sudan virus at 40–60%(6), and Bundibugyo virus at approximately 25%(7). Epidemics typically begin with a single instance of zoonotic transmission, followed by human-to-human transmission through direct contact with infected bodily fluids, contaminated fomites, or other forms of close contact(8). While most outbreaks can be traced to a single spillover event from an unknown reservoir via unknown mechanisms(8), recent epidemics have increasingly implicated persistent viral contamination in Ebola survivors as a significant source of transmission(9).

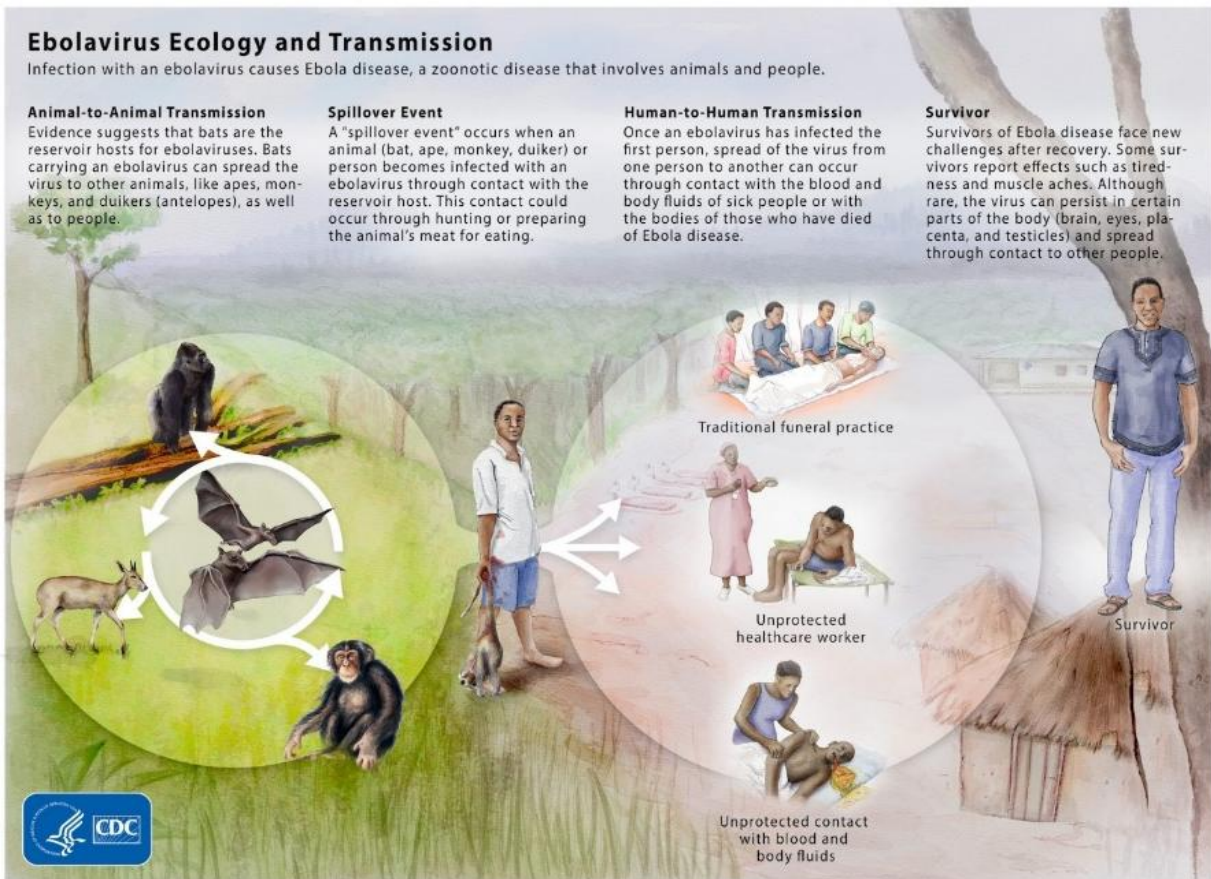


Figure 2: How Ebola virus disease spreads (Source : Centers for Diseases Control and Prevention)

Ebola epidemics have far-reaching direct and indirect socio-economic consequences. Direct impacts include loss of life and disruptions to trade and travel, while indirect effects encompass workforce absenteeism, lost wages, reduced tax revenue, informal healthcare costs (e.g., patient transport), and strain on human resources for health. Additional consequences include losses in the agriculture sector, declines in tourism and travel, reduced trade and retail activity, environmental damage, and disruptions to education. These effects often exacerbate existing inequalities, disproportionately affecting marginalised populations(4). Such challenges underscore the fragility of global health security in an interdependent world and the critical need for a robust global health system capable of mitigating these risks for the entire global community(10).

Since 1976, there have been 48 recorded Ebola outbreaks globally, with over 85% occurring in Africa (Figure 3). These outbreaks have resulted in a total of 34,932 cases and 15,407 deaths, equating to a global case-fatality rate of 44%. Of these, 29 epidemics occurred between 2010 and 2022, compared with 15 between 1999 and 2010, indicating a doubling in frequency. In the Democratic Republic of Congo (DRC), an Ebola outbreak was reported on average, every

five years between 1976 and 2014, but this interval has shortened, with outbreaks occurring almost annually between 2017 and 2022(6).

Over the past decade, the world has faced the two largest Ebola epidemics in recorded history, both of which were declared Public Health Emergencies of International Concern (PHEIC) by the World Health Organization (WHO). The first, the largest, longest, and deadliest EVD outbreak to date, occurred in West Africa between December 2013 and March 2016, resulting in 28,652 infections and 11,325 deaths across 10 countries(11). The second, the 2018–2020 outbreak in the DRC, was the second largest EVD epidemic on record and the only one to occur in an active conflict zone. This outbreak caused 3,481 cases (3,323 confirmed and 158 probable) and 2,299 deaths in North Kivu, Ituri, and South Kivu Provinces from August 2018 to June 2020(12).

The failure to prevent the spread of the 2014–2016 Ebola outbreak in West Africa exposed significant weaknesses in the implementation of the International Health Regulations (2005) (IHR). This legally binding international framework requires 196 countries, including all 194 WHO Member States, to establish and maintain the surveillance and response capabilities necessary to detect, assess, notify, and respond to public health emergencies with potential international repercussions(13,14). The magnitude of the outbreak prompted the United Nations Security Council to unanimously adopt a resolution establishing the United Nations Mission for Ebola Emergency Response (UNMEER)—the first UN emergency health agency. UNMEER was tasked with strengthening surveillance, supporting health workers, and mobilising resources, with its responsibilities later transferred to WHO upon achieving its primary objectives(13,15).

Although predicting the timing and location of future Ebola epidemics remains challenging, past events clearly demonstrate that the African region is particularly vulnerable and will likely continue to be disproportionately affected compared to other regions, despite global advances in vaccines, diagnostics, and treatments(9). Effective and timely responses are essential given the high morbidity, mortality, and socio-economic disruption caused by Ebola epidemics. This necessitates a proactive focus on high-impact strategies that ensure swift, reactive responses. Improved implementation of these strategies holds the potential to mitigate public health impacts and reduce the overall cost of responses.

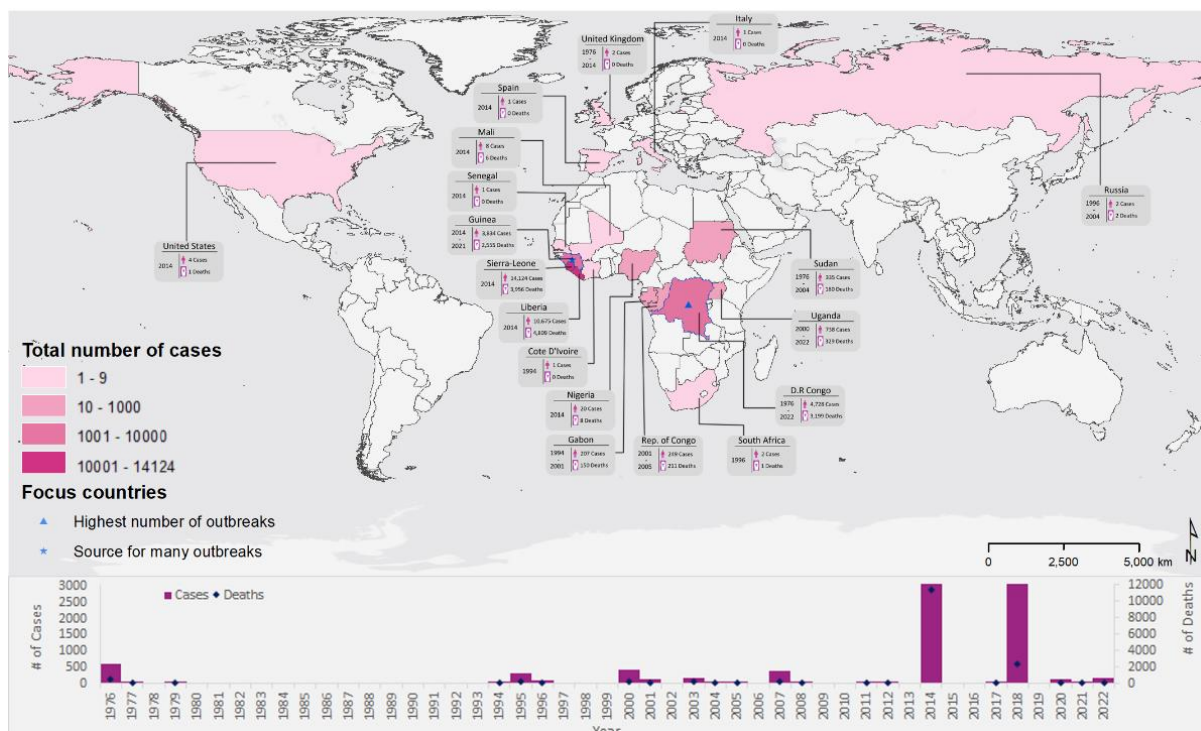


Figure 3: Ebola outbreaks around the world since 1976 (Source: author)

Before 2013, ED epidemics typically involved relatively small numbers of cases, were confined to rural areas, and were effectively controlled using basic public health measures, such as quarantine and containment(16). However, more recent epidemics have fundamentally altered the perception and understanding of Ebola epidemiology. These outbreaks have affected larger populations and spread to urban areas, presenting new challenges for control and containment.

While all Ebola epidemics are generally believed to have originated from zoonotic spillover events—where ebolaviruses are transmitted from wildlife to humans—recent outbreaks have reshaped our understanding of the mechanisms driving the emergence of these viruses (Table 1)(9).

Table 1: Ebola disease outbreak origins 2014 - 2022

Year	Disease	Location	Cases (CFR %)	Suspected cause
2014	EVD	Equateur, DRC	69 (71)	Spillover
2014-16	EVD	Guinea, Liberia, Sierra Leone	28,610 (39)	Spillover

Year	Disease	Location	Cases (CFR %)	Suspected cause
2017	EVD	Likati, Bas Uélé, DRC	8 (50)	Spillover
2018	EVD	Equateur, DRC	54 (61)	Spillover
2018-20	EVD	North Kivu, Ituri, DRC	3481 (66)	Spillover
2020	EVD	Equateur, DRC	130 (42)	Spillover; Viral persistence
2021	EVD	North Kivu, DRC	12 (50)	Viral persistence
2021	EVD	N'Zérékoré, Guinea	23 (52)	Viral persistence
2021	EVD	North Kivu, DRC	11 (82)	Viral persistence
2022	EVD	North Kivu, DRC	1 (100)	Viral persistence
2022	SVD	Mubende, Kampala, Uganda	164 (55)	Spillover

Controlling epidemics like Ebola across a wide spatial scale in a timely manner poses a complex optimisation challenge. Disease parameters, such as transmission and fatality rates, can vary significantly across different geographical regions. Furthermore, the mobility and migration of populations facilitate the spread of disease from one area (e.g., city, country, or continent) to another. This is compounded by the fact that resources for epidemic intervention are often limited and insufficient, forcing policymakers and healthcare providers to make strategic and rapid decisions about resource allocation to effectively control outbreaks of infectious diseases(17).

The West African epidemic persisted and spread rapidly due to the extremely weak health systems in the affected countries(13). The 2016 self-assessments identified major gaps in the implementation of the International Health Regulations (IHR) 2005, showing that no country in the WHO African Region had all the necessary IHR capacities, due to weak health systems(18). Additionally, misinformation, amplified by a lack of trust between communities and political and health authorities, led to widespread rejection of proposed interventions and response efforts. This mistrust resulted in unprecedented violence, including attacks and killings, during an epidemic response(19). During this outbreak, the World Health Organization (WHO) implemented a roadmap based on nearly 40 years of experience in controlling Ebola

virus disease (EVD), employing strategies that had previously proven effective. However, this unique context highlighted that in areas with high transmission and fragile health systems, standard outbreak control strategies must be complemented by novel approaches (18). For instance, in the absence of effective vaccines or medicines, Sierra Leone and Liberia resorted to the forced quarantine of contacts. This approach likely proved counterproductive, fostering negative behaviours such as hiding bodies or sick individuals and avoiding healthcare services. This suggests that epidemic control strategies rooted in social acceptance and local practices may be more effective(20,21).

The 2018–2020 EVD epidemic in North Kivu and Ituri, Democratic Republic of Congo (DRC), exhibited high transmissibility and mortality, exacerbated by chronic insecurity in the affected areas. Contributing factors included the presence of multiple armed groups, extreme poverty, displaced populations, and widespread mistrust of the government(22). However, this outbreak benefitted from advancements in understanding the molecular biology and pathogenesis of the virus, which enabled the deployment of an effective vaccine(23) and new specific therapies(24). Despite these advances, significant challenges remain in optimising the use of available tools to rapidly control epidemics. Deploying these resources effectively requires community trust, a factor that cannot be assumed, as the DRC epidemic demonstrated. Future responses must prioritise the development of acceptable and comprehensive control strategies(7).

1.2 | Theory of change

In the absence of primary prevention measures, managing an Ebola epidemic relies heavily on implementing secondary strategies during the outbreak(25). For instance, during the 2018–2020 epidemic in eastern Democratic Republic of Congo (DRC), which persisted for nearly two years despite the availability of effective vaccines and therapeutics, public health performance indicators were at times suboptimal. This was evidenced by an increase in community deaths, poor transmission control (as indicated by a high number of cases with no known contacts), and delays between symptom onset and isolation. Consequently, a strategic shift was required to adapt to the challenging context and achieve a rapid and substantial reduction in transmissibility(26).

The fourth Strategic Response Plan (SRP-4) was therefore developed, building on strategic directions that capitalised on lessons learned. Key measures included the detection and rapid isolation of cases, the intensification of multidisciplinary public health actions around

confirmed cases, and the strengthening of community engagement(26). In this context, and aligned with our research objectives, we proposed a *Theory of Change* (ToC) diagram to guide the identification of new strategic approaches to surveillance. This was inspired in part by the “micro-cerclage” strategy implemented in Guinea, which was developed after traditional methods failed to control the epidemic(27).

The proposed model integrates a combination of strategies, including the establishment of a decentralised early warning system, reliable contact tracing (understanding the key influencing factors is crucial for this), and more extensive investigations incorporating both epidemiological methods and real-time genomic sequencing. Additionally, a community-based contact isolation strategy was proposed where feasible and culturally appropriate. The primary targets of this strategic approach were alerts, suspected cases, and contacts(28), for whom intervention methods needed to be adjusted given that the epidemic had already persisted for over a year.

The expected outcomes of this new approach included an enhanced alert and response system, a reduction in secondary and tertiary cases, and the rapid interruption of transmission to achieve epidemic control. These outcomes, however, were contingent on several moderating factors. Chief among these was community involvement, which ensures that communities are both motivated and equipped to adopt desired behaviours, such as adherence to contact isolation and the implementation of infection prevention measures at the community level. Furthermore, the success of this approach depended on the continuation of other core interventions, including surveillance, case management, vaccination, infection prevention and control, and risk communication and community engagement (Figure 4).

Consequently, an intervention framework (Figure 5), incorporating key research areas, was developed to better inform, understand, and evaluate the effectiveness of interventions aimed at achieving rapid epidemic control. This research holds particular relevance as it was conducted under real-world conditions, seeking to understand and work within existing complexities rather than attempting to control or eliminate them as causal factors. Moreover, it engaged with populations directly affected by the interventions, ensuring that the findings were applicable to the target population, rather than relying on selected beneficiaries who might not represent the broader intervention context(29).

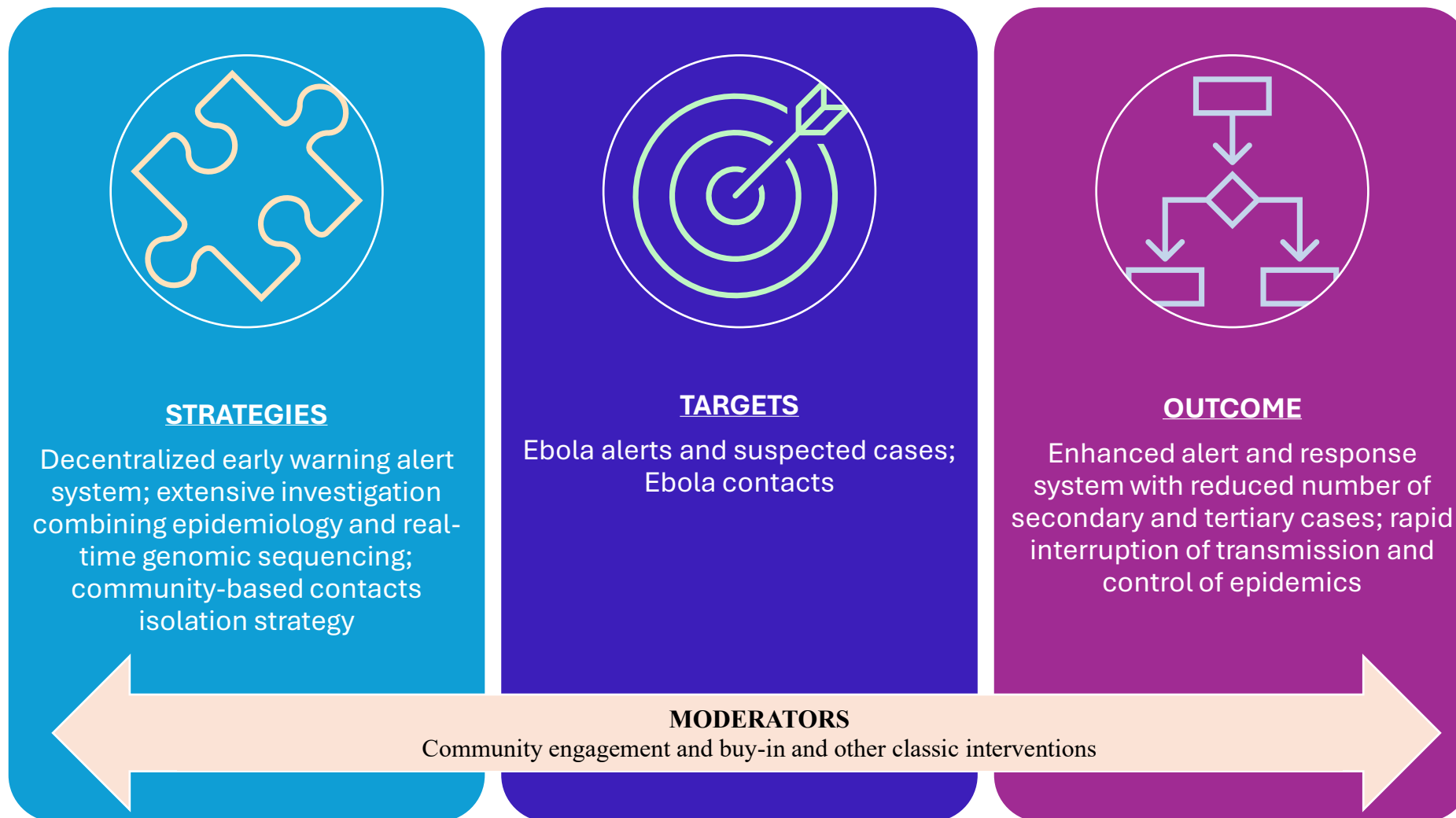


Figure 4: Theory of change framework (Source: author)

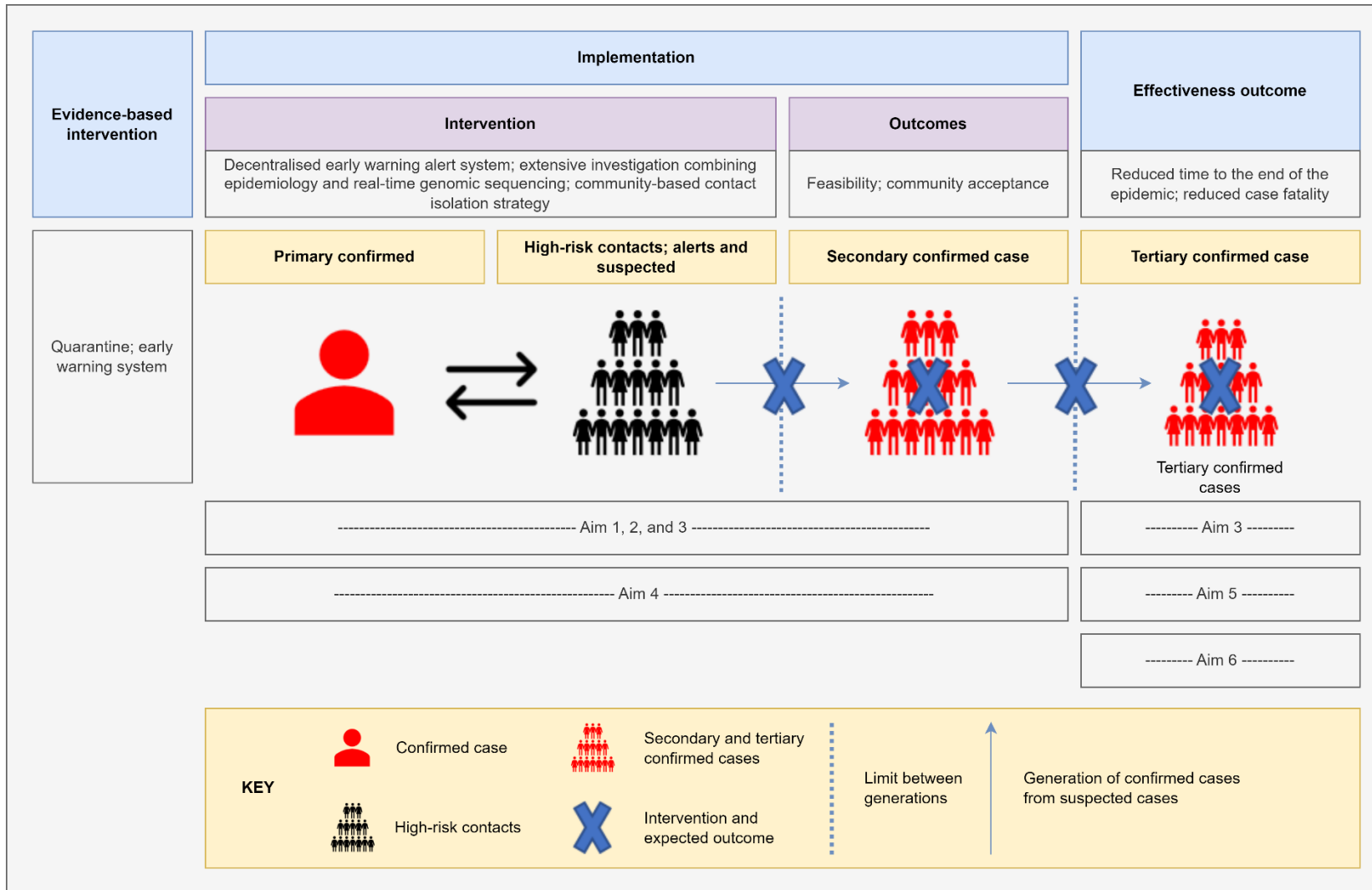


Figure 5: Intervention framework (Source: author)

Although Ebola virus disease has been extensively documented since its discovery in 1976, there remains a scarcity of published studies evaluating the effectiveness of specific containment strategies during an active epidemic. This gap highlights the importance of generating evidence to guide public health decision-making and optimise intervention outcomes.

1.3 | Hypothesis

This research hypothesises that the rapid control of an Ebola epidemic can be achieved through the application of innovative approaches, including a decentralised early warning alert system, reliable contact tracing, and community-based contact isolation.

1.4 | Research aims and objectives

The aim of this research is to enhance the response to Ebola and similar disease outbreaks by providing evidence-based strategies and approaches proven effective in certain settings, with adaptations for broader application where necessary. To achieve this, the specific objectives were:

1. To evaluate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of a decentralised early warning alert system in controlling Ebola epidemics;
2. To integrate epidemiological and genomic investigations to better understand the origins and dynamics of transmission during epidemics;
3. To provide evidence for the effectiveness of a community-based contact isolation strategy, centred on the participation of contacts and community engagement, as a potential approach for future outbreaks to rapidly mitigate onward transmission;
4. To identify factors associated with the reliability of 21-day follow-up among listed contacts, to inform and improve contact tracing efforts in future outbreak responses in similar contexts; and
5. To assess the feasibility and acceptance of applying community contact isolation and decentralised early warning system strategies in comparable outbreak scenarios.
6. To investigate how investment in preparedness capacities (IHR core capacities) will affect and contribute to the response to an Ebola epidemic.

2 | Articles

2.1 | Methodological contribution

Note: for each research objective, a research article was written and published, as detailed in the table below (Table 2).

This thesis represents the culmination of independent work conducted by the candidate, with significant intellectual and practical contributions at every stage of the research process. Across the six articles forming the core of this thesis, the candidate played a leading role in conceptualising, designing, and executing each study, ensuring a cohesive and impactful body of work.

The candidate independently conceived the research objectives for all six studies, guided by a deep understanding of the public health challenges posed by Ebola Virus Disease (EVD) and related epidemics. These objectives were strategically aligned to address critical gaps in the literature and to generate actionable insights for epidemic preparedness and response. For each study, the candidate designed the methodologies, collected and analysed data, and interpreted findings with minimal external direction. This reflects a high degree of autonomy and expertise in navigating complex public health challenges.

As the corresponding author for all six articles, the candidate bore primary responsibility for drafting, revising, and finalising the manuscripts for submission. This involved synthesising input from co-authors while maintaining intellectual leadership throughout the process. The candidate ensured that each article met the highest standards of academic rigour, contributing significantly to the dissemination of findings in peer-reviewed journals.

For the first article, evaluating the Early Warning, Alert, and Response System (EWARS) in the Democratic Republic of Congo (DRC), the candidate independently designed the study and analysed its sensitivity, specificity, and predictive values. Similarly, in the second article, the candidate integrated epidemiological and genomic investigations to elucidate transmission dynamics during the final cluster of the 2018–2020 EVD outbreak. Both studies required advanced analytical skills and a nuanced understanding of outbreak management, demonstrating the candidate's capacity to lead cutting-edge research.

In subsequent articles, the candidate extended his focus to community-based strategies, contact tracing, and preparedness. The third article's investigation of community isolation strategies

was entirely conceptualised and executed by the candidate, highlighting the importance of participatory approaches in outbreak response. Likewise, the fourth article's identification of factors affecting contact tracing reliability relied on the candidate's ability to derive practical insights from complex epidemiological data. The fifth and sixth articles further emphasised the candidate's expertise in applying these findings to broader health systems, including addressing coinfections and evaluating health system reforms in Guinea.

This body of work reflects the candidate's independent contributions as a researcher and practitioner. The studies were designed to complement one another, creating a comprehensive thesis that advances the field of epidemic preparedness and response. Each article stands as a testament to the candidate's intellectual autonomy, methodological precision, and commitment to addressing critical public health challenges in resource-constrained settings.

Table 2: Articles in this thesis addressing each research objective, and the candidate's contribution to each

Research objective	Associated article	Candidate contribution
1. To evaluate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of a decentralised early warning alert system in controlling Ebola epidemics	The findings are presented in the first article of this thesis: <i>Evaluation of Early Warning, Alert and Response System for Ebola Virus Disease, Democratic Republic of the Congo, 2018–2020</i> (Chapter 2.4.1, page 3530).	I conceived and designed the study; collected, analysed, and interpreted the data; wrote the first draft; incorporated co-authors' suggestions; and prepared the final version for submission. I served as the corresponding author.
2. To integrate epidemiological and genomic investigations to better understand the origins and dynamics of transmission during epidemics	The results are detailed in the second article of this thesis: <i>Investigation of and Strategies to Control the Final Cluster of the 2018–2020 Ebola Virus Disease Outbreak in the Eastern Democratic Republic of Congo</i> (Chapter 2.4.2, page 47).	I conceived and designed the study; collected, analysed, and interpreted the data; wrote the first draft; incorporated co-authors' suggestions; and prepared the final version for submission. I served as the corresponding author.
3. To provide evidence for the effectiveness of a community-based contact isolation strategy, centred on the participation of contacts and community engagement, as a potential approach for future outbreaks to rapidly mitigate onward transmission	These findings are reported in the third article of this thesis: <i>A Community-Based Contact Isolation Strategy to Reduce the Spread of Ebola Virus Disease: An Analysis of the 2018–2020 Outbreak in the Democratic Republic of the Congo</i> (Chapter 2.4.3, page 64).	I conceived and designed the study; collected, analysed, and interpreted the data; wrote the first draft; incorporated co-authors' suggestions; and prepared the final version for submission. I was responsible for the overall content as guarantor and served as the corresponding author.
4. To identify factors associated with the reliability of 21-day follow-up among listed contacts, to inform and improve contact tracing efforts in future outbreak responses in similar contexts	The findings are presented in the fourth article of this thesis: <i>Factors Associated with Reliable Contact Tracing During the 2021 Ebola Virus Disease Outbreak in Guinea</i> (Chapter 2.4.4, page 63).	I conceived and designed the study; collected, analysed, and interpreted the data; wrote the first draft; incorporated co-authors' suggestions; and prepared the final version for submission. I was responsible for the overall content as guarantor and served as the corresponding author.

