Recurrent outbreaks of Ebola Virus Disease in Africa: A Meta-analysis of case fatality rates

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Research Article

Keywords: Africa, Case fatality rate, Ebola virus disease, Meta-analysis, Outbreak

Posted Date: November 6th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-103255/v1

Version of Record: A version of this preprint was published at Public Health on November 6th, 2020. See the published version at https://doi.org/10.1016/j.puhe.2021.03.027.

Abstract

Background: In the last decade, Africa has witnessed several outbreaks of Ebola virus disease (EVD), each presenting with varying case fatality rate (CFR) and other socio-economic impacts. This study aims to summarise the CFR and identify potential factors that influenced the severity of EVD outbreaks in Africa.

Methods: This was a systematic review and meta-analysis of EVD outbreaks published between January 2010 and March 2020, using Web of Science, Scopus and PubMed databases. Only English articles and reports, including the number of cases and deaths during the outbreak in Africa, were considered. Quality of the included articles was assessed using the Murad's quality assessment tool. The analysis was conducted using Stata (version 12), pooled effect sizes were calculated using the random-effects model and heterogeneity was tested for using the I^2 statistic.

Result: Thirteen studies with 32,300 cases and 13,727 deaths were identified whose pooled CFR was 60% (95% CI: 47-73%). The most EVD-affected countries were DRC with 5 outbreaks and a pooled CFR of 65% (95% CI: 59-71%), followed by Uganda with 3 outbreaks and CFR= 83% (95% CI: 60-99%). Zaire ebolavirus caused the most outbreaks (10), with a CFR= 58% (95% CI: 45-71%). Besides, outbreaks with less than 1000 cases reported a higher CFR rate compared to those with more cases.

Conclusion: The study has revealed a considerably high CFR caused by the recurrent EVD outbreaks in Africa. It also notes an implementation gap of the prevention and control strategies, and thus identifies a need to strengthen the surveillance systems and response mechanisms to enable early detection and prompt control of future outbreaks.

Introduction

Ebola virus disease (EVD) is a multifaceted zoonosis; highly infectious in humans and endemic in the African region [1]. EVD is caused by Ebola viruses; these are negative-stranded RNA viruses, belonging to the *Filoviridae* family and are endemic to regions of the west and equatorial Africa [2]. The first EVD human case was identified in 1976 in Zaire, the now called Democratic Republic of Congo (DRC) [3]. The exact origin of the Ebola virus is still controversial, but in most outbreaks, it is suspected to be introduced into the human population via forest bats and other wild animals [4]. Usually, the first source of transmission is an animal found dead or hunted in the forest, trailed by person-to-person transmission from the first case to family members or even health care staff. Animal-to-human transmission happens when people come into contact with tissues and bodily fluids of infected animals [3]. EVD is known to present with flu-like symptoms; fever, sore throat, headache, and muscle pain, as well as severe complications such as symptoms of kidney and liver dysfunction, hemorrhagic diathesis, among others [5].

Within the past ten years, Africa has faced several recurrent outbreaks of EVD, with case fatality rates, usually around 25-90 % [1,2]. Besides the 2014-2016 Ebola outbreak in West Africa, which claimed more than 10,000 victims, Africa was again stricken with the recent 2018-2020 Kivu Ebola outbreak in the DRC [6]. This was the largest outbreak of EVD recorded in DRC and the second largest worldwide; it began in August 2018 and mainly concentrated in Eastern provinces of Kivu and Ituri [7]. This epidemic was caused by the Zaire ebolavirus species, which is the most lethal species of the six known Ebola virus species [8].

On 17 July 2019, World Health Organisation (WHO) announced the Kivu outbreak as a "Public Health Emergency of International Concern (PHEIC)" [9]. The overwhelming effects of this outbreak put the global health response in acute focus, with the potential of spreading to neighbouring countries [10]. It took major efforts for the Government, Ministry of Health (MoH) of DRC, WHO, and partners to implement outbreak response and control interventions. This was a key challenge due to the prolonged humanitarian crisis in North Kivu province, the unstable security situation and the mistrust of affected communities in response activities [7,11]. By 9th March 2020, DRC was declared free of this outbreak with 3,421 cases and 2,242 deaths, including 161 health care workers, and, with a fatality rate of 66.8% [6].

Current evidence links the severity of the Ebola outbreak to the type of Ebola species involved. The Ebola Zaire and Ebola Sudan species are the most pathogenic, while Ebola Bundibugyo species is reported to cause lower case fatality rates [2,12]. In the last decade, Africa has witnessed critical outbreaks within Ebola history, each presenting with varying case fatality rate (CFR) and other socio-economic impacts. Nevertheless, there has been no updated meta-analysis conducted on EVD. Therefore, we conducted an updated systematic review and meta-analysis to summarise the impact, in the form of CFR, and identify potential factors that influenced the severity of EVD outbreaks in the last ten years in Africa. Identifying such factors would be of vital help in formulating practical interventions in preventing and addressing future EVD outbreaks.

