Filovirus Outbreak Detection and Surveillance: Lessons From Bundibugyo

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The first outbreak of Ebola hemorrhagic fever (EHF) due to *Bundibugyo ebolavirus* occurred in Uganda from August to December 2007. During outbreak response and assessment, we identified 131 EHF cases (44 suspect, 31 probable, and 56 confirmed). Consistent with previous large filovirus outbreaks, a long temporal lag (approximately 3 months) occurred between initial EHF cases and the subsequent identification of Ebola virus and outbreak response, which allowed for prolonged person-to-person transmission of the virus. Although effective control measures for filovirus outbreaks, such as patient isolation and contact tracing, are well established, our observations from the Bundibugyo EHF outbreak demonstrate the need for improved filovirus surveillance, reporting, and diagnostics, in endemic locations in Africa.

The family *Filoviridae* has two genera of viruses, *Ebolavirus* and *Marburgvirus*, which are associated with similar clinical syndromes: Ebola hemorrhagic fever (EHF) and Marburg hemorrhagic fever (MHF). Investigators have identified 4 species of Ebola virus—*Zaire ebolavirus* (ZEBOV), *Sudan ebolavirus* (SEBOV), *Reston ebolavirus* (REBOV), *Cote d'Ivoire ebolavirus* (CIEBOV)—and 1 proposed species, *Bundibugyo ebolavirus* (BEBOV) [1], whereas a single species of Marburg virus, *Lake Victoria marburgvirus* (MARV) is known. EHF and MHF are notable for the overall severity of disease in humans, often with hemorrhagic characteristics and high case fatality. Considerable differences in the mortality of various Ebola viruses and strains of Marburg virus have been noted, ranging from a low of approximately 40% for *Bundibugyo ebolavirus* [2] to nearly 90% for *Zaire ebolavirus* [3, 4], and similarly, mortality among Marburg viruses have ranged from 25% to 90% [5]. Typical early symptoms of EHF and MHF, such as fever, fatigue, headache, muscle aches, vomiting, and diarrhea, are nonspecific [3, 6–11], making initial syndromic-based identification of these diseases a challenge. Serologic, molecular, and virologic data suggest that fruit bats are the zoonotic reservoir of filoviruses [12–16]; however, filovirus outbreaks are characterized by prolonged chains of familial and nosocomial person-to-person transmission, which occurs through direct contact, contact with bodily fluids, or contact with contaminated clothes or linens of an infected person [17–21].

In November 2007, EHF was confirmed by Viral Special Pathogens Branch, Centers for Disease Control and Prevention (CDC), Atlanta, GA, in diagnostic samples associated with an outbreak of illnesses with unknown etiology in Bundibugyo District, Uganda. Genetic sequencing demonstrated that infections were caused by a novel fifth *Ebolavirus* species, BEBOV [22], marking the first time a new filovirus species had been identified since 1994 [23]. In the following days, a large national and international outbreak response was started to contain the outbreak. Organizations involved in outbreak response included the Uganda Ministry of Health, Médecins Sans Frontières, the World Health Organization, the African Field Epidemiology Training Network, the Uganda Virus Research Institute, and the

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International Federation of Red Cross. Previous reports on this outbreak have focused on identification and the clinical and epidemiologic characteristics associated with EHF in Bundibugyo District [2, 22, 24]. The goal of this article is to discuss challenges and contrast characteristics of surveillance, case classification, and epidemiology of the 2007 Bundibugyo EHF outbreak with those from previous large filovirus outbreaks.

METHODS

Data Collection

Epidemiologic data collection and laboratory testing (polymerase chain reaction [PCR], antigen detection enzyme-linked immunosorbent assay [ELISA], immunoglobulin M ELISA, immunoglobulin G ELISA) was performed, using standardized procedures, as described previously [2]. Case report forms were filled out in the field at the time of the patient's initial presentation. In some cases, information regarding signs, symptoms, dates, and contacts were retrospectively collected by follow-up interview or by hospital chart review. Data collection and management was performed by and shared daily with multiple organizations involved in the acute outbreak response. Laboratory testing was performed at the Uganda Virus Research Institute, Entebbe, Uganda. In addition, sample aliquots were shipped to Atlanta, to the CDC for confirmatory laboratory testing. All data for this report was collected as part of public health surveillance and outbreak response. Whereas other reports have described slightly different aggregate case numbers [24], for this article, patient classification was based on confirmatory laboratory testing, combined with epidemiologic data, at CDC; finalized data was provided to the Uganda Ministry of Health.

