Investigation of, and strategies to control the final cluster of the 2018-2020 Ebola virus disease outbreak in eastern Democratic Republic of Congo

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Abstract

Background

On April 10, 2020, while the independent committee of the International Health Regulation (IHR) was meeting to decide whether the 10th Ebola outbreak in the DRC still constituted a Public Health Emergency of International Concern, a new confirmed case was notified in the city of Beni, the last epicentre of the epidemic. This study aimed to understand the source of this cluster and learn from the implemented control strategies for improved EVD outbreak response in 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 the last cluster of Beni; two males and six females, with a median age of 22 years (range 7 - 68 years). Five cases were likely nosocomially infected. A total of 1,028 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 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, undertaken in accordance with key guiding principles agreed with the affected community.

Conclusion

The 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.

1. Introduction

The Ebola virus disease (EVD) outbreak that affected eastern Democratic Republic of Congo (DRC) between April 2018 and June 2020 was the second largest recorded EVD outbreak globally (World Health Organization, 2021a). Although this was the 10th EVD outbreak in the DRC, it was the first in eastern DRC, an area which 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.) (World Health Organization, 2020a). The epidemic started in the province of North Kivu and spread to bordering Ituri province in the north and South Kivu in the south (Aruna et al., 2019). 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 (World Health Organization, 2019). 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 (World Health Organization, 2020b). 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 (Jombart et al., 2020).

Beni, a city in North Kivu of approximately 200,000 inhabitants, was the health zone most affected by the epidemic, with 737 cases, or 32% of all recorded EVD cases (World Health Organization, 2020c). 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 (Jombart et al., 2020). 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) count-down towards 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 a PHEIC, a new confirmed case was notified in the city of Beni, the last epicentre 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 PCR test of the last confirmed case, i.e. two 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) with a cycle-threshold values (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, and the public health implications.

2. Materials And Methods

2.1. 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 (Subissi et al., 2018). If the alert was validated, an ambulance was sent to bring the suspected case to an isolation centre 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 two consecutive negative results within 72 hours, after which they were discharged as non-cases 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), and in case of 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 deaths 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 the last exposure to the confirmed/probable case. In addition, all eligible contacts were vaccinated upon giving informed consent.

2.2. Case definition

A suspected case was defined as a person, living or dead, who has or had sudden onset of fever and at least three of the following signs: headache, vomiting, anorexia, diarrhoea, lethargy, stomach pain, muscle pain or joints, 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 and 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 (M. Keita et al., 2021).

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 (e.g., 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 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 health care facilities or in the community that was not otherwise characterized as a high-risk exposure (Reaves et al., 2014).

2.3. 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 2–8°C. Testing was performed on the same day. All laboratories used GeneXpert® Ebola (Cepheid, Sunnyvale, CA) polymerase chain reaction as a diagnostic tool, with cycle threshold (CT) values of less than 40 considered as a positive result.

2.4. 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 using 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 TruSeq Exome or Nextera Flex for Enrichment method, as previously described (Mbala-Kingebeni et al., 2019). Analysis of data was performed using an in-house pipeline for virus genomes, as previously described (Mbala-Kingebeni et al., 2019).

2.5. Data collection and analysis

Information on all confirmed and probable cases was collected from the EpiInfo database(Schafer et al., 2016). Additional data were collected on contact tracing, vaccination, and laboratory results in separate dedicated Excel databases. Data were analyzed using R statistical software (Team., 2014). The Global Positioning System (GPS) coordinates related to the mapping of confirmed cases was collected using Android™ Mobile Operating System in the households of cases, and maps made using ArcGIS® software(ESRI, 2011).

2.6. Ethical considerations

This study was approved by the Ethics Committee of the Kinshasa School of Public Health (approval number ESP/CE/03/2021).

3. Results

3.1. Epidemiological investigation of transmission chain

The index case (Case 1) was identified to be a male taxi driver who presented with EVD-like symptoms starting on 25 March 2020. He was hospitalized at community health centre 1 from 25-26 March 2020. Despite still presenting symptoms, he was discharged and stayed at home. After his symptoms worsened, he was admitted to community health centre 2 on April 9, where he passed away 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 centre 1 during the same period as case 1, in search of potential nosocomial transmissions. The investigation identified 24 patients, of whom five developed symptoms consistent with EVD. Case 2, who died on 29 March,

attended community health centre 1 at the same time as the index patient and was a sister of Case 4. She was HIV-positive and had stopped her anti-retroviral 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 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 four cases (3 to 6) were all confirmed positive for EVD, of which cases 4, 5 and 6 were isolated in the ETC during the confirmation of EVD, while case 3 died on April 11, with a post-mortem 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 centre, as being symptomatic. He 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).