Research objective	Associated article	Candidate contribution
<p>5. To assess the feasibility and acceptance of applying community contact isolation and decentralised early warning system strategies in comparable outbreak scenarios</p>	<p>These findings are reported in the third article of this thesis: <i>A Community-Based Contact Isolation Strategy to Reduce the Spread of Ebola Virus Disease: An Analysis of the 2018–2020 Outbreak in the Democratic Republic of the Congo</i> (Chapter 2.4.3, page 64).</p> <p>And in this case report, the fifth article: <i>Case Report: COVID-19 and Lassa Fever Coinfection in an Ebola-Suspected Patient in Guinea</i> (Chapter 2.4.5, page 75); and</p>	<p>I conceived and designed the study; collected, analysed, and interpreted the data; wrote the first draft; incorporated co-authors' suggestions; and prepared the final version for submission. I was responsible for the overall content as guarantor and served as the corresponding author.</p> <p>I wrote the first draft; incorporated co-authors' suggestions; and prepared the final version for submission. I served as the corresponding author.</p>
<p>6. To investigate how investment in preparedness capacities (IHR core capacities) will affect and contribute to the response to an Ebola epidemic.</p>	<p>These findings are reported in the sixth article of this thesis: <i>Investing in Preparedness for Rapid Detection and Control of Epidemics: Analysis of Health System Reforms and Their Effect on the 2021 Ebola Virus Disease Epidemic Response in Guinea</i> (Chapter 2.4.6, page 79).</p>	<p>I conceived and designed the study; collected, analysed, and interpreted the data; wrote the first draft; incorporated co-authors' suggestions; and prepared the final version for submission. I served as the corresponding author.</p>

2.2 | Site selection

This thesis was conducted in two countries that experienced the largest Ebola epidemics in history: Guinea and the Democratic Republic of Congo (DRC). My involvement in the response to these and subsequent outbreaks was substantial. Serving as Senior Field Coordinator, Deputy Incident Manager, and Incident Manager for the World Health Organization (WHO) across various locations, I contributed significantly to the operational management of these emergencies. These roles allowed me to initiate and implement innovative approaches, which are detailed in this thesis and were integral to the response efforts.

The thesis is based on field data that my team and I were directly involved in collecting, ensuring its relevance to real-world conditions and its direct application to outbreak response.

The research focused on districts that had experienced Ebola outbreaks and where innovative strategies were implemented to accelerate epidemic control. These included the provinces of North Kivu (Beni and Mabalako Health Zones) and Equateur (Ingende, Bomongo, Lolanga Mampoko, Lotumbe, and Bikoro Health Zones) in the DRC (Figure 6), as well as the prefecture of Nzérékoré in Guinea (Figure 7).

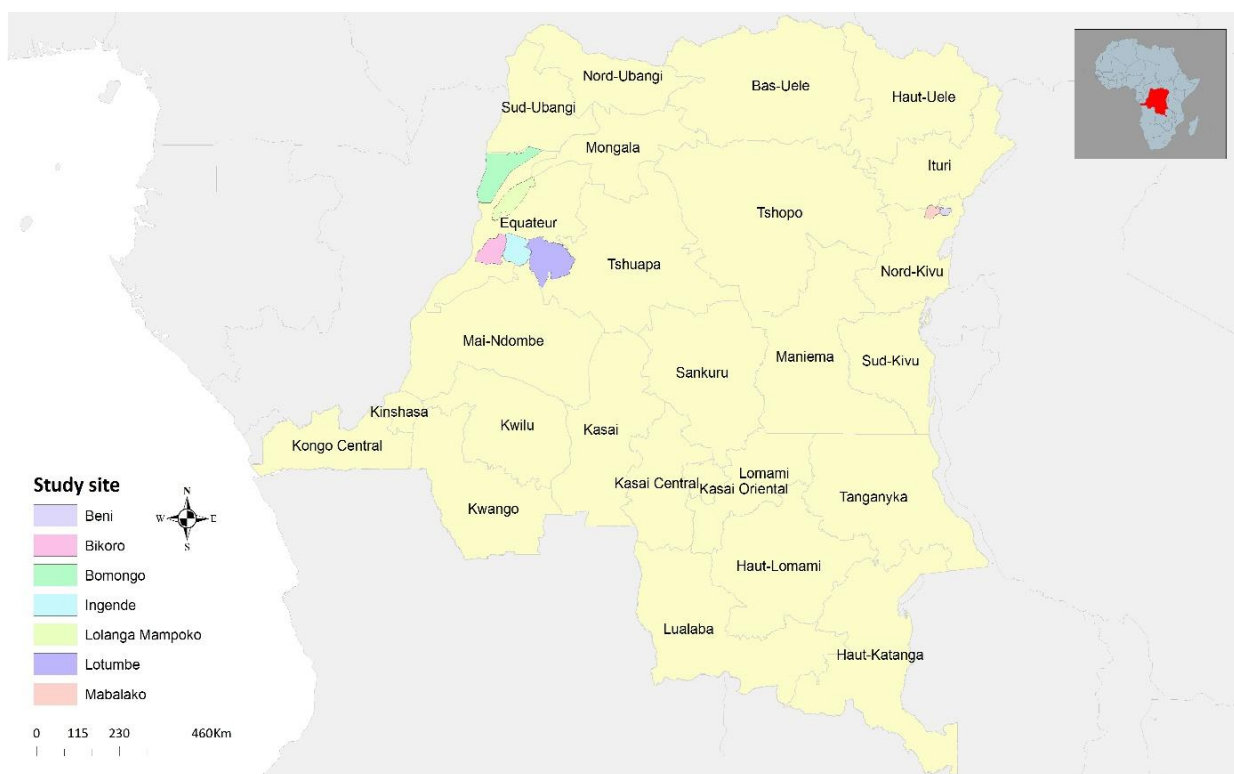


Figure 6: Study sites map in the Democratic Republic of Congo (Source: author)



Figure 7: Study sites map in Guinea (Source: author)

2.3 | Ethics

To support this work, I designed a research protocol that was reviewed and approved by the ethics committees in both countries (under reference numbers ESP/CE/03/2021 and 017/CNERS/21 respectively for the DRC and Guinea). All research was conducted in accordance with best practice.

2.4 | Chapter articles

Six peer-reviewed academic journal articles are now presented, comprising the main body of this PhD thesis, as indicated in Table 2 (page 32).

Evaluation of Early Warning, Alert and Response System for Ebola Virus Disease, Democratic Republic of the Congo, 2018–2020

Mory Keita, Héloïse Lucaccioni, Michel Kalongo Ilumbulumbu, Jonathan Polonsky, Justus Nsio-Mbeta, Gaston Tshapenda Panda, Pierre Celeste Adikey, John Kombe Ngwama, Michel Kasereka Tosalisana, Boubacar Diallo, Lorenzo Subissi, Adama Dakissaga, Iris Finci, Maria Moitinho de Almeida, Debarati Guha-Sapir, Ambrose Talisuna, Alexandre Delamou, Stephanie Dagron, Olivia Keiser, Steve Ahuka-Mundeke

The 10th and largest Ebola virus disease epidemic in the Democratic Republic of the Congo (DRC) was declared in North Kivu Province in August 2018 and ended in June 2020. We describe and evaluate an Early Warning, Alert and Response System (EWARS) implemented in the Beni health zone of DRC during August 5, 2018–June 30, 2020. During this period, 194,768 alerts were received, of which 30,728 (15.8%) were validated as suspected cases. From these, 801 confirmed and 3 probable cases

were detected. EWARS showed an overall good performance: sensitivity and specificity >80%, nearly all (97%) of alerts investigated within 2 hours of notification, and good demographic representativeness. The average cost of the system was US \$438/case detected and US \$1.8/alert received. The system was stable, despite occasional disruptions caused by political insecurity. Our results demonstrate that EWARS was a cost-effective component of the Ebola surveillance strategy in this setting.

Early case detection is important to control and prevent infectious disease outbreaks (1). The 5 identified purposes for early detection surveillance

are detecting the first case of the disease in a population previously free, detecting new cases in an area already infected, early detection of an abnormal increase in the level of a disease normally present at a base level, screening for individual cases of noncommunicable diseases, and the first detection of an invasive species in an area previously free of that species (2). The International Health Regulations (2005) (3) impose obligation on countries to develop, strengthen, and maintain their capacities to detect, verify, assess, report, and respond to any events that may constitute a public health risk and thereby prevent international spread. Public health surveillance systems are poorly developed in many low-income and middle-income countries, as demonstrated by recent Ebola outbreaks, which had devastating consequences in the health and economy of several countries (4–7).

Ebola virus disease (EVD), if not detected and reported early, can rapidly spread and result in high rates of illness and death (8,9). In recent years, the world has faced the 2 largest EVD epidemics in recorded history, both of which were declared public health emergencies of international

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DOI: <https://doi.org/10.3201/eid2712.210290>

concern by the director-general of the World Health Organization (WHO).

EVD case definitions are crucial surveillance tools, both for referring suspected cases and as screening tools to aid admission and laboratory testing decisions at health facilities (10). WHO has developed standard case definitions for alert, suspected, probable, and confirmed cases in the context of routine and community-based surveillance (11,12) (Appendix Table, <https://wwwnc.cdc.gov/EID/article/27/12/21-0290-App1.pdf>).

Insufficient command of these case definitions at the community and health-facility level has resulted in late detection of EVD outbreaks. For instance, recent epidemics in both West Africa and the Democratic Republic of the Congo (DRC) were officially declared 3 months after the effective start of the epidemics (13,14). The epidemic in DRC was the second largest EVD outbreak ever documented after the West Africa EVD epidemic (2013–2016); a total of 3,481 cases (3,323 confirmed and 158 probable) and 2,299 deaths were recorded in August 2018–June 2020 in North Kivu, Ituri, and South Kivu Provinces. This outbreak was particularly complex because it occurred in an active conflict zone (15). Public health performance indicators at the beginning of this EVD response were poor, including many community deaths, poor contact tracing, and delays between symptom onset and case isolation. A decline in incidence toward the end of 2019 was thought to be the result of improvement in the quality of surveillance activities, including prompt investigation, early detection and isolation of cases, enhanced community-based surveillance, rapid follow-up of high-risk contacts, and an adaptive vaccination strategy (16).

Soon after the declaration of the 10th EVD outbreak in the DRC, an Early Warning, Alert and Response System (EWARS) was implemented throughout North Kivu and Ituri Provinces, to report, collect, investigate, validate, and take early action (isolation, safe burial, or referral) on alerts that met the suspected case definition for EVD. We describe and evaluate this system as implemented in the subcoordination of Beni, established to manage the response across several health zones.

Methods

Description of the EWARS

The Alert Unit was the core functional unit around which the EWARS was organized (Figure 1); it was composed of an overall operational leader who coordinated activities, a database and information

administrator, a case management leader, a Safe and Dignified Burial (SDB) leader, 3 telephone operators, 1 alert monitoring officer, 1 database manager, 1 data clerk, and 1 archivist. The main role of the Alert Unit was to gather and scan alerts from various sources, coordinate the field investigations with the rapid intervention teams, and, if relevant, organize the referral and ambulance transfer or safe burial in collaboration with the case management or SDB team. All alerts and their outcomes were entered and archived into paper-based alert and investigation forms and a Microsoft Excel database (<https://www.microsoft.com>). There were 4 main sources of alerts: community, in which community health workers, community members, and political and administrative authorities raised alerts; active case finding conducted in health facilities and other structures (pharmacies, churches, traditional practitioners); surveillance sites, including contact tracing teams, vaccination sites, and points of entry/points of control (PoE/PoC); and finally, public and private health facilities that ensured passive reporting.

Two toll-free numbers were activated on August 26, 2018, to enable rapid and easy alert reporting from all the sources. Calls were directed to telephone operators in the Alert Unit, which was operational 24 hours per day, 7 days per week; a smaller team for night shifts comprised the operations leader and phone managers only. In active case finding, passive reporting, or PoE/PoC, the alert notifier completed an alert form, or for community and contact tracing alerts, the telephone operator or alert monitoring officer completed the form. When telephone operators received the alerts, they checked for duplication and conducted preliminary triage to prioritize them by epidemiologic and clinical factors. Rapid intervention teams were then notified to investigate the alert onsite.

Rapid intervention teams were made up of a field epidemiologist, an infection prevention and control (IPC) officer, a communication officer, and a psychosocial worker. All these response pillars were positioned in each health area covered by the alert system, from which a senior epidemiologist would organize rapid intervention teams. The investigation consisted of a detailed history, assessment of the epidemiologic link, clinical symptoms for validation against the suspected case definition (17), and initial listing of contacts. Investigation forms were stored in the Alert Unit, and copies were sent to Ebola treatment centers (ETC) for patients requiring admission. The rapid intervention team validated or invalidated the alert on

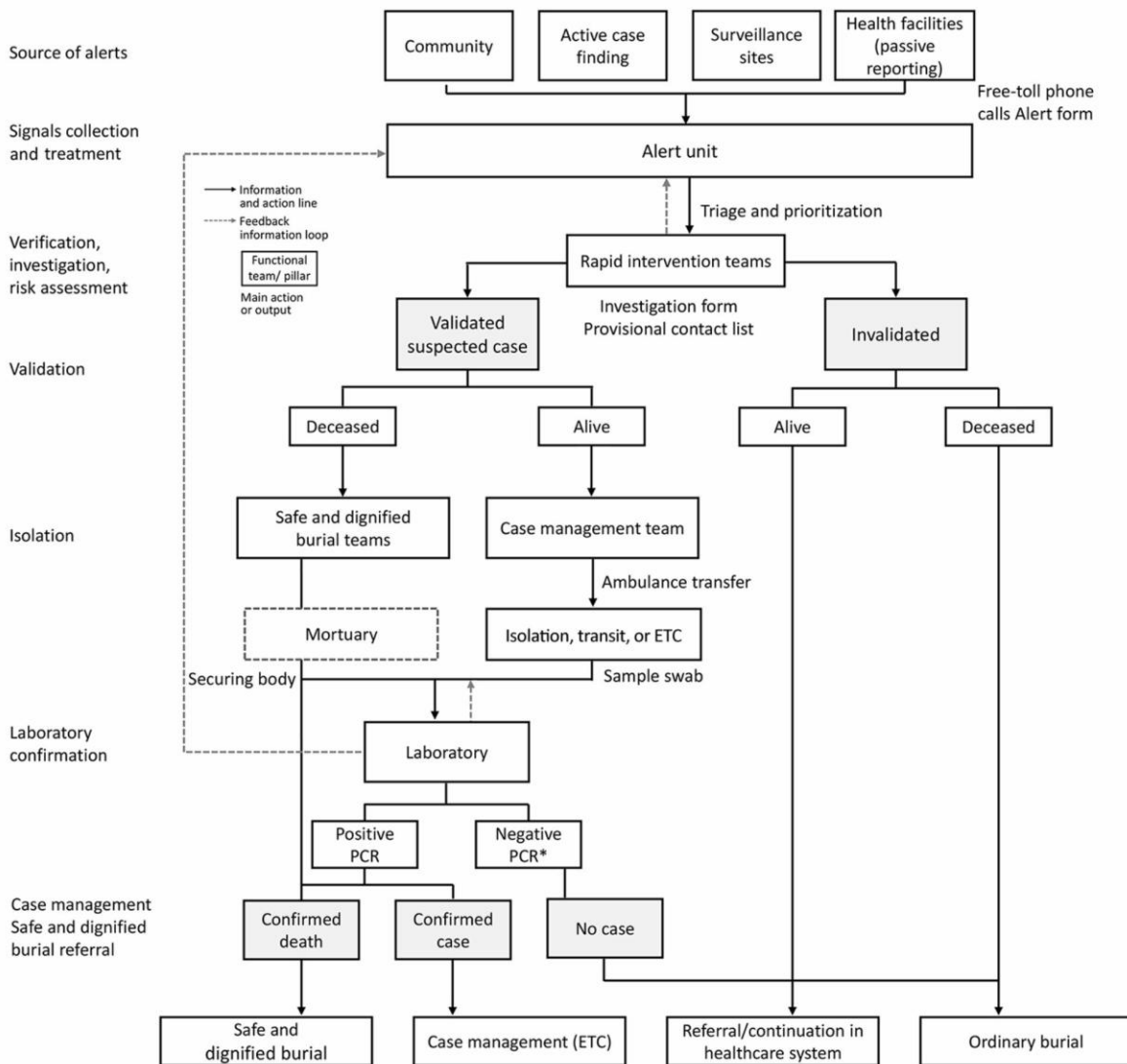


Figure 1. Organization of the Early Warning, Alert and Response System as used in the Democratic Republic of the Congo, August 2018–June 2020. Asterisk (*) indicates 1 negative result for a deceased suspected case-patient or 2 negative results within 72 hours for an alive suspected case-patient. ETC, Ebola treatment center.

the basis of the investigation findings and provided immediate feedback to the Alert Unit contact persons, who coordinated the next steps.

For invalidated alerts, the family can proceed with ordinary burial of deceased patients, whereas living patients were referred to public healthcare facilities for free healthcare. Living patients with validated alerts were immediately transferred to a transit center, isolation center, or ETC, depending on the patient’s condition and location. There was no additional validation at triage in ETC. To reduce

the risk that a transfer would refuse a patient, the intervention team would propose 2 options according to patient condition and preference: transfer the patient by ambulance or by motorcycles driven by Ebola survivors. After admission to the isolation center, patients followed the suspected case management algorithm: blood samples were taken and tested by using GeneXpert (Cepheid, <https://www.cephid.com>) within 3 hours after admission. Cases confirmed by PCR were immediately admitted to an ETC for treatment. Those patients with an

initial negative test were discharged pending a second negative result 72 hours later.

The SDB team were notified of validated alerts of deceased patients, then joined the rapid intervention team onsite to engage with the family. The body was secured and a swab sample taken and sent to the laboratory for testing. With family consent, SDB proceeded immediately. However, if the family refused, the body was kept at the mortuary until the laboratory result was available. If the result was negative, the body was returned to the family to proceed with ordinary burial; if the results was positive, SDB was mandatory and enforced by authorities.

Evaluation Approach and Data Sources and Indicators

We conducted a quantitative evaluation according to guidelines published by WHO (18) and the US Centers for Disease Control and Prevention (CDC) (19). We used the anonymized Alert Unit database, covering the health zones of Beni, Mutwanga, and Oicha, during August 5, 2018–June 30, 2020, to assess EWARS using the EVD suspected case definition as the standard. An alert was considered validated if it met the definition of an alert case by community-based surveillance or the definition of a suspected case by mobile teams or health stations or centers (12). An investigator would validate a suspected case on the evidence of clinical signs in the patient (Appendix Figure).

To assess the true sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) would require laboratory testing for all patients, which would not have been feasible. We calculated sensitivity as the proportion of alerts validated among all alerts meeting the suspected case definition, specificity as the proportion of invalidated alerts among all alerts not meeting the suspected case definition, PPV as the proportion of alerts that met the suspected case definition among all validated alerts, and NPV as the proportion of alerts that did not meet the suspected case definition among all invalidated alerts. We assessed timeliness as the median, range, and interquartile range (IQR) of the delay between the transmission of alert to the Alert Unit and the start of the onsite investigation. We evaluated representativeness through the geographic and demographic coverage of the alerts by comparing alert incidence by sex, age group, and health zone. We appraised usefulness by considering the number of confirmed and probable cases that were detected through the alert system. Finally, we assessed stability by

considering how the system was operating over time, disruptions, and sustainability of functioning beyond the emergency response phase, notably in relation with costs and human resources. We conducted all analyses using R statistical software version 4.0.3 (20).

Results

Outcomes of EWARS

During the study period, 195,601 alerts were received; 194,768 (99.6%) from the health zones of Beni, Mutwanga, and Oicha, and 833 (0.4%) from other health zones (Figure 2). A small number (52,240, 2.7%) were reports of community deaths.

On average, there were 280 alerts/day (range 2–955, median 127 alerts/day), although this value greatly varied over time. The number of daily alerts increased progressively, from 6 at the outset in August 2018 to a peak of 922 at the beginning of March 2020. We observed multiple sudden, short-lived decreases in the daily number of alerts, particularly in mid-November 2019 and early April 2020, coinciding with security incidents (see Stability) (Figure 3).

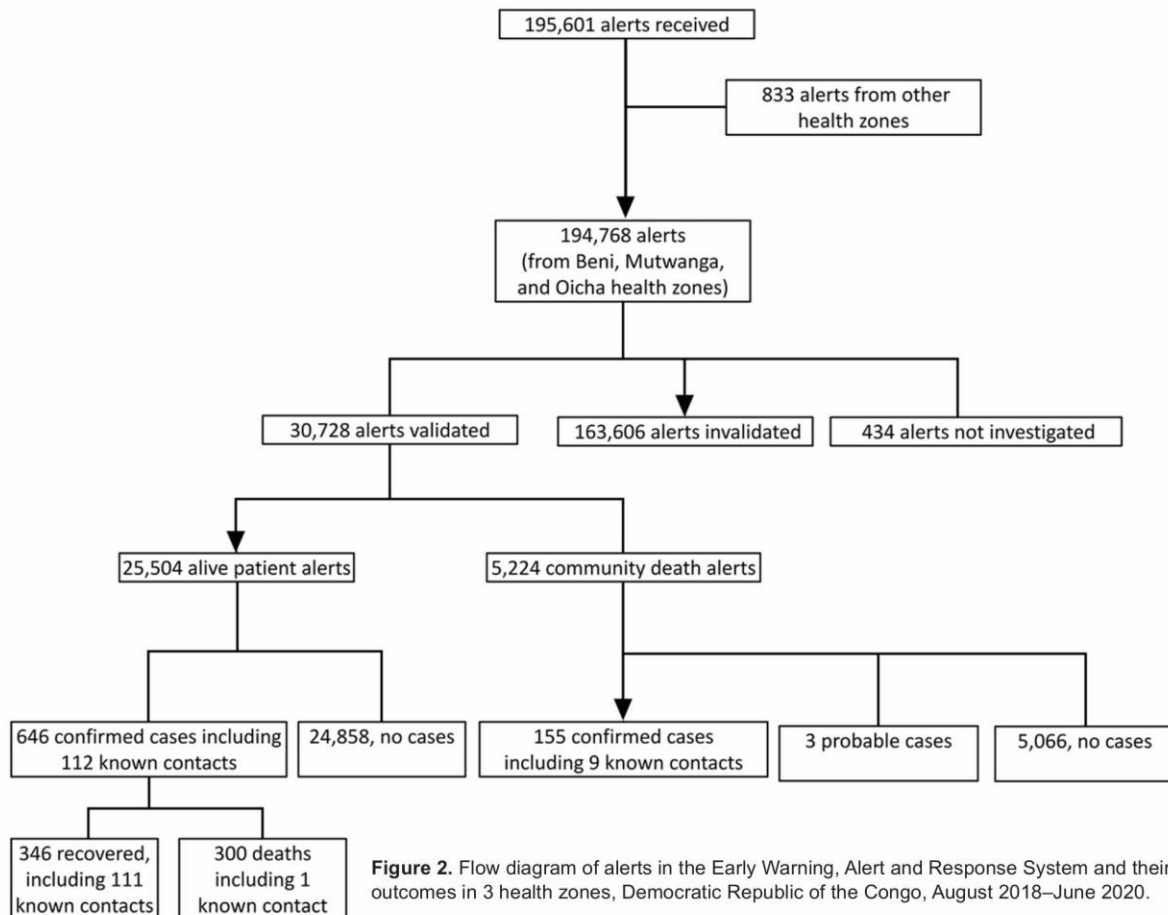
A total of 30,728 (15.8%) alerts were validated as suspected cases. Among those, 801 (2.6%) were finally classified as confirmed cases and 3 (<0.1%) as probable cases. No invalidated alerts became confirmed cases; the information recorded the first time remains in the database, and a new alert with the same information could be quickly detected.

Most (62.6%) alerts were raised by active case finding teams, followed by passive reporting from health facilities (19.0%), and community alerts (15.0%). The remainder (3.6%) originated from other sources (Table 1).

Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value

We excluded 434 alerts (0.2%) that were not investigated and 201 alerts (0.1%; 197 invalidated and 4 validated) that could not be classified according to the case definition because of missing data. A total of 17,927 (9.2%) alerts met the EVD suspected case definition. Sensitivity was 84.6% (95% CI 84.1%–85.1%) and specificity 91.2% (95% CI 91.0%–91.3%). PPV was 49.4% (95% CI 48.8%–49.9%) and NPV 98.3% (95% CI 98.2%–98.4%) (Table 2).

Indicators varied with time, health zone, and source of notification (Table 3). Overall, sensitivity increased over time, and specificity remained high throughout the study period. PPV decreased while NPV increased, which is consistent with the outbreak



dynamics and the decrease in incidence toward the end of the epidemic (Appendix Figure).

Sensitivity was higher for alerts arising from surveillance sites (98.0%, 95% CI 97.4%–98.7%), community alerts (91.4%, 95% CI 90.1%–92.7%), and active case finding (87.5%, 95% CI 86.9%–88.1%) and lower for those arising from passive reporting from health facilities (65.4%, 95% CI 63.8%–67.0%). Conversely, specificity was highest in health facilities (96.2%, 95% CI 96.0%–96.4%), and was high (>90%) for all other sources except surveillance sites. Sensitivity was higher in Beni (94.8%, 95% CI 94.4%–95.2%) than in Mutwanga (54.9%, 95% CI 52.4%–57.3%) and Oicha (64.3%, 95% CI 62.8%–65.8%), but specificity was higher in Mutwanga (96.4%, 95% CI 96%–96.7%) and Oicha (93.3%, 95% CI 92.8–93.8).

Timeliness

An investigation was initiated within 2 hours from the time of alert for 188,184 (96.6%) alerts. The

median time from alert transmission to the arrival of the investigation team on site was 11 minutes (IQR 10–15 minutes). Information about the time of investigation was not available for 3,475 (1.8%) alerts.

Timeliness of responses varied over time; substantial delays were observed at the outset of the system implementation, with greatest delays in Mutwanga (Figure 4). We saw no marked difference in timeliness by source of notification.

Representativeness

We observed substantial variations in the alert incidence between the health zones. On average, there were 241 (range 2–789) alerts/day in Beni, 42.3 (range 1–181) alerts/day in Mutwanga, and 25.4 (range 1–138) alerts/day in Oicha. The alert incidence in the population followed a similar pattern: an average of 36 alerts/1,000 inhabitants/week in Beni, 2.5 alerts/1,000 inhabitants/week in Oicha, and 2.4 alerts/1,000 inhabitants/week in Mutwanga. In Beni,

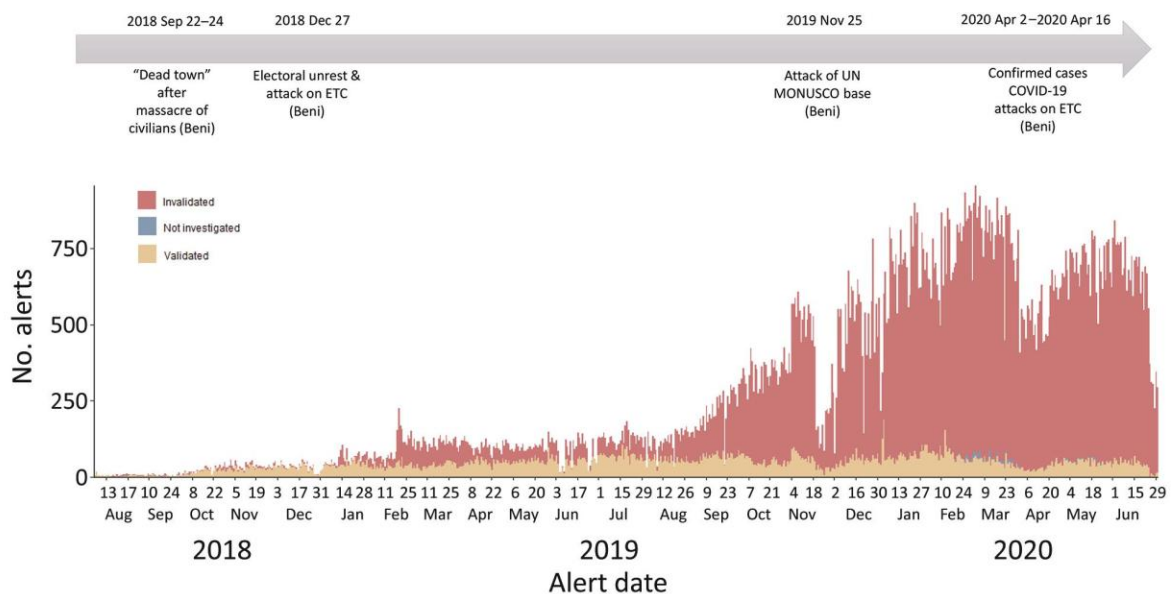


Figure 3. Trend in daily number of alerts from the Early Warning, Alert and Response System by final validation status in 3 health zones, Democratic Republic of the Congo, August 2018–June 2020. Key security incidents during the epidemic period are depicted along the timeline above the graphic. MONUSCO is the name of the UN peacekeeping force in the country. ETC, Ebola treatment center.

the incidence of alerts increased progressively from the outset (Figure 5). However, in Mutwanga and Oicha, incidence remained low until the beginning of November 2019, when it rapidly increased following community transmission.

We observed more alerts among female (56.3%) than male (43.4%) patients. Children <5 years of age were the most represented (23.6%), followed by patients 20–29 years of age (18.9%) and 10–19 years of age (18.9%); these percentages approximate the age and sex breakdown of the local population, with the exception of children 5–9 years of age, who were underrepresented (11%).

Usefulness and Cost

The EWARS system led to the detection of 801 confirmed and 3 probable cases, which equates to 242 alerts notified and 38 alerts validated for each case detected by the system. The total direct and indirect costs associated with EWARS implementation and maintenance was US \$353,525 over the 2-year period of operation (Table 4), yielding a minimum value of US \$1.8/alert and US \$438/case detected.