Methods

This study was done following the guidelines published in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13] and Meta-analysis of observational studies in epidemiology (MOOSE) guidelines for observational studies [14].

Literature search strategy

A detailed literature search was done in PubMed, Web of Science and Scopus to identify published papers and reports on EVD outbreaks (1st January 2010 to 25th March 2020). In the absence of a peer-reviewed publication for a known outbreak, data was retrieved from websites of WHO and CDC.

The following keywords were used to identify articles and reports of EVD outbreaks "ebola", "ebolavirus", ebola virus disease", "ebola virus disease outbreak" and "ebola outbreak". Also, the cross-referencing of primary articles was done to obtain the original articles. Since the number of EVD outbreaks is known and

few, efforts were made to find all information about these outbreaks from WHO websites and Ministries of Health of the respective countries (**Figure 1**).

Study selection

Articles and reports were included in the meta-analysis if they reported the total number of cases and the total number of deaths from the EVD outbreak. Studies that did not report original data and those that reported EVD outbreaks outside Africa were excluded. In cases of multiple publications, the one with complete data or the most recent one was used. In cases of controversy on the number of cases and deaths between articles, cross-reference with the respective ministries of health or WHO databases helped to reconcile these discrepancies.

Quality Assessment

The quality of the included articles and reports was assessed using the Murad's Quality assessment tool for case series and case reports [15]. The tool has eight leading questions under the four sections of selection, ascertainment, causality, and reporting. Four answers (yes, no, unclear and not applicable) were used to represent the extent to which the study meets the proposed criteria, as shown in **Supplementary table 1**. The discrepancy in the appraisal was resolved by discussion and consensus.

Data extraction

The study used a standardised data extraction form, and the following information was extracted (by KJ and THM) for each qualifying article and epidemic report: i) author; ii) country; iii) number of cases; iv) number of deaths; v) Case Fatality Rate (if reported); vi) month and year of the outbreak; vii) year of publication viii) and species involved. The overall papers included in the meta-analysis are shown in **Table 1**.

Statistical analysis

Data was collected in a Microsoft Excel® spreadsheet, and outcome measures were calculated. CFR was calculated as the number of deaths divided by reported cases. The effect size, the principal summary measure, was the proportion represented by CFR. Statistical analyses were performed using the *metaprop* command in Stata (version 12). The Freeman-Turkey double arcsine transformation was used which computed the weighted pooled estimate and performed the back-transformation on the pooled estimate, using the random-effects model. The confidence interval of each outbreak was calculated using the *Score method* in the *metaprop* command. The outbreak-specific proportions were weighted by the inverse of their variance, and the statistical significance was set at a P value of <0.05. The I^2 statistic was used to assess the heterogeneity between the outbreaks [16].

Random-effects meta-regression analyses and subgroup analyses were conducted to determine whether the following study characteristics could explain variability across outbreaks: species, country of the

outbreak, start (time) of the outbreak and number of cases in the outbreak. Sensitivity analysis was done by eliminating outbreaks that reported very few numbers or zero deaths.

The presence of publication bias was visualised by funnel plots to measure the asymmetry and quantitatively examined with Egger's linear regression test. The trim-and-fill method was used to adjust for potential publication bias.

Results

The study retrieval and selection strategy are illustrated in **Figure 1**. Of the 878 publications meeting initial search criteria, 65 papers were retrieved. On detailed evaluation, 53 articles were excluded leaving a total of 13, which were included in the meta-analysis.

Quality of the included articles

Basing on the Murad's quality assessment tool, the four domains of selection, ascertainment, causality and reporting were used to assess the potential bias in the selected articles. On evaluation, the included articles addressed most of the relevant questions in the four assessment domains, as shown in **Figure 2.**

Pooled Case Fatality Rate of EVD outbreaks

We used 13 articles (32,300 cases and 13,727 deaths) that reported on EVD outbreaks in the last ten years in Africa. Their CFR ranged from 28-100%. We used the random-effects model and calculated the pooled CFR, which was found to be 60% (95% CI: 47-73%), with P<0.001. However, there was significant heterogeneity observed among the outbreaks with I^2=99.6%, P<0.001, as shown in **figure 3.** In addition, sensitivity analysis by removing outbreaks that reported single case and those with CFR of 100% showed no effect on the observed heterogeneity (I^2=99.7%, P<0.001), but the pooled CFR reduced to 57% (95% CI:45-69%).

Factors influencing the CFR of EVD outbreaks

Meta-regression was done to explore the possible sources of the observed heterogeneity (**Table 2**). The analysis was done for four pre-selected factors; start (time) of the outbreak, species involved, country of outbreak and number of cases in the outbreak. Of these factors, the country of the outbreak (P=0.046) and the number of cases (P<0.001) were the only factors identified to cause the between-outbreak variance.

