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MAJOR ARTICLE

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 Demogratic 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

Received 11 May 2022; editorial decision 27 June 2022; accepted 29 June 2022

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https://doi.org/10.1093/ofid/ofac329

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 was 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,

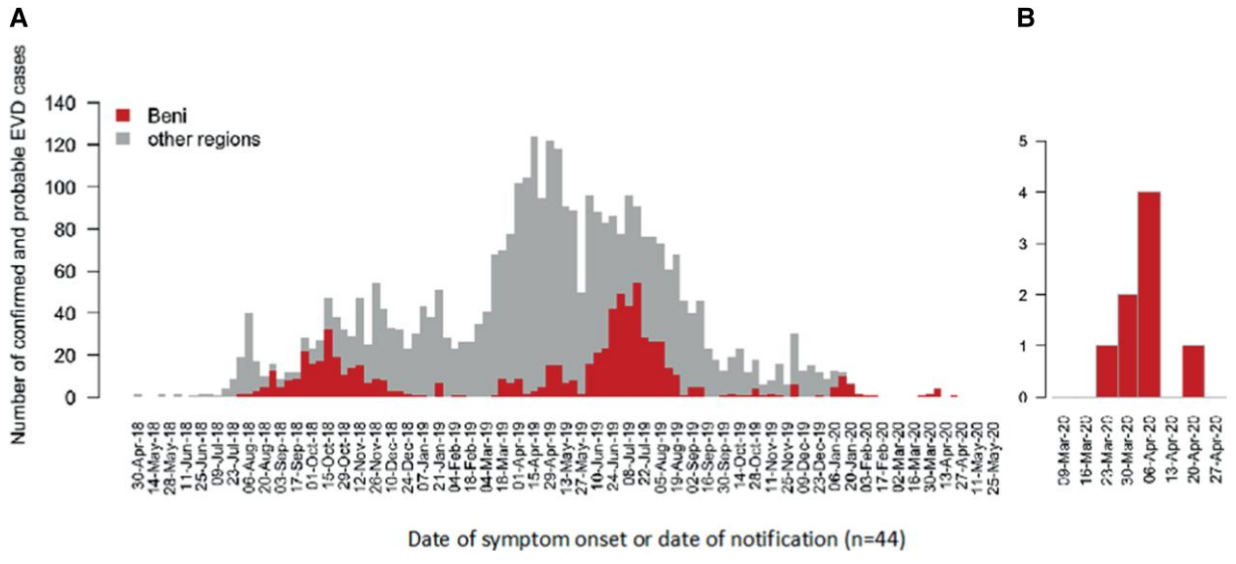

Figure 1. Epidemiological curve of confirmed and probable cases of EVD in Eastern DRC, 2018–2020. A, Epidemiological curve of confirmed and probable cases of EVD in Eastern DRC from April 2018 to June 2020. In red are the cases of Beni, in gray are the cases of all other regions, and the bars represent 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.

