

Feedback from operational stakeholders who manage or respond to outbreaks is that they are often too busy to review literature or obtain relevant background information to assist them with acute response. Unlike a traditional analytical outbreak investigation report, **Watching Briefs** are intended as a rapid resource for public health or other first responders in the field on topical, serious or current outbreaks, and provide a digest of relevant information including key features of an outbreak, comparison with past outbreaks and a literature review. They can be completed by responders to an outbreak, or by anyone interested in or following an outbreak using public or open source data, including news reports.

Keywords: Ebola; Ebola virus disease, outbreak; epidemiology; Democratic Republic of Congo; DRC; North Kivu; Bas-Uele; Equateur; viral persistence; zSVS-ZEBOV

Watching brief	
Title	Ebola Outbreaks in the Democratic Republic of Congo (DRC), 2017-2019
Author(s)	Phi-Yen Nguyen, University of New South Wales, Sydney, Australia
Date of first report of the outbreak	9/5/2017
Disease or outbreak	Ebola virus disease (EVD)
Origin (country, city, region)	Bas-Uele, Northeast DRC
Suspected Source (specify food source, zoonotic or human origin or other)	Zoonotic and human-to-human transmission of Ebola virus (EBOV), subtype Zaire [1,2,3]
	It was unclear how the first deceased victim contracted the virus, but past outbreaks have been linked to consumption of bush meat, especially non-human primates, and direct contact with infected animals [4].
Date of outbreak beginning	Several outbreaks have occurred in different parts of DRC since 2017. The three outbreaks described below are the eighth, ninth and tenth outbreaks of EVD since its discovery in 1976 in the DRC.
	2017 Bas-Uélé province outbreak



On 9 May 2017, the World Health Organization (WHO) was informed of a cluster of undiagnosed illness and deaths with haemorrhagic symptoms from 22 April 2017 in Likati health zone, Bas-Uélé province, northern DRC (near the Central African Republic border). Five blood samples were sent to the Institut National de Recherché Biomédicale (INRB) laboratory in Kinshasa, two of which tested positive for EBOV using RT-PCR.

On 11 May 2017, WHO declared the start of the outbreak after being notified by the Ministry of Health (MOH) of DRC of the first two confirmed EVD cases. By then, 9 suspected cases, including 3 deaths, have been reported [1].

2018 Équateur province outbreak

From 4 April to 9 May 2018, 32 EVD cases (including 18 deaths) were reported from Bikoro health zone, Équateur province, northwest DRC (near the Congo border), approximately 800km southwest of Likati, Bas-Uélé [5]. Five samples were sent to the INRB, two of which tested positive for EBOV using RT-PCR.

On 8 May 2018, WHO declared the start of the outbreak, after being notified by the MOH of DRC of two confirmed EVD cases [6].

2018 North Kivu province outbreak

On 28 July 2018, the MOH of DRC was informed of a cluster of haemorrhagic fever cases by the North Kivu health division, eastern DRC (near the Uganda border). Mangina, the epicentre of the outbreak [7], is approximately 700km southeast of Likati, Bas-Uélé and 1,300km east of Bikoro, Équateur [5]. Six blood samples were sent to the INRB laboratory, four of which tested positive for EBOV using GeneXpert-automated PCR.

On 1 August 2018, WHO declared the start of the outbreak after being notified by the Ministry of Health (MOH) of DRC of the four confirmed EVD cases. By 3 August 2018, 43 EVD cases (13 confirmed and 30 probable), including 33 deaths, had been reported in North Kivu province and the neighbouring Ituri province [8].

Date outbreak declared over

For EVD, the end of an outbreak will be declared 42 days (two 21-day incubation cycles of EBOV) after the last confirmed patient of the affected area tested negative for the disease for the second time.