Stability

The alert system operated 24 hours per day, 7 days per week, including a minimal night team to ensure continuity. Continuous communication and reporting

of alerts was possible by a comprehensive and stable mobile phone coverage covering all health areas. As such, alerts were collected and analyzed on a continuous basis, and reports were produced and distributed daily. However, despite the continuous availability of human resources and communication networks, the system was severely disrupted by security incidents. Security incidents coincided with decreases in the number of alerts, affecting both the reporting and investigation of alerts (Figure 3). The Alert Unit ceased operations following the standard 90-day period of heightened surveillance after the declaration of the end of the outbreak, as determined by WHO (21).

Discussion

During August 2018–June 2020, EWARS led to the notification and investigation of 194,768 alerts and the detection of 801 confirmed and 3 probable EVD cases. The evaluation showed an overall good performance of the system regarding the main attributes we assessed, highlighting the many strengths of such a system. However, it also revealed disparities in performance between the health zones covered by the system, reflecting differences in the timing of implementation and, most notably, unequal operating conditions (e.g., security incidents).

This system encompassed both event-based and indicator-based surveillance (22,23), resulting

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Table 1. Characteristics of Ebola virus disease alerts received in Beni subcoordination, Democratic Republic of the Congo, August 5, 2018–June 30, 2020

Characteristic	No. (%) alerts, n = 194,768
Year	
2018	3,211 (1.6)
2019	67,579 (34.7)
2020	123,978 (63.7)
Final alert status	
Invalidated	163,606 (84.0)
Validated	30,728 (15.8)
Not investigated	434 (0.2)
Alert initial status	
Deceased	5,230 (2.7)
Alive	189,538 (97)
Final case classification	
Not a case	193,964 (99.6)
Confirmed case	801 (0.4)
Probable	3 (<0.1)
Source of alert	
Active case finding	121,970 (62.6)
Health structure	36,911 (19.0)
Community	28,928 (15.0)
Other surveillance sites	6,959 (3.6)
Health zone	
Beni	167,503 (86.0)
Mutwanga	12,891 (6.6)
Oicha	14,374 (7.4)
Sex	
F	109,605 (56.3)
M	84,442 (43.4)
Unknown	721 (0.4)
Age group	
0–4	45,934 (23.6)
5–9	22,220 (11.4)
10–19	36,825 (18.9)
20–29	37,945 (19.5)
30–39	21,975 (11.3)
40–49	11,186 (5.7)
50–59	6,668 (3.4)
≥60	8,679 (4.5)
Unknown	3,336 (1.7)
Known contact of confirmed or probable case	
No	194,052 (99.6)
Yes	672 (0.3)
Unknown	44 (0.1)

in 7.8% of alerts meeting the definition of EVD suspected case, 4-fold higher than the event-based surveillance system at the community level during the Ebola outbreak in Sierra Leone in 2014–2016, and a 6-fold higher 49.4% PPV (24). Approximately 92% of our alerts did not meet the suspected case definition because of a time lag of days between symptom

onset, on which the alert launch was based, and the symptoms that were actually present in these patients during investigation.

Although the overall proportion of detected cases among alerts was low (0.4% of all alerts), EWARS aimed to be highly sensitive; actions taken around those confirmed cases successfully interrupted transmission chains and prevented further spread of the disease. Indeed, the system showed a high sensitivity and specificity (>80%) and a low PPV, which reflects the low EVD incidence in the population. All health areas covered by the system reported alerts that did not differ greatly from the population structure, thus suggesting a good demographic representativeness. The system presented prompt timeliness of investigation of alerts throughout its 2 years of operation. Finally, the minimum cost per alert or cases was relatively low compared with that for a nationwide telephone alert system established for rapid notification and response during the 2014–2015 Ebola disease epidemic in Sierra Leone (25).

This good performance of EWARS can be explained by the intensive, comprehensive, and continuous reporting flow. First, the system relied on the use of various sources of alerts, involving both passive and active case reporting from the community, health structures, and other surveillance sites. Second, it built upon a stable and extensive telephone network further supported by toll-free numbers, a means of communication that is easily accessible, acceptable, and already commonly used by all stakeholders involved in surveillance. Third, it adopted a decentralized approach for the organization of the investigation teams, which enabled comprehensive coverage of all health areas and prompt reactivity for early action. The existence of a dedicated team at the subcoordination level further supported the coordination of activities at the local level while aiding in the centralization and consolidation of the information circuit. The unceasing availability of all key actors of the reporting system (surveillance, investigation teams, alert unit, and case management/SDB) ensured the continuous reporting and actions around alerts in timely manner. How fast a system detects and responds effectively

Table 2. Evaluation results and overall characteristics of Ebola virus disease alerts from EWARS, Democratic Republic of the Congo, August 5, 2018–June 30, 2020*0

Alert system	Suspected case definition		Total	% (95% CI)			
	No. met	No. unmet		Sensitivity	Specificity	PPV	NPV
Validated	15,163	15,561	30,724				
Invalidated	2,764	160,645	163,409				
Total	15,245	184,104	194,133	84.6 (84.1–85.1)	91.2 (91.0–91.3)	49.4 (48.8–49.9)	98.3 (98.2–98.4)

*Total excludes 434 (0.2%) alerts that were not investigated and 201 (0.1%) alerts that could not be classified according to the case definition due to missing data. EWARS, Early Warning, Alert and Response System; NPV, negative predictive value; PPV, positive predictive value.

Table 3. Evaluation of EWARS alerts by source of Ebola virus disease alert and health zone, Democratic Republic of the Congo, August 5, 2018–June 30, 2020

Category	% (95% CI)			
	Sensitivity	Specificity	PPV	NPV
Source of alert				
Active case finding/IPC	87.5 (86.9–88.1)	91.7 (91.6–91.9)	51.2 (50.4–51.9)	98.7 (98.6–98.7)
Community	91.4 (90.1–92.7)	93.6 (93.3–93.9)	48.3 (46.6–50.0)	99.4 (99.3–99.5)
Health facility	65.4 (63.8–67.0)	96.2 (96.0–96.4)	64.5 (62.9–66.1)	96.4 (96.2–96.6)
Other surveillance sites	98.0 (97.4–98.7)	34.3 (33.0–35.6)	33.0 (31.7–34.2)	98.1 (97.5–98.8)
Health zone				
Beni	94.8 (94.4–95.2)	90.6 (90.5–90.8)	44.9 (44.3–45.5)	99.5 (99.5–99.6)
Mutwanga	54.9 (52.4–57.3)	96.4 (96–96.7)	68.2 (65.7–70.8)	93.8 (93.3–94.2)
Oicha	64.3 (62.8–65.8)	93.3 (92.8–93.8)	78.6 (77.2–80.1)	87.2 (86.6–87.9)

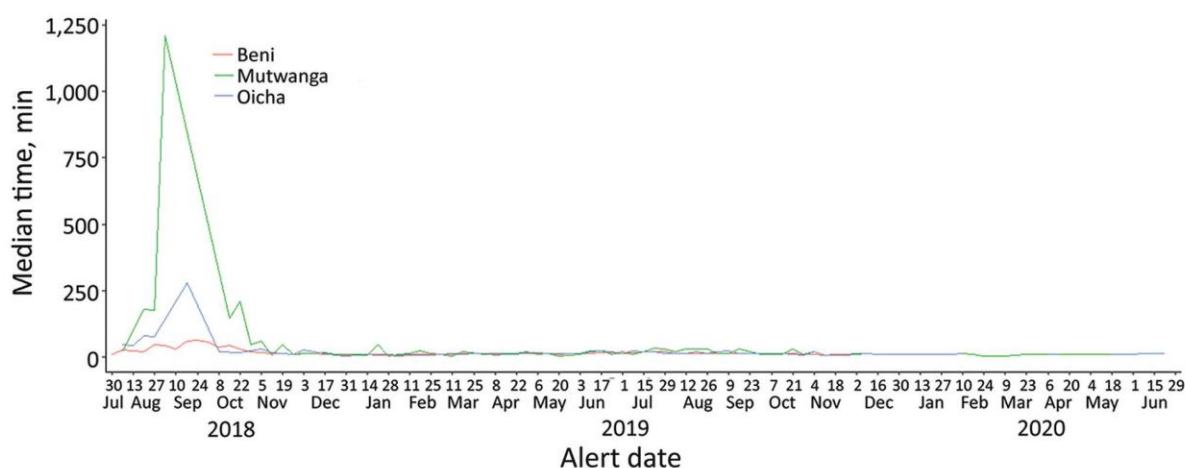
*EWARS, Early Warning, Alert and Response System; IPC, Infection Prevention and Control; NPV, negative predictive value; PPV, positive predictive value.

to a threat is the optimal measure of performance. Continuously evaluating and improving timeliness can identify performance bottlenecks and help to accelerate progress, improving detection speed and response quality (26).

The alert system performed better in Beni for all attributes we studied. In Mutwanga and Oicha, sensitivity was <80%, alert incidence was low (even after an increase in the number of daily alerts in late 2019), geographic coverage appeared less comprehensive as many health areas reported few alerts, and delays in investigation were longer, particularly at the outset. Mutwanga and Oicha are 2 rural health zones located at the epicenter of nonstate armed groups' territories, which greatly affected the operations. Surveillance and investigation activities faced regular security incidents and restrictions, long distances to alert sites, and poor road networks in many health areas. In this context, the alert system was initially implemented in Beni and progressively extended and strengthened in Mutwanga and Oicha. For example, in the early

phase, rapid intervention teams were staffed in the Beni subcoordination office only, such that alert investigations in Mutwanga and Oicha suffered longer delays. Surveillance and reporting capacities were also weaker in Mutwanga and Oicha. In November 2019, a training of response personnel (registered nurses, supervisors, and investigators) was organized to address the low incidence of alerts; to strengthen data management capacities, data managers were deployed, leading to a rapid increase in alerts from these health zones.

Despite the effects of security incidents, the EWARS continued to operate throughout the whole period, managing an increasing volume of alerts, leading to the detection of hundreds of cases. In a context of limited surveillance capacities and weak health systems, such an intensive and steadily reporting alert system was vital for the early detection of cases and interruption of the spread of the disease in the population. However, the system was conceived and implemented in an ad hoc manner within the frame-

**Figure 4.** Timeliness over time of alerts from the Early Warning, Alert and Response System, Democratic Republic of the Congo, August 2018–June 2020. Timeliness is defined as weekly median time (in minutes) from alert transmission to the start of the investigation.

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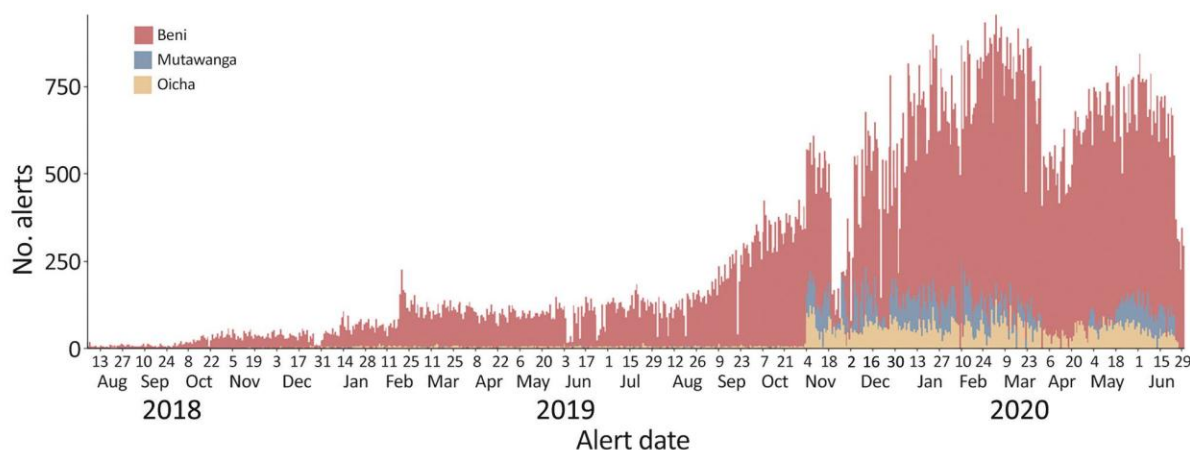


Figure 5. Trend in daily number of alerts in the Early Warning, Alert and Response System in 3 health zones in the Democratic Republic of the Congo, August 2018–June 2020.

work of the Ebola outbreak response, which limited its sustainability beyond the resources and time period of the outbreak response. The financial, logistical, and human resources needed to implement and maintain the system were made possible by dedicated response funds and the time-bound engagement of both national support teams and international financial and technical partners. The EWARS ceased operations within 12 weeks of the declared end of the outbreak. The long-term sustainability of systems such as EWARS remains unknown. An additional limitation was the challenge in assessing overall performance measures of the system, such as completeness, acceptability, and flexibility. We evaluated EWARS with regard to its objectives, but

we could not extrapolate the effects of the system on the overall outbreak dynamics.

In conclusion, the magnitude and duration of the 10th and largest Ebola outbreak in DRC, occurring in an active conflict zone, highlighted the need for prompt, functional, and effective infectious disease surveillance systems. We have demonstrated that the EWARS implemented was a cost-effective component of this surveillance system. Our findings underscore the importance of early-warning systems, along with the necessity of ensuring efficiency and sustainability beyond the duration of the emergency response phase. As such, Integrated Disease Surveillance and Response is a relevant framework to further strengthen the International Health Regulations (2005) core

Table 4. Costs for EWARS in Beni, Mutwanga, and Oicha, Democratic Republic of the Congo, August 2018–June 2020*

Health zone	Item	Implementation period costs, USD			Total cost, USD
		2018 Aug 5–Dec 31	2019 Jan 1– Dec 31	2020 Jan 1–Jun 30	
Beni	Prime staff for alerts management teams	6,000	25,200	12,600	43,800
	Prime staff for data managers	900	10,350	5,400	16,650
	Ambulance rental	6,000	72,000	36,000	114,000
	Fuel	9,600	36,000	18,000	63,600
	Purchase of telephones	175	NA	NA	175
	Purchase of materials†	5,500	12,000	6,000	23,500
	Communication credit	750	3,600	2,100	6,450
	Green numbers‡	15,200	15,200	NA	30,400
Oicha	Prime for alerts management teams	NA	12,150	6,300	18,450
	Prime for data managers	NA	5,400	2,700	8,100
	Communication credit	NA	1,200	600	1,800
Mutwanga	Prime for alerts management teams	NA	7,200	5,400	12,600
	Prime for data managers	NA	7,200	5,400	12,600
	Communication credit	NA	800	600	1,400
Total		44,125	208,300	101,100	353,525

*Expenditures included direct and indirect costs. EWARS, Early Warning, Alert and Response System; NA, not applicable.

†Flip charts, markers, printed forms.

‡Telephone numbers 0820800001 and 0999009405, which health workers and community members could use for no charge. WHO covered this expense.

capacities (27,28). The need to evaluate and learn from field implementation of surveillance systems in infectious disease outbreaks, even in such difficult contexts, is an opportunity to better understand response efforts and improve future responses (29).

Acknowledgments

We thank the alert unit team and all the actors who have been involved in the EWARS in Beni, Mutwanga, and Oicha, DRC.

About the Author

Dr. Keita is a medical doctor and public health specialist, currently working as technical officer for risk assessment with the WHO Regional Office for Africa. During the 10th EVD outbreak in DRC, he was deployed as senior field coordinator in Beni. His research interests include infectious diseases epidemiology, risk assessment, public health response in humanitarian and emergency settings, health systems strengthening, healthcare management, and global health policy.

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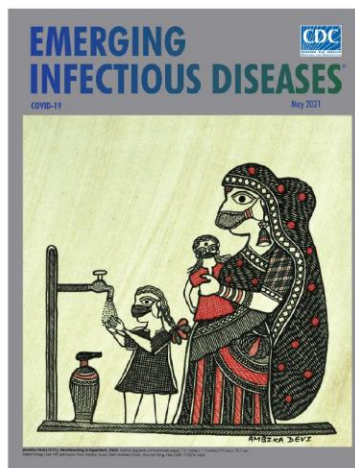
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- Coordinated Strategy for a Modeling-Based Decision Support Tool for COVID-19, Utah, USA
- Clinical Laboratory Perspective on Human Infections Caused by Unusual Nonhemolytic, Lancefield Group B *Streptococcus halichoeri*
- Case Series of Laboratory-Associated Zika Virus Disease, United States, 2016–2019
- Successful Control of an Onboard COVID-19 Outbreak Using the Cruise Ship as a Quarantine Facility, Western Australia
- Whole-Genome Sequencing of Shiga Toxin-Producing *Escherichia coli* OX18 from a Fatal Hemolytic Uremic Syndrome Case
- Coccidioidomycosis and COVID-19 Co-Infection, United States, 2020
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Investigation of and Strategies to Control the Final Cluster of the 2018–2020 Ebola Virus Disease Outbreak in the Eastern Democratic Republic of Congo

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Background. On April 10, 2020, while the independent committee of the International Health Regulation was meeting to decide whether the 10th Ebola outbreak in the Democratic Republic of Congo still constituted a Public Health Emergency of International Concern, a new confirmed case was reported in the city of Beni, the last epicenter of the epidemic. This study aimed to understand the source of this cluster and learn from the implemented control strategies for improved response in the future.

Methods. We conducted a combined epidemiological and genomic investigation to understand the origins and dynamics of transmission within this cluster and describe the strategy that successfully controlled the outbreak.

Results. Eight cases were identified as belonging to this final cluster. A total of 1028 contacts were identified. Whole-genome sequencing revealed that all cases belonged to the same cluster, the closest sequence to which was identified as a case from the Beni area with symptom onset in July 2019 and a difference of just 31 nucleotides. Outbreak control measures included community confinement of high-risk contacts.

Conclusions. This study illustrates the high risk of additional flare-ups in the period leading to the end-of-outbreak declaration and the importance of maintaining enhanced surveillance and confinement activities to rapidly control Ebola outbreaks.

Keywords. Ebola; outbreak; investigation; strategies to control.

The Ebola virus disease (EVD) outbreak that affected the Eastern Democratic Republic of Congo (DRC) between April 2018 and June 2020 was the second largest recorded EVD outbreak globally [1]. Although this was the 10th EVD outbreak in the DRC, it was the first in the Eastern DRC, an area that has experienced prolonged conflict and displacement for over 25 years. A total of 3481 confirmed and probable cases were detected, resulting in 2299 deaths and 1162 people surviving the disease (case fatality ratio [CFR], 66.0%; final outcome was missing for 20 cases) [2]. The epidemic started in the province of North Kivu and spread to Ituri province in the north and South Kivu in the south [3]. Due to the spread of EVD in

Goma, the provincial capital of North Kivu and Uganda, the outbreak was declared a public health emergency of international concern (PHEIC) in July 2019 [4]. North Kivu and Ituri are highly populated provinces that have been affected by persistent insecurity, with at least 420 attacks on health facilities recorded during the outbreak period [5]. Additionally, the mobility of the population, including tracing contacts of EVD cases, has posed a challenge to control the outbreak, leading to new outbreaks in areas that had previously successfully interrupted local chains of transmission [6].

Beni, a city in North Kivu of ~200 000 inhabitants, was the health zone most affected by the epidemic, with 737 cases, or 32% of all recorded EVD cases [7]. Its position at the crossroads between commercial hubs including Butembo and the nearby Ugandan border, the presence of the airport, and constant insecurity made it a challenging context for outbreak control [6]. The outbreak in Beni peaked in July 2019, after which it started to decrease, and Beni was the last health zone with recorded cases. After Beni's last confirmed case tested negative on March 2, 2020, the 42-day (twice the theoretical maximum EVD incubation period) countdown toward declaring the end of the epidemic started.

On April 10, 2020, while the independent committee of the International Health Regulation (IHR) was meeting to decide whether this 10th Ebola outbreak in the DRC still constituted

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a PHEIC, a new confirmed case was reported in the city of Beni, the last epicenter of the epidemic. The notification came after 52 consecutive days without a confirmed case of EVD in the DRC and 40 days after the last negative polymerase chain reaction (PCR) test of the last confirmed case, that is, 2 days before the declaration of the end of the epidemic. The notified case was a death in the community, with a sample taken on April 9 by a laboratory technician and tested at the Beni laboratory, producing a positive result the following day by GeneXpert Ebola (Cepheid, Sunnyvale, CA, USA) with a cycle threshold value (for which higher values indicate lower RNA levels) of 19.0 with the nucleoprotein (NP) gene target and 22.9 with the glycoprotein (GP) gene target. The sample was also sent for further verification and sequencing to the Butembo laboratory, which confirmed the positive result.

We describe a combined epidemiological and genomic investigation to understand the source and the strategy that led to the control of the final cluster of the outbreak, as well as public health implications.

METHODS

EVD Alert System and Epidemiological Investigation

Alerts of possible suspected cases were raised at community or health facility levels and subsequently triaged. For suspicious patient alerts, Rapid Response Teams (RRTs) composed of epidemiologists, infection prevention and control (IPC) officers, communications officers, and psychosocial workers immediately carried out epidemiological investigations, after which the alert was either validated or invalidated [8]. If the alert was validated, an ambulance was sent to bring the suspected case to an isolation center, where a sample was taken and the disease diagnosed. Patients with positive results were transferred to the Ebola Treatment Centre (ETC), while patients with negative results were required to have 2 consecutive negative results within 72 hours, after which they were discharged as noncases and continued a course of appropriate care.

For death alerts, RRTs including the Safe and Dignified Burial (SDB) team were deployed for outreach, investigation, and preparation of the body and collection of a swab sample. Samples were tested using GeneXpert Ebola (Cepheid, Sunnyvale, CA, USA), and in case of a positive result, mandatory SDB was conducted in accordance with the recommendations of the Ministry of Public Health. If the result was negative, the body was returned to the family for an ordinary burial. However, all individuals who died were, as far as possible, systematically recorded and buried with dignity and in security.

For each confirmed case, all contacts made during the symptomatic period were listed, contacted, and followed up for 21 days from last exposure to the confirmed/probable case. In addition, all eligible contacts were vaccinated upon giving informed consent.

Case Definition

A suspected case was defined as a person, living or dead, who presently had or had previously had sudden onset of fever and at least 3 of the following signs: headache, vomiting, anorexia, diarrhea, lethargy, stomach pain, muscle or joint pain, difficulty swallowing or breathing, hiccups, unexplained bleeding, or any sudden unexplained death. A probable case was considered to be any suspected case evaluated by a clinician or a patient who met the suspected case definition, with a notion of contact with a confirmed or probable case, who had died without having laboratory confirmation by PCR. A confirmed case of EVD was defined as any suspected case with a confirmed laboratory PCR result [9].

A contact was defined as a person with no symptoms who had physical contact with an EVD patient within the past 21 days. Physical contact could be proven or highly suspected, such as having shared the same room or bed, cared for a patient, touched body fluids, or closely participated in a burial (eg, physical contact with the corpse). A high-risk exposure was defined as a percutaneous or mucous membrane exposure to or direct skin contact with the blood or body fluids of an EVD patient or corpse without appropriate personal protective equipment. A low-risk exposure was defined as a household contact who was not involved in providing care for and did not have close contact with the EVD patient in health care facilities or in the community and did not have what was otherwise characterized as a high-risk exposure [10].

Laboratory Investigation

Blood samples were collected for living suspected cases, while oral swabs were taken for deceased cases. The samples were immediately transported to the closest laboratory, maintaining the temperature between 2°C and 8°C. Testing was performed on the same day. All laboratories used GeneXpert Ebola (Cepheid, Sunnyvale, CA, USA) polymerase chain reaction as a diagnostic tool, with cycle threshold (CT) values of <40 considered a positive result.

Sample Collection and Sequencing

All positive samples were aliquoted and sent to the mobile laboratory of the Institut National de Recherche Biomédicale (INRB) deployed in Butembo and to the Pathogen Genomic Laboratory in Kinshasa for sequencing. Complete viral genome sequencing was done with the iSeq100 and MiSeq Desktop sequencer (Illumina Technologies, San Diego, CA, USA) using the KAPA RNA HyperPrep library preparation kit (KAPA Biosystems, Wilmington, MA, USA) followed by the TruSeq Exome or Nextera Flex for Enrichment method, as previously described [11]. Analysis of data was performed using an in-house pipeline for virus genomes, as previously described [11].

Data Collection and Analysis

Information on all confirmed and probable cases was collected from the EpiInfo database [12]. Additional data were collected on contact tracing, vaccination, and laboratory results in separate dedicated Excel databases. Data were analyzed using R statistical software [13]. Global Positioning System (GPS) coordinates related to the mapping of confirmed cases were collected using the Android Mobile Operating System in the households of cases, and maps were made using ArcGIS software [14].

RESULTS

Epidemiological Investigation of Transmission Chain

The Beni health zone was the last to report confirmed cases, despite having gone 50 consecutive days without a confirmed case before the occurrence of a new cluster (Figure 1). The index case of this cluster (Case 1) was identified to be a male taxi driver who presented with EVD-like symptoms starting on March 25, 2020. He was hospitalized at community health center 1 from March 25 to 26, 2020. Despite still presenting symptoms, he was discharged and stayed at home. After his symptoms worsened, he was admitted to community health center 2 on April 9, where he died a few hours after admission. The swab sample taken from his corpse confirmed EVD infection. A comprehensive investigation was conducted, and all potential contacts were identified (in health facilities and in the community). Focus was placed on identifying patients who attended community health center 1 during the same period as case 1, in search of potential nosocomial transmissions.

The investigation identified 24 patients, of whom 5 developed symptoms consistent with EVD. Case 2, who died on March 29, attended community health center 1 at the same time as the index patient and was a sister of case 4. She was HIV-positive and had stopped her antiretroviral treatment (efavirenz, lamivudine, and tenofovir) several months earlier. Her first swab was positive with a CT of 38.0 with the nucleoprotein (NP) gene target, and an additional swab produced a CT of 40 with the same gene target. She was thus initially classified as a non-EVD case. However, her contacts were listed and followed up as a matter of precaution. After the final review of the outbreak in July 2020, she was reclassified as a confirmed EVD case.

The remaining 4 cases (3–6) were all confirmed positive for EVD, of whom cases 4, 5, and 6 were isolated in the ETC during the confirmation of EVD, while case 3 died on April 11, with a postmortem swab confirming the presence of Ebola virus in bodily fluids. Through further investigation among the social connections of case 1, we identified a friend (case 7) who had cared for him and transported him to the health center as being symptomatic. The friend was confirmed to be positive and admitted to an ETC but absconded the following day. Finally, another instance of community transmission was discovered connected to case 6, who had infected her mother (case 8) (Figure 2).

Epidemiological Summary

In total, 8 cases were identified within the last cluster of Beni. Of these, 7 were identified as confirmed cases during the outbreak,

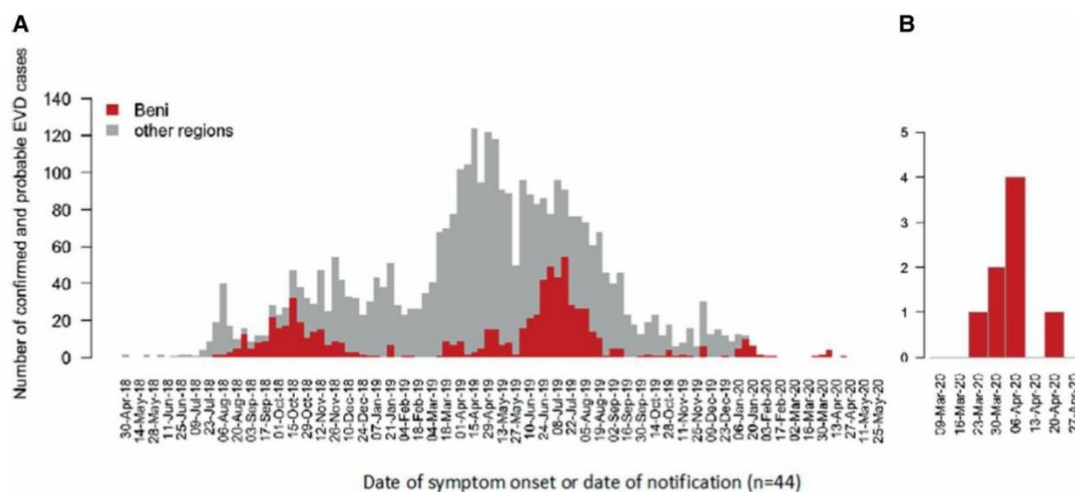


Figure 1. Epidemiological curve of confirmed and probable cases of EVD in Eastern DRC, 2018–2020. A, Epidemiological curve of confirmed and probable cases of EVD in Eastern DRC from April 2018 to June 2020. In red are the cases of Beni, in gray are the cases of all other regions, and the bars represent weekly number of EVD cases. B, Epidemiological curve of the last cluster of the 2018–2020 outbreak located in Beni. For 1 case, date of notification was used, as the date of symptom onset was unknown. Abbreviation: EVD, Ebola virus disease.

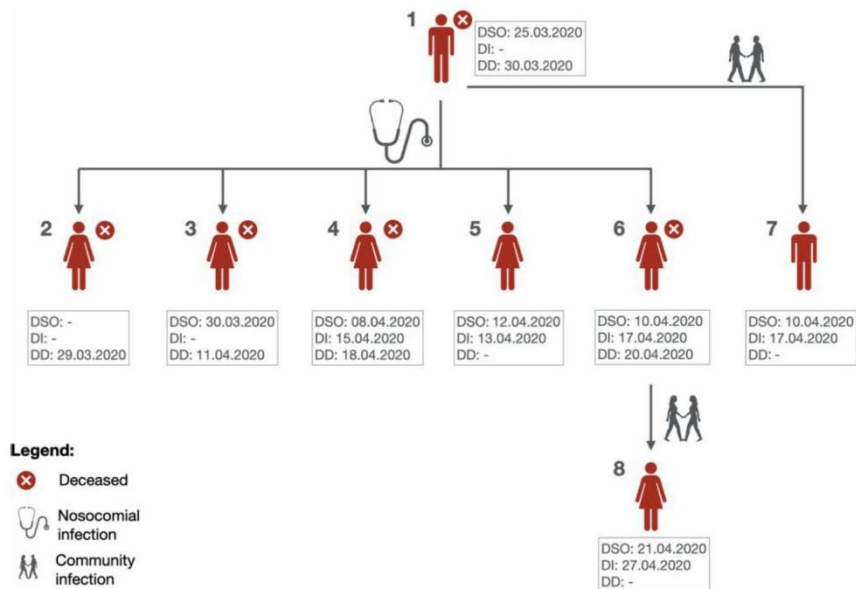


Figure 2. Transmission chain of the last cluster in Beni, DR Congo, March–April 2020. Abbreviations: DD, date of death; DI, date of isolation; DSO, date of symptom onset.

while the eighth case was classified as a confirmed case in July 2020 after final revision of the case classification. Two cases were male and 6 were female, with a median age (range) of 22 (7–68) years. Five (63%) cases died, of whom 3 were community deaths. All cases resided in the same neighborhood as case 1, where community health center 1 was also located (Figure 3). Five cases were likely nosocomially infected within this health center. A total of 1028 contacts were identified around these 8 confirmed cases, including 844 high-risk contacts. Of those contacts, 971 (94%) were successfully traced and followed up, and 781 (76%) were vaccinated.