3.2. Epidemiological summary

In total, eight cases were identified within the last cluster of Beni. Of these, seven were identified as confirmed cases during the outbreak, 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 six were female, with a median age of 22 years (range 7 - 68 years). Five (63%) cases died, of which three were community deaths. All cases resided in the same neighbourhood as case 1, where the community health centre 1 was also located (Figure 3). Five cases were likely nosocomially infected within this community health centre. A total of 1,028 contacts were identified around these eight confirmed cases, including 844 high-risk contacts. Of those contacts, 971 (94%) were successfully traced and followed up, and 781 (76%) were vaccinated.

3.3. Sequencing investigation

Whole Genome Sequencing (WGS) results were available for seven 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 (Inrb-drc, 2021).

3.4. 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 categorised according to the type of contact into high or low risk contacts. Confinement in two 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 agreed to drive its implementation (acceptance through community engagement, flexibility, listening to and acting on the needs and concerns expressed by communities). This confinement was also guided by the WHO 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; infection prevention and control (IPC) measures and monitoring of quarantined persons implemented (World Health Organization, 2021b).

The first facility was community health centre 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 centre was closed for new patients and visitors. All other close contacts of confirmed cases, such as family members, neighbours, and health providers from community health centre 1, were placed in the second confinement facility. In both confinement facilities, contacts were screened two times per day for 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 guidance on how to act in accordance with infection prevention measures. All contacts were provided three meals per day during the confinement period. Moreover, communities around the confinement facilities were sensitized and given information on confinement facilities and their importance, in order to gain community acceptance of such facilities. Finally, a vaccination campaign targeting the contacts was conducted.

4. 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 eight flare-ups originated from persistently infected EVD survivors and delayed the end of the epidemic by 11 months (Subissi et al., 2018). 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 Beni area in February 2020, but to earlier cases of 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 (Coltart et al., 2017). During this outbreak, a total of 1,162 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 (Diallo et al., 2016), this large number of survivors poses a risk for future flare-ups (World Health Organization, 2021c)(A. K. Keita et al., 2021). Additionally, people who recover from EVD can, in rare cases, have a relapse of the disease and subsequently infect others, as was the case of an individual who infected 91 people during the same outbreak (Mbala-Kingebeni et al., 2021).

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 is a crucial but often neglected activity (Polonsky et al., 2021). However, the last hypothesis seems least likely as it would mean there was an undetected continued chain of transmission happening for more than 6 months.

This final cluster in the 10th EVD epidemic of DRC was rapidly stopped, with a total of just eight 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 i.e., 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 high vaccination rate among contacts likely also helps explain why this outbreak was rapidly contained. 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 (Polonsky et al., 2021).

As the risk to have flare-ups in the 42 days period as well as in the 90 days post-Ebola period remains high, it is of utmost importance to continue surveillance and maintain rapid response capability (Christie et al., 2020)(Thompson et al., 2019). 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, sensitizing and also vaccinating their close contacts is also an important strategy to prevent future outbreaks (Keita et al., 2020).

Community confinement likely helped to control rapidly 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, wellbeing, and livelihoods of those affected, as was observed during previous EVD outbreaks and the ongoing COVID-19 pandemic (Okware et al., 2015)(Polonsky et al., 2022)(Wang et al., 2021). 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 (Polonsky et al., 2022)(Gillespie et al., 2016).

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 a consideration of a contacts 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.

Declarations

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Mory Keita: Conceptualization, Methodology, Data curation, Writing – original draft, Visualization, Validation, Writing – review & editing. Jonathan Polonsky: Methodology, Data curation, Validation, Supervision, Writing – review & editing. Iris Finci: Software, Writing – original draft. Placide Mbala-Kingebeni: Methodology, Data curation, Investigation, Writing – review & editing. Michel Kalongo Ilumbulumbu: Methodology, Data curation, Writing – original draft, Investigation. Adama Dakissaga: Software, Data curation, Investigation. John Kombe Ngwama: Methodology, Validation, Investigation. Michel Kasereka Tosalisana: Methodology, Validation, Investigation. Steve Ahuka Mundeke: Methodology, Supervision, Validation, Writing – review & editing. Abdou Salam Gueye: Methodology, Supervision, Validation, Writing – review & editing. Stephanie Dagron: Supervision, Validation, Writing – review & editing. Olivia Keiser: Methodology, Supervision, Validation, Writing – review & editing. Ibrahima Soce Fall: Methodology, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare no competing interests.