Case Classification

Final case classification was based on signs and symptoms, history of contact, and laboratory testing. The assignment of history of contact was based on the question, ''Did the patient have a contact with a known suspect case anytime in the 3 weeks before becoming ill?'' along with the name of the contact provided on the case investigation form at the time of presentation. Information regarding history of contact, on the case investigation form, was limited to a single contact per case. Cases of disease were classified as suspect, probable, or confirmed cases; or characterized as not a case of EHF. A suspect EHF case was defined as the occurrence of 1 of the following in a resident of or visitor to Bundibugyo District after 1 August 2007: (1) sudden onset of fever, plus at least 4 of the following signs or symptoms: vomiting, diarrhea, abdominal pain, conjunctivitis, skin rash, unexplained bleeding from any site, muscle pain, intense fatigue, difficulty swallowing, difficulty breathing, hiccups, headache; or (2) sudden onset of fever, plus history of contact with a suspect, probable, or confirmed EHF case; or (3) any sudden, unexplained death. A probable EHF case was defined as an individual meeting the suspect case definition, with a history of contact with a probable or confirmed EHF case in the 3 weeks prior to development of signs and symptoms, plus at least 3 of the following signs or symptoms: vomiting, diarrhea, unexplained bleeding, conjunctivitis, or skin rash. A confirmed case was defined as a suspect or probable case with laboratory confirmation of infection. An individual was defined as not being a case of EHF if within 3 days or more following the onset of symptoms, the individual demonstrated the absence of Ebola virus infection by laboratory testing, or the individual did not meet the clinical definition of a suspect EHF case.

During the acute stage of the outbreak response, the above suspect case definition was liberally applied as a surveillance and prevention tool for the identification and isolation of potential EHF cases within Bundibugyo district. As such, a number of ill persons were investigated during the outbreak response who did not meet the final criteria for a suspect EHF case. In this report, all potential EHF cases for which surveillance information was collected (including those whose symptoms did not meet the final criteria as a suspect case) during the outbreak response are considered investigated cases.

RESULTS

Case Classification

In total, 192 cases of illness in Bundibugyo District were investigated during the EHF outbreak response (Figure 1). Of these, a definitive laboratory outcome was obtained for 101 cases: 56 individuals were identified as confirmed cases of EHF, and 45 individuals were classified as not cases of EHF. Among the remaining 91 individuals, for whom a laboratory outcome was not available, 16 individuals were classified as not a case, on the basis of not having the clinical signs and symptoms congruent with the suspect case definition. For the remaining cases, 75 met the suspect EHF case definition, and 31 of those individuals met the probable EHF case definition (44 remained classified as suspect cases).

In summary, 131 total cases of suspect ($n = 44$), probable ($n = 31$), or confirmed ($n = 56$) EHF were identified in Bundibugyo District. Of the 131 cases, 42 had fatal outcomes (32%). In contrast, only 7% of investigated illnesses that were classified as not a case of EHF had fatal outcomes (Table 1). Among all suspect, probable, and confirmed EHF cases, no trend for increasing or decreasing case fatality was noted over the course of the outbreak, when cases were classified on the basis of the month of symptom onset ($P = .5827$; Cochran–Armitage trend test).

Outbreak Dynamics

The first suspect EHF case identified in Bundibugyo District developed a fever on 20 August (Figure 2) and subsequently died