Sequencing Investigation

Whole-genome sequencing (WGS) results were available for 7 confirmed cases, showing similar sequences and supporting the results of the epidemiological investigation, which indicated that all cases belonged to the same cluster. However, the sequence was not directly linked to the latest Beni cluster of February 2020. The closest sequence to this cluster was identified as a case from the Beni area with symptom onset in July 2019 (Figure 4), with a difference of just 31 nucleotides [15].

Outbreak Control Measures

As this was the final cluster of the outbreak and was a surprise, much stricter and wide-ranging prevention measures were implemented in order to contain the outbreak. All contacts of confirmed cases at the time were listed, identified, and categorized according to the type of contact into high- or low-risk contacts.

Confinement in 2 designated facilities was proposed to all contacts, with priority given to those at highest risk. This confinement was designed in accordance with key guiding principles to drive its implementation (acceptance through community engagement, flexibility, listening to and acting on the needs and concerns expressed by communities) (Figure 5). This confinement was also guided by the World Health Organization recommendations, which state that if a decision to implement quarantine is taken, the authorities should ensure that those in quarantine are adequately supported. This means adequate food, water, protection, hygiene, and communication provisions, as well as infection prevention and control (IPC) measures and monitoring of quarantined persons [16].

The first facility was community health center 2, where all health providers and patients who were in contact with the index case were asked to remain for 21 days from the date of last contact, during which time the health center was closed for new patients and visitors. All other close contacts of confirmed cases, such as family members, neighbors, and health providers from community health center 1, were placed in the second confinement facility. In both confinement facilities, contacts were screened 2 times per day for the presence of EVD-like symptoms to detect and isolate new cases promptly. Psychologists were assigned to provide support during the confinement period. Communications officers were assigned to communicate the infection risk and give guidance on how to act in accordance with infection prevention measures. All contacts were provided 3 meals per day during the confinement

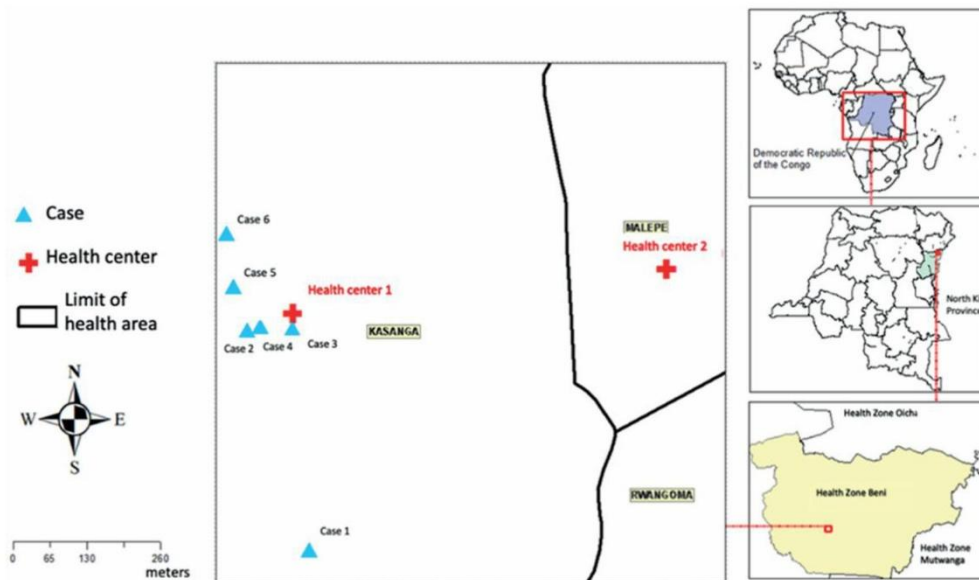


Figure 3. Geographic distribution of cases by residence.

period. Moreover, communities around the confinement facilities were sensitized and given information on the confinement facilities and their importance in order to gain community acceptance of such facilities. Finally, a vaccination campaign targeting the contacts was conducted.

DISCUSSION

This study illustrates how high the risk of additional flare-ups continues to be in the period following the last case detection. In the West African EVD epidemic, at least 8 flare-ups originated from persistently infected EVD survivors and delayed the end of the epidemic by 11 months [8]. To date, it is not known how the index case of this last EVD cluster got infected. As he was a taxi driver, he might have had more and closer interactions with a larger than average number of individuals, which makes contact tracing and finding the source of infection more difficult. As a result of genomic investigation, it was discovered that, contrary to expectations, the virus genome of the index case of the final cluster was not linked to the latest cases detected in the Beni area in February 2020, but to earlier cases from the same area detected in July 2019. This has led to different hypotheses on how this cluster arose: sexual transmission from, or relapse of disease in, an EVD survivor or an undetected chain of transmission [17]. During this outbreak, a total of 1162 persons recovered from EVD, the second highest number of EVD survivors after the West African epidemic, and as Ebola virus can be detected in the sperm of male EVD survivors up to

500 days after recovery [18], this large number of survivors poses a risk for future flare-ups [19, 20]. Additionally, people who recover from EVD can, in rare cases, have a relapse of the disease and subsequently infect others, as was the case for an individual who infected 91 people during the same outbreak [21].

Lastly, there might have been a hidden chain of transmission, missed by the surveillance system, that was detected very late, after a number of generations of disease, which is why reinforcing surveillance activities and assessing their performance are crucial but often neglected activities [22]. However, the last hypothesis seems least likely, as it would mean that there was an undetected continued chain of transmission happening for >6 months.

This final cluster in the 10th EVD epidemic of the DRC was rapidly stopped, with a total of just 8 cases over 72 days (from reporting the index case to declaring the end of the epidemic). There are several reasons why the containment of this cluster was successful.

As this was the end of the epidemic, the containment strategy involved a new, stricter measure—community confinement; that is, very high-risk contacts were brought to designated confinement facilities. Community confinement ensures that if contacts become cases, they are rapidly detected and transferred to the ETC, reducing the risk of further transmission. Thirty-one contacts with very high risk of exposure were thus confined, likely helping contain the spread of the infection. Additionally, 84% of the confined contacts and 76% of all contacts were successfully vaccinated. Such a high vaccination rate

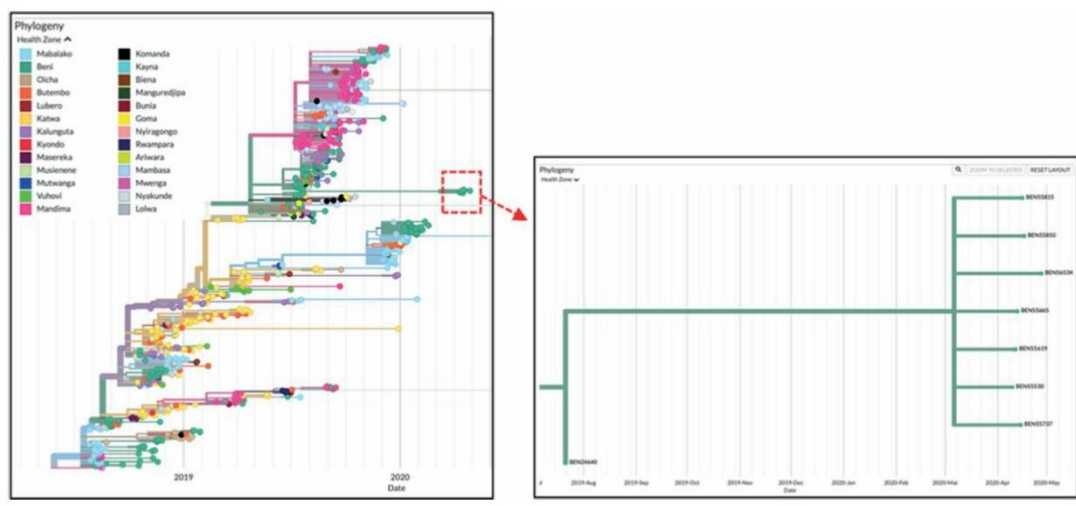


Figure 4. Sequencing results.

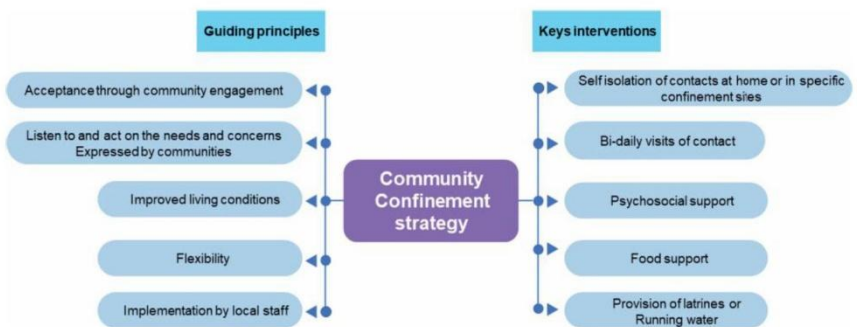


Figure 5. Key aspects of community confinement strategy.

among contacts likely also helps explain why this outbreak was rapidly contained. The approach of listening and acting on the needs and concerns expressed by affected families and influential community members is also likely to have contributed to this. The successful strategy of community confinement could have served to promote trust, and thus enhance other interventions in need of such trust. Indeed, proactive listening to the concerns of different subgroups and culturally sensitive and appropriate strategies are crucial to rollout of vaccines and to minimizing vaccine hesitancy [23]. Another possible contributing factor is the fact that EVD demonstrates a highly overdispersed offspring distribution, which leads both to a tendency to transmission driven by superspreading events and to stochastic extinction of small, isolated clusters of disease [22].

As the risk to have flare-ups in the 42-day period as well as in the period 90 days post-Ebola remains high, it is of utmost importance to continue surveillance and maintain rapid response capability [24, 25]. As this cluster was detected within 42 days of the last EVD case, all activities were under continuation: alerts, alert investigation, etc., and the index case was detected within a reasonable time. Additionally, following up EVD survivors and sensitizing and vaccinating their close contacts are important strategies to prevent future outbreaks [26].

Community confinement likely helped to rapidly control this outbreak and could be considered as a measure in other outbreaks, especially in early stages, which present the best opportunities for successful interruption of transmission. However, such quarantining could substantially negatively impact the health, well-being, and livelihoods of those affected, as

was observed during previous EVD outbreaks and the ongoing COVID-19 pandemic [27–29]. Therefore, such a strategy requires clear communication and effective engagement with those persons affected and the surrounding community to maximize acceptance and the chances of successful implementation [28, 30].

Overall, this study illustrates the major concern of additional flare-ups in the period leading to the end-of-outbreak declaration and the importance of enhanced surveillance (combining epidemiological and genomic surveillance and investigation) and consideration of a contact-confinement strategy to rapidly control Ebola outbreaks. This approach may be applied more broadly to other settings and for other directly transmitted and highly pathogenic infectious diseases.

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Author contributions. M.K., J.P., and I.S.F. designed the study. M.K., I.F., and M.K.I. wrote the first draft. P.M.K. and S.A.M. generated and interpreted the sequencing data. M.K.I., J.K.N., and M.K.T. conducted epidemiological investigations. M.K., A.D., I.F., and M.K.I. analyzed and interpreted the data. P.M.K., S.A.M., A.S.G., O.K., S.D., and I.S.F. supervised the methodology, review, & editing. All authors read and contributed significantly to the final manuscript.

Patient consent. (a) The patient's written consent was obtained. (b) The design of the work was approved by the Ethics Committee of the Kinshasa School of Public Health (approval number ESP/CE/03/2021).

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A community-based contact isolation strategy to reduce the spread of Ebola virus disease: an analysis of the 2018–2020 outbreak in the Democratic Republic of the Congo

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ABSTRACT

Introduction Despite tremendous progress in the development of diagnostics, vaccines and therapeutics for Ebola virus disease (EVD), challenges remain in the implementation of holistic strategies to rapidly curtail outbreaks. We investigated the effectiveness of a community-based contact isolation strategy to limit the spread of the disease in the Democratic Republic of Congo (DRC).

Methods We did a quasi-experimental comparison study. Eligible participants were EVD contacts registered from 12 June 2019 to 18 May 2020 in Beni and Mabalako Health Zones. Intervention group participants were isolated to specific community sites for the duration of their follow-up. Comparison group participants underwent contact tracing without isolation. The primary outcome was measured as the reproduction number (R) in the two groups. Secondary outcomes were the delay from symptom onset to isolation and case management, case fatality rate (CFR) and vaccination uptake.

Results 27324 EVD contacts were included in the study; 585 in the intervention group and 26739 in the comparison group. The intervention group generated 32 confirmed cases (5.5%) in the first generation, while the comparison group generated 87 (0.3%). However, the 32 confirmed cases arising from the intervention contacts did not generate any additional transmission (R=0.00), whereas the 87 confirmed cases arising from the comparison group generated 99 secondary cases (R=1.14). The average delay between symptom onset and case isolation was shorter (1.3 vs 4.8 days; $p<0.0001$), CFR lower (12.5% vs 48.4%; $p=0.0001$) and postexposure vaccination uptake higher (86.0% vs 56.8%; $p<0.0001$) in the intervention group compared with the comparison group. A significant difference was also found between intervention and comparison groups in survival rate at the discharge of hospitalised confirmed patients (87.9% vs 47.7%, respectively; $p=0.0004$).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Isolation of cases, quarantines of their close contacts and other forms of physical isolation are approaches to reducing social and physical contact of individuals with the potential to transmit infection.

WHAT THIS STUDY ADDS

⇒ A community-based contact isolation strategy implemented in the Democratic Republic of Congo to curtail an Ebola virus disease (EVD) outbreak was found to effectively interrupt transmission from the first generation of isolated contacts. Further, the survival rate of patients hospitalised with EVD was significantly increased by this strategy, due to improved timeliness of case detection.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings demonstrate the importance of a community-based approach in implementing contact isolation and have relevance for policy choices regarding whether to isolate contacts or quarantine entire populations, which is particularly pertinent in resource-limited settings. Applied in various infectious disease contexts, a community-based contact isolation strategy can save lives of isolated contacts that develop infection and also prevent onward transmission to others.

Conclusion The community-based contact isolation strategy used in DRC shows promise as a potentially effective approach for the rapid cessation of EVD transmission, highlighting the importance of rapidly implemented, community-oriented and trust-building control strategies.

INTRODUCTION

The 10th Ebola virus disease (EVD) outbreak in the Democratic Republic of Congo (DRC) was declared on 1 August 2018 in North Kivu province's Mabalako Health Zone (HZ).¹ This outbreak—the first recorded in the Eastern part of the country—quickly reached large urban cities, before spreading to two other provinces, Ituri and South Kivu.

The Province of North Kivu is home to 6.6 million people of which 3.2 million live in extreme poverty. Around 2.5 million people live in the largest urban areas of Goma (around 1.2 million), Butembo (690 000) and Beni (570 000).² Insecurity in the region (with over 120 armed groups active) triggered mass population movements with more than a million internally displaced people and made containment of this 10th outbreak much more challenging.^{3–4} As result, this outbreak became the second largest EVD outbreak globally, after the 2013–2016 West Africa Ebola Epidemic⁵ with a total of 3481 cases (3323 confirmed and 158 probable) and 2299 deaths were recorded.¹

Control of EVD outbreaks has been found to be achievable through a mixed approach involving risk communication and community engagement (RCCE), early case detection, rapid isolation and care, contact tracing (CT), and the safe and dignified burial of deceased confirmed or suspected cases.^{6,7} The biological features of the Ebola virus, requiring contact with body fluids for a possibility of human-to-human transmission, place the notion of contact at the centre of the interruption of such virus-driven outbreaks.⁸ Therefore, CT is among the key EVD control measures, consisting of the identification and listing, tracing (ie, locating and establishing initial contact), and finally, regular follow-up.⁹ The core aim is to limit the spread of the infectious disease by offering early support and care as well as isolation if the contact develops disease.¹⁰

Accordingly, during the 2013–2016 West Africa EVD Epidemic—in which more than 28 000 cases were documented—CT was implemented as a key component of the surveillance pillar to prevent further transmission.^{11,12}

However, poor performance was identified as one of the principal weaknesses of the response.¹³ For example, CT was successfully performed for only 26.7% of all EVD cases in Liberia, leading to the detection of just 3.6% of new cases¹² (this is despite the fact that CT was less logistically complex because quarantine was enforced through the presence of army personnel and police officers, which theoretically ensured contacts remained in place at all times).⁶ This enforced quarantine was likely counterproductive and may have led to negative public health behaviours, such as hiding bodies or sick persons, and not seeking healthcare. This suggests that epidemic control interventions rooted in RCCE, social acceptance and local practices may be a more effective alternative.^{14–16} In addition, CT becomes extremely challenging and impractical beyond the early stages of large and rapidly expanding outbreaks, during which time the

Box 1 Defining 'community-based contact isolation' as distinct from quarantine

This manuscript examines a community-based isolation of EVD contacts, which in this manuscript is different from enforced quarantine. Quarantine is usually understood to be an enforced mechanism, whereby a legal obligation is impressed on a contact that may go on to develop infection. This can also include police or military enforcement, either through spot checks or on-site guarding.⁴⁹

The concept of community-based contact isolation (as used in this manuscript), on the other hand, is a voluntary mechanism, where contacts are advised, encouraged, supported, and even incentivised—but not obliged—to self-isolate. It builds largely on Rosenthock's health belief model including the perceived susceptibility; perceived severity and perceived benefits of the intervention.⁵⁰

The specific design and strategy used in the 2018–2020 EVD outbreak in DRC is discussed further later in this manuscript.

DRC, Democratic Republic of Congo; EVD, Ebola virus disease.

number of contacts grows exponentially and overwhelms the capacity to respond.¹⁷ Recent analyses indicate that the prevention of new clusters of cases may have been more effective at bringing that epidemic to an end than the reduction of secondary infections achieved through enhanced surveillance activities such as CT.¹⁸

In the 2018–2020, EVD outbreak in Eastern DRC, where more than 250 000 contacts were recorded,¹ public health performance indicators were initially poor. This included many community deaths, poor CT⁹ and delays between symptom onset and case isolation.¹⁹ In response to the persistence of the outbreak, a number of initiatives and strategies were pursued, including the decentralisation of interventions in the health areas (health area approach), the establishment of a unit to search for lost to follow up contacts, and the contact isolation of contacts (Nota Bene: we use the term 'community-based contact isolation' as distinct from 'quarantine', box 1).

The lack of previous studies on community-based contact isolation precluded the use of this strategy in the early stages of this outbreak as the effectiveness of such strategies has been demonstrated only in modelling studies on the impact of quarantine.^{16,20–22} Furthermore, evidence concerning the acceptability of such an intervention was deemed necessary, as previous efforts to control EVD spread have often resulted in clashes and conflict due to the fact that outbreaks often overlap with other major community needs that are neglected by political authorities. This is a particular risk when control measures do not align with local practices and expectations. In one instance in Womey village, Nzerokore prefecture, local inhabitants interpreted Ebola responders disinfecting households with bleach sprays as spreading EVD, leading to the killing of members of the Ebola response team.²³ Further issues included inadequate public health messaging, distrust of those providing the health messages, political instability and regional conflict.^{24,25} Taken together, this allowed EVD to

spread and kill thousands, when early containment could possibly have been within reach.²⁶

This study aimed to provide evidence of the effectiveness of a contact isolation strategy that is more focused on contact participation, and community engagement that could be implemented in future epidemics to rapidly mitigate onward transmission.

METHODS

Study design

A quasi-experimental (ie, non-randomly assignment) study was designed to compare isolated contacts to those who were not isolated (see 'description of the intervention' for definitions). As this intervention was implemented in support of the response to the EVD outbreak, participant recruitment was organised through existing Ebola response mechanisms at the initial stage of alert response: whenever a new case was confirmed and reported, a psychosocial team (a team including those trained in psychological and social first aid) visited the person and his/her family to deliver the result. The surveillance team then completed a case investigation and updated the contact list.

At this point, in collaboration with the RCCE team, the study was explained to contacts to obtain their informed consent. When fully oriented and consent was provided, contacts were assigned to one or other group by the intervention team (ie, field epidemiologists), considering the rapid risk assessment based on the type of contacts.²⁷ Since we could not confine all contacts given their number and geographical dispersion, priority was given to high-risk contacts, an approach taken in Spain with contacts of the first secondary case of the 2014–2016 Ebola epidemic that occurred outside Africa.²⁸ However, if a high-risk contact did not consent to isolate, they were placed in the non-isolated group.

A contact was defined as a person who is currently asymptomatic but had physical contact with an EVD patient within the past 21 days. Physical contact could be proven or highly suspected, such as having shared the same room or bed, cared for a patient, touched body fluids or closely participated in a burial (eg, physical contact with the corpse). A high-risk exposure was defined as a percutaneous or mucous membrane exposure to, or direct skin contact with blood or other body fluids of an EVD patient or corpse without appropriate personal protective equipment. A low-risk exposure was defined as a household contact that was not involved in providing care to, or having close contact with, an EVD patient in healthcare facilities or in the community that was not otherwise characterised as a high-risk exposure.²⁹

Description of the intervention

Intervention group participants were isolated in specific community sites of their preference (ie, either households or rehabilitated structures, defined as a transitional facility where living conditions have been improved to

allow several individuals to stay and live there temporarily, including the installation of additional tents) for the 21-day follow-up period. In community site settings, certain contacts were grouped together on the same site, usually within their own households, thereby separating them from the rest of the community. Additional tents for contacts (to reduce contact with each other) as well as toilets, water and a solar electricity supply system were added in some areas. The use of individual utensils was encouraged (spoons and bowls were distributed). Hygiene measures were strengthened by distributing soap, hydroalcoholic solutions and installing multiple hand hygiene units to minimise cross-contamination risk. Psychosocial support was delivered according to the inter-agency standing committee guidelines on mental health and psychosocial support in emergency settings³⁰ and financial support provided to approximately compensate for loss of income. Risk communication, awareness and sensitisation were delivered on a daily basis to isolated contacts. As part of community engagement efforts, the security services were explicitly excluded from the process, despite the outbreak occurring within a conflict zone.

Meanwhile, comparison group participants underwent CT without isolation and were allowed to continue their daily activities while receiving non-regular psychosocial and food support. In both groups, daily follow-up of contacts was undertaken for a period of 21 days from the date of last contact with the index case (defined for this context as the case that led to the contacts under investigation) and vaccination performed according to the same strategy ('ring vaccination') (figure 1).

The community contact isolation strategy was designed in line with various principles that guided preparation for, and implementation of, CT³¹:

- ▶ Acceptance through community engagement: All affected families were actively engaged and the rationale for contact isolation and measures being taken explained (ie, isolation and prompt treatment of suspected patients, vaccination of contacts, protection of other family members and compensatory measures in terms of lost economic gain at the family level). Influential family members, local government or religious leaders were engaged to support this engagement.
- ▶ Listen to and act on the needs and concerns expressed by communities: The strategy was guided by community feedback, adapting the implementation of activities accordingly (eg, daily meal menus were suggested by contacts themselves and supported by the intervention team). The choice of contact isolation site was not imposed. Communities were welcome to express any concerns about contact isolation, and the strategy could be adapted accordingly.
- ▶ Flexibility: The strategy was adapted: to local conditions (eg, urban vs rural villages); the relative availability of contact isolation sites (especially in urban areas); and consideration of the choice of people to confine.

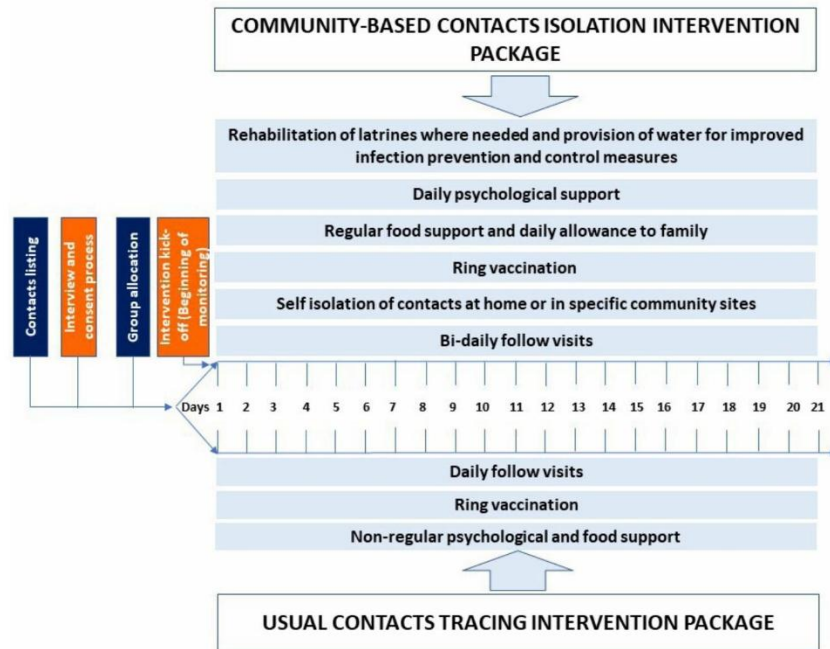


Figure 1 Community-based contact isolation study protocol, Beni and Mabalako sub-coordination, Democratic Republic of the Congo, June 2019–May 2020.

- Improved living conditions: Transmission of EVD often occurs in areas with poor access to water, sanitation and hygiene. Therefore, the strategy sought to improve these conditions by providing additional latrines and water supply to contact isolation sites in the respect of infection, prevention and control protocols.
- Implementation by local staff: All work to set up and/or adapt the contact isolation sites (eg, construction of toilets, installation of water tanks, installation of electrical panels, construction of fences, guarding of

sites) was entirely performed by local staff, who were financially compensated for their work.

Setting

The intervention was implemented in two HZs (Beni and Mabalako), from 12 June 2019 to 18 May 2020. While the outbreak was short-lived in some locations, these two HZs experienced continuous transmission over the epidemic’s 2-year duration and were the first and last two HZs to report confirmed cases, respectively (figure 2).

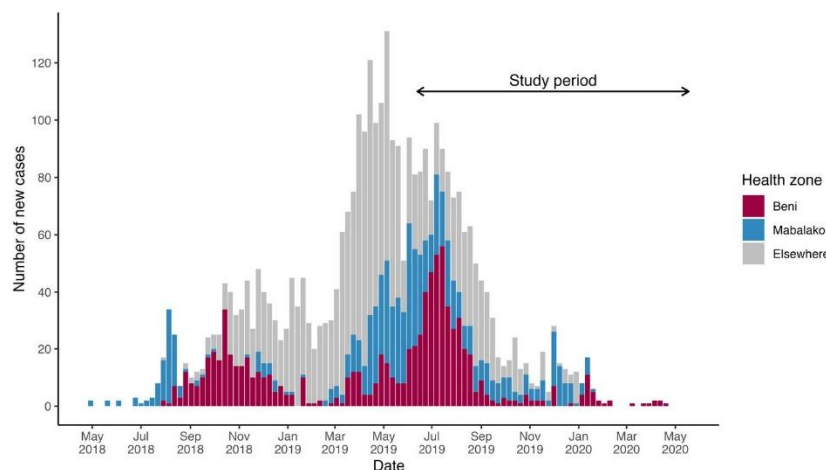


Figure 2 Evolution of the weekly number of confirmed and probable cases of Ebola virus disease by Health Zone, Democratic Republic of the Congo, May 2018–June 2020

Data sources and measurement

Data were collected from the investigation forms of EVD alerts, suspected and confirmed cases, individual contact listing and monitoring sheets including vaccination status, and inpatient records by field epidemiologists and data managers. Intervention group participants were compared with the comparison group over the same period.

As a measure of effectiveness, the primary outcome was measured as the reproduction number (R , the average number of secondary cases generated from index cases) in the two groups.³² The first known recorded contacts that were included in the study were considered the first generation. Confirmed cases among this group were considered the primary confirmed cases. The second generation corresponds to contacts of the primary confirmed cases. Confirmed cases from this generation were considered the secondary confirmed cases.

Secondary outcomes included the successful follow-up rate of contacts in the two groups, the delay from symptom onset to isolation and case management and the case fatality rate (CFR).

Statistical methods

Being integrated into the outbreak response strategy, there were no sample size targets or limits, with the study continuing until the last contact completed the 21-day followed up.

Both primary and secondary outcome measures were summarised using simple descriptive statistics including mean, SD and percentage. Outcome measures were tested for differences between isolated and non-isolated. Comparisons between means were tested using the two-sample t-test, and differences between frequencies were tested using the χ^2 test. The Mantel-Haenszel test was

used to test the overall difference between the intervention and comparison group. Logistic regression analyses were performed to assess predictors of death among confirmed patients. Statistical significance was defined as $p < 0.05$ (two sided). R V.4.0.2³³ and STATA V.14.1 (Stata) were used to perform different analyses.

Patient and public involvement

Opinions of the health district management team, local leaders, local political and administrative authorities, and community members were obtained and integrated to improve the intervention package before the initiation of the study.

