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## Review

# The 2018/19 Ebola epidemic the Democratic Republic of the Congo (DRC): epidemiology, outbreak control, and conflict

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## SUMMARY

The Democratic Republic of Congo (DRC) (formerly Zaire) was the location of the first Ebola outbreak, in 1976, and since then there have been a total of ten outbreaks in different parts of the country. The current outbreak, the first in eastern DRC (North Kivu and Ituri provinces), began in July 2018, and by December 2019, there had been 3262 cases and 2232 deaths. Within weeks of the first reported cases, the World Health Organisation (WHO) and the DRC Ministry of Health (MOH) initiated a major response programme, with laboratory support, international agencies providing personnel, and material resources. Unlike previous Ebola outbreaks, including the west Africa epidemic, a proven vaccine, and trial therapeutic agents have been available as part of the outbreak response. Two therapeutic agents, mAb114 and REGN-EB3, both monoclonal antibody derived, have shown case fatality rates (CFR) of around 30%, compared to the overall of 66%. Despite these positive interventions, the outbreak has continued for eighteen months. Underlying the outbreak response has been a high number of violent incidents by local militias, and community mistrust and lack of involvement that has hampered many aspects of the response programme. As a result, many cases are not reported early and not transferred to treatment centres, deaths and increased transmission occur in the community, and the response programme is reaching only a proportion of the cases. New strategies to improve community participation, and integrate the Ebola response into the existing health structure are planned to improve the programme effectiveness.

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## Introduction

The current (2018/19) outbreak of Ebola virus disease (EVD, Ebola) in the Democratic Republic of Congo (DRC) is the largest outbreak that has occurred in that country, and is the second largest of all EVD outbreaks, following the 2014 West Africa

outbreak. While transmission pathways, morbidity and case fatality rates, and population impact have been similar to previous outbreaks, three factors have been unique to this situation, affecting both the spread of the disease, and strategies available for management.

The first, and the most negative factor, has been the extremely difficult and dangerous security situation in the outbreak affected area of north east DRC, having an impact on all aspects of the management of the outbreak.

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The second and third, potentially positive factors, have been the availability and field use of a vaccine against EVD, and, for the first time in an Ebola outbreak, the use of recently developed therapeutic agents. While longer term analysis of the effectiveness of these two inputs is required, they offer control and management options not previously possible.

### Ebola virus disease epidemiology and transmission

The biology of the Ebola virus, and the epidemiology and routes of transmission of EVD are now well known [1,2]. Forest fruit bats are regarded as the principal reservoir and may be eaten directly. Other forest animals, particularly monkeys may be infected from fruit bats and subsequently eaten as bush meat. Human to human transmission then occurs by body fluids of symptomatic cases to family and other close contacts [3]. High transmission rates occur at traditional funerals of cases, and then spread by infected funeral attendees to other villages and locations, leading to a gradual expansion of the outbreak [4]. If admitted to health facilities, without strict infection control and protective clothing, transmission is a high risk to health staff [5].

### Ebola virus disease in the DRC

DRC [then Zaire] is the country where EVD was first described, in the outbreak occurring in Yambuku in 1976 [6]. A similar, though unrelated outbreak was occurring at the same time in southern Sudan [7]. The Zaire outbreak was initially linked to a hospital, and then spread to the adjoining rural area, and resulted in 318 reported cases, and a case fatality rate (CFR) of 81%. Since 1976, there have been nine further reported outbreaks of EVD in DRC [8]. Many of these were small outbreaks, in rural areas, and apparently self limiting. The largest outbreak was centred around the town of Kikwit in 1995, with 317 cases and 245 deaths [9]. Timely infection control, case finding, education and supervision of burials helped to bring this large outbreak under control [10].

In the two years before the beginning of the current outbreak, there have been two EVD outbreaks in DRC, both in geographic areas distant from the current outbreak, and resulting in far fewer cases [11,12].

### Development of the current outbreak in DRC

The current outbreak in DRC is affecting the provinces of North Kivu and Ituri in north eastern DRC, an area bordering Uganda, Rwanda and South Sudan, Figure 1.