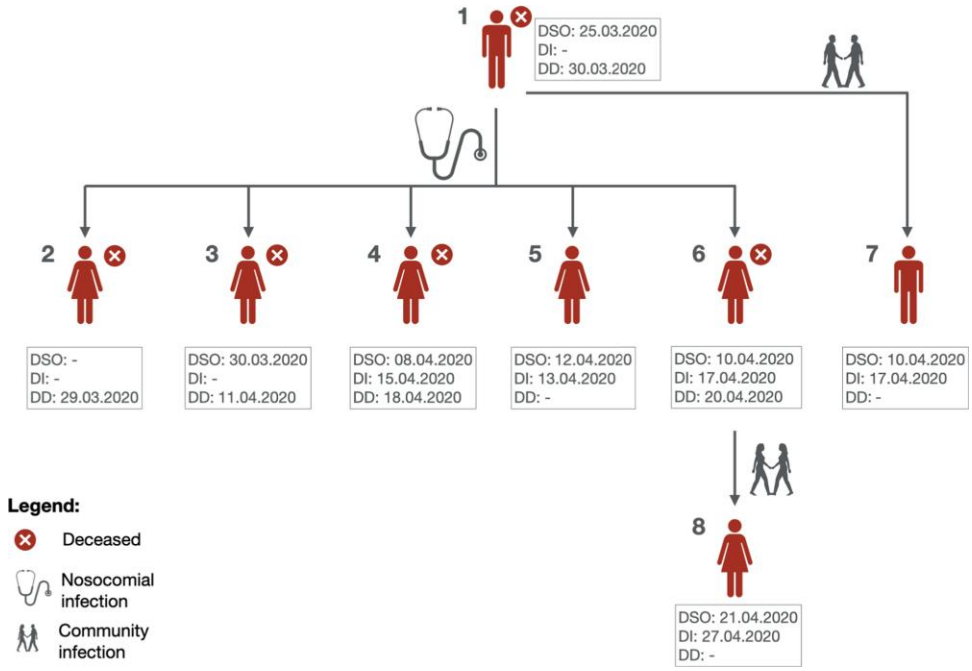

Figure 2. Transmission chain of the last cluster in Beni, DR Congo, March–April 2020. Abbreviations: DD, date of death; DI, date of isolation; DSO, date of symptom onset.

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

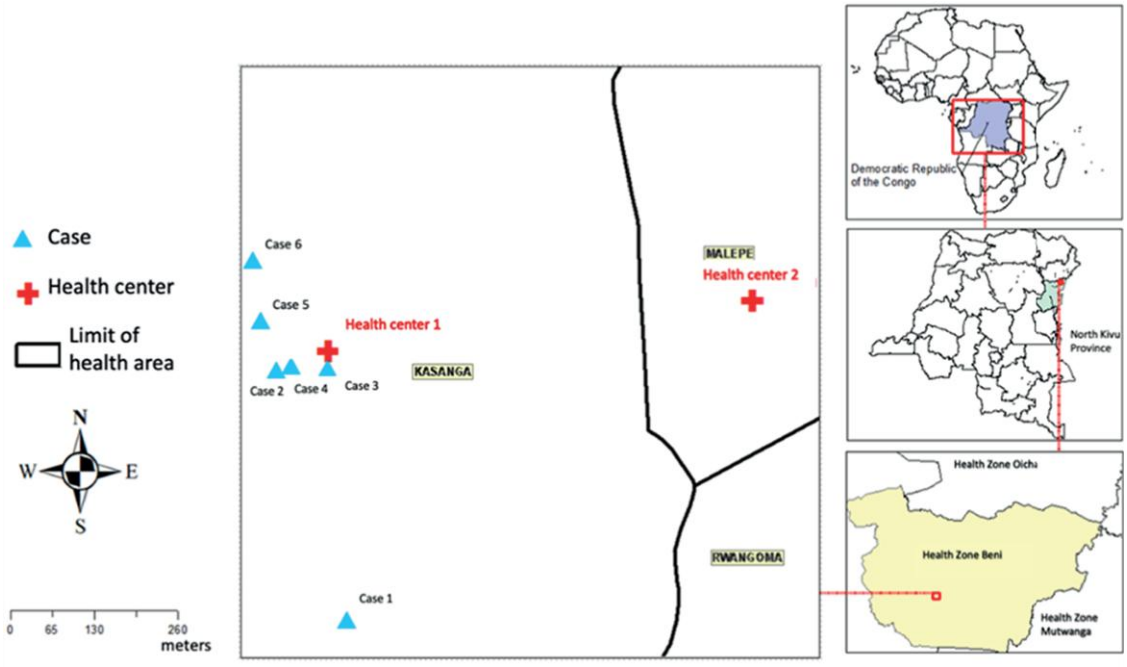

Figure 3. Geographic distribution of cases by residence.