RESULTS

Participants and descriptive data

A total of 27 324 contacts met the eligibility criteria and were included in the study (figure 3); 585 contacts underwent contact isolation while 26 739 did not. The characteristics of the two groups were quite similar regarding gender ($p=0.346$), but intervention group were slightly older with regard to age (median of 25.9 years vs 24.3 years; $p=0.013$). However, the risk of exposure (determined by the nature of the relationship with the index case and the type of contact) was significantly higher in the intervention group, as high-risk contacts were prioritised for isolation (table 1).

Primary outcome

A total of 32 primary confirmed cases resulted from the 585 isolated contacts (54.7‰) compared with 87 of the 24 384 non-isolated contacts (3.57‰). There were no secondary confirmed cases arising from the 32 primary confirmed cases in the intervention group, whereas 99

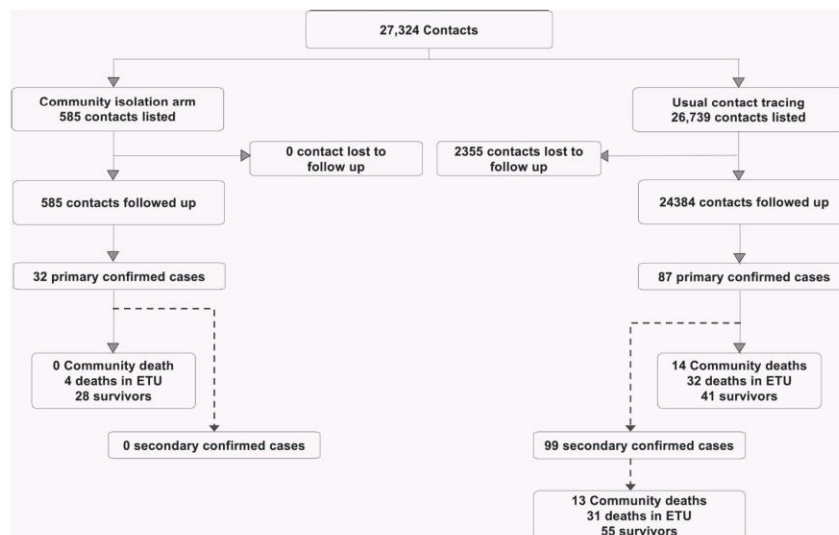


Figure 3 Flow diagram of the progress of contacts and their outcome through the intervention and comparison arms of the study, Beni and Mabalako sub-coordination, Democratic Republic of the Congo, June 2019–May 2020. ETU: Ebola Treatment Unit

Table 1 Baseline characteristics of study participants according to intervention arm, Beni and Mabalako sub-coordination, Democratic Republic of the Congo, June 2019–May 2020.

Characteristic	Intervention arm (community contact isolation)	Comparison arm (standard community contact tracing)	P value
Age (years)	n=520 250.9 (24.6; 27.2)	n=24586 240.3 (24.1; 24.5)	0.013
Gender			
Male	301	13140	0.346
Female	283	13414	
Type of contacts			
1	58	4871	
2	113	7130	<0.00001
3	225	6331	
4	105	2794	
Relation with the index case			
Nosocomial	69	882	
Household family members	168	3817	<0.00001
Community	214	13400	

secondary confirmed cases arose from the 87 primary confirmed cases from the comparison group.

Secondary outcomes

There were significant differences between the intervention and comparison groups in all the secondary outcomes explored (table 2). The average delay between symptom onset and case isolation was shorter (1.3 vs 4.8 days; $p<0.000$), CFR lower (12.5% vs 48.4%; $p<0.000$) and vaccination uptake higher (86.0% vs 56.8%; $p<0.000$) in the intervention group compared with the comparison group. A significant difference was also found between intervention and comparison groups in survival rate at discharge of hospitalised confirmed patients (87.9% vs 47.7%, respectively; $p=0.0004$) (figure 4).

The multivariable regression analysis showed that neither age, gender nor vaccination status had an impact on CFR in confirmed cases admitted to Ebola Treatment Centres. However, the risk of death was more than six times greater in the comparison group compared with the intervention group (table 3).

DISCUSSION

To the best of our knowledge, this is the first comparative study conducted during an ongoing EVD epidemic to demonstrate the effectiveness of contacts isolation. The approach was based on enhanced risk communication

Table 2 Assessment of intervention and comparison groups according to primary and secondary objectives, Beni and Mabalako sub-coordination, Democratic Republic of the Congo, June 2019–May 2020.

Characteristic	Intervention arm (community contact isolation)	Comparison arm (standard community contact tracing)	P value
No of secondary cases	32	87	–
Average delay between symptom onset and isolation (days)	1.3 (n=32)	4.8 (n=86)	0.0000
Case fatality rate	12.5% (n=32)	48.4% (n=186)	0.0001
Vaccination uptake among contacts	86.0% (n=585)	56.8% (n=26739)	0.0000

and individual commitment without any obligation or constraint on EVD contacts, unlike enforced quarantine, and therefore, is a less restrictive contact isolation strategy.

The 2018–2020 eastern DRC outbreak lasted nearly 2 years despite the availability of effective vaccine³⁴ and therapeutics³⁵ from the outset of the response. Public health performance indicators were poor, with increasing community deaths, poor CT (indicated by the high number of cases that had no known contacts), and delays between symptom onset and isolation.^{9 19 34} The change in strategy to adapt to a difficult context was necessary, and led to a rapid and drastic reduction in transmissibility which reduced incidence and helped bring the outbreak under control.³ The contact isolation strategy was then implemented to avoid a new spread of the epidemic, especially as the security situation was more critical.

Although implemented after the peak of the epidemic, this strategy played an important role in accelerating control as it contributed to rapidly stopping the remaining transmission chains. The overall comparison between intervention and comparison group showed a significant difference in the outcome indicators, namely the reproduction number, CFR, delay from symptom onset to case isolation and vaccination uptake among contacts. Moreover, for all confirmed cases from the intervention group, the average delay between the date of vaccination and the onset of symptoms was less than ten days, meaning that all these cases were already in incubation at the time they were vaccinated. This implies that, even vaccinated, these contacts could have contaminated other people if they were not isolated as vaccine is effective when administered early to contacts. Ring vaccination is known to be most effective in contacts of contacts (second ring) than contacts (first ring), as

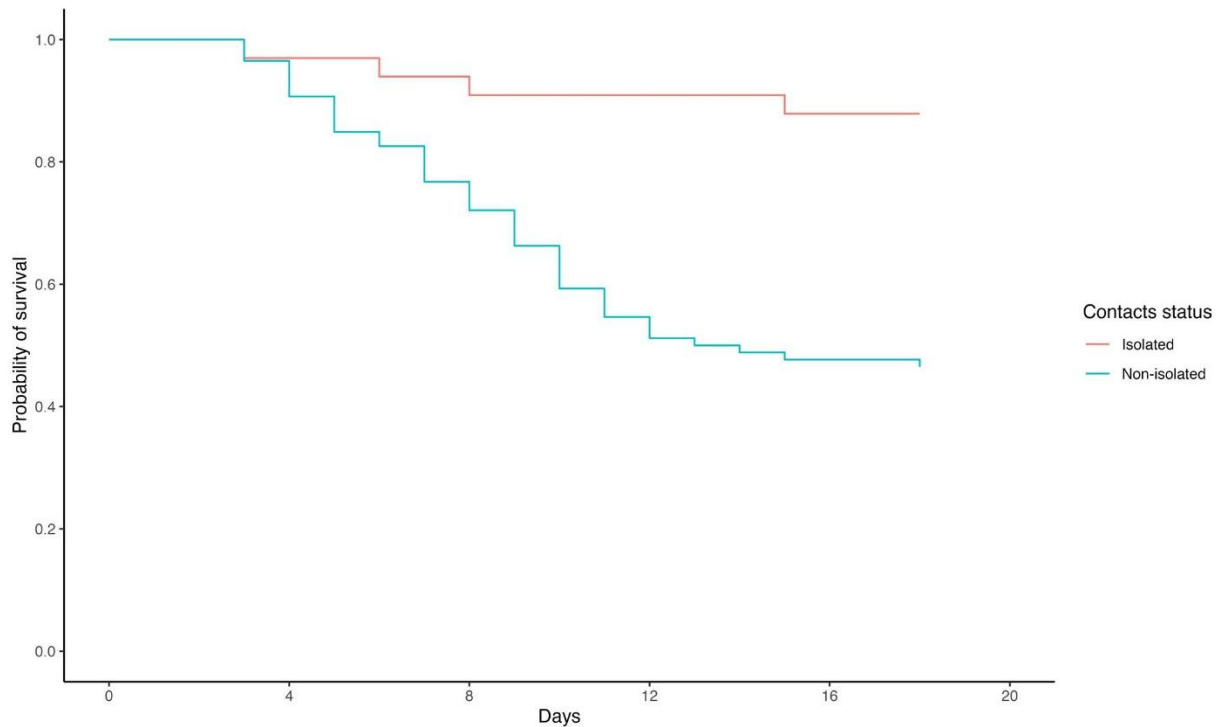


Figure 4 Kaplan-Meier survival curves for confirmed Ebola virus disease case-patients among the intervention (isolated) and comparison (non-isolated) groups, Beni and Mabalako sub-coordination, Democratic Republic of the Congo, June 2019–May 2020.

some contacts are often exposed several days before the confirmation of their primary case.³⁶ The rapid control of the recent Sudan Virus Disease outbreak in Uganda,³⁷ in which no vaccine was available for contacts, may be

associated with the isolation of high-risk contacts applied by the health authorities especially when confirmed cases were reported in Kampala.

Survival analysis showed a higher survival of confirmed cases from the intervention group than the comparison group. The higher survival rate may be attributable to the early detection of confirmed cases in the intervention group, as supported by the shorter delay from symptom onset to case isolation in this group. This delay was reported as one of the factors associated with EVD death in Guinea during the 2013–2016 West Africa Ebola Epidemic.³⁸ This survival difference is likely not treatment-related as there was no difference between the two groups. All hospitalised patients received one of the two specific molecules that had already been validated in the first stage of a clinical trial conducted during the same epidemic.³⁵ Finally, the security context is unlikely to have had an impact as both groups were in the same localities, and therefore, subject to the same conditions.

In contrast to the traditional quarantine, the community-based contact isolation strategy applied in eastern DRC from June 2019 to May 2020 is unique in its method of implementation, and the acceptance by those concerned. First, it only involved contacts, as opposed to the general population (ie, it was targeted). Second, it was designed by a multidisciplinary team including social scientists. The methodological approach based on community participation and engagement, inclusion of

Table 3 Results of multivariable analysis of predictors of death among confirmed cases, Beni and Mabalako sub-coordination, Democratic Republic of the Congo, June 2019–May 2020.

Multivariable analysis			
	OR adjusted	95% CI	P value
Contact isolation			
Isolated (ref)	1		
Non-isolated	6.45	(1.46 to 28.38)	0.01
Sex			
Male (ref)	1		
Female	1.02	(0.44 to 2.38)	0.95
Vaccination			
Vaccinated (réf)	1		
Non vaccinated	1.04	(0.31 to 3.47)	0.94
Age group			
0–35 years (ref)	1		
36–65 years	0.31	(0.01 to 5.64)	0.43
66 years plus	0.71	(0.05 to 8.88)	0.79

participants' expectations and the support of psychosocial experts at all levels mitigated the negative impact of contact isolation on mental health. No cases of mental disorders were reported among the isolated population in contrast to what is reported in the quarantines during COVID-19.³⁹ The implementation was also guided by WHO recommendations on quarantine, which state that if a decision to implement it is taken, the authorities should ensure that those in quarantine are adequately supported. This means adequate food, water, protection, hygiene and communication provisions; infection prevention and control (IPC) measures; and the monitoring of quarantined persons.⁴⁰ Introducing quarantine measures early in an outbreak may delay the introduction of the disease to a new country or area and may delay the peak where local transmission is ongoing. However, if not implemented properly, quarantine may also create additional sources of contamination and dissemination of the disease.⁴¹ In addition, quantitative models have also shown that quarantine and symptom monitoring of contacts with suspected exposure to an infectious disease are key interventions for the control of emerging epidemics.⁴²

The novel community-based contact isolation strategy drawing on these concepts of quarantine was applied during the 2018–2020 North-Kivu outbreak and has great potential for future outbreaks for which CT and isolation is recommended, including, but not limited to, EVD. This includes Marburg Virus Disease, an emerging and increasingly frequent viral haemorrhagic fever in Africa, caused by a virus of the same family of Filoviridae as Ebola Virus.^{43 44} For the first time since 1975, two concurrent outbreaks of Marburg Virus Disease occurred in Africa in 2023, in Equatorial Guinea and Tanzania.⁴⁵ In Equatorial Guinea, more than 200 people were quarantined, and movement was restricted along its border.⁴⁶ While the availability of the EVD vaccine has markedly reduced transmission during EVD outbreaks, there is a possibility of relapse up to 5 years after infection.⁴⁷ This reinforces the need to consider, strengthen and more broadly apply community contact isolation strategies for the rapid containment of future outbreaks. This will require trust from affected populations, which should not be taken for granted. However, the strategy itself can also serve to engender this trust, and therefore, also strengthen the positive effect of other interventions requiring this trust, which includes all five core pillars of EVD response (ie, case management, case finding and CT, IPC, safe and dignified burial, and risk communication and community engagement).⁷

Limitations

As allocation to the group was not random, but rather based on the risk associated with the type of contact, some high-risk contacts who did not want to be isolated may be motivated to falsely report not having been in close contact with a confirmed or probable case. This potential bias is likely to be mitigated by the validation of

the group assignment by field epidemiologists. Moreover, the impact is not significant as it would to some extent rebalance the level of risk that was estimated to be higher in the intervention group.

The size of the intervention and comparison groups was vastly different, with the comparison group being approximately 45 times the size of the intervention group. This reflects the radical, more costly and somewhat experimental nature of the contact isolation strategy, which resulted in only a small proportion, including the most high-risk, contacts being proposed for the intervention. However, our analysis of baseline characteristics revealed the groups to be broadly similar in most sociodemographic characteristics. Furthermore, the imbalance in participant numbers between groups would not have negatively impacted the statistical power of the assessment, which was sufficient in the small of the two groups.⁴⁸

CONCLUSION

The rapidly evolving nature of the 2018–2020 Kivu epidemic has shown that unaddressed EVD transmission chain can escalate into further (and lethal) transmission. Therefore, CT strategies—including in areas with such weak health systems and conflict—should consider methods of rapid identification and isolation of contacts accompanied by a range of supportive interventions and with community engagement. This study has shown that doing so can help interrupt disease transmission when done using the community-based contact isolation approach. More than just saving lives through limiting onward transmission, it also has the added advantage of engaging affected individuals, as well as key and trusted community actors, which can help to engender and maintain trust in the response. Further, it limits the need to use more costly forms of containment such as enforced quarantine or regional lockdowns. In short—for the ease of the strategy's implementation, the integration of social sciences, the engagement of affected communities and trust built among them (which is itself key to the overall effectiveness of an outbreak response)—the community contact isolation strategy should be considered on a case by case basis as a potentially effective and efficient method of saving lives.

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Factors Associated with Reliable Contact Tracing During the 2021 Ebola Virus Disease Outbreak in Guinea

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Abstract

Background In 2021, an Ebola virus disease (EVD) outbreak was declared in Guinea, linked to persistent virus from the 2014–2016 West Africa Epidemic. This paper analyzes factors associated with contact tracing reliability (defined as completion of a 21-day daily follow-up) during the 2021 outbreak, and transitively, provides recommendations for enhancing contact tracing reliability in future.

Methods We conducted a descriptive and analytical cross-sectional study using multivariate regression analysis of contact tracing data from 1071 EVD contacts of 23 EVD cases (16 confirmed and 7 probable).

Results Findings revealed statistically significant factors affecting contact tracing reliability. Unmarried contacts were 12.76× more likely to miss follow-up than those married (OR = 12.76; 95% CI [3.39–48.05]; $p < 0.001$). Rural-dwelling contacts had 99% lower odds of being missed during the 21-day follow-up, compared to those living in urban areas (OR = 0.01; 95% CI [0.00–0.02]; $p < 0.01$). Contacts who did not receive food donations were 3× more likely to be missed (OR = 3.09; 95% CI [1.68–5.65]; $p < 0.001$) compared to those who received them. Contacts in health areas with a single team were 8× more likely to be missed (OR = 8.16; 95% CI [5.57–11.96]; $p < 0.01$) than those in health areas with two or more teams (OR = 1.00; 95% CI [1.68–5.65]; $p < 0.001$). Unvaccinated contacts were 30.1× more likely to be missed compared to vaccinated contacts (OR = 30.1; 95% CI [5.12–176.83]; $p < 0.001$).

Conclusion Findings suggest that contact tracing reliability can be significantly influenced by various demographic and organizational factors. Considering and understanding these factors—and where possible addressing them—may be crucial when designing and implementing contact tracing strategies during future outbreaks in low-resource settings.

Keywords Ebola virus disease · Contact tracing · Surveillance · Guinea

Abbreviations

CI Confidence interval
EVD Ebola virus disease

OR Odds ratio
WHO World Health Organization

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1 Introduction

The largest, longest, and deadliest outbreak of Ebola virus disease (EVD) occurred in West Africa from December 2013 to March 2016, causing 28,652 infections and 11,325 deaths in 10 countries. Of these, 99% occurred in just three countries: Guinea, Sierra Leone, and Liberia. Seven years after the outbreak was declared over, Guinea faced a new EVD outbreak. This outbreak, near the epicenter of the previous, lasted from 14 February to 19 June 2021, and resulted in 12 known deaths [1, 2]. Evidence had previously suggested that EVD outbreaks typically begin with a single case of zoonotic transmission followed by human-to-human transmission via direct contact or contact with infected bodily fluids or contaminated fomites [3]. However, the 2021 Guinea epidemic—as well as other recent epidemics and investigations—showed that EVD outbreaks may be caused by virus persisting in and transmitting from a survivor months or, in this case, years later [4, 5].

Regardless of origin, once an outbreak has occurred, the biological features of EVD—requiring a contact with body fluids for a possibility of human-to-human transmission—make contact tracing a foundational strategy to interrupt the outbreak [3]. Contact tracing is defined by the World Health Organization (WHO) as the monitoring process through which people who have been in close contact with someone infected with a pathogen during the time when they were infectious are closely followed and observed for development of any relevant signs or symptoms indicative of disease. As applied to EVD control, contact tracing consists of the identification and listing of contacts; tracing them (i.e., locating them and establishing initial contact); and finally, daily follow-up with them for the 21-day period of EVD's incubation period, with the core dual aims of limiting the spread of an infectious disease through isolation and offering early support and treatment to any suspected case [6]. Contact tracing was a key element in containing the 2014–2016 EVD outbreak in West Africa [7], as well as other recent outbreaks in Democratic Republic of Congo (DRC) [8, 9] and Guinea [10].

The successful interruption of EVD transmission through contact tracing—meaning systematic and complete listing and subsequent 21-day follow-up can only be ensured if it is rapidly implemented upon identification of an associated EVD case, which generally includes the time taken for laboratory confirmation [7]. The completeness of the 21-day follow-up is considered a key performance indicator for overall surveillance and containment, because it impacts the duration of the outbreak and response. The definition of contact implies that a contact is not symptomatic, as for known contacts, the presence of a single

symptom suggests the person should be categorized as a suspected EVD case requiring additional public health actions, such as isolation and clinical support. Therefore, for EVD, a contact is not sick, is not systematically quarantined (though it is recommended to reduce movements and travel) and is seen by contact tracers to assess their health and promptly detect EVD symptom onset up to twice a day (according to their willingness to be followed up).

However, while contact tracing is understood to be a critical tool for containing outbreaks (and a significant amount of labor is therefore assigned to its function), critical assessments of the factors effecting its performance are limited in number and rigor. This is despite known issues in recent outbreaks. For example, a recent study estimating the completeness of contact tracing during the 2018–2020 EVD outbreak in eastern DRC (using the capture and recapture method) highlighted that contact tracing efforts performed well at identifying contacts during the listing stage, but performed poorly during the contact follow-up stage [11]. Some efforts to improve effectiveness have focused on improving contact monitoring tools by digitizing as much as possible [12], for example, but few studies have focused on other factors.

In this study, we describe and analyze contact tracing activities as conducted in urban and rural areas of the Nzerekore Health District from February to May 2021. The main objective of the study was to understand the factors associated with the reliability of 21-day follow-up among listed contacts, so as to inform and help guide contact tracing efforts in response to future outbreaks in similar contexts.

2 Methods

2.1 Setting

The study was conducted in the Nzerekore health district in the Republic of Guinea. The district covers about 3632 km² and has an estimated population of 497,667 inhabitants in 2021 according to the Third General Census of Population and Housing (RGPH3) [13]. It is composed of seventeen health areas. The EVD outbreak occurred from 14 February to 19 June 2021.

2.2 Study Design and Participants

We conducted a descriptive and analytical cross-sectional study. Participants consisted of all contacts identified by epidemiological investigation teams for confirmed and probable cases during the data collection period (February to May 2021). The definition of contact was aligned with the WHO definition: any person with no sign or EVD symptom and who had been exposed to any confirmed (alive or dead) or

probable EVD patient or with their bodily fluids within the past 21 days.

Accordingly, contacts were categorized into four types: Category 1 were people who had direct contact with body fluids, such as blood, saliva, vomit, breastmilk, or sperm of an EVD-infected patient; Category 2 had directly touched the alive or dead EVD-infected patient's body; Category 3 had touched clothes of the EVD case or had shared the same linens or utensils; and Category 4 have slept in, eaten in, or otherwise shared the same house with an EVD-infected patient [6].

The contact tracing mechanism was designed at the operational level (i.e., by the response coordination committee) and implemented at the tactical level (i.e., in the community). Local agents including community One Health platform members were identified and trained to become contact tracing-specific Community Relays (ReCo). Generally, 6 to 8 contact-tracing ReCo would work under a designated supervisor and would see 15–20 contacts daily. While all contacts had only one ReCo, some health zones had two or more supervision teams coordinating their work, depending on: the uncertainty of the initial investigation; the dispersion of contacts (i.e., the geographical grouping of contacts in a zone); the relative presence of contacts classed as high risk; and the overall number of listed and unreported contacts in a given area. As per WHO guidance regarding the incubation period for EVD [6], the follow-up period was 21 days from the day following last contact with the index case. The supervisor was responsible for listing the contacts as completely as possible; partially filling the individual contact-tracing form that would later be given to the ReCo; and summarizing the information in a form for transmission to the surveillance pillar team. This information was then supplemented with additional information, thereby constructing a contact linelist.

The contact linelist is an outbreak-specific database of identified contacts, detailing each contact's socio-demographic information; pertinent information about the index case; and the maximum theoretical date of last exposure (for greater precaution and operational ease, generally defined as the date the index case was isolated from the community). For every day of follow-up, the contact was either 'seen' (that is, directly observed and interviewed to note any visible signs and symptoms), or 'not seen'. Contacts not seen were also divided into different categories: those not seen for a day or two ('single absence'); those not seen for three consecutive days ('lost to follow-up'); those that moved outside of their registered health districts (were 'displaced'); those that had never been traced; and known exposures without identification (classified as 'unknown contacts'). A contact's status could vary throughout the tracing period (e.g., if they were lost to follow-up, but then successfully traced). During this response, a surveillance unit (alternatively called

a 'cell') was established with the sole focus of analyzing the characteristics of contacts who were lost to follow-up or displaced. The aim was to inform and reinforce the overall contact tracing strategy by trying to identify and trace contacts that were never seen, lost to follow-up, or displaced.

During the listing process, different sources of information or an unclear or unfinished case investigation occasionally led to one person being listed multiple times for the same index case. In addition, some contacts may have been exposed to two different confirmed cases. For this study, such duplicates were identified and only one record kept for purposes of analysis. Where a contact already being contact traced had a new exposure to another case, they were followed for a second time—i.e., such that the contact tracing procedure recommenced based on the date of isolation of the more recent case (Fig. 1). Such contacts were then flagged as 'recycled', and their initial follow-up information excluded from analyses to avoid duplication.

2.3 Data

Databases of alerts, cases (suspected, confirmed, and probable), and contacts were examined. The main indicator being sought was the 'completeness' of contact follow-up over the full 21-day incubation period (this being defined as the consistent physical presence and willingness to answer all questions from a surveillance team regarding the occurrence of one or more symptoms). 'Non-completeness' was therefore defined as any failure to attend one or more days of follow-up for any reason.

Socio-demographic variables (age, gender, occupation, residence, and marital status), as well as several key performance indicators (vaccination status; number of contact tracing teams and whether the contact was receiving food support from the response team) were included for analysis so as to assess the impact of various factors on contact tracing completeness. Additional analyses included: delay in notification of suspected cases (time between the onset of symptoms and notification to contact tracing staff); alert delay (time between the onset of symptoms and initiation of alert by contact tracer); and isolation delay (time between the onset of symptoms and isolation of suspected case).

2.4 Analysis

STATA[®] version 14.1 (Stata Corporation, College Station, Texas, United States of America) and R version 4.0.2 were used [14] to perform different analyses (described below). The analyses were performed without imputation of missing values, due to the very low percentage of missing data (0.01%). We used univariable and multivariable logistic regressions to analyze the association between the dependent variable and the independent variables specified above.

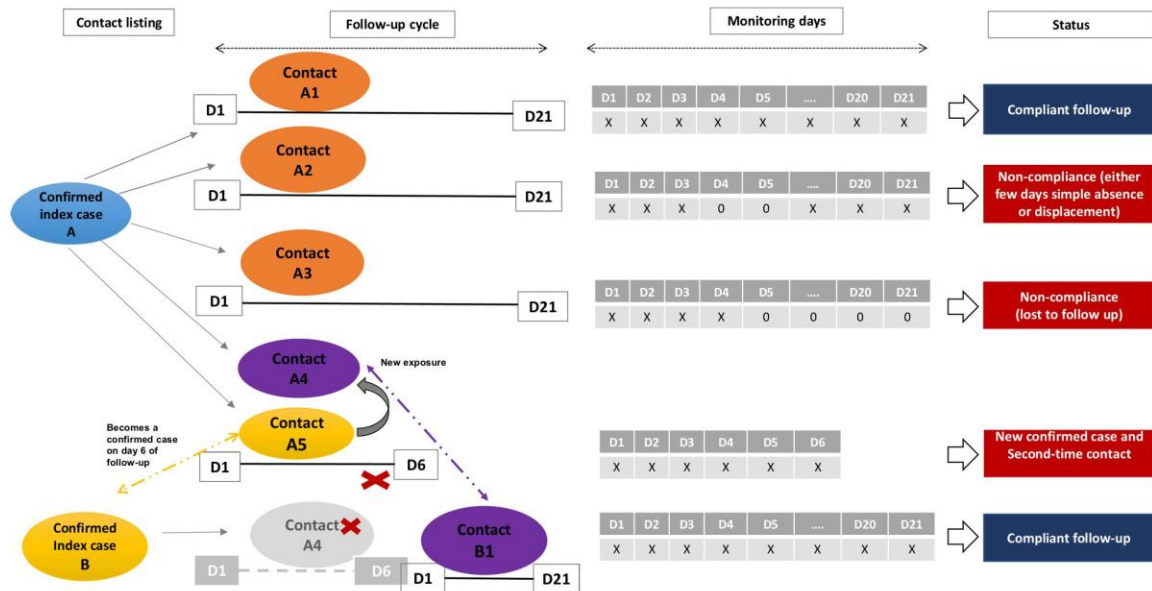


Fig. 1 Follow-up procedure for EVD contacts and completeness criteria

In the multivariable analysis only univariable predictors with a p value ≤ 0.2 were considered and we used a bottom-up stepwise procedure to select the final variables that were retained. We calculated crude and adjusted Odds Ratio (OR) with their 95% confidence intervals (CI). Different models were compared based on the Akaike Information Criterion (AIC). Multicollinearity among predictors was checked by the variance inflation factor. The final model was validated using the coefficient of discrimination.

3 Results

3.1 Characteristics of the EVD Cases

A total of 23 EVD cases (16 confirmed and 7 probable) were reported between the outbreak's declaration on 14 February 2021 and the end of the epidemic on 19 June 2021. All cases were reported in the Prefecture of Nzerekore, with five sub-prefectures affected. Initial investigations revealed that 8/16 (50%) of confirmed cases were known and followed as contacts at time of detection. Further investigation indicated that seven confirmed cases (43.8%) were epidemiologically linked but were not recorded as contacts prior their confirmation. One confirmed case was recorded as a contact but was not followed up by contacts tracing teams (Fig. 2). For confirmed cases, the delay to report varied between 1 and 11 days; the delay to alert between 1 and 9 days; and the delay to isolation between 1 and 11 (Fig. 3).

3.2 Characteristics of the EVD Contacts

The overall contact follow-up rate was 95%, while the overall completeness rate was 52.8% (these numbers are not identical as contacts could be followed up without 100% success, as previously described).

Of the 1071 contacts analyzed, 688 (64.2%) were aged 25 years and above; 510 (47.62%) were male and 561 female (52.6%); 706 (66.9%) were married; 450 (42.6%) were health workers; 786 (73.4%) were residing in urban areas; and 573 (54.3%) were high school graduates. A total of 905 (85.8%) received food aid, and 1030 (97.63%) were vaccinated against EVD (Table 1).

3.3 Univariable Analysis of Factors Associated with Non-completeness Contact Tracing

In the univariable analysis, multiple factors had statistically significant associations with EVD contact tracing completeness. This included: age, education, and employment in certain occupations. It also included whether a contact lived in an urban or rural area; and whether or not the area had more than one contact tracing team. Data for each is presented in turn.