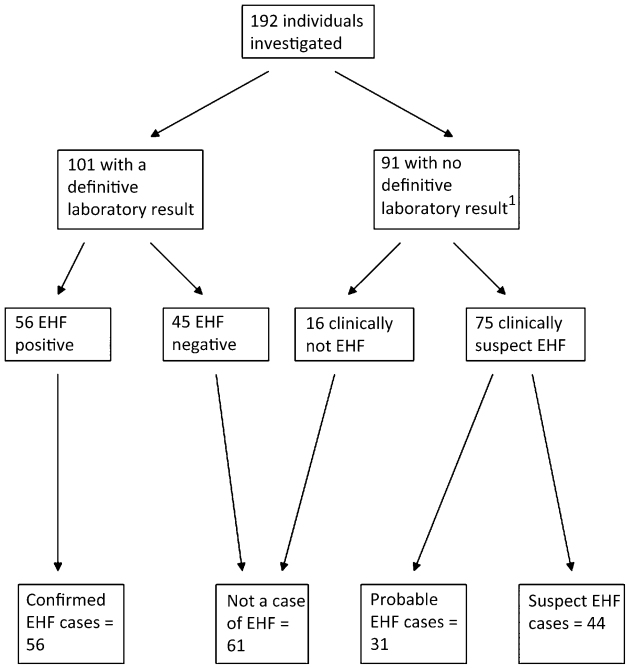

Figure 1. Classification of cases investigated during the Ebola hemorrhagic fever outbreak response, Bundibugyo District, Uganda, 2007. EHF, Ebola hemorrhagic fever. [1]Includes investigated cases that had no laboratory testing and investigated cases with an inconclusive laboratory result.

on 4 September 2007. No cases meeting the suspect EHF case definition with symptom onset prior to this date were identified; however, owing to the delayed investigation (full outbreak response occurred in early December 2007), whether this individual is the actual index case of the outbreak remains unclear. The first laboratory-confirmed case developed symptoms on 14 September and later recovered.

Case counts remained relatively low through most of September and October. A peak in case detections occurred in late November and early December. This peak was largely associated with secondary transmission from a single individual who developed signs and symptoms of illness in early November, was hospitalized on 16 November, and died with severe hemorrhagic disease on 23 November. This individual had prominent status in the community, and numerous members of the local population had contact with this individual, either shortly before his death, or at his funeral. In total, 27 people developed EHF following contact with this individual (including 22 laboratory-confirmed cases); 11 of these cases died. Secondary transmission from this individual accounted for 21% of the case total in the Bundibugyo District outbreak. In contrast, only 2 instances of tertiary transmission (transmission from a secondary case) were identified. Of the 27 secondary cases, we note there is a single secondary EHF case with an exceptionally long incubation period (25 d). It remains possible that whereas this case did have contact with the index EHF case in this cluster, transmission occurred following contact with a different individual infected with BEBOV.

Table 1. Case Fatality Rates Among Ebola Hemorrhagic Fever (Suspect, Probable, or Confirmed) and Illnesses Ruled as Not a Case of Ebola Hemorrhagic Fever Among Illnesses Investigated During the Bundibugyo Outbreak Response

	Fatal Cases/Total Number of Cases	Case Fatality Rate
Suspect, probable, and confirmed EHF cases	42/131	32.0%
Not a case of EHF	4/61	6.6%

NOTE. EHF, Ebola hemorrhagic fever.

DISCUSSION

Challenges in Case Identification and Classification

Although the use of structured of case investigation forms (including use during retrospective follow-up investigations) allowed us to standardize clinical information on cases, there are clear limitations with this approach. For instance, a large portion of information was collected during triage, and may not capture the whole range of signs and symptoms subsequently experienced by EHF cases. Similarly, whereas chart reviews were performed for those case patients who had developed disease prior to recognition of the outbreak, the clinical information extracted from the written record was often limited. In addition, although follow-up interviews were performed on some surviving cases, actual signs and symptoms reported during follow-up interview may have been subject to recall bias. Regardless of these limitations, we do note strong concordance between severity of disease and classification as a case of BEBOV infection. As described, among all cases meeting the final suspect, probable, or confirmed case definition, case fatality was 32% (and case fatality was 40% among laboratory confirmed cases diagnosed on the basis of an acute diagnostic sample [2]), whereas only 7% of identified illnesses that were classified as not a case of EHF had a fatal outcome.