2017 Bas-Uélé province outbreak

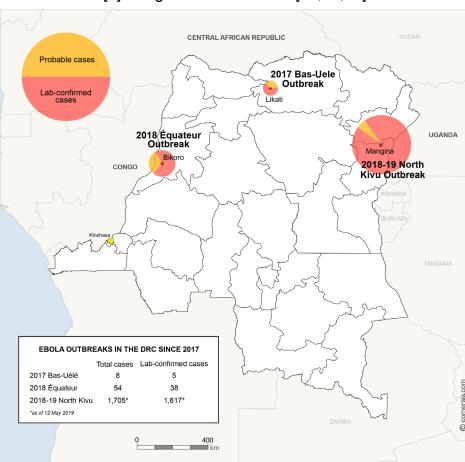


	On 2 July 2017, WHO declared the end of the outbreak in Bas-Uélé [9].
	2018 Équateur province outbreak
	On 24 July 2018, WHO declared the end of the outbreak in Équateur [10].
	2018 North Kivu province outbreak
	N/A – ongoing as of 12 May 2019.
	2017 Bas-Uélé province outbreak
	Because of the remote and isolated nature of Likati district, the outbreak was contained within the boundary of Bas-Uélé province. Cases were reported from four health areas:
	 Nambwa (3 confirmed and 2 probable, including 3 deaths);
	Muma (1 confirmed, no death);
	Ngayi (1 probable, including 1 death);
	Mabongo (1 confirmed, no death) [11].
	2018 Équateur province outbreak
	Cases were reported from three health areas in Équateur province:
Affected countries &	Bikoro (10 confirmed and 11 probable, including 18 deaths);
regions	 Iboko (24 confirmed and 5 probable, including 12 deaths);
	Wangata (4 confirmed, 3 deaths) [10].
	2018 North Kivu province outbreak
	As of 12 May 2019, cases were reported from the following 21 health zones:
	 North Kivu province: Beni, Biena, Butembo, Kalunguta, Katwa, Kayna, Kyondo, Lubero, Mabalako, Manguredjipa, Masereka, Musienene, Mutwanga, Oicha, Vuhovi (1,465 confirmed and 76 probable, including 1,024 deaths);
	 Ituri: Bunia, Komanda, Mandima, Nyakunde, Rwampara, Tchomia (152 confirmed and 12 probable, including 100 deaths) [12].



Figure 1: Location of epicentres and number of cases for Ebola outbreaks in the DRC since 2017, adapted with permission from comersis.com [5] using data from who.int [10,11,12]

Number of cases (specify at what date if ongoing)



Clinical features

Initial presentation of EVD is non-specific and can be misdiagnosed as other diseases such as malaria, typhoid, and other viral haemorrhagic fevers (including dengue or Lassa fever) [13].

According to WHO's case definition, an EVD case is classified as "suspected" if either of the following symptoms applies:

- a sudden onset of high fever (39-40°C) and at least three of the following symptoms: headaches, anorexia, stomach pain, vomiting, diarrhoea, lethargy, aching muscles or joints, difficulty swallowing, difficulty breathing, hiccups; or
- · inexplicable bleeding; or
- sudden, inexplicable death.



A case is classified as "probable" if it is evaluated by a clinician, or if a diseased patient has an epidemiological link with a confirmed case.

A case is classified as "laboratory confirmed" if a blood sample is tested positive for virus antigen via reverse transcriptase-polymerase chain reaction (RT-PCR) or detection of IgM antibodies directed against EBOV [14].

For the three outbreaks, cases were alerted to the MOH of DRC by the referral health centre upon showing symptoms of acute haemorrhagic fever. The common symptoms for most of the early cases were high fever and intense fatigue [15,16,17]. No detailed description was given for any haemorrhagic symptom that accompanies fever (e.g. conjunctival bleeding, gastrointestinal bleeding or bleeding from venipuncture site).

Bodily fluids contact

Initial transmission of EBOV occurs through contact with an infected animal, such as a fruit bat or a primate. After that, EBOV can be transmitted from human to human via direct contact with blood or bodily fluids (urine, saliva, sweat, faeces, vomit, breast milk and semen) of an infected or deceased person [18].

The virus can remain in bodily fluids secreted from immunologically privileged sites, including semen, breast milk, ocular fluid and spinal column fluid, even after the infected person has recovered from EVD [19]. However, the amount of viral shedding in each type of fluid is not well quantified [18].