Odds indicates that contacts in the 0–24 age group were 1.6 \times more likely to be missed with follow-up than those above 25 years of age (OR = 1.62; 95% CI [1.27–2.06]; $p < 0.001$). Unmarried contacts were 4.27 \times more likely to miss follow-up than married contacts (OR = 4.27; 95%

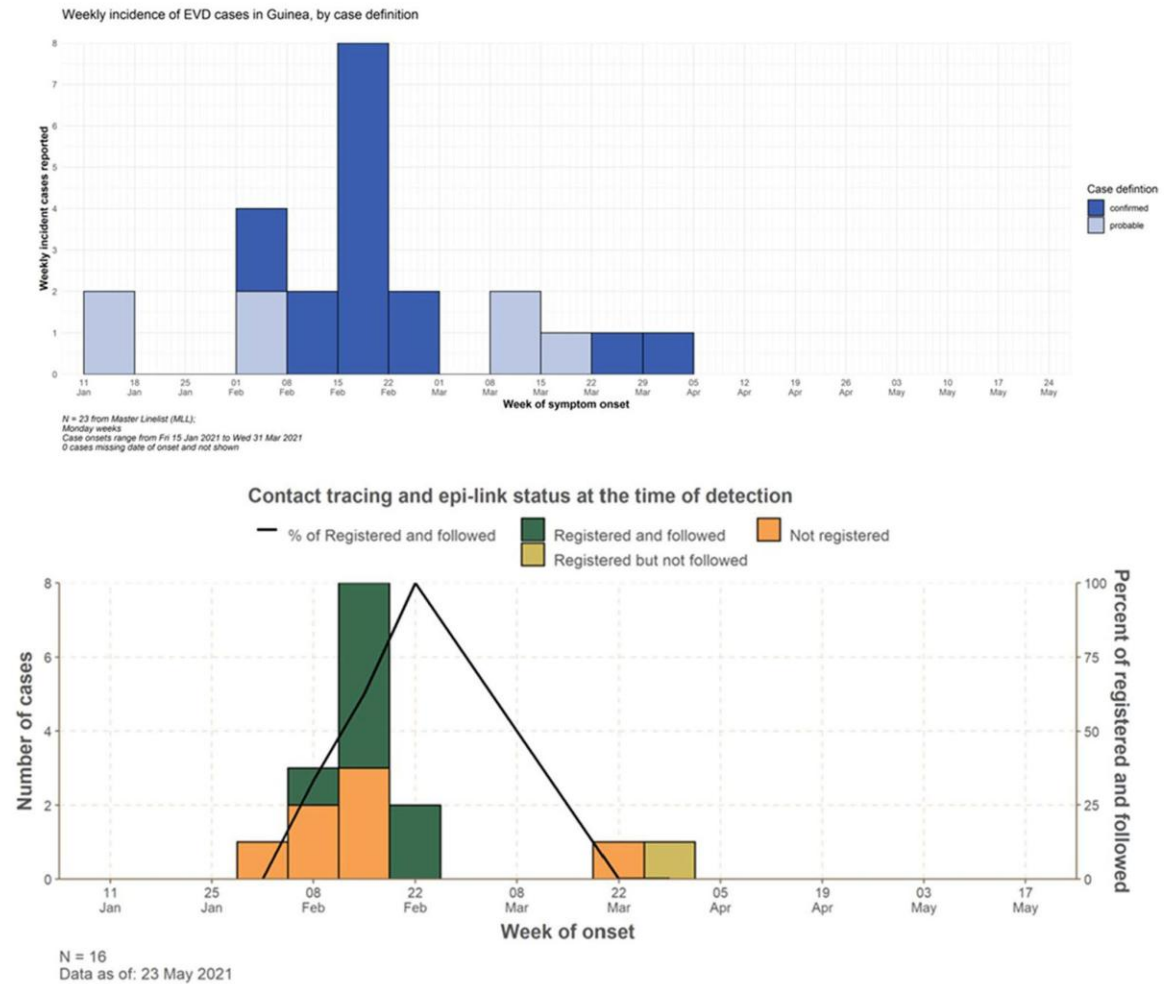


Fig. 2 **A** Number of EVD cases (confirmed and probable) by week of symptom onset in Guinea between February and May 2021. **B** Number of confirmed EVD cases by week of onset and contact tracing status including epidemiological link ('epi-link') at time of detection

between February and May 2021. Here, 'epi-link' refers to a known link with a preceding confirmed case (i.e., previously registered as a contact of another case) or not at the time of detection

CI [1.56–11.67]; $p < 0.01$). Contacts with no education or with primary or secondary education were 3.5, 2.9, and 2.3× (respectively) more likely to discontinue follow-up than those with tertiary education (OR = 3.58; 2.94; 2.30; 95% CI [2.13–6.03]; [1.70–5.10]; [1.42–3.71]; $p < 0.001$; $p < 0.001$; $p < 0.001$). Contacts with certain occupations were also more likely to miss follow-up. This included those with occupations, such as farmer, housekeeper, laborer, merchant, and nurse/midwife, who were 7.4, 6.6, 6.3, 5.5, and 4.0× (respectively) more likely to miss follow-up than doctors (OR = 7.46; 6.63; 6.32; 5.55; 4.09; 95% CI [2.41–23.05]; [2.23–19.67]; [2.08–19.19];

[1.70–18.10]; [1.39–12.05]; $p = 0.01$; $p < 0.01$; $p < 0.001$; $p < 0.01$; $p < 0.01$). Those contacts who lived in rural areas had 93% lower odds of missing the 21-day follow-up, compared to those living in an urban community (OR = 0.07; 95% CI [0.04–0.10]; $p < 0.001$). In areas with a single follow-up team, contacts were 1.7× more likely to miss follow-up compared to areas with two or more teams (OR = 1.70; 95% CI [1.39–2.32]; $p < 0.01$). Unvaccinated contacts were 13.8× more likely to be missed compared to those vaccinated (OR = 13.8; 95% CI [4.19–45.54]; $p < 0.001$) (Table 2).

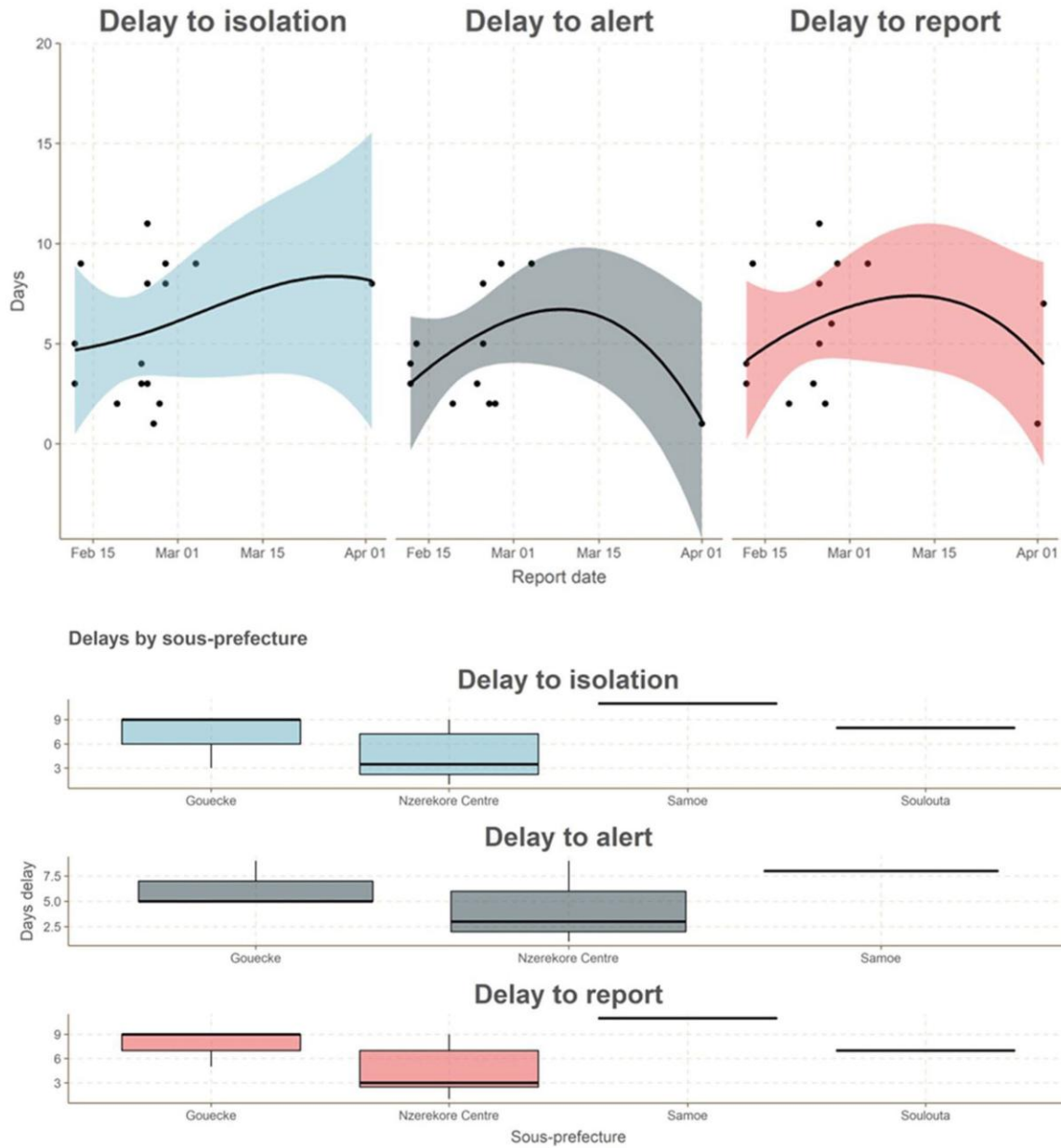


Fig. 3 **A** Evolution of delays to isolation, to alert, and to report over time of EVD confirmed and probable cases in Guinea between February and May 2021. **B** Delays to isolation, to alert, and to report of

EVD confirmed and probable cases by affected sous-prefecture in Guinea between February and May 2021

3.4 Multivariable Analysis of Factors Associated with Non-completeness Contact Tracing

As in the univariable analysis, in the multivariable analysis, multiple factors were significantly associated with EVD

contact tracing completeness. This included: age, gender, whether contacts lived in a rural or urban community, whether contacts received food donations, and whether or not the area had more than one contact tracing team. Data for each is presented in turn.

Table 1 Characteristics of EVD contacts in Nzerekore in the 2021 outbreak

Independent variables	Count	Percentage
Age groups (years)	<i>N</i> =1071	
0–24 years old	383	35.76
25 years and over	688	64.24
Sex	<i>N</i> =1071	
Male	510	47.62
Female	561	52.38
Marital status	<i>N</i> =1055	
Married	706	66.92
Widowed/divorced	38	3.60
Unmarried	311	29.48
Educational level	<i>N</i> =1055	
Unschoolled	231	21.90
Primary level	155	14.69
Secondary level	573	54.31
Higher level	96	9.10
Contact occupations	<i>N</i> =1055	
Doctors	27	2.56
Nurses/midwives/students	423	40.09
Merchants	57	5.40
Cultivators	108	10.24
Housewives	293	27.77
Other non-health public professionals	147	13.93
Residence of contact	<i>N</i> =1071	
Urban	786	73.39
Rural	285	26.61
Household receiving food donations	<i>N</i> =1055	
Yes	905	85.78
No	150	14.22
Number of assigned contact tracing teams	<i>N</i> =1055	
One	380	36.02
Two or more	675	63.98
Vaccination status	<i>N</i> =1055	
Vaccinated	1030	97.63
Unvaccinated	25	2.37

Odds also showed that contacts in the 0–24 age group were 2.3× more likely to miss follow-up than those in the 25+ age group (OR=2.38; 95% CI [1.70–3.34]; $p < 0.001$). Female contacts had 22% lower odds of missing the 21-day follow-up (OR=0.78; 95% CI [0.51–0.98]; $p = 0.03$) compared with men. Unmarried contacts were 12.76× more likely to miss follow-up than those married (OR=12.76; 95% CI [3.39–48.05]; $p < 0.001$). Contacts living in rural area had 99% lower odds of missing the 21-day follow-up compared to those living in urban area (OR=0.01; 95% CI [0.00–0.02]; $p < 0.01$). Contacts who did not receive food donations during the follow-up period were 3× more likely to be missed (OR=3.09; 95% CI [1.68–5.65]; $p < 0.001$)

compared to those who received food donations. Contacts in health areas with a single team were 8× more likely to miss follow-up (OR=8.16; 95% CI [5.57–11.96]; $p < 0.01$) than those in health areas with two or more teams (OR=1.00; 95% CI [1.68–5.65]; $p < 0.001$). Unvaccinated contacts were 30.1× more likely to be missed compared to those vaccinated (OR=30.1; 95% CI [5.12–176.83]; $p < 0.001$) (Table 3).

4 Discussion

With the increasing frequency of EVD outbreaks in Africa [15] and the established role of contact tracing in containing transmission [16], there remains a need to understand the various factors that contribute to contact tracing success and failure. Indeed, to the authors' knowledge, only one study roughly similar to this was conducted (in Port-Loko, Sierra Leone) [17].

Contact tracing completeness was a significant problem, though was certainly less so than has been documented elsewhere. The average contact follow-up rate was more successful compared with the earlier 2013–2016 West Africa EVD Epidemic in Guinea [18], Sierra Leone [19] and Liberia [20], and also compared with other recent outbreaks such as one in the Democratic Republic of Congo [8]. This is possibly the result of the post-2014 epidemic reforms undertaken by Guinea. Therefore, in the 2021 EVD outbreak in Guinea, many response staff had received training through Field Epidemiology Training Programs (FETPs) [10]. However, overall contact tracing completeness was still low (52.8%), which may explain the long delay between the onset of symptoms and notification and isolation that were identified. This has significant implications for survivability and containment [21]. In sum, despite the relatively high rate of follow-up in our study compared with other outbreaks, half of all confirmed cases were not previously known as contacts. This could have led to intense community transmission as experienced in previous outbreaks [22]. This was likely mitigated by the overall high vaccination rate among contacts (the result of earlier vaccination campaigns as well as ones rolled out in response to this outbreak) that may have contributed to the rapid interruption of the epidemic [23].

Taken together, it is clear that contact tracing is an integral part of any EVD response; is often not fully successful despite its importance; and is also poorly understood and under-discussed in the literature base. To help to address this research gap, this study investigated predictive factors for the completion of contact follow-up in the 2021 EVD epidemic in Guinea. Three factors related to the contacts themselves—and two related to the organization of the response—were associated with the relative completeness of contact tracing.

Table 2 Factors associated with non-completeness of contact tracing in Nzerekore during the 2021EVD outbreak, using univariable analysis

Independent variables	Odds ratio (OR)	95% CI	<i>p</i> value
Age groups (years)			
25 years and over (ref)	1		
0–24 years old	1.62	[1.27–2.06]	0.000***
Sex			
Male (ref)	1		
Female	0.78	[0.61–1.00]	0.05*
Marital status			
Married	1		
Widowed/divorced	3.15	[0.36–26.87]	0.29
Unmarried	4.27	[1.56–11.67]	0.00***
Educational level			
Superior (ref)	1		
Secondary	2.30	[1.42–3.71]	0.00***
Primary	2.94	[1.70–5.10]	0.000***
Unschooling	3.58	[2.13–6.03]	0.000***
Contact occupations			
Doctors (ref)	1		
Nurses/midwives/students	4.09	[1.39–12.05]	0.01*
Merchants	5.55	[1.70–18.10]	0.00***
Cultivators	7.46	[2.41–23.05]	0.000***
Housewives	6.63	[2.23–19.67]	0.00**
Other non-health public professionals	6.32	[2.08–19.19]	0.00***
Residence of contact			
Urban (ref)	1		
Rural	0.07	[0.04–0.10]	0.000***
Household receiving food donations			
Yes (ref)	1		
No	1.47	[1.04–2.09]	0.02**
Number of contact tracing teams			
Two or more (ref)	1		
One	1.70	[1.39–2.32]	0.00***
Vaccination status			
Vaccinated	1		
Unvaccinated	13.8	[4.19–45.54]	0.00***

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Younger contacts (i.e., those under 25 years old) were more likely to miss follow-up than older ones. This finding contrasted with what was observed by Jonathan et al. examining the 2019–2020 Kivu epidemic in DRC, who found that contacts in older age groups had a significantly higher probability of being missed than contacts in the youngest age group (defined in the study as 0–15 years) [11]. It is possible the discrepancy in examined age ranges could explain this difference, or it could be explained by cultural differences and varied prior experiences with EVD between the two countries. In Guinea, for example, youth often have a strong influence on discourse and beliefs within the community around issues such as EVD [24]. This can have a negative effect: during the earlier West Africa epidemic in Guinea,

young people were primarily responsible for various attacks that occurred against response teams, and were often very resistant to public health interventions [25].

In Guinea, male contacts were also more likely to miss follow-up than female contacts. This is consistent with a study in the DRC, where male contacts had slightly (though statistically significantly) greater odds of being lost to follow-up [11]. Similarly, in Sierra Leone, being female was also associated with successful contact tracing over a 21-day follow-up period [17]. A possible theory is that women are often more routinely present at home [26]. Conversely, male contacts are generally more likely to work outside the home and therefore less likely to be physically present when tracing teams arrive at

Table 3 Factors associated with non-completeness of contact tracing in Nzerekore during the 2021 EVD outbreak, using multivariable analysis

Independent variables	Adjusted odds ratio (aOR)	95% CI	<i>p</i> value
Age groups (years)			
25 years and over (ref)	1		
0–24 years old	2.38	[1.70–3.34]	0.000***
Sex			
Male (ref)	1		
Female	0.70	[0.51–0.98]	0.03**
Marital status			
Married (ref)	1		
Widowed/divorced	2.79	[0.27–28.29]	0.38
Unmarried	12.76	[3.39–48.05]	0.000***
Residence of contact			
Urban (ref)	1		
Rural	0.01	[0.00–0.02]	0.000***
Household receiving food donations			
Yes (ref)	1		
No	3.09	[1.68–5.65]	0.000***
Number of contact tracing teams			
Two or more (ref)	1		
One	8.16	[5.57–11.96]	0.00***
Vaccination status			
Vaccinated	1		
Unvaccinated	30.1	[5.12–176.83]	0.00***

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

households. One alternative may be to consider, circumstantially, remote contact tracing via telephone. However, this may be ineffective, because of frequently poor network coverage; the possibility that a contact lacks the necessary equipment, phone credit, or phone charge to make and receive calls; and the possibility that a contact may develop illness without self-reporting under an unobserved contact tracing system. Another possible resolution would be for contact tracing teams to arrange visits away from the home, though this introduces logistical challenges as well as the possibility of stigmatizing a contact at their place of work and in the wider community.

Unmarried contacts were significantly more likely to miss follow-up than those who were married. This result is consistent with the findings of a study on the effect of knowledge and perceptions of risks on Ebola-preventive behaviors in Ghana, which demonstrated that the never married and divorced persons were significantly less likely to take action to avoid Ebola than those who were married [27]. Marriage's effect on preventive health behaviors is extensively documented in the literature [28, 29]. For Ebola, it is believed married persons may be worried about the consequences for their close relatives.

Urban-dwelling contacts were more likely than rural-dwelling contacts to miss follow-up. A similar trend was observed in Sierra Leone [17]. This may be related to associations related to profession: economic, and professional activities in rural areas are often limited to a relatively defined geographical area, which may naturally limit contacts' overall movement thereby easing contact tracing activities.

When contacts were provided with food donations (compared to when they were not), this resulted in very significant differences in contact tracing completeness. This may be particularly important in rural areas. As in many sub-Saharan African countries, Guinea is a developing country where roughly 21.8% of households are living in a food-insecure state. Rural populations are the most vulnerable, where 71.1% experience food insecurity [30]. As contact tracing requires a physical presence test, the follow-up of contacts can limit economic activities, and therefore make it difficult for some contacts to remain compliant for the full duration of the contact tracing window. This finding aligns with the community-based containment strategy implemented in DRC, which also evidenced a positive effect of food support on contact compliance [21].

Health areas with two or more teams were more likely to complete the 21-day follow-up. This is presumably due to better supervision and support of the contact tracing teams, and echoes findings from a previous study examining the West Africa epidemic [18]. However, it is important to note that the composition of the contact tracing teams—in addition to their number—should be considered. Multidisciplinary teams are often advised, so that visits to contacts can be limited to one or two visits per day. For example, the Ugandan authorities recently decided to send a single multidisciplinary team to provide an integrated response to Sudan Virus Disease hotspots, rather than sending multiple separate teams to operate in silos [31]. This approach provides an opportunity to present the community with a single point of contact from which a relationship may be built between the people responding to the outbreak and those affected by it. This, in turn, may allow for mutual understanding and the building of trust, thus enabling responders and community members to work together as partners thereby better containing the outbreak.

There was a strong association between whether individuals had been vaccinated for EVD and contact tracing completeness. This agrees with a recent study in the DRC, where vaccination uptake was demonstrated to be significantly higher among contacts who accepted community isolation (i.e., those who voluntarily self-quarantined at a dedicated site and were regularly monitored over the 21-day incubation period) [21]. This finding is likely because those accepting vaccination were already prone to wider acceptance of the milieu of public health interventions that comprised the

overall EVD response. In other words, it is not vaccination that improved contact tracing completeness per se, but rather that those accepting vaccination were more accepting of the response and therefore contact tracing. While intuitive, this nevertheless has important implications when conducting contact tracing in future outbreaks, in that it may be prudent to commit more resources to tracing individuals who indicate reticence in this way. It also highlights the critical role of effective risk communication in public health interventions [32].

Whether these factors are shared in other countries at other times cannot be predicted using the results of this study—indeed, these findings corroborate the conclusions of some prior reports but disagree with others. What is clear is that certain demographic factors, and certain factors related to the organization of a response, can have significant effect on the probability of successful contact tracing. Understanding and considering these (perhaps context-specific) factors and using this knowledge to adjust resource allocation and contact tracing strategies, is evidently crucial to improve the completeness of contact tracing in future epidemics.

5 Conclusion

This study confirms that the completeness of 21-day follow-up in the 2021 EVD outbreak in Guinea was influenced in a statistically significant way by factors related to: the socio-demographic characteristics of contacts (such as age, gender, and education); and factors related to the organization of the response (including the overall number of contact tracing teams for a given area, and the support provided to contacts during their follow-up period such as food donations). This has important implications for how contact tracing during outbreaks of viral hemorrhagic fevers and other infectious diseases in similar contexts is designed and organized. Examining and understanding these factors—and adapting contact tracing accordingly, especially when related to organizational factors within the control of the response—may be key to saving lives and shortening life-threatening epidemics.

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manuscript and approved the final version. MK is responsible for the overall content as guarantor.

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Data Availability Data are available on reasonable request.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval The study was approved by the National Ethics Committee for Health Research (CNER) in Republic of Guinea (approval number 001/CNERS/21).

Consent for publication Participants' consent was obtained.

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2.4.5 | Case Report: COVID-19 and Lassa Fever Coinfection in Ebola Suspected Patient in Guinea

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Case Report: COVID-19 and Lassa Fever Coinfection in an Ebola Suspected Patient in Guinea

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Abstract. In this case report, we describe a clinical presentation and therapeutic history of a unique case diagnosed with Lassa fever and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a 23-year-old man from Yomou prefecture in southeast Guinea identified with suspected Ebola Virus Disease (EVD) in the midst of an ongoing outbreak of that disease in the same region. On May 3, 2021, he was admitted to the Nzérékoré Epidemic disease treatment center where his clinical condition deteriorated significantly. Laboratory testing performed on the same day reveals a negative EVD polymerase chain reaction (PCR). Three days later, the patient was tested positive for SARS-CoV-2 and Lassa fever by reverse transcriptase PCR (RT-PCR) assays. Laboratory examination also indicated severe hematological and biochemical deteriorations in the patient. This case substantiates the need for systematic differential diagnosis during epidemic-prone disease outbreaks to better manage severely unwell patients.

INTRODUCTION

Emerging infectious diseases such as Ebola Virus Disease (EVD), COVID-19, and Lassa fever pose significant epidemic threats.^{1,2}

In Guinea, the ongoing COVID-19 pandemic has already resulted in more than 23,501 cases and 168 recorded deaths³ (from March 12, 2020 to June 19, 2021). The country has also been facing the resurgence of EVD officially declared on February 14, 2021.⁴ As of June 10, 2021, a total of 23 cases, including 16 confirmed cases (10 recovered and 5 deaths) and 7 probable cases, have been recorded in the district of Nzérékoré, located in the country's southeast.⁵

In addition to the ongoing COVID-19 pandemic and EVD outbreak and to further complicate matters, on May 17, 2021, the Ministry of Health (MoH) declared a Lassa fever epidemic in the Prefecture of Yomou.

Lassa fever is caused by the Lassa virus. It is a viral hemorrhagic fever (VHF) that is endemic in West Africa (primarily in Sierra Leone, Guinea, Liberia, and Nigeria⁶). The primary reservoir host is the multimammate rodent *Mastomys natalensis*, which often lives close to human populations.⁷ In recent years, several advancements in Lassa fever identification have been made, such as improved diagnostics through real-time polymerase chain reaction (PCR) for genomic signatures and the successful utilization of sequencing technology to diagnose and characterize the virus.⁸

The concurrent COVID-19, Ebola, and Lassa fever outbreaks pose unique and significant risks to local populations in Guinea, especially as the country's situation is characterized by community reluctance (i.e., rejection of directions from national or international experts) and frustration following the

drawn-out COVID-19 pandemic and the recent 2013–2016 West Africa Ebola Epidemic. Thoroughly understanding comorbidity is also paramount, there are no reports for human infection with Lassa fever and COVID-19 as of this report.

CASE REPORT

A 23-year-old man from Yomou district in southeastern Guinea was identified with suspected EVD on May 3, 2021 at the Nzérékoré Regional Hospital. The patient presented with fever (38.8°C), anorexia, asthenia, chest pain, muscle pain, joint pain, abdominal pain, and insomnia. He was isolated, transferred, and admitted to the Ebola Treatment Center (ETC) the same day. Physical exam findings on admission included a temperature of 39.4°C, blood pressure of 170/100 mm of Hg, respiratory rate of 26 breaths/minute, blood oxygen saturation of 97.2%, and pulse rate of 100 beats/minute. Samples (blood and swabs) were collected and tested for acute viral infection. Polymerase chain reaction testing was performed using the Fosun COVID-19 reverse transcriptase PCR (RT-PCR) Detection Kit (Fosun Pharma, Shanghai City, China) to confirm the suspected COVID-19 infection. The Lassa fever was confirmed by RealStar[®] Lassa Virus RT-PCR Kit (Altona Diagnostics, Hamburg, Germany). The Xpert[®] Ebola (Cepheid, Sunnyvale, CA) was used to confirm the suspected EVD infection. The Marburg virus disease test was carried out using the RealStar filovirus RT-PCR Kit (Altona Diagnostics). While EVD and Marburg tests were negative, the patient was found to be Lassa fever positive and COVID-19 positive by PCR. Further laboratory testing (blood biochemical tests) showed that hepatic (increased levels of alanine aminotransferase [ALT] and aspartate aminotransferase [ASAT]) and kidney functions (an elevated creatinine level) were seriously altered and required immediate treatment (Table 1).

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On May 4, 2021, the patient left the Nzérékoré ETC of his own accord and without informing hospital staff. He returned to his village in Yomou. Upon being informed of the situation, a family member brought him to a local EVD Treatment Unit (ETU) where biosafety measures were put in place, and the patient was admitted. The patient was then transferred back to the Nzérékoré ETC for further testing and investigation (Figure 1).

On May 6, 2021, readmittance to the ETC was deemed necessary because of the appearance of new symptoms such as respiratory distress and the further deterioration of the patient's clinical condition (asthenia, abdominal pain, and oliguria). More laboratory testing was conducted to guide medical actions.

Hematology performed with Sysmex pocH-100i™ Automated Hematology Analyzer (Sysmex Corporation, Kobe, Japan) and biochemistry with Piccolo Xpress® (Abaxis, Inc., Union City, CA) showed a severe deterioration of hepatic, renal, and hematological functions (Table 1). The treatment plan consisted of rehydration, the provision of oxygen therapy and antibiotics, and other symptomatic treatments.

Despite attempts at several treatments including oxygen therapy and ultimately resuscitation, the patient rapidly deteriorated and died on May 7, 2021 with respiratory distress and organ failure symptoms.

To better understand the chains of transmission and to appreciate the potential risks and extent of the viruses' circulation, the MoH collaborated with the WHO and other partners to carry out a thorough case investigation. This case investigation found 30 contacts and public health actions were initiated immediately. Further to few days' rejection of response activities implementation, the community accepted the strategy of community confinement (i.e., no movement of contacts outside their village until the end of the follow-up period) with food support. Contact follow-up

continued until the end of the 21-day period without any secondary cases being detected.

DISCUSSION

Many cases of Lassa fever have been described with specific conditions.⁹⁻¹¹ However, the unusual association of two epidemic-prone diseases (Lassa fever and COVID-19) in the context of an ongoing Ebola outbreak is a unique and previously unreported case.

The case reported here was admitted to the ETC with symptoms that included those in the EVD case definition.¹¹ Additionally, he presented a respiratory distress syndrome that is common in Lassa fever (up to 20% of cases)^{12,13} as well as in COVID-19.¹⁴ Laboratory testing showed liver and kidney failure, which directed the clinical management team to conduct further testing as early identification of Lassa fever is one of the critical points for maximizing the benefit of further available care such as antiviral therapy.¹⁵

The hematological analysis showed polycythemia in which the hematocrit and/or Hb concentration are elevated in peripheral blood and may reduce the blood flow and the amount of oxygen that reaches heart, brain, and other vital organs increasing the risk of clots within a blood vessel causing a stroke or death.¹⁶⁻¹⁸ He had a high risk of vascular thrombosis, which is well described in patients dying of COVID-19. This supports the reported statement that the thrombotic complications are central determinants of the high mortality rate in COVID-19 and that thrombosis prevention strategies remain important.¹⁶ The biochemical analyses carried out on May 3 and May 7, 2021 showed elevated levels of ALT and ASAT markers more than 100 time arguing for acute hepatitis. The kidney function marker measured by creatinine and blood urea nitrogen were at least increased seven times the upper limit of normal.