Review of epidemiologic data from the 2007 Bundibugyo investigation underscores the difficulty in assigning case definitions when investigating filovirus outbreaks. As with any pathogen that has not been well characterized, there is a circular logic in prospectively using cases definitions based on signs and symptoms to identify cases, which will subsequently be used to describe the signs and symptoms of the disease. Furthermore, although predefined case definitions represent a valuable activity in outbreak planning and response, the reality is often more complex. Investigators developing case definitions may not be the same personnel attempting to determine whether an ill person should be characterized as a case of EHF for purposes of isolation. As would be expected, medical personal attempting to

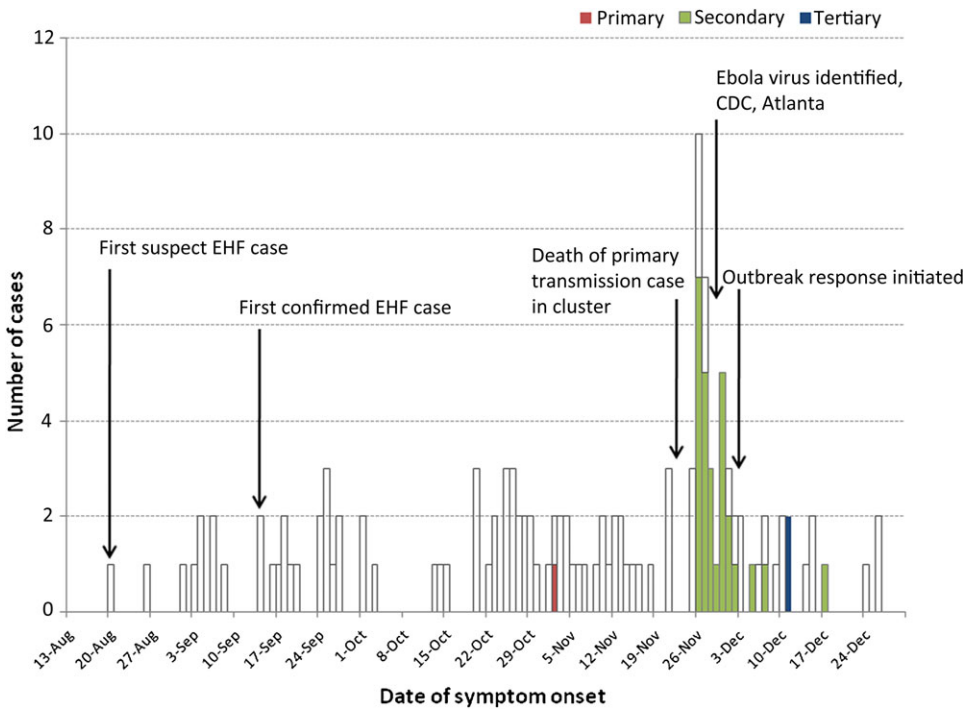

Figure 2. Distribution of suspect, probable, and confirmed Ebola hemorrhagic fever cases, based on the date of onset of symptoms, Bundibugyo District, Uganda, 2007. EHF, Ebola hemorrhagic fever. Date of onset of symptoms of the individual associated with a large cluster of transmission events is shown in red. Date of onset of secondary cases and tertiary cases from this individual are shown in green and blue, respectively.

triage sick individuals during a filovirus outbreak may rely on clinical judgment in addition to epidemiologically assigned criteria in assessing patients.

In some filovirus outbreaks with extremely high case fatality (for instance, outbreaks due to ZEBOV and the MARV outbreaks in the Democratic Republic of Congo [DRC] and Angola, in which 80%–90% of cases have a fatal outcome [3, 7, 8, 10, 25–27]), severe illness, death, or both are expected to be strongly predictive of filovirus infection. In the case of BEBOV infection, fewer than half of cases had a fatal outcome. Common signs and symptoms of EHF are largely nonspecific and may mimic other tropical infections. For instance, common signs and symptoms of laboratory-confirmed cases of BEBOV infection included fever, fatigue, headache, nausea, vomiting, abdominal pain, muscle pain, joint pain, and diarrhea, and among those with a well-documented contact history, the average time from last contact to symptom onset was 6.3 days [2].

As previously described, many illnesses investigated in Bundibugyo District were classified as not a case of EHF on the basis of laboratory testing or signs and symptoms. Because filovirus outbreak control is reliant on identifying cases and minimizing person-to-person transmission, it remains important to identify all potentially infectious individuals. In 2004, during the concomitant Ebola virus and measles virus outbreaks in Yambio, Sudan, both viruses spread within families and within groups of contacts, with similar signs and symptoms of illness during the early stages of infection [28]. In that setting, it was difficult to clinically and epidemiologically differentiate severe measles from EHF, leading to isolation of patients with measles and EHF together. Only retrospective testing was able to differentiate the diseases. We believe the combination of broad (highly sensitive) surveillance criteria and rapid laboratory diagnostic capacity (highly specific) to correctly classify ill persons as having or not having EHF will maximize the ability to identify the virus, provide medical care, and prevent further spread of the virus from infectious individuals. Such a system will also allow those who do not have a filovirus infection to be released back into the community or triaged to receive appropriate medical care.