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Figures

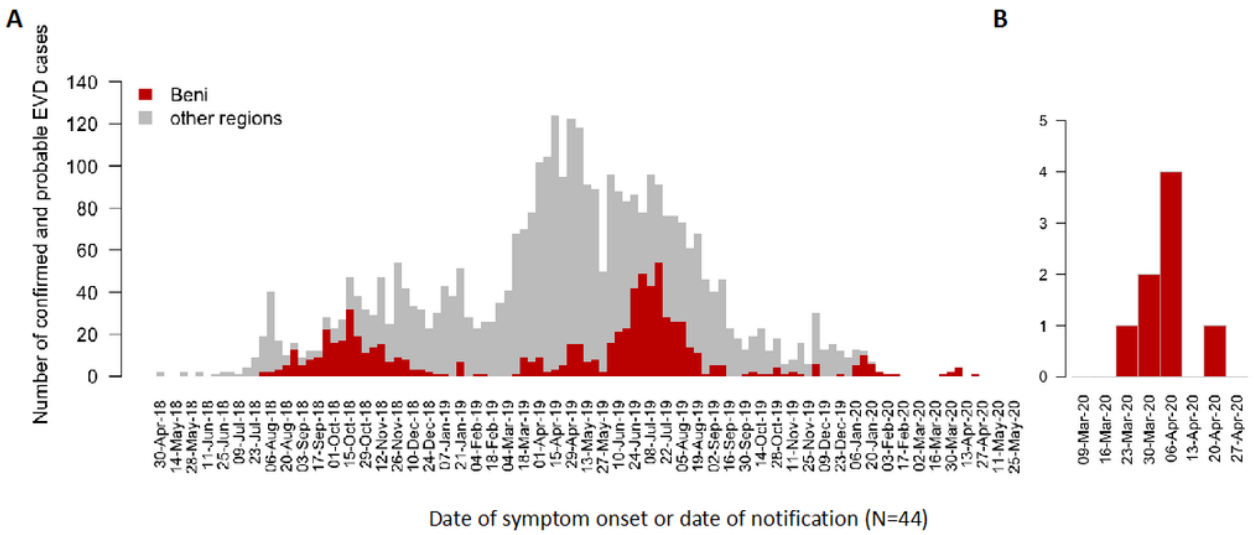

Figure 1

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 the cases of Beni, in grey the cases of all other regions, the bars represent weekly number of EVD cases; B – Epidemiological curve of the last cluster of the 2018-2020 outbreak located in Beni. For one case, date of notification was used as date of symptom onset was unknown.