Outbreaks were, first, categorised according to the start (time) of the outbreak; 1st half of the year (5 outbreaks) and 2nd half of the year (8 outbreaks). On subgroup analysis, there was no heterogeneity noted among EVD outbreaks that started in the 1st half of the year. However, substantial heterogeneity remained among outbreaks that started in the second half of the year (I^2=99.7%, P<0.001) (**Table 2**).

Regarding the species causing the outbreak, outbreaks caused by Sudan ebolavirus (2 outbreaks) showed no heterogeneity, unlike Zaire ebolavirus outbreaks (10) which showed a significant heterogeneity (I^2=99.7%, P<0.001). It was also noted that Sudan ebolavirus had the highest CFR of 80%, followed by Zaire ebolavirus (58%) and Bundibugyo ebolavirus (55%), as shown in **table 2**. However, Zaire ebolavirus was responsible for 10 outbreaks out of the 13 recorded outbreaks.

According to the region/country of the outbreak, outbreaks (3) in Uganda (East Africa) and DRC (Central Africa-5 outbreaks) showed no significant heterogeneity on subgroup analysis. However, outbreaks from West Africa (5) had persistent heterogeneity (99.8%, P<0.001). In the last ten years, DRC was noted to have the most number of EVD outbreaks (5 outbreaks) with a CFR of 65% (95% CI: 59-71%), followed by Uganda (3 outbreaks), with CFR=83% (95% CI: 60-99%) (**Figure 4**). The West African countries included: Liberia, Sierra Leone, Guinea, Mali and Nigeria, each with one EVD outbreak.

When sub-grouped according to the number of cases in each outbreak, outbreaks with less than 1000 cases (9 outbreaks) showed no significant heterogeneity, compared to those with above 1000 cases (4 outbreaks) which showed substantial heterogeneity (I^2= 99.9%, P<0.001) (**Figure 5**). It was noted that four countries reported EVD outbreaks with above 1000 cases, which included; Liberia, Sierra Leone, Guinea and DRC.

Publication bias

Publication bias was assessed in the EVD articles using visual inspection of the funnel plot, which showed a slight asymmetry in the outbreaks, implying probable publication bias towards small EVD outbreaks (**Figure 6**). However, further evaluation using Egger's test showed no significant publication bias in EVD outbreaks (P= 0.872). Nevertheless, when the trim-and-fill analysis was executed, the adjusted CFR was 55.5% (95%CI: 44.3-69.6%), after filling in 2 missing outbreaks.

Discussion

The study aimed to quantify the severity and the potential factors influencing EVD outbreaks in Africa for the last ten years. The analysis showed that the pooled CFR of EVD was 60%; this value is slightly lower than the previously reported CFR of 65% [12,28]. This could be because of the fewer outbreaks used in the analysis, thereby affecting the accurate estimation of the effect size. On the other hand, it may be due to the improving health care systems and increasing awareness about EVD within the past decade, enabling people to know how to prevent and control the disease, thus having less CFR [29,30,31].

The study noted that on average, Africa reported at least one EVD outbreak each year in the last decade, with the most recent being the 2018-2020 Kivu EVD outbreak [6]. Despite the considerable efforts taken in the control and prevention of EVD, Africa still faces recurrent outbreaks of EVD [24]. This implies an implementation gap in the surveillance and response mechanisms towards EVD outbreaks and thus should be addressed if future outbreaks are to be avoided or controlled.

The analysis revealed several factors that influenced the CFR of EVD outbreaks, which included country of the outbreak and number of cases involved in the outbreak, as the most significant. The difference in the health care capacity, surveillance systems and outbreak response mechanisms in African countries may all explain why EVD affects these countries differently. Countries with robust surveillance systems and fast response to outbreaks have been reported to register fewer cases and thus fewer fatalities attributed to EVD [24,32]. In the last ten years, DRC was noted as the most affected country by EVD outbreaks. It should be noted that apart from DRC being endemic to EVD [33], the country has several social and political challenges hindering effective implementation of the prevention and control measures of EVD as well as other infectious diseases in general. For example, the political instability in DRC combined with lack of community trust affects the effective response and control of EVD outbreaks [7,11]. Political crises dismantle social, economic and health systems, resulting in internally displaced people (IDP) and refugees, thereby predisposing communities to several other infectious diseases [34,35]. Early case identification, diagnosis and prompt control and response measures are hardly impossible in a country with a weak health system and political unrest. Therefore, there is an urgent need for extra efforts towards peace-talks to solve the political turmoil in not only DRC but also other countries facing the same challenge.

In addition, the study noted that the biggest EVD outbreaks with a massive number of cases and deaths registered less CFRs. In this case, their CFRs should be interpreted with caution considering the deaths involved in these outbreaks. Thus the impact of these outbreaks on the health systems, social lifestyle, as well as the economy [36,37,38] should not be overlooked just based on overall CFR.

The time when the outbreak started was found to affect the CFR of EVD, where outbreaks that began in the 1st half of the year had a higher CFR (68%) compared to those in the second half of the year (55%). This finding is in line with a previous study that found a link between the month of the year and EVD outbreaks [12]. However, the reasons behind this link are uncertain and therefore need further investigation.