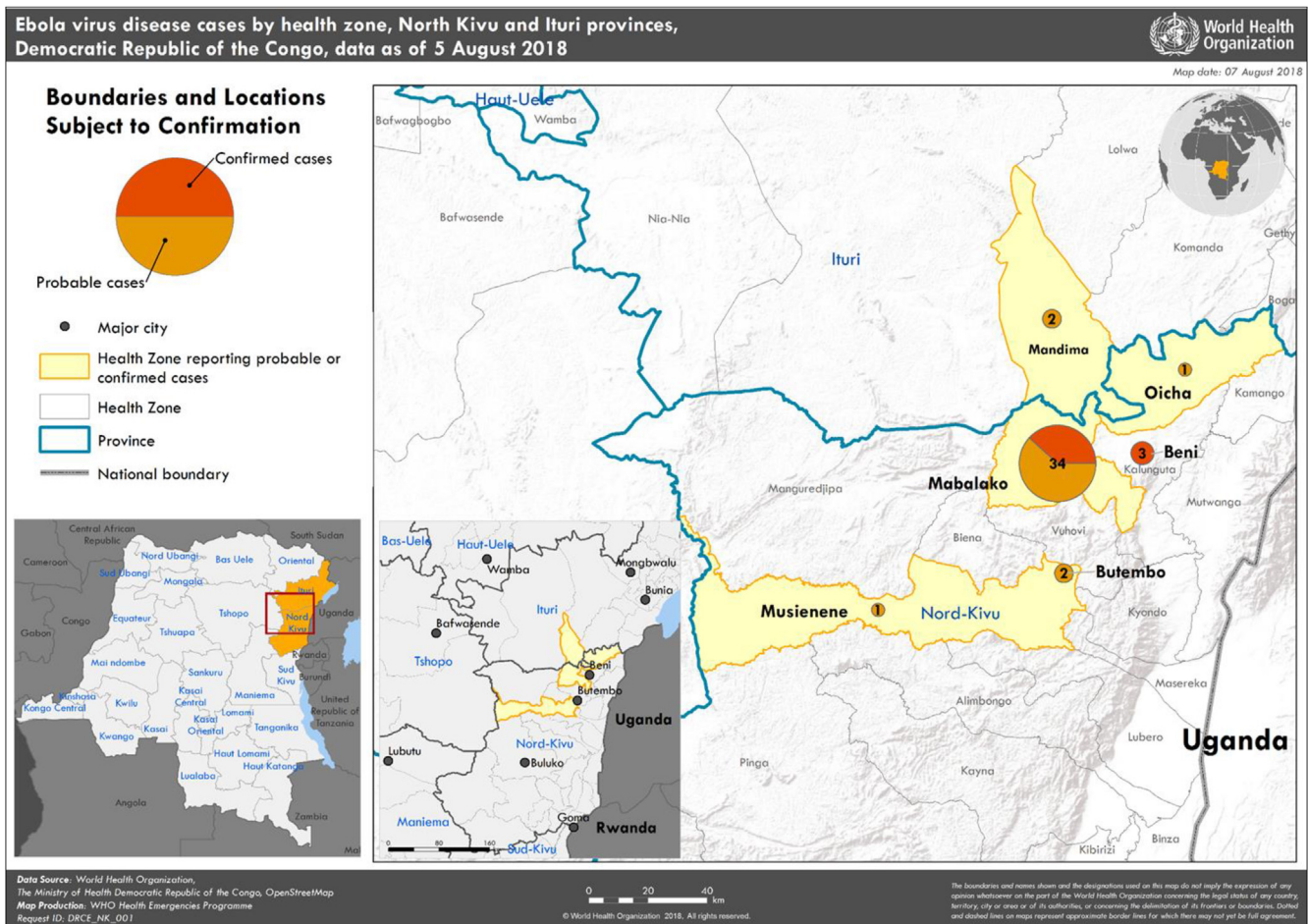


Figure 1. Geographical distribution of confirmed and probable Ebola virus disease cases in North Kivu and Ituri provinces, Democratic Republic of Congo, 5 August 2018.