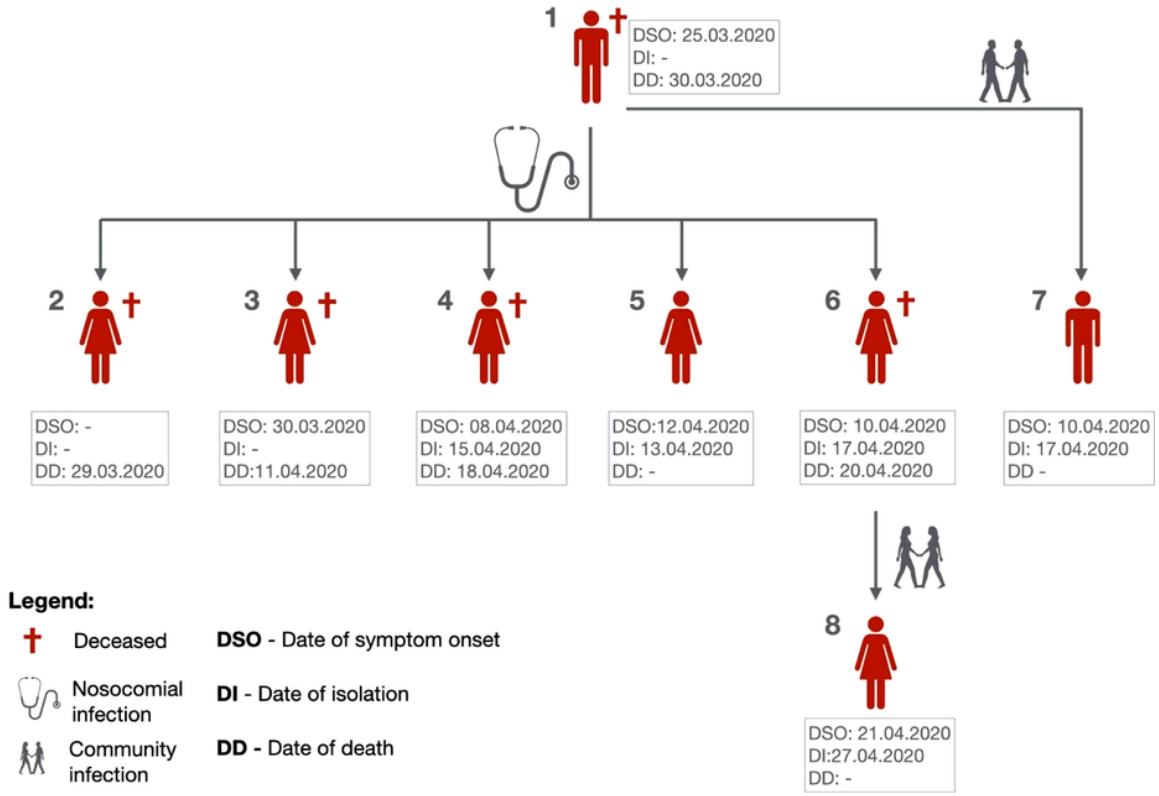

Figure 2

Transmission chain of the last cluster in Beni, DR Congo, March-April 2020

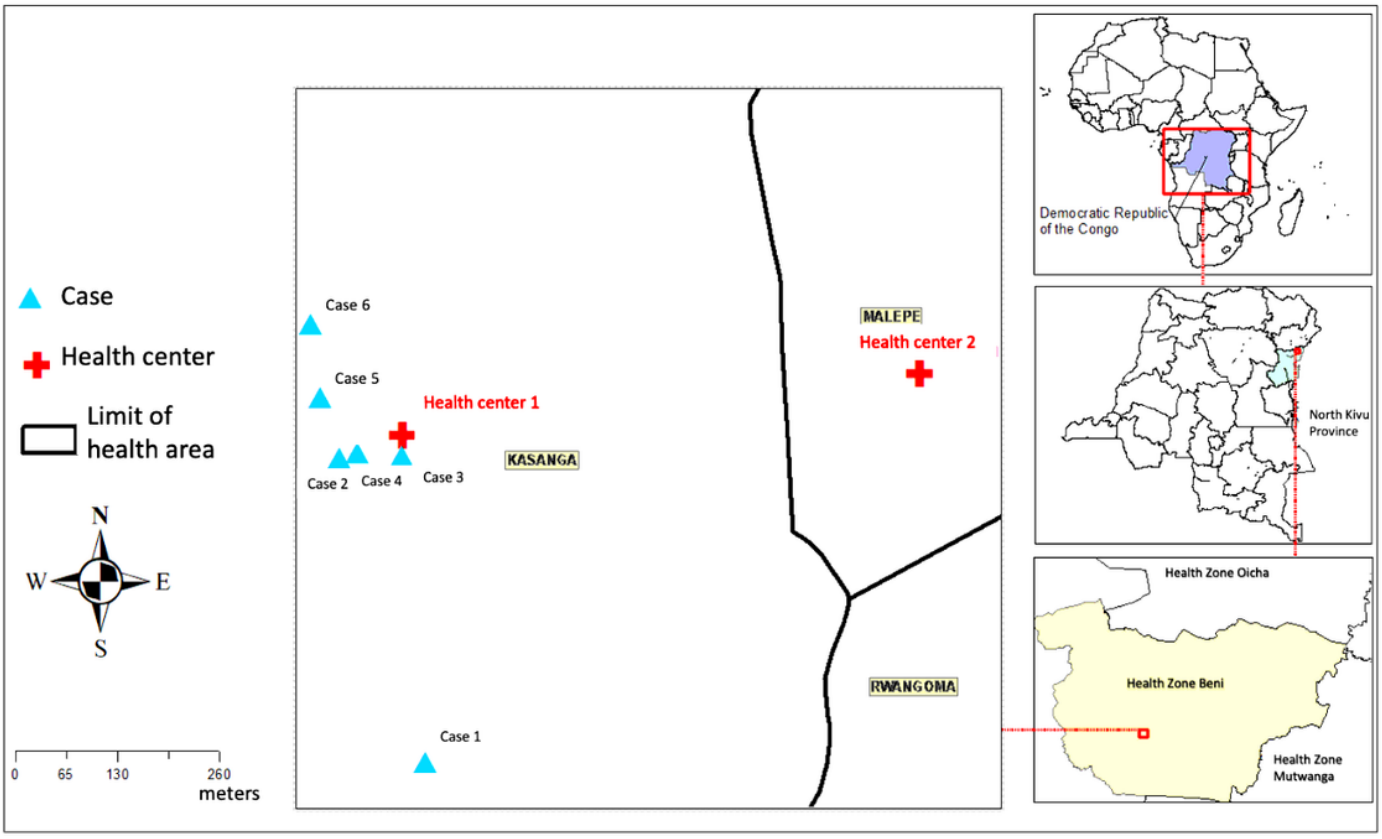

Figure 3

Geographic distribution of cases by residence

Figure 4

Sequencing results