The species involved in EVD outbreaks were found to have varying CFRs, where the Sudan ebolavirus had the highest CFR, followed by Zaire ebolavirus and Bundibugyo ebolavirus. This finding is dissimilar from other studies which report Zaire ebolavirus to have the highest CFR [3,39]. The reason for this may be the few outbreaks used to estimate the CFR of Sudan ebolavirus. Besides, the analysis revealed that Zaire ebolavirus was responsible for over 70% of the EVD outbreaks in the last decade. The species was responsible for the two biggest EVD epidemics in history, including the 2014-2016 West African outbreak and the 2018-2020 Kivu outbreak [8]. Given the pathogenicity of the Zaire ebolavirus, efforts are required to speed up the wide-scale use and accessibility of the recently approved Ebola Zaire vaccine (rVSV-ZEBOV) [40,41,42]. This would help to reduce the case fatalities and impact of future EVD outbreaks. Nevertheless, vaccines against other Ebolavirus species or a comprehensive vaccine against all the species should be considered in future vaccine developments.

Limitations of the study

The estimated effect size (CFR) could have been affected by the considerable heterogeneity, which could not be fully explained by the pre-identified factors nor solved by sensitivity analysis. It should be noted that these studies used different methods of data collection and were from different locations, making heterogeneity unavoidable. In addition, due to limited data and disaggregated information from these outbreak reports and studies, we could not examine the effect of all potential factors, such as age, gender, among others, on the CFR of EVD outbreaks.

Conclusion

The study revealed that on average, Africa registered at least one EVD outbreak in the last decade. Although the study noted a moderate CFR of EVD, the overall socio-economic impact of these outbreaks should not be overlooked. The study also found out that Zaire ebolavirus was responsible for most of the EVD outbreaks and DRC and Uganda reported the highest number of outbreaks. The study noted surveillance and an implementation gap in the prevention and control of EVD given the recurrent outbreaks. Therefore there is a need to strengthen the surveillance systems and response mechanisms in the EVD endemic countries to allow early detection as well as prompt control of future outbreaks. Lastly, the study identifies a need to speed up the Ebola vaccine development and approval for extra protection from future EVD outbreaks.

Data Availability Statement

All the relevant data supporting the results conclusions of the study are included in the manuscript.

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Tables

Table 1: Characteristics of the outbreaks

Author	Month and year	Country	Species	Cases	Deaths	CFR (%)
WHO 2012 [17]	June-August, 2012	Uganda	SUDV	24	17	71
Kratz et al. 2015 [18]	August-November, 2012	DRC	BDBV	62	34	55
Shoemaker et al. 2012 [19]	May-2011	Uganda	SUDV	1	1	100
WHO 2016 [20]	Dec 2013-June 2016	Liberia	EBOV	10675	4809	45
WHO 2016 [20]	Dec 2013-June 2016	Sierra Leone	EBOV	14124	3956	28
Keïta et al. 2017 [21]	Dec 2013-June 2016	Guinea	EBOV	3811	2543	67
Diarra et al. 2016 [22]	October 2014-January 2015	Mali	EBOV	8	6	75
Fasina et al. 2014 [23]	July-October 2014	Nigeria	EBOV	20	8	40
Bell et al. 2016 [24]	August-November, 2014	DRC	EBOV	66	49	74
WHO 2017 [25]	May-July 2017	DRC	EBOV	8	4	50
WHO 2018 [26]	May-July 2018	DRC	EBOV	54	33	61
WHO 2020 [6]	August 2018-March 2020	DRC	EBOV	3444	2264	66
MOH-Uganda 2019 [27]	Junuary-2019	Uganda	EBOV	3	3	100

Note: EBOV- Zaire ebolavirus, SUDV- Sudan ebolavirus, BDBV- Bundibugyo ebolavirus, CFR-Case fatality rate

Table 2: Moderators of the CFR of the EVD outbreaks

				Heterogeneity		Effect of moderator	
Moderator	No. of studies	Prop. of CFR (95% CI)	P value	I^2 Within	P value	I^2 between	P Value
Start (time) of the outbreak						99.64%	0.264
1st half of the year	5	0.68 (0.56-0.80)	<0.001	0.0%	0.450		
2nd half of the year	8	0.55 (0.41-0.69)	<0.001	99.7%	<0.001		
Ebola Species						99.64%	0.516
SUDV	2	0.80 (0.54-0.98)	<0.001	--	--		
BDBV	1	0.55 (0.43-0.67)	<0.001	--	--		
EBOV	10	0.58 (0.44-0.71)	<0.001	99.7%	<0.001		
Country of outbreak						99.54%	0.046*
Uganda	3	0.83 (0.60-0.99)	<0.001	--	--		
DRC	5	0.65 (0.59-0.71)	<0.001	39.8%	0.160		
West Africa	5	0.49 (0.32-0.66)	<0.001	99.8%	<0.001		
Number of cases						94.99%	<0.001*
Below 1000	9	0.65 (0.54-0.75)	<0.001	42.1%	0.090		
Above 1000	4	0.51 (0.33-0.69)	<0.001	99.9%	<0.001		

***=**Significant

Declarations

Funding Statement

None

Ethical approval

No ethical approval required since secondary data was used and no human nor animal subject used directly involved in the study.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contribution

Conceptualisation and Methodology were done by JK and XJ. Data curation, Validation and Formal analysis by THM and JK. Writing – original draft by JK, Writing – review & editing by JK, THM and XJY, while Supervision was done by XY. All authors have agreed with the final draft of the manuscript.