Mode of transmission (dominant mode and other documented modes)

An infected person can only transmit EBOV once he or she develops signs and symptoms [18]. The incubation period is approximately 2-21 days [21]. Healthcare workers (HCWs) and burial personnel are at high risk of contracting EVD because of close contacts with the infected person and handling of instruments (needles and syringes) containing bodily fluids [22,23]. Hence, infectious control measures in hospitals and safe burial practices are critical in transmission control.

Fomite transmission

Theoretically, fomite transmission is possible because EBOV was detected in visible dried blood stains [20] and could persist on glass surface and in the dark for 6 days in a laboratory-controlled setting [24]. However, EBOV does not remain infectious if allowed to dry on environmental surfaces, especially in routinely disinfected wards [20].



	Airborne transmission (aerosol or large droplets)
	Experiments have demonstrated transmission of EBOV without direct contact among animals [25,26], suggesting the possibility of transmission via aerosol or large droplets secreted by the infected animal. In mechanically produced aerosols, EBOV was found at sufficient levels to cause lethal infections in primates [27,28]. However, airborne transmission from human to human is uncertain in previous outbreaks [29]. In pathology specimens of the lung, abundant Ebola virus is found [30], and the Kikwit outbreak in 1995 suggests airborne transmission in at least five cases [31].
	<u>Others</u>
	EBOV cannot be transmitted by food (except for consumption of bushmeat in certain parts of the world), mosquito bites, or casual contact with a survivor [18]. However, sexual transmission from recovered survivors and vertical transmission from mother to baby have been documented [32].
Demographics of cases	Demographic details were not available for the 2017 Bas-Uélé province outbreak.
	2018 Équateur province outbreak
	7 out of 54 reported cases (13%) were HCWs [10]. The median age was 40 years (range 8-80) and 40% were females. 71% of confirmed cases had contact with infected patients, and 58% of confirmed cases attended funerals before the onset of disease [16].
	2018 North Kivu province outbreak
	As of 12 May 2019, among 1,705 reported cases, 56% were female, and 29% were children aged less than 18 years. 101 cases (6%) were HCWs [12].
	2017 Bas-Uélé province outbreak
Coop fotolity water (OFD)	By 2 July 2017, 4 out of 8 reported cases were fatal. The overall CFR is 50%. The number of fatalities among confirmed cases was not published [11].
Case fatality rate (CFR)	2018 Équateur province outbreak
	By 24 July 2018, 33 out of 54 reported cases (17 out of 38 confirmed cases) were fatal. The overall CFR was 61%; the CFR among confirmed cases is 45% [10].



	2018 North Kivu province outbreak
	As of 12 May 2019, 1,124 out of 1,705 reported cases (1,036 out of 1,617 confirmed cases) were fatal. The overall CFR is 65.9%; the CFR among confirmed cases is 64.1% [12].
Complications	The initial non-specific presentation of the disease is followed with abdominal pain, severe vomiting and diarrhoea, leading to fluid loss and hypovolemic shock [13]. Patients are also prone to systemic inflammatory response syndrome, characterised by symptoms commonly associated with bacterial sepsis (fever, tachycardia, hyperventilation and leukopenia). Haemorrhage is only observed in a minority of patients [33].
	The combination of hypovolemia, septic shock and haemorrhage eventually results in multi-organ dysfunction, particularly the renal, hepatic and coagulation systems. This happens typically by the second week of the disease and rapidly leads to organ failure and death [33].
	Ebola survivors may develop ocular complications such as uveitis, which can lead to vision loss [34].
Available prevention	Wearing of personal protective equipment (PPE) can reduce the risk of EBOV transmission by introducing a physical barrier against the infected person's bodily fluids [35]. However, emphasis on proper donning and doffing technique and double gloving [36,37] is crucial to minimise the risk of self-contamination during removal of PPE [38].
	Several vaccines for EVD are being evaluated in clinical trials [39,40,41,42]. One vaccine, called rVSV-ZEBOV, has been demonstrated in phase I-III clinical trials to be safe and immunogenic in humans [43]. This vaccine consists of recombinant vesicular stomatitis virus (VSV) vector expressing a surface glycoprotein from the Zaire Kikwit 1995 strain [44].
	rSVS-ZEBOV is recommended by the Strategic Advisory Group of Experts on Immunization (SAGE) for use against subtype Zaire if no licensed vaccine is available [45]. It was approved for compassionate use by the DRC's Ethics Committee during the early stage of the 2018 Équateur province and 2018 North Kivu province outbreaks [46,47] based on the genomic analysis of early cases' pathogen samples [48].
	In May 2019, SAGE recommended an additional vaccine alternative for lower risk individuals, for whom the Ad26.ZEBOV/MVA-BN is being considered [49]. The