The first reported cases occurred in North Kivu province at the end of July 2018 [13]. Samples from several patients were confirmed as EVD at the national laboratory in Kinshasha on 1/8/2018, and the outbreak was reported at that time to the World Health Organisation (WHO). The strain was identified as the Zaire strain, but with some local variation [14]. Health staff reported that similar cases may have occurred in the preceding two months, suggesting the epidemic may have started in May, with probable spread before any control measures were initiated. As of 3/8/2018, there were 13 confirmed cases, 30 probable, and 33 deaths [13]. The cases were occurring in both North Kivu and Ituri provinces. By November 2018, there had been 279 cases and by early March 2019, 897 cases (832 confirmed) with a case fatality rate of 63% [15]. The number of cases increased dramatically from March 2019, to 2713 cases in July 2019 (CFR 67%), and 3191 cases by the end of September 2019 [16]. Figure 2 shows the monthly number of cases from August 2018 to December 2019.

The dramatic increase from March 2019 coincided with an upsurge in local violence and insecurity, and with increasing mistrust among local community with the control programme [17]. This resulted in fewer cases coming to treatment centres and a breakdown in contact tracing, leading to increased transmission in the community. The apparent low case number in November 2019 coincided with attacks on response teams and reduced reporting.

## Methods

The following sources of information were accessed for the review:

- PUBMed using the search terms "Ebola outbreak DRC", "Ebola outbreak DRC and restricted to papers published after 2017", "Ebola vaccine", "Ebola treatment", "Ebola infection control", "Ebola community involvement".
- Google scholar, using the same search terms as above.
- Pro Med mail updates
- World Health Organisation (WHO) Regional Office for Africa, Ebola Outbreak Weekly External Situation Reports and Disease Outbreak News
- WHO protocols and information bulletins on Ebola
- CMRE (Comite Multisectoriel de la Riposte a la Maladie a Virus Ebola), the coordinating body of the DRC Ministry of Health, daily and weekly reports
- Communication with, and direct reporting from, health staff working in the outbreak in DRC.

## Results

- The national and international response to the outbreak and strategy.

Although Ebola had not been previously described in this area of DRC, there was a rapid response by both the DRC Ministry of Health and the World Health Organisation following reporting of the first suspected cases. Through the DRC MOH and WHO there was a rapid influx of personnel, equipment, and supplies to the outbreak area, though the lack of developed infrastructure and the ongoing insecurity made this a difficult and complex process. The overall strategy involved surveillance and reporting of cases, contact tracing, setting up of laboratories, admission of suspected cases to appropriate health facilities and management of confirmed cases, infection prevention and control, vaccination of contacts, and screening of mobile populations adjacent to neighbouring countries [13].

Because of the limitations of existing health facilities, and the major infection risks in managing suspected and confirmed Ebola cases, dedicated Ebola Treatment Centres (ETC's) were set up, involving MOH, WHO, and international government and non government organisation (NGO) staff. Later in the outbreak, a network of "Transit Ebola Treatment Centres" was created to bring facilities nearer to distant communities.

- Epidemiology and geographic spread of the outbreak.

Neither the primary source nor the index case for the outbreak have been established, but it is assumed that eating of bush meat and local family and community spread, through contact with symptomatic cases and traditional funerals, occurred before the first reported and diagnosed cases in Mabalako Health Zone of North Kivu province in late July 2018. Geographically, the outbreak spread from the initial area, southwards to the cities of Beni and Butembo, and to Katwa and Kanya further south, and further cases were reported to the north in Ituri province [18]. While locations such as Beni and Butembo are "cities" from the size of their populations, large parts of them are sprawling, crowded areas with poor housing and infrastructure, high risk factors for urban transmission.

Investigations into the spread of cases confirmed that most transmission was occurring in the community, both rural and urban. There are no clear descriptions of specific routes of transmission, though most cases are ultimately linked to a previous case, and clusters or hot spots of infection occur in multiple locations. It is estimated that there was at least a five

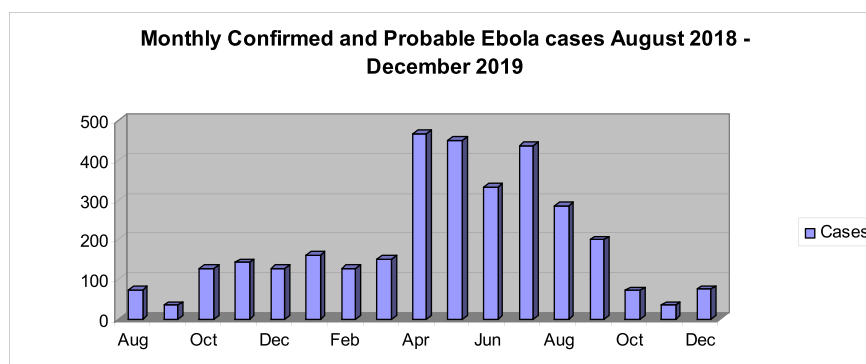


Figure 2. Monthly confirmed and probable Ebola cases: August 2018–December 2019.