Figures

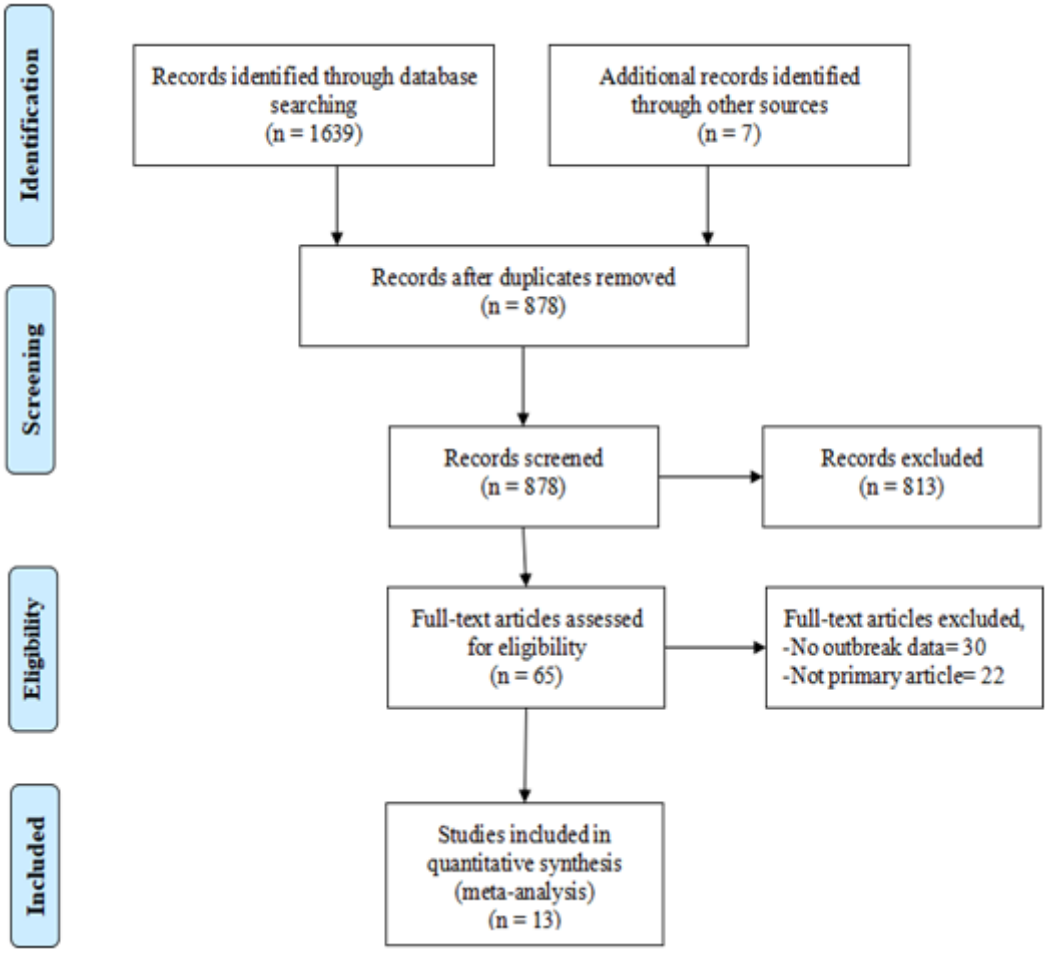

Figure 1

The PRISMA flow-chart diagram of data extraction

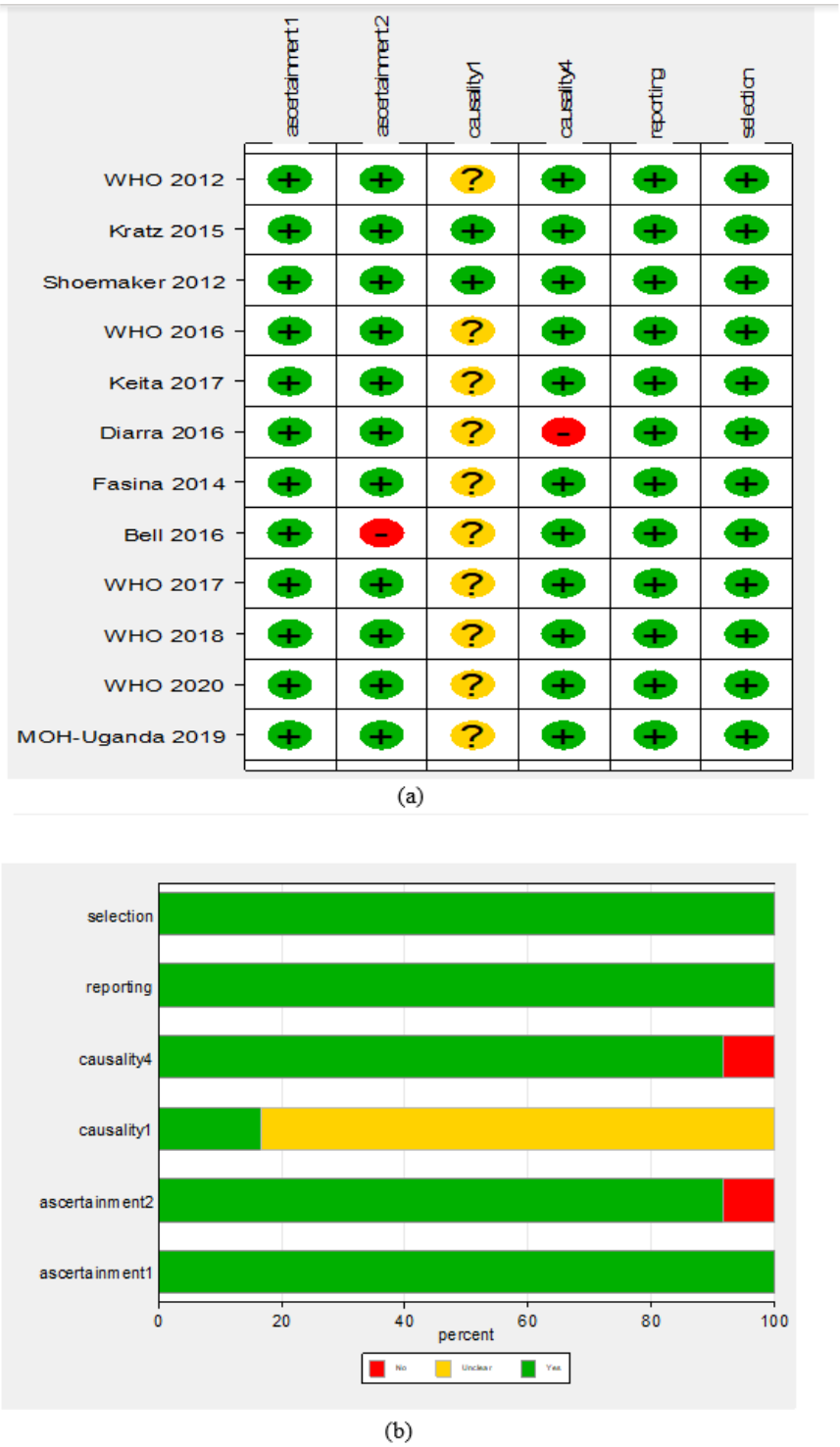

Figure 2