	Ad26.ZEBOV/MVA-BN is a two-dose, multivalent vaccine consisting of an adenovirus-26 vector (Ad26.ZEBOV) and a modified vaccinia Ankara vector (MVA-BN) encoded with Ebola glycoproteins, which have been demonstrated in phase I-II randomised controlled trials (RCT) to be safe and immunogenic for human volunteers [50,51].
Available treatment	Current treatment for EVD is limited to supportive care and symptomatic treatment only. Rehydration via oral or IV route is routinely encouraged to prevent hypovolemic shock. Transfusion of whole blood or coagulation regulators (e.g. clotting factors, fibrinolysis inhibitors, etc.) is administered to counteract haemorrhage. Some patients require anticoagulants to reduce risk of thrombosis and disseminated intravascular coagulation following haemorrhage. Intensive care, including dialysis, hemofiltration, intubation, and mechanical ventilation, is required for patients with multi-organ system failures, but is limited to developed-country settings [52].
	Several experimental therapies are under development, including antivirals, interferons, antibodies and interfering RNA [53], although none have successfully completed human RCT. There is increasing interest in convalescent therapy, in which patients receive whole blood or plasma from Ebola survivors, which has improved survival rates in past outbreaks [54]. It is recommended by WHO as an interim empirical treatment during outbreaks [55].
	A cocktail of three chimeric monoclonal antibodies, named ZMapp, demonstrated strong antiviral activity in preliminary studies and prevented death even when administered in the late stage of the disease. However, the human RCT (PREVAIL II) only succeeded in demonstrating safety, not efficacy, due to insufficient enrolment [56].
	A phase II-III RCT is underway in the DRC to compare the safety and effectiveness of 3 new therapies against Zmapp: mAb114 (a single monoclonal antibody), remdesivir (an antiviral) and REGN-EB3 (a monoclonal antibody cocktail). The trial is enrolling EBOV patients in Beni, with plans to include patients from other Ebola treatment units [57].
Comparison with past outbreaks	Case fatality rate The 2018 Équateur province outbreak reported CFR of 61%, which is comparable to previous outbreaks of the same scale,



such as the 2014 outbreak (69 cases, CFR 71%) or the 2008 outbreak (32 cases, 47%) [58].

The 2018 North Kivu province outbreak was the most severe outbreak in the history of the DRC, with 1,705 cases and CFR of 65.9%, which is comparable to other large outbreaks such as the 2007 outbreak (264 cases, 71%) or the 1995 outbreak (315 cases, 79%) [59].

The 2012 outbreak reported a lower CFR (36 cases, 36%). However, it was caused by a different virus, *Bundibugyo ebolavirus* [48].

Causative agents

All three outbreaks were caused by *Zaire ebolavirus*, which is the causative agent behind the 2014-2016 outbreak in West Africa and all previous outbreaks in the DRC except for the 2012 outbreak [58,60]. Phylogenetic analysis shows that the EBOV strains behind the 2018 Équateur outbreak are genetically linked to the 2014 outbreak, which occurred at the neighbouring Tshuapa province [61].

Geographic footprint

Like most previous outbreaks, the Bas-Uélé and Équateur outbreaks were geographically contained due to the remote nature of their epicentres. The Bas-Uélé outbreak's epicentre is a forested region of Likati health zone, with a population density of only 7 people/km² [62]. The Équateur outbreak's epicentre is Bikoro health zone, which is 280km by road from the provincial capital, Mbandaka [6].