day delay from the onset of symptoms before admission and isolation, allowing a window for ongoing transmission [19]. The spatial occurrence in different, often distant, locations may be explained by movement to markets and towns from different rural areas. The possibility of different original foci is unlikely, but more detailed sequencing of strains from different areas may help to clarify this.

While most surviving cases do not get a recurrence of infection, in December 2019 a previous patient in Mabalako health area relapsed, and was the source of EBV infection to at least a further 28 cases [18]. The relapse was confirmed from preliminary sequencing results of the original and subsequent strains. This is the first documented relapse case in this outbreak.

Although there has been considerable concern of regional spread, with adjacent borders to neighbouring Rwanda, Uganda, and South Sudan, as of November 2019 only one episode of transmission outside of DRC has been reported. This occurred in a family who had entered Uganda from DRC, with one family member being infected after arrival in Uganda [20]. However, no onward transmission has been reported.

### 3. Laboratory diagnosis facilities and methods.

The WHO recommended strategy for laboratory diagnosis of EBV at the periphery is the Gene Expert PCR, for blood or salivary samples [21]. The method was shown to have good performance characteristics, [22], with results positive 3–4 days after the onset of symptoms. Samples are taken from both suspected cases at treatment centres, and where possible from deaths in the community.

### 4. Surveillance, reporting, contact tracing and screening

Case definitions for suspected and confirmed cases of EVD are detailed in WHO guidelines [23]. Suspected cases that fulfil the basic WHO case definition of fever  $\pm$  other EBV related symptoms plus contact with an Ebola case in the previous 21 days are referred, through the local rural or urban health centre, to an Ebola Treatment Centre or one of the transit treatment centres. There are many cases where this referral is delayed, or not possible because of the security situation. As in West Africa, relatively few, less than 10%, present with haemorrhagic symptoms. Based on laboratory testing, suspected cases may be designated as a confirmed case, or if EBV negative, managed separately according to their clinical diagnosis. Up to 95% of suspected cases are shown to be Ebola negative, an indication of the wide range of other febrile infections endemic in the area [24]. Data on confirmed cases, and outcome, are collected and collated by the Ministry of Health and the WHO, providing daily and weekly reports.

Where possible, contact tracing teams follow up each confirmed case. Owing to the frequently insecure situation and difficult terrain, it is estimated that 30–50% of contacts may not be initially registered [25], resulting in the potential for further ongoing transmission.

To minimise the risk of the spread to neighbouring countries, screening points were established at the many border crossings. Screening consisted of temperature monitoring [26] with over 2m screenings undertaken. This successful programme has no doubt contributed to the containment of the epidemic within DRC.

### 5. Case management

Before the availability of the trial therapeutic agents, the management of confirmed cases was supportive and symptomatic, primarily electrolyte and fluid maintenance, nutritional support, and treatment of any co-infections. Clear guidelines for supportive management have been prepared by WHO [27].

While some patients begin recovery at this stage, others progress to a more severe and often fatal condition. Uncontrolled infection by Ebola leads to an impairment of immunity with a cytokine storm, coagulopathy, systemic bleeding, multi-organ failure and a high fatality rate [28,29].

Increasing understanding of the pathogenesis has led to the development of novel agents aimed inhibiting the uncontrolled immune and cytokine response.

The first experimental therapeutic agent ZMapp (a combination of three monoclonal antibodies), was used in a preliminary trial towards the end of the West Africa outbreak. While some reduction in mortality was observed, the numbers recruited were too small to determine if there was a significant benefit [30].

In November 2018, the DRC MOH and WHO began a randomised controlled trial of four experimental therapeutic agents under the Monitored Emergency Use of Unregistered and Investigational Interventions [MEURI] protocol. The agents were ZMapp, Remdesivir (an antiviral agent), Mab114 and REGN-EB3, the latter two being monoclonal antibody agents. Patients were enrolled at four ETC's, in Beni, Katwa, Butembo and Mangina [31].