Methodology Quality (a) Details of study quality (b) Summary of assessment

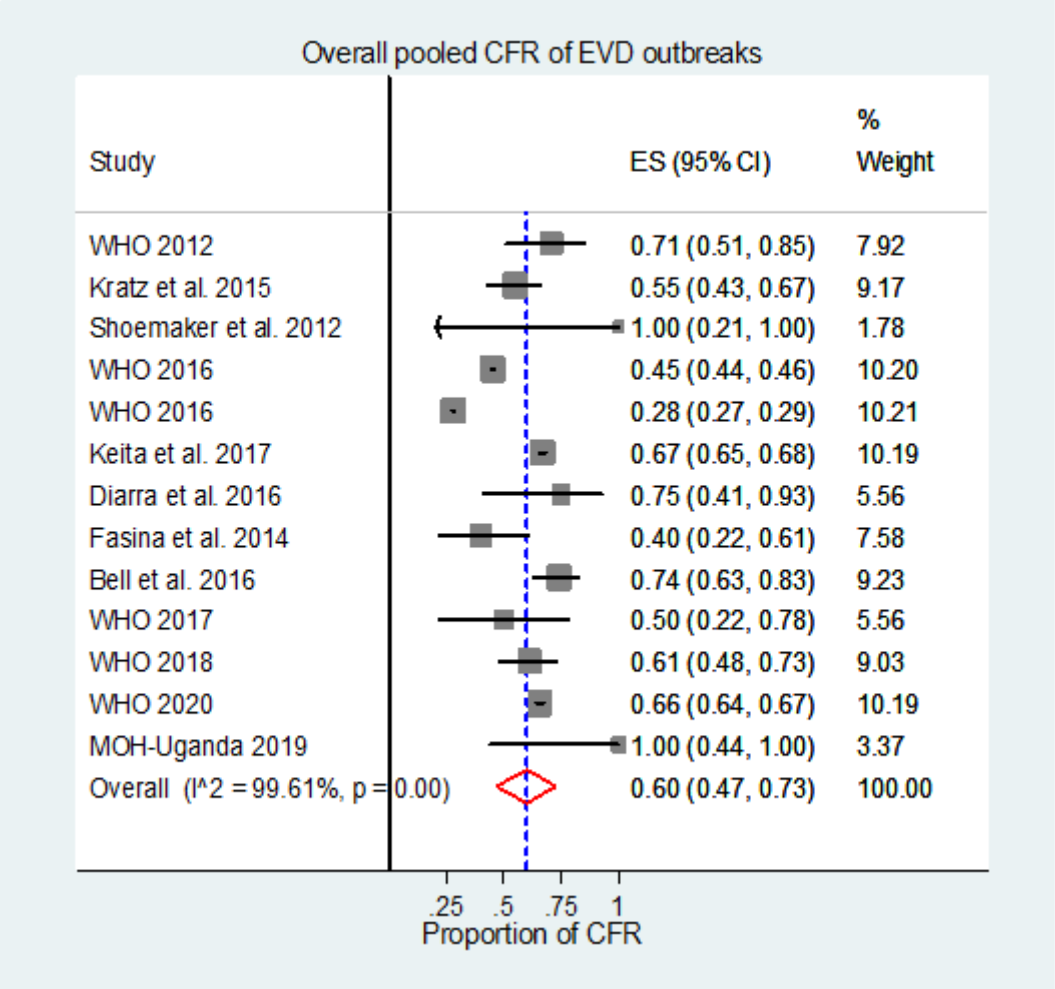

Figure 3

A Forrest plot of the pooled proportion of case fatality rates (CFR) of the EVD outbreaks.