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

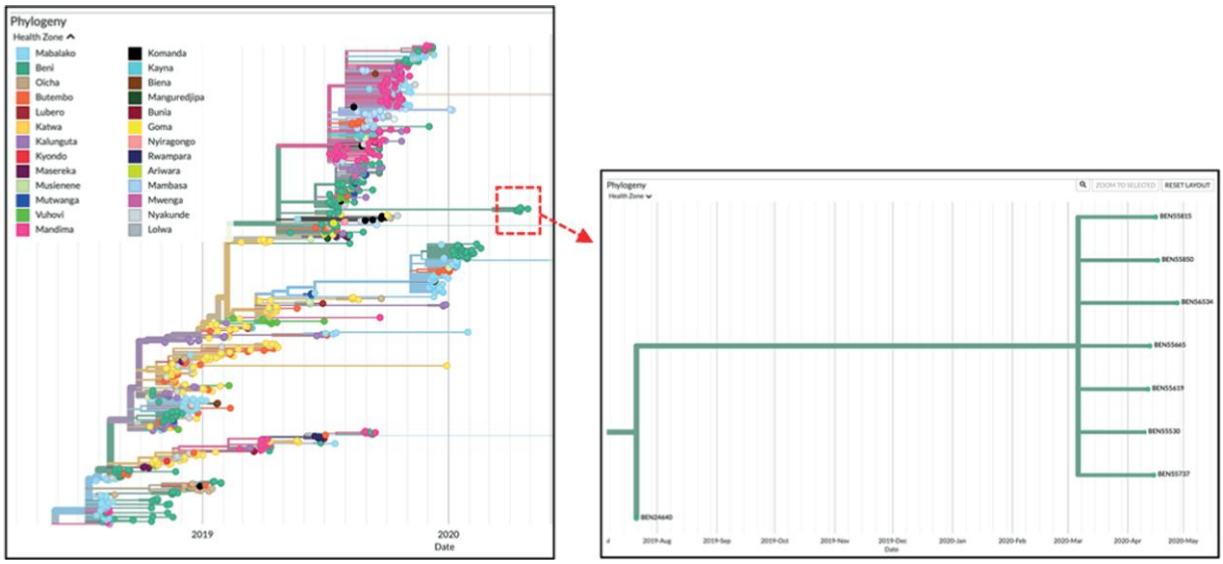

Figure 4. Sequencing results.

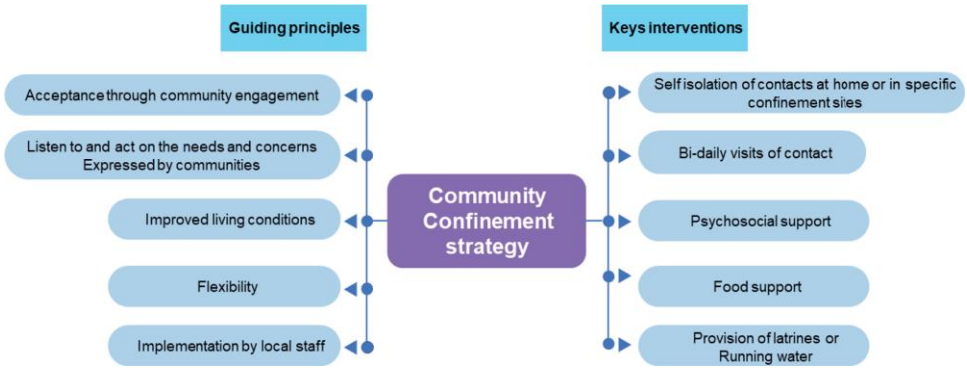

Figure 5. Key aspects of community confinement strategy.

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.

Acknowledgments

The authors thank the families and community members who participated in the study.

Financial support. This study was partially supported by the World Health Organization as it was implemented during the outbreak response.

Disclaimer. The views expressed are those of the authors and not necessarily those of their affiliated institutions.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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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