Preliminary data were reviewed in August 2019, and showed superiority of mAb114 (mortality 34%) and REGN-EB3 (mortality 29%) over ZMapp (mortality 49%) and Remdesivir (mortality 53%). The RCT was stopped, and further patients were randomised to either mAb114 or REGN-EB3 [32]. These two agents are now used wherever logistically possible in all treatment centres, though problems of insecurity and supplies limit their availability. In addition to the reduced overall mortality, both agents showed a further reduced mortality in patients treated early in the course of disease, mAb114 11%, and REGN-EB3 6%.

It is important to note however that despite these potentially good survival rates in certain ETC's, when conditions allow a full treatment regimen to be followed, the overall mortality rate since August 2018 has shown little reduction from around 60%.

Underlying the management of individual patients, is the high risk of infection transmission within the treatment centres.

### 6. Infection control in treatment centres and the community

Several studies in West Africa highlighted issues of infection control, that were responsible for a high risk of transmission both in treatment centres and in the community [33]. In that outbreak, over 600 HCW's were infected, with more than 300 deaths. Many of the lessons of the West Africa epidemic have formed the basis for improved infection control strategies and equipment in the DRC [34,35].

Suspected cases are first admitted to the triage area, until laboratory results are available. Confirmed cases are then moved to the treatment wards. Within an ETC, strict infection prevention and control (IPC) practices are followed, with

rigorous adherence to personal protective equipment (PPE), protocols for IV access and other clinical procedures, and environmental and ward decontamination.

The Ebola Treatment Centres in the current DRC outbreak (when not being attacked or looted) may be compared to small field hospitals [36].

They are designed to provide the necessary clinical management for patients, but also with an equal emphasis on strict infection prevention protocols in each part of the centre.

By December 2019, WHO data indicated that over 150 health care workers had been infected. It is likely that many of these acquired infection in the community, either as front line care for new cases, or through other family or neighbour contacts. There is no definite evidence of HCW infection within ETC's.

Infection control and prevention of transmission in the community is more complex than in the controlled area of a treatment centre. In the outbreak region, local people often present first to local health centres, where facilities for infection prevention, and trained staff, are limited. Transmission is likely to occur at this level, before suspected cases are transferred to an ETC or transit treatment centre. Earlier studies in Uganda have emphasised the importance of community involvement in Ebola infection prevention [37]. Improvement of infection prevention strategies at border areas, have improved infection control compliance [38].

The greatest risk, as in all previous Ebola outbreaks, has been traditional burials, where part of the cultural activity is for large numbers of relatives and friends to attend and touch the deceased. In an outbreak in Uganda [39], and in earlier outbreaks in DRC [40], there has been progress by local red cross volunteers and community groups to organise safe burials, but this has often created tensions within the community.

A study in the 2018 DRC Equateur outbreak [41] demonstrated the importance of refresher training of health care workers in IPC practices. After the training, compliance with protocols was significantly improved at rural health centres as well as at district hospitals.

In September 2019, the DRC MOH and WHO launched revised IPC guidelines and training targeting more than 3,000 nurses, doctors, and community healthcare workers. The new guidelines comprised an IPC toolkit and protocols, covering subjects from hand washing and decontamination, to PPE, and the training of 400 additional IPC supervisors in the community [42].

#### 7. Vaccination, strategy, implementation, and possible effectiveness

An investigational vaccine, rVSV-ZEBOV, which has shown to be safe and protective against the Zaire strain of the Ebola virus, is recommended by the Strategic Advisory Group of Experts on Immunization [SAGE-I] for use in Ebola outbreaks caused by the Zaire strain of the virus, [43]. The vaccine consists of a vesicular stomatitis virus [VSV], an animal virus that has been genetically engineered to contain an immunogenic protein from the Zaire Ebola virus.

This vaccine was trialled in a major study towards the end of the West Africa outbreak, and was shown to be safe, and protective against the Ebola virus [44]. It was first used in the field during the relatively small Ebola outbreak in Equateur Province of DRC in 2018 [45].