In contrast, the North Kivu outbreak has extended to urban locations, including Beni (population 420,000) and Butembo (population 1 million) [7,63]. It is comparable to the 1995 outbreak in Kikwik (population 500,000) [64].

Impact on HCWs

The proportion of HCWs among total EVD cases are lower (6-13%) [10,12] compared to previous Ebola outbreaks (25-31%) [22].

Vaccination

This is the first time a vaccination strategy was adopted in the DRC for Ebola response [65]. An extensive ring vaccination campaign with rSVS-ZEBOV has been carried out since August 2018, covering more than 120,000 high-risk individuals, including



	children, contacts and front-line HCWs. 80% of identified cases (776) had their rings defined and their contacts gave consent for vaccination. 90% of consented contacts were vaccinated, indicating high coverage [66]. Acceptance of vaccination among families and HCWs is high [67]. To date, Merck & Co. has shipped 100,0000 rSVS-ZEBOV doses to the DRC and agreed to maintain a global emergency stockpile of 300,000 doses. However, in view of the scale of recent Ebola outbreaks, an option to increase the stockpile may be revisited in the future [68].
Unusual features	By 12 May 2019, over 93,400 contacts have been registered, 14,459 were under surveillance, and 114,498 contacts have been vaccinated with rSVS-ZEBOV [12]. In April 2019, WHO published preliminary results from the observational study of this campaign, claiming an overall vaccine efficacy of 97.5% (95% CI 95.8-98.5%). Out of all vaccinated contacts, 71 contracted EBOV (0.076%). The report concludes that ring vaccination with rSVS-ZEBOV demonstrates protective effects on secondary degree contacts and lowers fatality rate among those contracting EBOV (CFR was 16% among those contracting within 9 days post-vaccination and 0% among those contracting 10 days or more post-vaccination) [66].
	However, despite unprecedented advancements in vaccines, diagnostics, experimental treatment and accumulated institutional experience, the response strategies that were successful in containing the Équateur outbreak failed to replicate the same result in the North Kivu outbreak. Since October 2018, new clusters continue to emerge in multiple health zones [7].
Critical analysis	Phylogenetic analysis Genome sequencing confirmed that the two EBOV strains behind the outbreaks in Équateur and North Kivu provinces are genetically distinct. The 2018 Équateur strain is genetically closer to the 2014 outbreak that hit the neighbouring Tshuapa province [61]. On the other hand, samples from Mangina and Beni (2018-2019 North Kivu outbreak) are genetically closer to the sample from Likati (2017 Bas Uélé outbreak) [69].
	The three EBOV strains seem to be independent lineages diverging from a single clade in 1976-1977 (the first Ebola outbreak in the DRC) [61]. This raises the possibility of a single origin reservoir that has been propagating EVD across



geographic distances in the DRC, either through habitat fragmentation or migration. A similar hypothesis emerged for the 2014 outbreak, in which bats were identified as the main zoonotic reservoir of EBOV and their spatial-temporal migration patterns were said to correlate with hot spots of EVD outbreaks in West Africa [70].

Persistence of the outbreak

The current North Kivu-Ituri outbreak is characterised as a complex humanitarian emergency because efforts to contain the outbreak were hampered by a multitude of interlinked issues.

Security deterioration & community resistance

Unlike the other two, the North Kivu outbreak occurred in a war zone – the Kivu province is the stronghold of the opposition, with over 100 active armed groups in conflict for over 25 years [71]. Ebola treatment centres (ETCs) and HCWs have been repeatedly attacked by militants [71,72,73].

Besides armed groups, HCWs have frequently encountered community resistance in multiple locations, especially in Beni [74,75]. The tension between HCWs and the civilians stems from frustration over unmet health needs, postponement of presidential elections due to the Ebola outbreak and the resulting suspicion of the Ebola response as a political ploy by the incumbent government [76]. In rural areas, residents are generally distrustful of health personnel because of past violent acts by outsiders and the perceived high death rates at ETCs [73].