Adding to challenges faced in syndromic-based case identification and classification, at times during the EHF outbreak in Bundibugyo District there was a reluctance to collect diagnostic samples due to the perception that specimens were being collected for reasons other than diagnostic testing. This was particularly the case for retrospective investigation and classification of individuals who had an illness consistent with EHF prior to the outbreak response. At times we noted a similar hesitancy in sharing clinical records among partner organizations, the result of the lack of communication between groups due to being overwhelmed by urgent patient care and outbreak response issues. We believe it remains a crucial responsibility of every group involved in outbreak response to scientifically characterize clinical, laboratory, and epidemiologic aspects of filovirus outbreaks (particularly in the case of a novel virus, such as BEBOV) to develop improved prevention measures and

Table 2. Timeliness of Outbreak Detection and Response for Large (>100 Cases) Filovirus Outbreaks

Location, year (disease)[1]	Onset of first identified case	Date of preliminary assessment or report	Date of international outbreak response	Time between onset and outbreak response	Total number of cases identified	Reference
Zaire, 1976 (EHF)	1 September 1976	21 September 1976	19 October 1976	>1.5 months	318	[3]
Sudan, 1976 (EHF)	27 June 1976	4 October 1976	29 October 1976	>4 months	284	[6]
Democratic Republic of Congo, 1995 (EHF)	6 January 1995	1 May 1995	11 May 1995	>4 months	315	[4]
Democratic Republic of Congo, 1998–2000[2] (MHF)	October 1998	23 April 1999	8 May 1999	~7 months	154	[10]
Uganda, 2000 (EHF)	30 August 2000	8 October 2000	21 October 2000	>1.5 months	425	[9, 29, 30]
Congo/Gabon, 2001 (EHF)	25 October 2001	24 November 2001	16 December 2001	>1.5 months	124	[25]
Congo, 2003[3] (EHF)	25 December 2002	28 January 2003	19 February 2003	>1.5 months	143	[26]
Angola, 2005 (MHF)	October 2004 (presumed)	9 March 2005	27 March 2005	>5 months	374	[27, 31]
Democratic Republic of Congo, 2007 (EHF)	Late May 2007	21 August 2007	17 September 2007	>3.5 months	264	[32]
Uganda, 2007 (EHF)	20 August 2007	5 November 2007	3 December 2007	>3 months	131	[24], current manuscript

NOTE. [1] Ebola hemorrhagic fever (EHF) or Marburg hemorrhagic fever (MHF).

[2] Numerous introductions occurred over the course of 2 years within a gold-mining village.

[3] At least 3 independent introductions.

outbreak response guidelines for future human outbreaks. We additionally believe that efforts to increase dialog and collaborative activities between partner organizations, both prior and during outbreak response, will help alleviate these issues in future outbreak responses.

Common Characteristics of Filovirus Outbreaks

There are common, recurrent themes that characterize most large (100 or more cases) filovirus outbreaks. For example, filovirus outbreaks often involve long temporal lags between initial cases and subsequent outbreak identification and response. In the instance of Bundibugyo District, >2 months elapsed between initial EHF cases and preliminary investigation, and >3 months elapsed before filovirus-specific outbreak control measures were fully implemented. Similar lag periods have also been associated with many previous filovirus outbreaks (Table 2). As shown, in large filovirus outbreaks, the time from initial spill-over events to recognition and implementation of a full-scale outbreak response has consistently been >1 month, and often much longer. Although outbreak response following etiologic identification tends to occur rapidly, the long temporal lag between early cases and subsequent outbreak recognition fosters the perpetuation of person-to-person transmission in community and hospital settings. We believe this observation demonstrates the importance of improving surveillance for filovirus infections in endemic areas of sub-Saharan Africa. With improved surveillance and rapid outbreak detection, it is possible to quickly intervene and limit person-to-person transmission and geographic dissemination in outbreak settings, thus minimizing the time and overall size of future filovirus outbreaks.