TABLE 1
Dynamic of hematology and biochemistry profile of the patient between admission 1 and 2

Laboratory	Reference range	First day of admission (May 3, 2021)	Second day of admission (May 7, 2021)
Hematology			
Hematocrit (%)	26.0–50.0	46.1	47.3
Hemoglobin (g/dL)	8.0–17.0	16.3	18.2
White blood cells (×10 ³ /μL)	3.0–15.0	5.1	14.7
Mean corpuscular volume (fL)	86.0–110.0	79.9	74.5
Mean corpuscular hemoglobin (pg)	26.0–38.0	28.2	28.7
Neutrophils (%)	45.0–95.0	85.2	77.7
Lymphocytes (%)	5.0–55.0	12.1	15.1
Platelets (×10 ³ /μL)	50–400	52	72
Biochemistry			
Glucose (mg/dL)	73–118	153	118
Blood urea nitrogen (mg/dL)	7–22	28	168
Creatinine (mg/dL)	0.6–1.2	2.1	15.3
T bilirubin (mg/dL)	0.2–1.6	0.9	4.4
Albumin (g/dL)	3.3–5.5	2.3	1.5
Aspartate transaminase (U/L)	11–38	1,018	> 2,000
Alanine transaminase (U/L)	10–47	288	1,344
Creatine kinase (U/L)	30–380	1,771	4,775
Sodium (mmol/L)	128–145	123	125
Potassium (mmol/L)	3.6–5.1	2.9	Very high (results falling outside of the highest display range set in the analyzer).
C-reactive protein (mg/L)	0.0–7.5	40.8	81.9

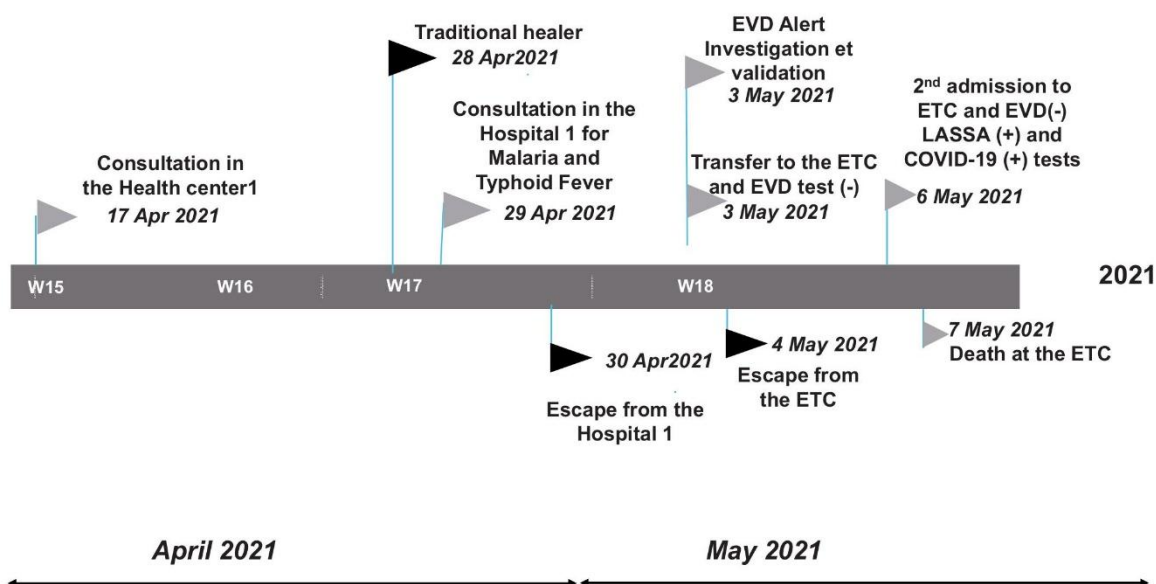


FIGURE 1. Therapeutic itinerary of the COVID-19 and Lassa fever coinfection patient from his village (the health district of Yomou) to the regional capital (Nzérékoré), April to May 2021.

This case also clarifies the need for laboratory testing that can run differential diagnoses between various diseases that share the same symptoms and expression, especially those that are endemic, epidemic-prone, or contemporaneously pandemic. Since the case lived in a highly rural area of the district of Yomou where the reported frequency of COVID-19 is among the lowest in the country suggests that the COVID-19 incidence might be underestimated in African countries as several reports have suggested.^{19,20}

The reemergence of Lassa fever in Guinea was of grave concern. This patient twice left without notice from medical centers foregoing the opportunity for proper and timelier care. His subsequent return in a seriously deteriorated condition was too late for available care to prove effective. The patient's source of infection remains unknown both for COVID-19 and Lassa fever. Moreover, subsequent confirmation of both diagnoses led to an in-depth investigation that revealed no evidence of COVID-19 coexisting cases with the patient during his first hospitalization and excluded any possible contamination that occurred there. Although Lassa fever is endemic in this area,^{6,21} the source could be related to human-to-human or zoonotic transmission. The COVID-19 contamination may have occurred anywhere else given the spread of the disease in Guinea.

This event is a fundamental reminder that endemic and epidemic-prone diseases continue to occur during the COVID-19 pandemic affecting the capacities of exhausted healthcare professionals.²²⁻²⁴ The first-ever outbreak of Marburg Virus Disease in the West African region was recently reported in Guinea,²⁵ few weeks after declaring the end of the EVD outbreak.²⁶

Cross-border issues may be a significant factor in this case as of May 25, 2021, a Lassa fever outbreak was ongoing in Liberia, and suggest an epidemiological link between

the outbreaks that must be investigated and taken into account.^{20,21} This case makes it clear how important it is to identify, track, and predict the spread of disease so that all levels of government can respond quickly and deploy the resources necessary to stop its spread.

Finally, as one epidemic can hide another, this case clarifies the need to expand disease-specific surveillance to areas surrounding the outbreak's known geography. In this case, the extension of Ebola surveillance into neighboring districts allowed us to identify and diagnose this Lassa fever index case, facilitating the prompt declaration of a Lassa fever epidemic and the rapid implementation of control measures to limit the virus' spread in Guinea and Liberia.

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Investing in preparedness for rapid detection and control of epidemics: analysis of health system reforms and their effect on 2021 Ebola virus disease epidemic response in Guinea

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ABSTRACT

The 2014–2016 West Africa Ebola Virus Disease (EVD) Epidemic devastated Guinea's health system and constituted a public health emergency of international concern. Following the crisis, Guinea invested in the establishment of basic health system reforms and crucial legal instruments for strengthening national health security in line with the WHO's recommendations for ensuring better preparedness for (and, therefore, a response to) health emergencies. The investments included the scaling up of Integrated Disease Surveillance and Response; Joint External Evaluation of International Health Regulation capacities; National Action Plan for Health Security; Simulation Exercises; One Health platforms; creation of decentralised structures such as regional and prefectural Emergency Operation Centres; Risk assessment and hazard identification; Expanding human resources capacity; Early Warning Alert System and community preparedness. These investments were tested in the subsequent 2021 EVD outbreak and other epidemics. In this case, there was a timely declaration and response to the 2021 EVD epidemic, a lower-case burden and mortality rate, a shorter duration of the epidemic and a significant reduction in the cost of the response. Similarly, there was timely detection, response and containment of other epidemics including Lassa fever and Marburg virus disease. Findings suggest the utility of the preparedness activities for the early detection and efficient containment of outbreaks, which, therefore, underlines the need for all countries at risk of infectious disease epidemics to invest in similar reforms. Doing so promises to be not only cost-effective but also lifesaving.

INTRODUCTION

In recent decades, emerging infectious disease outbreaks have occurred at an

SUMMARY BOX

- ⇒ Infectious diseases with epidemic potential, in particular Ebola virus disease (EVD), have demonstrated in Guinea (2014–2016), that a single unidentified transmission chain in a susceptible area (ie, an area with a weak health system and absence of an Early Warning Alert System) can quickly escalate beyond straightforward containment.
- ⇒ The 2014–2016 West African EVD epidemic was a compelling reminder of the need to strengthen preparations in all countries worldwide for improved global health security.
- ⇒ After this 2014–2016 EVD epidemic, the Guinean government and partners invested in strengthening epidemic preparedness and response capacity, which contributed to rapidly detect and respond to several subsequent epidemics.
- ⇒ Health reforms and investment in outbreak preparedness implemented in Guinea after 2014–2016 EVD outbreak collectively served to the early detection of the 2021 EVD outbreak and its rapid control (shorten duration of response and prevent international spread).
- ⇒ Governance and technical autonomy of epidemic response structures are needed as well as building trust with the community for rapid control of epidemics.

increasing scale and frequency.¹ Along with the recent and ongoing COVID-19 pandemic, these outbreaks should be a wake-up call for all countries to invest in preparedness to avoid their health systems being overwhelmed during health crises.²

Such preparedness activities may seem out of reach especially where health systems

generally perform poorly like most African countries,³ which are also prone to epidemics. During the COVID-19 pandemic, low-income groups were more affected in terms of morbidity and mortality. Furthermore, gender inequalities and family violence also increased during lockdowns further impacting on women.⁴ Epidemics can also create or incur indirect economic losses such as work-force absenteeism, wages not earned, lower tax revenue, informal health costs (eg, for patient transport), negative impacts on human resources for health, losses in the agriculture sector, reduced tourism and travel, reduced trade and retail activity, environmental impacts and/or educational losses, all of which can serve to exacerbate existing inequalities, especially for marginalised populations.^{5,6}

One profound example of these consequences of global health inequalities is the 2014–2016 EVD epidemic in West Africa. The epidemic exposed major health system weaknesses including severe shortages of skilled health workers and a general lack of preparedness within the health system for the prevention, detection and containment of the outbreak at its source.^{7,8} Subsequently, the largest, longest and deadliest outbreak of EVD in human history occurred, causing 28 652 infections and resulting in 11 325 deaths across 10 countries with 99% of fatalities occurring in three neighbouring countries: Guinea, Sierra Leone and Liberia.⁹ The direct fiscal costs of the 2014 EVD epidemic were estimated to be around 6 billion USD, while the estimated economic burden ranged from 2.8 to 32.6 billion USD in lost gross domestic product.¹⁰

Investment in epidemic preparedness is crucial, because its cost is small compared with the unmitigated impact of a health emergency.¹ Adequate investment in epidemic preparedness capacities can help communities and countries avoid or at least minimise the impacts of outbreaks. However, as the results of this investment in preparedness are not immediate and visible (especially when successful),⁷ many governments inadequately invest in building preventative capacities and implementing preventive interventions during the ‘preoutbreak’ period.¹¹

Nevertheless, building on lessons learnt from the West African EVD disaster, and in line with the Joint external evaluation (JEE) report of International Health Regulations, 2005 (IHR, 2005) core capacities,¹² Guinea invested in preparedness and health emergency management capacity after the 2014–2016 EVD epidemic.¹³ The country then was able to rapidly detect and respond to several epidemics from 2017 to 2020, including yellow fever, measles, anthrax, Lassa fever, food-borne illness, circulating vaccine-derived poliovirus type 2 (cVDPV2) and COVID-19.¹⁴ The country has also been stress testing its capacity to respond to several concurrent epidemics (yellow fever, COVID-19, EVD, Lassa fever and Marburg virus disease) from 2020 to 2021. This latest EVD outbreak declared on 14 February 2021 was reported in Nzerekore, near the epicentre of the previous outbreak¹⁵ and lasted only 5 months.

Based on field experience, as a result of participating in both EVD outbreaks as well as other outbreaks and preparedness capacity building activities, we described in this paper, health system reforms conducted in Guinea before, during and after the 2021 EVD outbreak that may have contributed to a more effective response and its rapid containment.

THE ‘PREOUTBREAK’ PERIOD (FROM THE END OF 2014–2016 EVD OUTBREAK LEADING UP TO THE 2021 EVD OUTBREAK)

The 2014–2016 EVD epidemic evidenced the need for the affected countries, and other low-income countries with similarly weak health systems, to build stronger health systems and surveillance mechanisms in order to prevent future outbreaks from escalating in a similar fashion.¹⁶ Accordingly, Guinea implemented WHO recommendations by maintaining 90 days of postepidemic enhanced surveillance, during which several capacity-building activities, such as Integrated Disease Surveillance and Response (IDSR) cascade trainings from national to community level and data management training for Health District Management Team, were carried out to strengthen the country’s capacities.¹⁷ Subsequently, the government achieved key preparedness activities related to IHR core capacities (discussed hereafter).

Scaling up IDSR capacity

Challenges in the transmission and management of surveillance data contributed to the delay in detecting and confirming the EVD outbreak.¹⁸ There was a shortage of IDSR-trained public health workers, leading to under-reporting of cases and problems with data completeness, accuracy and reliability.¹⁹ In 2015, the Guinean Ministry of Health (MoH) begun IDSR strengthening^{19,20} to have surveillance and early warning systems that transmitted information from the community level to the health centre level, which was then sequentially relayed to the district level, the regional level and, finally, to the central or national level.

Joint External Evaluation

Guinea conducted its first JEE²¹ in April 2017 using the third version of the JEE that has 19 technical areas and 48 indicators.¹² The JEE helped determine the country’s baseline capacities as required under the IHR (2005). The country was found to have no capacity on 18 indicators, limited capacity on 20 indicators, developed capacity on nine indicators and demonstrated capacity on one indicator. The JEE informed the development of the National Action Plan for Health Security

National Action Plan for Health Security

Guinea’s national health security action plan²² was developed and validated in April 2019 due to extensive work that brought together 19 focal points of the IHR technical areas and partners. This 4-year plan (2019–2023) involved the sectors of health, livestock, environment and the Ministry of Agriculture.²³

Simulation exercises (SIMEX)

During the 2014–2016 EVD outbreak in West Africa, WHO and others within the public health community emphasised the need for simulation exercises to ensure that public health emergency response systems were in place to manage the importation of EVD into high-priority, non-affected countries.²⁴

In October 2018, the National Health Security Agency (ANSS) of Guinea, with the support of partners including WHO, organised tabletop exercises and drilled simulation exercises for the response to a possible cholera outbreak. These simulation exercises revealed that the preparedness and response mechanisms including Regional Epidemic Alert and Response Teams (ERARE), Prefectural Epidemic Alert and Response Teams (EPARE), Epidemic-prone diseases Treatment Centers (CT-Epi), Public Health Emergency Operations Centers (PHEOCs) are in place and capable of being operational at any time. Additionally, the strong involvement of the administrative and political authorities and the commitment of the communities in the localities visited revealed their interest in the emergency response teams.²⁵

One health

In the wake of the 2014–2016 EVD outbreak, Guinea was targeted for substantial support and capacity building from the USA and other nations to facilitate the recovery and renewal of its health system incorporating a One Health approach.^{26 27} In November 2016, an interministerial meeting held in Dakar, Senegal, resulted in formalised commitments from the three nations (Guinea, Liberia and Sierra Leone) to strengthen resilience to health threats by establishing a Regional Strategic Roadmap to institutionalise the One Health approach. Since then, Guinea has made significant progress towards establishing National One Health platforms to coordinate health security interventions in collaboration with international partners.²⁸

Creation of decentralised structures

Based on experiences in the 2014–2016 EVD epidemic in Guinea, the ANSS acquired decentralised structures for its operationalisation. They include 8 ERARE; 33 EPARE; 33 CT-Epi and 33 PHEOCs. Normative documents were developed to guide and assist the staff of these facilities.²⁵

Risk assessment and hazard identification

Guinea conducted a risk assessment in October 2017 to develop a multihazard plan as recommended by the JEE report.¹² The exercise involved a risk assessment and vulnerability mapping in the country, using the Strategic Tools for Assessing Risk and Vulnerability Risk Assessment and Mapping approach. Six hazards with a high risk of occurrence and impact on communities in Guinea, including EVD, were identified²⁹ and a multihazard plan developed.

Expanding human resource capacity

The state of the Guinean health workforce is one of the country's bottlenecks in advancing health outcomes. The 2014–2015 EVD outbreak provided a policy window to invest in the workforce and reform the health system.¹³ The Government of Guinea launched its Field Epidemiology Training Programme (FETP) in 2016. Since then, it has graduated 179 staff from the frontline (ie, district-level) programme and 16 from the intermediate programme and 10 advanced FETP graduates who participated in the Burkina Faso (Formerly West Africa) Field Epidemiology and Laboratory Training Programme.³⁰

Strengthening community preparedness

In the 2014–2016 post—Ebola agenda—setting for health system strengthening, the MoH Guinea recruited 5000 Healthcare Workers (HCW) and deployed in rural areas. A number of health centres were rehabilitated and logistics support provided to health districts for field activities, such as vaccination campaigns and training, and local contracting of 10–15 community health workers per subdistrict for epidemic-prone diseases surveillance.³¹

THE OUTBREAK PERIOD (14 FEBRUARY 2021 TO 19 JUNE 2021)

On the 14 February 2021, a case of EVD was identified in N'zerekore. Thereafter, reactive interventions—including establishing an Emergency Operations Centre (EOC); the reinforcement of an Early Warning Alert System (EWAR); and the reinforcement of active readiness capabilities in districts adjacent to N'zerekore were set up to contain the 2021 EVD outbreak.

Emergency operation centres

Once EVD was detected, it was crucial to have a well-prepared workforce (sufficient in both skills and numbers); updated response plan; standard operating procedures (SOPs) and protocols for field epidemiology and laboratory investigations, case identification, management, and contact tracing protocols. These SOPs and protocols were implemented through functional EOC that provided leadership with clear lines of command and with daily review of the outbreak.⁷ EOC activation procedures and outbreak management were coordinated mainly at district and regional (Nzerekore) in 2021.

Early Warning Alert System

EWAR³² help in: detecting the first case of the disease in a population previously free of disease; detecting new cases in an area already affected by disease; detecting of an abnormal increase in the level of a disease normally present from a baseline level in a timely fashion; screening for individual cases of a non-communicable disease; and first detecting an invasive species in an area previously free of that species.³³

In Guinea, the WHO supported the strengthening of the alert system.³⁴ A green number (a toll-free telephone line) was set up over the outbreak period that community



members could call to alert the health system of any health event in the community, including but not limited to EVD-related concerns.

Active readiness in non-affected health districts

Based on the conclusion of the WHO rapid risk assessment (a very high risk at the national level, an increased risk at the regional level, and a low risk at the global level); and considering lessons learnt from prior EVD experiences (including the need to move fast and use national expertise much as possible), dedicated full response capacity was rapidly established in N’zerekore—the areas of active transmission. Additionally, an active response mode in the six health districts bordering N’zerekore was also developed and implemented, due to their proximity to known cases. Scaling up active readiness in other health districts and regions also occurred through reinforcing the existing IDSR mechanism with daily alerts and reporting.

THE 2021 EVD POST-OUTBREAK 90 DAY’S SURVEILLANCE PERIOD

The ANSS and the WHO maintained enhanced vigilance in the region until the end of the 90 days following the declaration of the end of the EVD epidemic in Guinea. Additionally, as part of the monitoring and evaluation of ‘HR’s capacities, the Guinean MoH with technical support of WHO conducted the After-Action Review

of three outbreaks (EVD in Nzerekore, Marburg virus disease in Gueckedou and Yellow Fever in Koundara) in December 2021.³⁵ Lessons learnt and best practices identified during this exercise will help to improve the country preparedness for better response to future outbreaks.

WAS GUINEA BETTER PREPARED FOR THE 2021 EVD OUTBREAK?

Timely outbreak response

The 2014–2016 West Africa EVD outbreak went on unobserved for over 3 months³⁶; the outbreak that began in December 2013 was not officially declared until 23 March 2014 despite the first alert being issued on 24 January 2014. Further, the declaration of a Public Health Issue of International Concern (PHEIC), which would motivate financial and logistic support to the countries most affected and elevated the emergency to one demanding global attention, was not declared until 8 August 2014.³⁷ On 7 March 2015, the WHO (in collaboration with MERCK) availed the only advanced experimental vaccine, a full year after the epidemic’s onset, as part of a clinical trial.³⁸ The Report of the EVD Interim Assessment Panel commissioned by the WHO stated that there were “significant and unjustifiable delays occurred in the declaration” in relation to the delay between the WHO being informed of the 2014–2016 EVD epidemic in West Africa and declaring it a PHEIC.³⁹

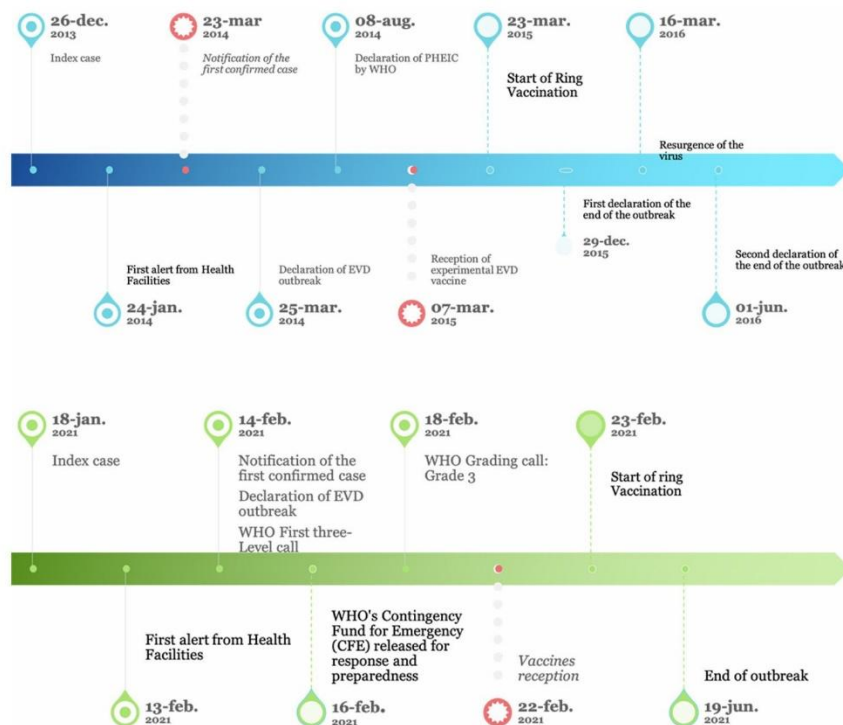


Figure 1 Timelines of the major events during the 2014–2016 (blue) and 2021 (green) EVD outbreaks in Guinea. EVD, Ebola Virus Disease; PHEIC, Public Health Issue of International Concern.

Table 1 Summary of the Case Fatality Rate (CFR) for the first and second EVD outbreaks in Guinea

EVD cases	Year of outbreak					
	2014–2016			2021		
	Number of cases	Number of deaths	Case fatality rate (CFR)	Number of cases	Number of deaths	Case fatality rate (CFR)
Confirmed cases	3358	2088	62%*	16	5	31%*
Probable cases	456	456	–	7	7	–
Total number	3814	2544	67%†	23	12	52%†

*CFR among confirmed EVD cases.
 †Global CFR.
 CFR, Case Fatality Rate; EVD, Ebola Virus Disease.

During the 2021 EVD outbreak, the national health authorities and the WHO rapidly reacted on notification of the suspected epidemic.⁴⁰ The outbreak that commenced on 15 January 2021 (the date of symptoms onset of the first case) was reported as an alert on 28 January 2021, after a cluster of deaths in the subprefecture of Gouécké, N’zerekore Region. The official outbreak declaration was made on 14 February 2021, that is, within 2 weeks after alert reporting and at the same day the WHO activated its emergency procedures to support the response⁴¹ (figure 1).

Following the declaration, a swift outbreak response was enacted with the deployment of a national support team from ANSS rapidly to thoroughly conduct an investigation of the confirmed cases and roll out specific tools for rapid epidemic control.⁴⁰ With the support of WHO, the government availed vaccines that were already in existence on 23 February 2021, that is, within 1 week of the outbreak declaration. The two new Food and Drug Administration-approved therapeutic drugs (Mab-114 and Regeneron) for EVD were availed to treat eight of the confirmed EVD cases, all of whom survived.

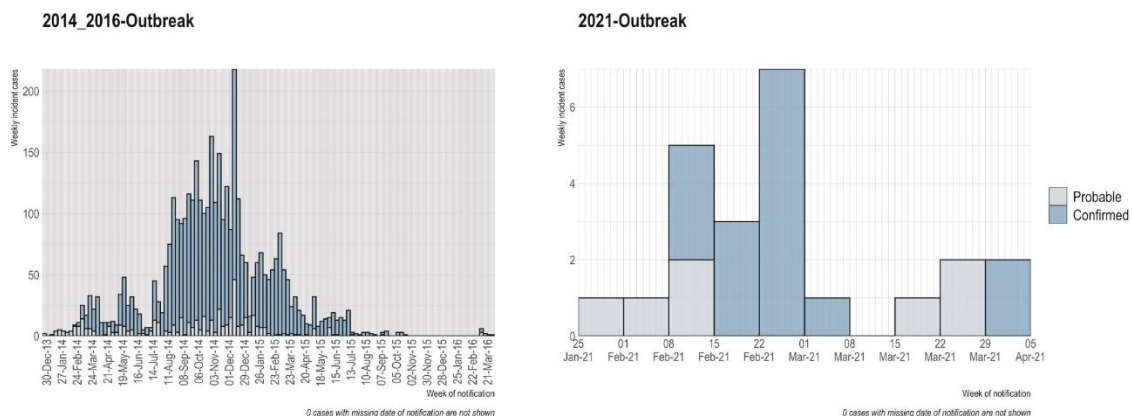
The country opened an isolation centre within 48 hours of the declaration of the outbreak, compared with the 3 weeks it took following declaration of the 2014–2016 West Africa EVD epidemic.⁴²

Efficient contact tracing and case investigations

The newly trained FETP graduates played leading roles in response to the 2021 EVD outbreak in the south-eastern part of the country, including alert validation, case investigations, active case finding, contact tracing, and data management. Their contributions as well as those of the community workers in local one-health platforms, led to the successful follow-up of >95% of EVD contacts, an essential component of successful EVD response.³⁰ The one-health platforms contributed to the investigation of the source of the outbreak that is reportedly to be a persistent virus linked to the 2014–2016 EVD outbreak but not a new spillover from animal to humans.¹⁵

A reduction in the case fatality rate

The disease incidence and lethality was reduced.⁴⁰ The overall lethality decreased from 2544/3814 (67%) in


Figure 2 Comparison of the epidemiological curves of the two EVD outbreaks 2014–2016 and 2021 in Guinea. EVD, Ebola Virus Disease.

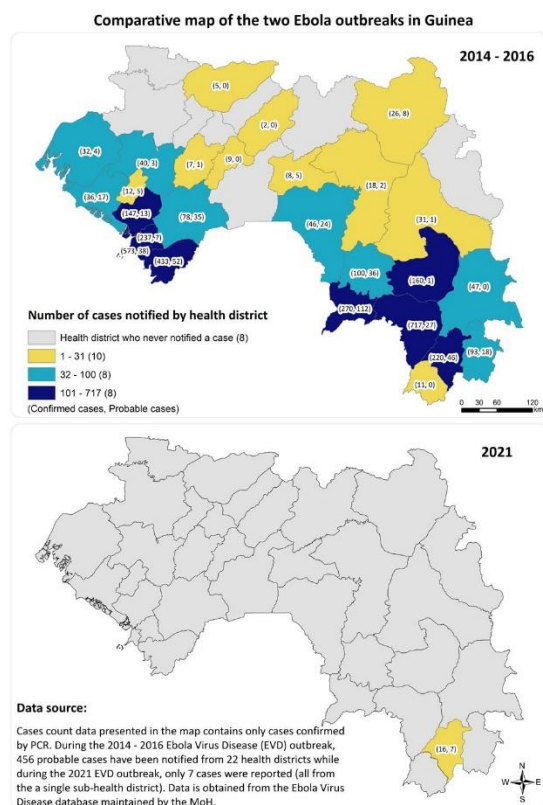


Figure 3 Comparison of the spread of the two EVD outbreaks 2014–2016 and 2021 in Guinea. EVD, Ebola Virus Disease; MoH, Ministry of Health.

the 2014–2016 epidemic, to 12/23 (52%) in the 2021 outbreak, while the lethality of confirmed cases was reduced from 62% in 2014–2016 to just 31% in 2021. While this may be due to more readily accessible vaccination and therapeutic interventions, the rapid availability of these interventions nevertheless rested on the preparedness activities undertaken in Guinea before the 2021 outbreak (table 1).

Shorter duration of the outbreak

The 2014–2016 West Africa EVD epidemic was controlled after more than 2 years, while the 2021 epidemic only lasted 5 months (figure 2). While the first one cost billions of dollars,¹⁰ the second one cost around 45 million.⁴³

Rapid control of the spread of the outbreak

While the initial outbreak spread over to 30 out of 38 Health Districts in the country, the subsequent outbreak was contained within one health district (figure 3).

Early detection of other epidemics

The extension of EVD surveillance into neighbouring districts identified a unique case of Lassa Fever and SARS-CoV-2 coinfection in a patient from Yomou prefecture in southeast Guinea on 6 May 2021. An alert was raised

regarding the individual whose signs and symptoms of illness were commensurate with EVD infection followed prompt declaration of a Lassa fever epidemic and the rapid implementation of control measures to limit the virus’ spread in Guinea.⁴⁴

In addition, a Marburg virus disease (MVD) outbreak was confirmed in Gueckedou on 9 August 2021. This is the first time it has been detected in Guinea and West Africa. An improved preparedness confined this case to a single confirmed case.⁴⁵

WHAT WAS THE OVERALL EFFECT OF HEALTH REFORMS ON EPIDEMICS DETECTION AND RESPONSE?

Admittedly, Guinea seemed better prepared for the 2021 epidemic than in 2014–2016. While the impact of enhanced preparedness and response activities contributed to the early detection of and response to other epidemics such as yellow fever, measles, anthrax, Lassa fever, food-borne illness, cVDPV2,¹⁴ the institutional reforms undertaken had mixed effects on the COVID-19 response.^{46 47} Guinea delayed in declaring and taking strong action for political reasons, as 2020 was an election year. The president of the independent national electoral commission was one of the early and most visible victims.⁴⁸

Furthermore, trust between political authorities and communities is never guaranteed. For instance, the community deaths reported in the village of Kpaghalaye during the 2021 epidemic,⁴⁹ which resulted in the latest confirmed case preferring to remain hidden in the community until he recovered as opposed to accepting admission to the treatment centre.

Thus, governance and technical autonomy of epidemic response structures as well as building trust with the community are needed in addition to health sector reforms to improve emergency preparedness.