These incidents were disruptive to contact tracing, safe burials and vaccination – the three pillars of Ebola prevention.

Ineffective contact tracing

More than half of reported EVD cases were not on existing lists of identified contacts, suggesting a potential weakness in contact tracing, or that the source of infection was not an identified case [73,77]. The reported barriers to identifying and monitoring contacts were low engagement of community health workers, particularly traditional healers, and heightened insecurity [74].

In addition, continuous movement of more than a million refugees and internally displaced people (IDP) in and out of North Kivu and Ituri provinces [78] creates barriers to effective contact tracing. The towns of Beni and Butembo, in particular,



see constant traffic, often unreported, across the DRC-Uganda border for micro-commerce activities, family visits and trafficking [71].

• Suboptimal infection prevention and control (IPC) measures

IPC practices – wearing gloves, washing hands, disinfecting infected wards and quarantining – remain inadequate in public and private health centres, as reflected in a high incidence of EVD among HCWs [12,79]. Infected but undiagnosed HCWs might be an important focal point that transmit EVD to community cases, who visit health facilities for other illnesses [74,80]. Supplies of PPE may also be short.

Another important source of infection is informal clinics belonging to traditional healers, which serve a majority of hard-to-reach communities. Their large number and unregistered nature demands multiple supervisory visits to ensure compliance with IPC standards. On the other hand, these traditional healers can be potentially engaged as CHWs for community education on sanitation and hygiene [74].

Viral persistence – A possible mechanism for perpetual flare-ups?

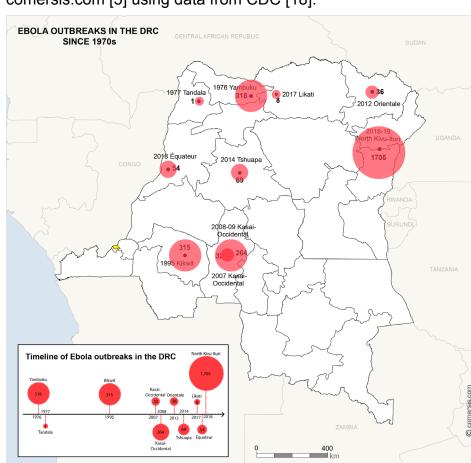
Despite having declared the end of the Ebola outbreak in March 2015, Liberia still faced several flare-ups throughout 2015 that were from persistently infected survivors, instead of an active reservoir [81]. Another phylogenetic investigation showed that a female EVD survivor from the 2014 Liberia outbreak might have transmitted EBOV to her son one year later [82]. These examples raised the question of whether persistently affected survivors are a source of unidentified transmission chains in the DRC outbreaks. However, this hypothesis is challenged by the fact that the DRC was not the main affected area in 2014 and does not have a large number of survivors present, compared to Sierra Leone. Liberia and Guinea.

One important link to consider is sexual transmission. Several flare-ups from Liberia, Guinea and Sierra Leone were attributed to sexual intercourse with persistently infected male survivors [83,84]. Serological and genomic data from EVD male survivors demonstrated persistence of viral RNA in semen [85,86] that lasted beyond the WHO-defined waiting period for declaring a country to be free from EVD [84]. This opens up another avenue for community health education: safe sex practices such as sexual abstinence or condom use must be included in the community education package for contacts of EVD survivors [84].



Why have multiple, genetically distinct outbreaks arisen in the DRC within a period of 24 months?

Figure 2: Geographical locations and timeline of all Ebola outbreaks in the DRC since 1970s, adapted with permission from comersis.com [5] using data from CDC [18].



Key questions

How can socio-political barriers to disease control be best addressed?

How effective are vaccination campaigns in reducing the spread of the disease in the 2018 North Kivu outbreak, and have cases occurred in vaccinated contacts?

How long will the immunity last among vaccinated people?

How should vaccines be given in view of heightened risk of outbreak expansion? Should the current ring vaccination strategy be replaced by geographical vaccination, covering areas of high population density?



	Have persistently infected survivors played a role in the North Kivu outbreak?
	What health promotion strategies are needed regarding prevention of sexual transmission among survivors?
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