The vaccine is a post exposure vaccine, one dose being required. The vaccine is offered to frontline health care workers, and in the community to contacts, and contacts of contacts, of symptomatic cases. A ring vaccination strategy is used in an attempt to both protect contacts from disease, and break the chain of transmission from the symptomatic case [46]. The strategy is similar to that used in the later stages of the Global Smallpox Eradication Campaign [47].

The ring is not necessarily a contiguous geographic area but captures a social network of individuals and locations that may include dwellings or workplaces further afield, where the index patient spent time while symptomatic, or the households of individuals who had contact with the patient during the illness or after his or her death. Experience suggests that each ring may be composed of an average of 150 persons [48].

Contacts are defined as individuals who, in the last 21 days, lived in the same household, were visited by the patient after they developed symptoms or visited the patient or were in close physical contact with the patient's body, body fluids, linen or clothes. Contacts of contacts are defined as neighbours, family, or extended family members at the closest geographic boundary of all contacts, plus household members of all high-risk contacts who do not live in the same locality as the patient [49].

While the ring vaccination protocol is epidemiologically based, because of the security situation and logistic difficulties, it is not always possible to be fully implemented.

Changing strategies when insecurity makes it difficult to reach people have included providing pop-up vaccination stations at health posts and increasing the number of people vaccinated within communities with ongoing transmission, sometimes vaccinating whole villages.

In September 2019, a decision was made by the health authorities of DRC and WHO to introduce a second experimental Ebola vaccine [50]. The vaccine (Ad26.ZEBOV) is a monovalent vaccine based on adenovirus type 26 (Ad26) vector expressing the glycoprotein (GP) of the Ebola virus Mayinga variant.

This vaccine is given in two doses 56 days apart. Unlike the, rVSV-ZEBOV vaccine, this vaccine will be used for populations not directly exposed to Ebola cases, in an attempt to broaden the area of protected population, and reduce the risk of spread to new geographical areas [51].

#### 8. The effect of insecurity and violence on the implementation of the programme and spread of the outbreak

In normal infection and epidemiological practice, it is difficult to comprehend the complexity and difficulty, and indeed, danger, of the situation in the outbreak area. Since March 2019, increased activity of militia groups, increasing political uncertainty, and direct attacks on the Ebola response programme, have had a major effect on the functioning of the health teams. Treatment centres have had to be evacuated, and the work of community outbreak teams and contact tracing interrupted. This is resulting in lack of treatment of known cases, but more importantly, inability to locate new cases and their contacts, leading to increased and unreported transmission.

A study by Wannier *et al.* [52] demonstrated increased transmission rates in areas with recently reported violent events compared to those without. In a detailed review, Kalenga *et al.* [53], have detailed the violent events from August 2018 to May 2019 which can be linked to interruptions of the response programme. Further studies have demonstrated a

similar impact of the violence and militia groups on interruptions to the programme [54,55].

#### 9. The problem of poor community involvement

In any major epidemic response, there is a dilemma between the need to act quickly and decisively, and the need to involve the affected community in participation and decision making. This dilemma is often compounded by the lack of understanding or knowledge of local cultural practices by non local, or non national, decision makers and health staff. These issues have become increasingly relevant in the response to the Ebola outbreak in eastern DRC.

In a study by Masumbuku *et al.* [56], surveys among the affected population showed both general mistrust with the Ebola response, partly related to years of mistrust of any government or external action, and specific opposition because of conflicts with local cultural practices. These include the traditional eating of bush meat, regular gatherings at family or village events, and, most importantly in relation to risks of Ebola transmission, traditional funeral practices.

The importance of understanding, and adapting programme response to, traditional beliefs and practices was demonstrated in several studies during the West Africa epidemic and in Uganda [57–59].

### Situation at 31 December 2019

By the end of 2019, there have been 3262 confirmed cases, and 2232 deaths, a CFR of 66%, [60]. 56% of the cases were female, and 28% children under the age of eighteen years. 168 cases were health care workers. 76 new confirmed cases were reported in the month of December, in health zones in both North Kivu and Ituri provinces. All cases were linked to known chains of transmission.

The 19th December WHO Disease Outbreak News report has investigated in detail the high number of cases in children [60].