Large outbreaks tend to occur in remote locations, where proper medical, public health, transportation, and communication infrastructure are limited. The transmission (and often amplification) of filovirus infections in hospital settings has been well described [3, 4, 6, 10, 17]. Whereas the use of personal protective equipment is recommended for medical personnel in outbreaks, transmission of filoviruses in health care settings can be largely prevented by basic infection control precautions and proper disposal of potentially infectious items [33, 34]. Widespread filovirus transmission events typically involve hospital settings where available protective equipment is limited or unavailable, and these events underscore the need for improved infection control measures in areas that have potential for filovirus infections.

Although the index case is often not identified, most filovirus outbreaks are typically the result of a single or small number of initial zoonotic transmission events that lead to subsequent prolonged chains of person-to-person transmission. Most human filovirus infections associated with large outbreaks in the previous 30 years have been the result of person-to-person transmission (with the notable exception of an outbreak of MHF in northern DRC from 1998 to 2000, which involved multiple

zoonotic introductions associated with mining activities [10]). Although the infectious nature of person-to-person transmission of filoviruses is limited to direct contact, contact with bodily fluids, or contact with contaminated objects (and so is less efficient than aerosol or food- or waterborne transmission), large filovirus outbreaks continue to occur, demonstrating the potentially explosive nature of filoviruses in resource-challenged parts of Africa.

We identified a large cluster of secondary EHF cases associated with transmission from a single individual in Bundibugyo District. This is not the first occurrence of a focus of secondary infections from a single individual accounting for a large portion of overall infections in a filovirus outbreak. For instance, Khan et al described 2 individuals who accounted for 20% of all infections during the outbreak of EHF in Kikwit, DRC [4]. Despite the large number of secondary cases associated with this single individual in Bundibugyo District, we documented only 2 tertiary cases of EHF in this chain of transmission. Importantly, the onset of symptoms in secondary cases occurred approximately at the same time as the implementation of the international outbreak response. Others have previously described the importance of surveillance and patient isolation in filovirus outbreak control [31, 35]. We believe the absence of a tertiary wave of infections in this instance demonstrates the efficacy of established outbreak control measures in controlling filovirus outbreaks.

CONCLUSION

The outbreak associated with BEBOV resulted in over 100 cases of EHF in Uganda in 2007. Although it was due to a novel Ebola virus, this outbreak had characteristics that were similar to those of other large filovirus outbreaks. Importantly, the long delay between initial cases and filovirus detection and response allowed for chains of person-to-person transmission. Although filovirus outbreaks often occur in remote, underdeveloped, resource-limited settings, outbreak detection and management is largely reliant on basic case identification and infection control practices. Based on lessons from previous outbreaks, we note the following as surveillance measures for ministries of health and international public health organizations working in endemic areas to consider:

1. Education to rural medical personnel on the signs and symptoms of filovirus infections, such that early chains of transmission can be identified by local populations. For instance, in response to numerous outbreaks of EHF that occurred in the Republic of Congo and Gabon from 1994 to 2003, educational activities were provided to medical staff and individuals in rural areas on EHF disease and risk factors for Ebola virus infection. These activities may have contributed to the absence of documented EHF in this area since 2005.
2. Implementation of basic infection control procedures, including patient isolation, disinfection of contaminated materials, and contact precautions (including gowns and gloves), in rural hospitals, such that individual or small clusters of filovirus cases can be contained without transmission amplification in the health care setting.
3. Improve the capacity for local medical staff and public health personnel to identify, collect standardized information, and report suspect filovirus infections to the ministry of health or national public health authorities.
4. Pre-establish an effective network to collect and transport diagnostic specimens, including preplacement of sample collection materials and secure packaging and shipping containers at rural health centers, and identifying the most appropriate transportation mechanisms (personal transport, public transport, air transport) to rapidly delivery diagnostic specimens to the national (or other appropriate) laboratory.
5. Improve the capacity to do filovirus diagnostic testing in-country to avoid the temporal lag associated with shipping diagnostic specimens internationally, such that outbreak measures can be implemented as rapidly as possible in the event of an actual filovirus infection.

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