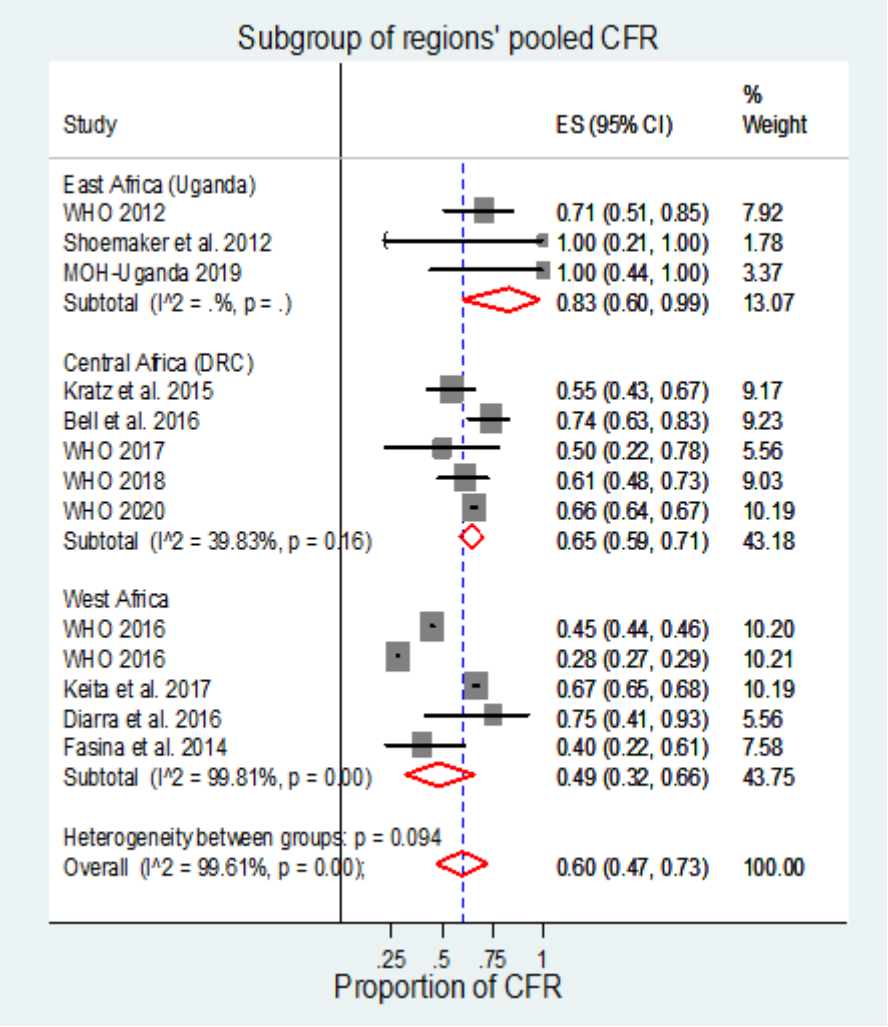

Figure 4

A Forrest plot of the pooled proportion of case fatality rates when sub-grouped according to country of EVD outbreaks.