CONCLUSION

While specifically appraising the epidemiological consequences of any one intervention is not possible, the overall effect may indicate such activities represent important preparedness and early warning investments that all countries at risk of epidemics should consider. The WHO Regional Office for Africa’s (AFRO’s) three flagship projects which incorporate lessons learned from COVID-19, EVD, and other health emergencies is a viable model for Member States to develop their capacities to prepare for, detect and respond to public health emergencies.⁵⁰

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3 | Conclusion and perspectives

This chapter concludes the thesis by synthesising the findings of six interlinked studies focused on public health emergency preparedness and response, particularly in the context of Ebola Virus Disease (EVD) and related epidemic challenges in sub-Saharan Africa. These studies collectively address critical aspects of epidemic management, ranging from early warning systems and contact tracing to community-based strategies and health system preparedness.

The work presented in this thesis underscores the importance of timely and efficient responses to infectious disease outbreaks, especially in resource-constrained settings. Using both empirical data and analytical methods, the studies explore how integrated approaches can strengthen health system resilience, improve outbreak containment, and minimise the societal and economic impacts of epidemics. From evaluating the Early Warning, Alert, and Response System (EWARS) in the Democratic Republic of Congo (DRC) to examining health reforms in Guinea post-EVD, the findings provide actionable insights for global health security.

The chapter also explores cross-cutting themes that emerge across the studies, such as the critical role of community engagement, the utility of data-driven surveillance systems, and the value of sustained investments in health security infrastructure. Through this integrative analysis, it aims to provide a cohesive narrative that positions the findings within the broader context of global public health challenges, offering pathways for future advancements in epidemic control.

3.1 | Key insights from the articles

The studies presented in this thesis represent a diverse yet interconnected body of work, each addressing a crucial element of epidemic preparedness and response. Together, they build a nuanced understanding of the challenges and opportunities in managing public health emergencies, particularly in regions characterised by fragile health systems and complex socio-political landscapes.

3.1.1 | *Synthesis of findings*

3.1.1.1 | *Early warning and surveillance systems*

Effective early warning and surveillance systems are fundamental to epidemic preparedness and response, as they enable the rapid detection and containment of infectious disease

outbreaks. In the context of the 2018–2020 Ebola Virus Disease (EVD) outbreak in the Democratic Republic of Congo (DRC), the Early Warning, Alert, and Response System (EWARS) demonstrated its critical role in managing one of the most complex public health emergencies in recent history(30).

The implementation of EWARS in North Kivu and Ituri provinces provided a systematic approach to detecting and responding to EVD cases in real time. With its core operational unit—the Alert Unit—EWARS integrated diverse sources of information, including community reports, active case finding, and surveillance at health facilities and points of entry. The system proved robust despite significant challenges, including ongoing conflict and limited resources(30). Its performance metrics were notable: over 194,000 alerts were received during the outbreak period, with 15.8% validated as suspected cases. Sensitivity and specificity exceeded 80%, and 97% of alerts were investigated within two hours of notification, reflecting the system's operational efficiency(30).

In addition to timeliness, EWARS enhanced community engagement by incorporating input from local health workers, community members, and traditional leaders. This participatory approach helped build trust in the system and increased the reporting of suspected cases. Furthermore, the system's cost-effectiveness—estimated at \$438 per case detected—highlighted its feasibility in resource-constrained settings(30).

However, the study also identified areas for improvement. Insufficient understanding and application of standard EVD case definitions at community and health facility levels led to delays in case detection during the early stages of the outbreak. This underscores the need for continuous training and capacity-building initiatives to enhance system reliability and responsiveness(30).

The EWARS experience in the DRC illustrates the importance of adaptive surveillance systems tailored to the unique challenges of each outbreak. By integrating technological, community-based, and operational elements, such systems can provide a robust foundation for outbreak detection and containment. These insights inform not only the design of future early warning mechanisms but also broader health system strengthening efforts in low-resource settings.

3.1.1.2 | *Cluster control strategies*

The success of early warning systems like EWARS is ultimately measured by their ability to trigger effective responses. During the 2018–2020 Ebola Virus Disease (EVD) outbreak in the Democratic Republic of Congo (DRC), the identification and management of the final cluster of cases demonstrated how rigorous investigations and decisive interventions can prevent a resurgence of infections. On April 10, 2020, just two days before the outbreak’s expected end-of-epidemic declaration, a new confirmed case in the city of Beni disrupted 52 consecutive days without confirmed EVD cases. This incident highlighted the persistent risk of flare-ups even during the final stages of an epidemic(31).

To understand and contain this cluster, a combined approach of epidemiological and genomic investigation was employed. Eight cases were identified, all tracing back to a single chain of transmission from a 2019 case in the same area. Genomic sequencing revealed minimal variation—only 31 nucleotide differences—between the cluster’s cases and their source, reinforcing the epidemiological link. This integration of genomic data provided critical insights into the cluster’s transmission dynamics and supported a targeted response(31).

The control strategy for this cluster centred on community confinement. High-risk contacts were advised to stay within specific community settings, with resources such as food and essential supplies provided to ensure compliance. Unlike enforced quarantines, this approach relied on voluntary participation and community trust, minimising resistance while effectively limiting movement. Enhanced contact tracing further supported these efforts, with over 1,000 contacts identified and closely monitored. Eligible individuals were vaccinated promptly, adding a crucial layer of protection against further transmission(31).

Timely isolation of suspected cases was another cornerstone of the response. Rapid testing enabled the swift confirmation of infections, shortening the time between symptom onset and medical intervention. This reduced the likelihood of onward transmission and ensured that cases received appropriate care. The ability to implement these measures quickly and effectively was pivotal in containing the cluster before it could escalate(31).

This response yielded important lessons for future epidemic management. First, it underscored the necessity of maintaining heightened vigilance and operational readiness even as case numbers decline. Outbreaks are rarely linear, and complacency during their final stages can allow undetected transmission chains to re-emerge. Second, the emphasis on community

engagement demonstrated how trust-building and supportive measures can enhance the acceptance and effectiveness of containment efforts. Providing food and other resources during confinement, for instance, alleviated potential hardships and fostered cooperation. Finally, the integration of genomic analysis into the response framework illustrated the value of advanced scientific tools in informing and refining intervention strategies(31).

The Beni cluster exemplifies how a well-coordinated, community-centred approach can effectively manage the complexities of outbreak control. By combining epidemiological precision with locally adapted interventions, the response not only halted transmission but also reinforced the importance of aligning technical strategies with community needs. These experiences offer invaluable guidance for managing future outbreaks and ensuring that even the most challenging clusters can be contained.

3.1.1.3 | Community-based strategies

The successful containment of the Beni cluster during the 2018–2020 Ebola Virus Disease (EVD) outbreak underscored the critical role of targeted interventions and swift responses. However, such efforts must extend beyond individual clusters to address the broader dynamics of epidemic transmission. Community-based strategies offer a powerful framework for outbreak control, combining local engagement with evidence-based interventions to reduce transmission and enhance trust in public health efforts. These strategies, deeply rooted in the specific socio-cultural contexts of affected regions, proved particularly effective in the Democratic Republic of Congo (DRC)(32).

One notable example of a community-based approach was the implementation of contact isolation strategies in Beni and Mabalako health zones during the 2018–2020 outbreak. Unlike traditional quarantines, which often rely on enforcement and may provoke resistance, the community-based contact isolation model emphasised voluntary participation and support. Contacts at high risk of developing EVD were encouraged, incentivised, and supported to remain in designated isolation sites within their communities for the duration of their monitoring period. This approach reduced potential exposure to others while addressing the socio-economic challenges that might otherwise discourage compliance. Food and essential supplies were provided, fostering cooperation and minimising hardship(32).

The impact of this strategy was striking. Among the intervention group, the average delay between symptom onset and isolation was significantly reduced—from 4.8 days in the

comparison group to just 1.3 days. This improvement not only curtailed the opportunity for onward transmission but also ensured earlier access to care, leading to better survival rates. Furthermore, the reproduction number (R) among the intervention group was effectively reduced to zero, with no secondary cases arising from the first-generation contacts in isolation. In contrast, contacts who were not isolated generated secondary cases, underscoring the critical role of the isolation strategy in breaking transmission chains(32).

The success of community-based contact isolation was not merely a function of logistical coordination but also of community engagement and trust-building. Past outbreaks had revealed that mistrust of public health authorities often undermines containment efforts. In response, the strategy in the DRC was carefully designed to align with local practices and priorities. Health workers and community leaders were engaged as advocates, fostering dialogue and ensuring that the interventions were culturally sensitive and contextually relevant. This participatory approach strengthened the legitimacy of the measures and increased public acceptance(32).

These lessons from the DRC illustrate the potential of community-driven strategies to transform epidemic response. By prioritising local engagement and addressing the social determinants of compliance, public health authorities can achieve both technical and relational success. The voluntary nature of isolation, combined with tangible support for affected individuals, proved to be a humane and effective alternative to coercive measures(32).

Community-based strategies are not only practical but also scalable. The principles demonstrated during the DRC outbreak—engaging local actors, providing material support, and building trust—are broadly applicable to other infectious disease outbreaks and health crises.

3.1.1.4 | Factors in contact tracing

The success of community-based strategies in managing EVD outbreaks underscores the importance of local engagement and trust in epidemic response. However, the effectiveness of these strategies often hinges on the foundational public health function of contact tracing. Identifying, monitoring, and supporting individuals exposed to infectious diseases remains a cornerstone of outbreak control. The 2018–2020 EVD outbreak in the Democratic Republic of Congo (DRC) and the 2021 outbreak in Guinea reveal critical insights into the factors influencing the reliability and effectiveness of contact tracing.

Contact tracing is inherently resource-intensive and requires meticulous execution to achieve its dual objectives: preventing further transmission and ensuring early intervention for those who may become symptomatic. Despite its central role, the effectiveness of contact tracing can be undermined by various demographic, logistical, and systemic factors. A study of the 2021 Guinea outbreak highlighted key determinants of contact tracing reliability. Rural-dwelling contacts were far more likely to complete the 21-day follow-up period compared to their urban counterparts, suggesting that smaller, more cohesive communities may facilitate better engagement. Conversely, contacts in urban areas, where populations are more mobile and dispersed, were significantly more challenging to monitor(33).

Demographic factors also played a significant role. Unmarried contacts were more likely to be missed during follow-ups than married individuals, perhaps reflecting the social support structures that facilitate accountability and compliance. Similarly, contacts who were unvaccinated or who did not receive material support, such as food donations, were less likely to adhere to the required monitoring protocols. These findings highlight the importance of integrating supportive measures into contact tracing strategies to incentivise compliance and reduce barriers to participation(33).

The number and capacity of contact tracing teams further influenced outcomes. Health areas with multiple teams achieved significantly higher follow-up rates compared to areas with a single team, underscoring the importance of adequate resourcing and workforce distribution. In Guinea, well-coordinated, decentralised contact tracing operations enabled rapid response to outbreaks in challenging and dispersed settings, but gaps in team capacity sometimes hindered efforts(33)(34).

Beyond operational challenges, trust and community acceptance emerged as pivotal factors. Historical experiences of marginalisation and mistrust of government authorities can undermine compliance with public health interventions. In Guinea, distrust was mitigated by leveraging local actors, including community health workers and traditional leaders, as intermediaries. These actors not only facilitated better communication but also helped to personalise the process, fostering greater cooperation from affected communities(33).

The lessons from these outbreaks underscore the multidimensional nature of contact tracing. While technical and logistical considerations are critical, the human and social dimensions—trust, support, and engagement—are equally influential. These findings point to the need for a

holistic approach to contact tracing, one that integrates demographic insights, community dynamics, and resource allocation.

3.1.1.5 | Complex coinfections

The factors influencing contact tracing effectiveness reveal how outbreaks are shaped by both individual and systemic dynamics. These challenges become even more pronounced when multiple infectious diseases circulate simultaneously, complicating diagnosis, response coordination, and resource allocation. Coinfections during epidemic-prone diseases underscore the need for robust, integrated systems capable of addressing overlapping health emergencies. The 2021 case of a patient in Guinea presenting with both Lassa fever and COVID-19 in the midst of an ongoing Ebola Virus Disease (EVD) outbreak illustrates the complexities of managing such scenarios(35).

In May 2021, during Guinea's resurgence of EVD, a young man was admitted to a treatment centre with symptoms initially suspected to be Ebola. However, further diagnostic testing revealed concurrent infections with Lassa fever and COVID-19. This case underscores the critical importance of differential diagnosis in outbreak settings, where the symptoms of multiple diseases often overlap. Misdiagnosis or delayed identification of coinfections can lead to inappropriate treatment protocols and increased mortality risk(35).

The management of this patient highlighted key challenges and lessons for handling coinfections. First, it demonstrated the need for integrated diagnostic capacity at the point of care. In this case, real-time PCR testing for multiple pathogens enabled the rapid identification of Lassa fever and COVID-19, guiding appropriate treatment. Without such capabilities, the patient's conditions might have gone unrecognised, potentially resulting in further transmission of both diseases and suboptimal care(35).

Second, the case revealed the operational strain that coinfections can impose on healthcare systems. In regions already overwhelmed by an Ebola outbreak, the simultaneous management of Lassa fever and COVID-19 required additional resources and coordination among different response teams. This strain was compounded by community resistance, which delayed response implementation in some areas. Efforts to build trust, such as providing food support during community confinement, were critical to overcoming these challenges(35).

Moreover, the socio-political context in which coinfections occur cannot be ignored. Epidemics often exacerbate existing tensions, and the introduction of new public health interventions for additional diseases may be met with scepticism or resistance. In Guinea, pre-existing frustration from the prolonged COVID-19 pandemic and the memories of the 2013–2016 West African Ebola epidemic created a challenging environment for public health authorities. Addressing these tensions required careful community engagement and clear communication to build trust and foster cooperation(35).

This case also highlights the importance of strengthening surveillance systems that can simultaneously monitor multiple diseases. Coinfections and concurrent outbreaks demand a shift from siloed responses to a more integrated approach that considers the full spectrum of potential public health threats. Investments in diagnostic capacity, workforce training, and multi-disease preparedness are essential to mitigate the risks posed by overlapping epidemics.

3.1.1.6 | Preparedness and health systems reform

The challenges posed by complex coinfections highlight the broader need for robust health systems capable of responding to overlapping public health emergencies. The experience of Guinea following the 2014–2016 West African Ebola Virus Disease (EVD) epidemic provides compelling evidence of how targeted health system reforms can enhance preparedness and response capacity. These investments not only improved the country’s ability to manage the 2021 EVD outbreak but also bolstered its capacity to address concurrent health crises, including Lassa fever, COVID-19, and Marburg virus disease(34).

In the wake of the devastating 2014–2016 EVD epidemic, Guinea undertook significant reforms aimed at strengthening its health security. These efforts included scaling up Integrated Disease Surveillance and Response (IDSR), conducting Joint External Evaluations (JEE) to assess International Health Regulation (IHR) capacities, and developing a National Action Plan for Health Security (NAPHS). By decentralising emergency operations through the establishment of regional and prefectural Emergency Operation Centres, Guinea enhanced its ability to detect and respond to outbreaks rapidly and efficiently(34).

The value of these reforms became evident during the 2021 EVD outbreak. Unlike the earlier epidemic, the response to the 2021 outbreak was characterised by early detection, rapid intervention, and effective containment. The outbreak was declared over within five months, with a significantly lower case burden and mortality rate compared to the 2014–2016 epidemic.

This success was attributed to the foundational improvements in surveillance, workforce capacity, and community engagement that had been implemented in the intervening years(34).

One of the most impactful reforms was the introduction of an Early Warning, Alert, and Response System (EWARS), which provided a streamlined mechanism for identifying and responding to potential outbreaks. Coupled with community preparedness initiatives, this system allowed for the rapid mobilisation of resources and personnel, even in remote and conflict-affected areas. Simulation exercises and risk assessments further reinforced the country's readiness, enabling stakeholders to identify gaps and refine response strategies before crises occurred(34).

Another critical component of Guinea's preparedness was its focus on fostering trust and collaboration with communities. The response to the 2014–2016 epidemic had been hampered by mistrust and misinformation, leading to resistance and delayed containment. In contrast, the 2021 outbreak response emphasised community-driven approaches, with local leaders and health workers playing a central role in communication and intervention efforts. This approach not only improved public compliance but also reinforced the legitimacy of public health measures(34).

The economic benefits of these reforms were also significant. By investing in preparedness, Guinea reduced the costs associated with emergency responses, which are typically much higher when outbreaks are allowed to escalate unchecked. The ability to detect and contain outbreaks early not only saves lives but also minimises disruptions to health systems, economies, and societies(34).

Guinea's experience underscores the importance of sustained investment in health system strengthening. The reforms implemented after the 2014–2016 epidemic served as a blueprint for building resilience and adaptability, offering valuable lessons for other low-resource settings at risk of infectious disease outbreaks. As this chapter transitions to broader reflections on the findings, the case of Guinea provides a compelling argument for the integration of preparedness into long-term health system planning, ensuring that countries are equipped to face future public health challenges with confidence and efficiency.

3.1.2 | *Cross-cutting themes*

The examination of preparedness and health system reform highlights the multifaceted nature of epidemic response, where technical, operational, and social dimensions converge. From enhancing surveillance systems and contact tracing to managing coinfections and fostering community trust, the interconnectedness of these elements underscores the need for a holistic approach to public health emergencies. While each intervention plays a distinct role, cross-cutting themes emerge that unify these efforts and provide broader lessons for strengthening health systems and outbreak response. The following section explores these themes, offering insights into how they inform and shape effective strategies across diverse epidemic contexts.

3.1.2.1 | Community engagement as a foundation

A recurring theme across the studies is the indispensable role of community engagement in outbreak response. Whether implementing voluntary contact isolation, fostering compliance with contact tracing, or managing coinfections in complex socio-political contexts, trust and collaboration with affected populations were paramount. In the Democratic Republic of Congo (DRC) and Guinea, involving community leaders and health workers as intermediaries ensured that public health measures aligned with local customs and priorities. This participatory approach not only improved intervention acceptance but also strengthened the legitimacy of the response(32)(35). It was equally founded on a Human Rights-Based Approach (HRBA), which emphasises the promotion and realisation of human rights principles—universality, indivisibility, equality and non-discrimination, participation, and accountability. This approach includes a focus on building the capacities of 'duty-bearers' to meet their obligations and of 'rights-holders' to assert their rights, encompassing all civil, cultural, economic, political, and social rights, as well as the right to development(36).

The success of these efforts underscores the importance of building trust before and during outbreaks. Community resistance often stems from historical mistrust of authorities or inadequate communication during health crises. By addressing these concerns proactively, public health responses can foster cooperation and reduce barriers to effective implementation(32).

3.1.2.2 | Interdependence of systems and strategies

The studies illustrate how different components of epidemic response—surveillance, contact tracing, isolation, and treatment—are deeply interconnected. Early warning systems, for example, provide the data necessary to guide contact tracing and case management, while

community-based isolation strategies rely on robust surveillance to identify and support high-risk contacts. The ability to integrate these systems into a cohesive framework is critical for achieving timely and efficient responses(30)(32).

This interdependence also highlights the importance of capacity-building at all levels of the health system. In both the DRC and Guinea, decentralised emergency operations and well-trained local teams were pivotal in ensuring rapid and context-specific responses. Investments in these areas not only improve preparedness but also enhance resilience to future outbreaks(34).

3.1.2.3 | Equity and resource allocation

Equity emerged as a key consideration in the design and implementation of outbreak responses. Factors such as geographic location, socio-economic status, and access to healthcare resources influenced outcomes during the DRC and Guinea outbreaks. Rural communities, for instance, demonstrated higher contact tracing follow-up rates due to their cohesion and accessibility, while urban settings faced challenges related to mobility and resource constraints(33).

Efforts to address these disparities included targeted resource allocation, such as providing food and essential supplies to isolated contacts, and prioritising vaccination campaigns for high-risk populations. These measures not only enhanced compliance but also ensured that interventions were accessible to those most in need(31)(32).

3.1.2.4 | Preparedness as a cost-effective investment

The experiences of Guinea demonstrate the long-term benefits of investing in preparedness. By strengthening surveillance systems, decentralising emergency operations, and conducting regular simulations, the country was able to contain the 2021 EVD outbreak with fewer cases, lower costs, and reduced disruption. This underscores the cost-effectiveness of proactive measures compared to reactive responses, which are often more expensive and less effective(34).

Preparedness also extends beyond technical capacities to include governance and community trust. Establishing clear roles and responsibilities, fostering collaboration among stakeholders, and building confidence in public health institutions are critical components of a resilient health system(34). As part of efforts to strengthen global health emergency preparedness and

response, amendments to the International Health Regulations (2005) (IHR) were adopted in June 2024. These notably expanded the purpose and scope of the IHR, as outlined in Article 2, to include preparedness for the international spread of disease(37). While uncertainties remain regarding the final outcome, the Pandemic Accord currently under negotiation highlights preparedness, readiness, and health system resilience in Article 6, where consensus has been reached. This reflects Member States' commitment to investing more in preparedness and enhancing core IHR capacities(38).

3.2 | Theoretical and practical implications

The findings of this thesis have significant theoretical and practical implications for the fields of epidemic preparedness, response, and health system strengthening. They provide a deeper understanding of the dynamics of public health emergencies and offer actionable recommendations for improving future responses in low-resource settings.

3.2.1 | Theoretical contributions

Theoretical contributions of the research include:

- The integration of multidimensional frameworks. The studies underscore the need for a multidimensional approach to epidemic management, integrating surveillance, community engagement, and health system reforms. They highlight how different components of public health responses—early warning systems, contact tracing, isolation, and case management—interact and reinforce one another. This interdependence suggests a need for theoretical frameworks that account for these synergies rather than treating each intervention in isolation. For instance, the effectiveness of community-based contact isolation during the DRC outbreak was contingent on robust early warning systems and trust-building measures. These findings challenge linear models of outbreak response, advocating for frameworks that prioritise adaptability and interconnectedness(32,34).
- The role of trust and social determinants. This thesis contributes to a growing body of literature recognising the centrality of social determinants, human rights and trust in public health responses. By demonstrating how community engagement influences compliance with interventions, the findings suggest that trust-building should be considered a core element of epidemic preparedness. Theoretical models of epidemic

response must therefore move beyond technical efficiency to incorporate relational dynamics and socio-cultural factors(32,33,39).

- Resilience and adaptive capacity. The experiences in Guinea and the DRC highlight resilience as a critical attribute of health systems facing complex emergencies. Theoretical contributions from this thesis propose resilience not just as the capacity to absorb shocks but as the ability to adapt and transform in response to evolving challenges. This perspective is particularly relevant for regions where concurrent outbreaks and socio-political instability complicate response efforts (32,34).

3.2.2 | *Practical applications*

Practical applications of research findings include the need for:

- Strengthening surveillance and early warning systems: practical recommendations include investing in surveillance infrastructure such as Early Warning, Alert, and Response Systems (EWARS), which proved effective in the DRC. These systems should be decentralised and integrated with community-level reporting mechanisms to ensure timely detection and response, particularly in conflict-affected or remote areas(30).
- Enhancing community-centric approaches: public health interventions should prioritise community engagement, leveraging local leaders, health workers, and culturally tailored communication strategies. The success of voluntary isolation strategies in the DRC and trust-building measures in Guinea demonstrate the importance of aligning public health actions with community needs and values. Such approaches not only improve compliance but also strengthen the legitimacy of health authorities(32,33).
- Addressing equity in resource allocation: interventions should account for geographic and socio-economic disparities. Targeted support for vulnerable populations, such as providing food and essential resources during isolation, can enhance the accessibility and acceptability of public health measures. Resource allocation strategies must prioritise equity to ensure that no community is left behind during an outbreak response(32).
- Investing in preparedness for cost-effectiveness: the case of Guinea illustrates the economic advantages of investing in health system reforms before outbreaks occur. Preparedness activities—such as regular simulation exercises, training programs, and decentralised emergency operations—reduce response costs and improve outcomes

when outbreaks do arise. Policymakers should view these investments as not only lifesaving but also cost-effective in the long term(34).

- Integrating multi-disease responses: coinfections and concurrent outbreaks require an integrated response strategy. Building diagnostic capacity to detect multiple pathogens simultaneously and fostering collaboration across response teams are critical for managing overlapping epidemics. This approach minimises resource duplication and enhances the overall effectiveness of public health efforts(35).
- Capacity building at all levels: developing the workforce capacity of health systems, particularly at local and regional levels, is essential for scalable and sustainable epidemic responses. Training programs should focus on enhancing technical skills, leadership, and coordination capabilities to ensure preparedness at every level of the health system(34).

3.3 | Limitations and challenges

The findings of this thesis are derived from localised epidemics in Guinea and the DRC, where tailored strategies were successfully implemented. However, their generalisability to other outbreaks remains limited. While decentralised alert systems may have broader applicability across varying contexts, the feasibility of implementing community-based contact isolation strategies in widespread, geographically dispersed epidemics—such as the DRC's mpox outbreak affecting all 26 provinces(40)—is significantly constrained.

In such disseminated epidemics, a targeted approach focusing on hotspot areas with intense, community-based transmission may offer a viable alternative. This is particularly relevant in semi-urban settings, where the strategy could be adapted to local dynamics. Crucial to its success is the active involvement of affected communities and families, alongside tangible support, such as the provision of food and financial assistance, to sustain isolated contacts.

Moreover, regular qualitative assessments of community acceptance and perceptions are essential to refine and adapt these strategies. Incorporating feedback mechanisms would ensure that interventions remain contextually appropriate and effective over time. These challenges underscore the importance of balancing technical strategies with social considerations, particularly in resource-constrained settings.

3.4 | Perspectives for future research and practice

The findings and implications of this thesis not only address pressing challenges in epidemic preparedness and response but also point to critical areas for future exploration and practice. As the global health landscape continues to evolve, driven by emerging pathogens, shifting socio-political contexts, and the lingering impacts of the COVID-19 pandemic, there is an urgent need to translate these insights into actionable strategies that bolster resilience and equity in public health systems.

One of the key areas for future research lies in refining and scaling integrated surveillance systems. While EWARS have demonstrated effectiveness in specific contexts, questions remain about its adaptability to diverse epidemiological and socio-political environments. Future studies could explore how these systems perform in urban versus rural settings or in regions with limited internet or phone connectivity and technical infrastructure. Additionally, the role of artificial intelligence and machine learning in enhancing the predictive capacity of surveillance systems warrants further investigation.

Community engagement, a cornerstone of effective outbreak responses, also requires deeper exploration. While the importance of trust and local participation has been well-established, future research could examine innovative methods to sustain this engagement beyond crisis periods. For instance, how can public health authorities build enduring partnerships with communities to ensure readiness for future emergencies? The use of participatory action research, where communities co-design interventions alongside researchers and practitioners, could provide valuable insights into this question.

Another critical area for future practice is the development of frameworks that address the complexities of overlapping outbreaks and coinfections. As demonstrated by the Lassa fever and COVID-19 case during the EVD outbreak in Guinea, simultaneous epidemics strain diagnostic, operational, and resource capacities. Future research could focus on designing integrated diagnostic protocols and response strategies that enable health systems to manage multiple diseases simultaneously. Additionally, practice-based innovations, such as multi-disease emergency response teams, could be tested and evaluated in real-world settings.

Equity must remain central to both research and practice in epidemic response. The findings from Guinea and the DRC underscore the disparities in access to healthcare and public health resources across different communities. Future initiatives should focus on designing

interventions that are explicitly tailored to reach the most vulnerable populations. This includes addressing systemic barriers such as geographic isolation, socio-economic inequality, and gender-based disparities that exacerbate health inequities during crises.

Lastly, the economic dimensions of preparedness deserve further attention. While the cost-effectiveness of investing in health system resilience has been demonstrated, there is a need for more granular analyses of the return on investment for specific preparedness activities. For example, how do investments in training programs, simulation exercises, or decentralised emergency operations centres translate into reduced response costs and improved health outcomes during actual outbreaks? These insights could provide compelling evidence for policymakers to prioritise sustained funding for epidemic preparedness.

In practice, these perspectives call for a paradigm shift toward integrated, proactive, and inclusive approaches to public health. Preparedness must be viewed as an ongoing commitment rather than a reactive response to crises. This includes embedding epidemic response planning into broader health system strengthening initiatives, fostering cross-sectoral collaboration, and ensuring that community voices remain central to decision-making processes.

3.5 | Conclusion

This thesis has explored the intricate and interconnected dimensions of epidemic preparedness and response, drawing on lessons from the 2018–2020 Ebola Virus Disease (EVD) outbreak in the Democratic Republic of Congo (DRC), the 2021 EVD outbreak in Guinea, and the broader challenges of concurrent health emergencies. Through an analysis of early warning systems, community-based strategies, contact tracing, complex coinfections, and health system reforms, it has underscored the critical importance of integrated, equitable, and community-driven approaches to managing public health crises.

At its core, the findings reveal that effective epidemic response requires more than technical interventions. It demands systems that are adaptable, holistic, and grounded in the realities of affected populations. Early warning and surveillance systems like EWARS demonstrated their potential to rapidly detect outbreaks, while community-based strategies showed how local engagement can transform compliance and intervention effectiveness. The success of these approaches depended not only on their technical design but also on the trust and legitimacy they fostered within communities.

The thesis also highlighted the importance of preparedness as a proactive investment. Guinea's post-2014 reforms, which strengthened its health system and response capacity, provide a compelling example of how sustained efforts can mitigate the devastating impacts of outbreaks. These lessons are particularly relevant for low-resource settings, where the cost of reactive responses often far outweighs the investments required to build resilience.

As global health faces mounting challenges, including the emergence of novel pathogens and the persistence of socio-economic inequalities, this research points to critical priorities for the future. These include advancing integrated surveillance systems, addressing the complexities of concurrent outbreaks, and ensuring equity in resource allocation. It also calls for sustained focus on building trust with communities, recognising that their engagement is not just a component of public health responses but a foundation for their success.

In conclusion, this thesis has shown that while the challenges of managing public health emergencies are significant, they are not insurmountable. By learning from past experiences and prioritising integrated, equitable, and community-centred approaches, health systems can not only respond to crises more effectively but also strengthen their capacity to prevent them. In doing so, they can move closer to achieving the broader goal of health security and resilience for all.

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