As of 17 December 2019, over a quarter of all confirmed EVD cases have been children aged less than 18 years (28%, 898/3233). Children from 1–4 years of age accounted for 9% (293/3233) of reported EVD cases and children under 1 year of age accounted for 6% (182/3233) of reported cases. The age distribution of EVD cases has remained relatively constant throughout the outbreak. The case fatality ratio among children aged 1–4 is 78% and among children under 1 year is 70%. These figures are similar to those observed in the 2014–16 West Africa EVD outbreak.

The data from this outbreak reveal a relationship between a person's age group and their pathway to care for EVD infection. Of persons who have died from EVD, death in the community occurred among 44% (80/182) of deaths among children under 1 year of age and 49% (145/294) of deaths among children 1–4 years of age. In contrast, 26% (575/2248) of deaths among persons aged 18 years or older were in the community. If a child infected with EVD presents to a health care facility (HCF), they do so, on average, sooner than adults after symptom onset. Although they present sooner, the proportion of children with EVD being referred from a HCF to an ETC is lower than adults. Among all cases admitted to a HCF, 38% of cases aged 1–4 years and 32% of cases aged less than 1 year die outside of ETCs, without referral, compared to 15% of cases aged 18 years or older.

These findings emphasise the need for strengthening the programme at the community level.

### Discussion

The response to the current outbreak in DRC has faced more difficulties than any previous Ebola outbreak. Without the violence, insecurity, and increasing community mistrust, the outbreak may have been resolved within months, rather than continuing for over a year, with the resulting high case numbers and mortality. The availability of two effective vaccines, novel therapeutic agents, and lessons from the West Africa outbreak, could have contributed to an earlier resolution of the crisis.

The situation in the countries affected by the West Africa outbreak, Guinea, Sierra Leone and Liberia were not free from political strife, two had had recent civil wars, and there were, in different locations, high community resistance and violence towards the response programme. Also, the geographical area affected, and the total number of cases, were far greater than in the current DRC outbreak. However, there was not the total breakdown in civil order that has occurred in some of the main cities affected, such as Beni and parts of Butembo, nor was the West Africa outbreak occurring in an environment where militia groups and longstanding military violence totally dominated the region. While there is a UN peace keeping force in eastern DRC, the complexity of the different militias and allegiances limit their ability to control the violence. It is in this context that all aspects of the programme in the current DRC outbreak must be considered.

The initial response was timely and appropriate, national and WHO inputs were started within days of the first confirmed case, and a coordinated programme of surveillance, infection control, and treatment centres initiated. Emergency protocols were agreed and implemented for the vaccination programme and the use of novel therapeutic agents. While full evaluation of their impact is still to be assessed, it is likely that they will form part of the initial response plans for future Ebola outbreaks.

There have, however, been increasing concerns, and evidence, that this specifically medical centred approach, has been limited by the lack of understanding in some aspects of the response programme of traditional beliefs and customs.

A recent workshop convened by the Ebola Anthropology Group [61] has highlighted some of these issues. Overall, it was felt that "Systems were designed around the disease, not those affected. Technical solutions were insufficient in the face of communities afflicted by precipitous losses of trust.

Community engagement often meant little more than issuing instructions".

A detailed anthropological study in the forest zone of Guinea during the West Africa outbreak [62] has shown how far apart the medical model, and the communities perception of Ebola and the response, may be.

An important recommendation from the workshop above, and recently from some of the agencies working in DRC, is that the Ebola response should be integrated into existing local health systems (which may themselves need considerable input), rather than be a separate, centralised, short term response. [63]. A more integrated, multidisciplinary strategy, with extensive community involvement, is now being considered within DRC [64].

In July 2019, WHO declared the outbreak a Public Health Emergency of International Concern (PHEIC) [65]. This is unusual for an outbreak where significant transmission in

neighbouring countries has not occurred. While such status will potentially increase funding and external support for the outbreak, a large expansion of outside input may do little to encourage community participation.

## Conclusion

The Ebola epidemic in DRC as of January 2020, continues, though with lower new case numbers than at the height of the outbreak. For future Ebola outbreaks, the proven medical interventions of the vaccines available, the efficiency of the treatment centres and the new therapeutic agents provide an optimism that has not existed for previous Ebola outbreaks. However, as has been demonstrated in both the current DRC outbreak, and in the earlier West Africa outbreak, community understanding and involvement are essential from the beginning of the outbreak response, and must be integrated into the medical interventions and strategy.

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