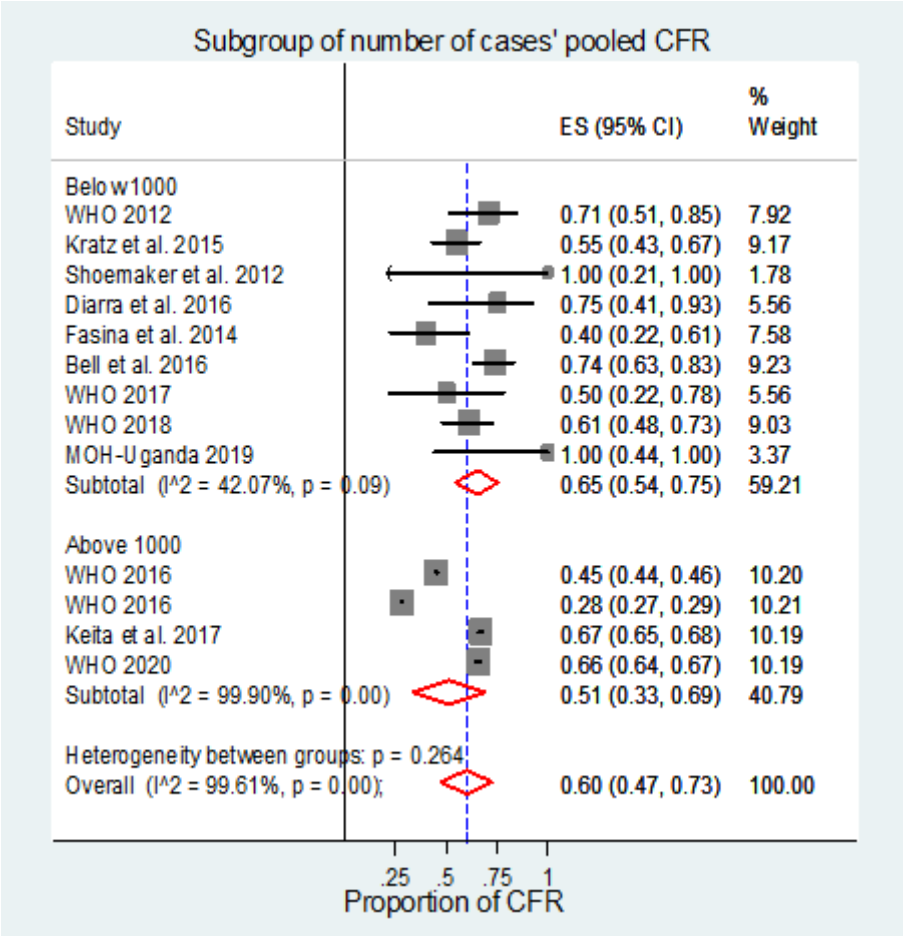

Figure 5

A Forrest plot of the pooled proportion of case fatality rates when sub-grouped according to number of cases.

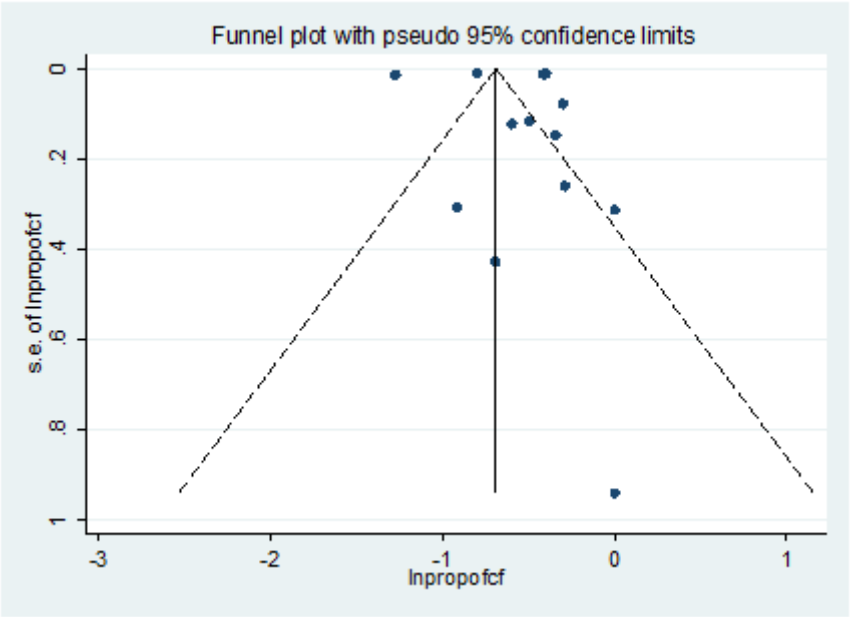

Figure 6

Funnel plot of EVD outbreak articles (Egger's test, P= 0.872). lnpropcf = Inverse proportion of case fatality

Supplementary Files

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- SupplementaryTable1.docx