How severe and prevalent are Ebola and Marburg viruses? A systematic review and meta-analysis of the case fatality rates and seroprevalence

Luke Nyakarahuka1,2,5*, Clovice Kankya2, Randi Krontveit3, Benjamin Mayer4, Frank N. Mwiine2, Julius Lutwama5 and Eystein Skjerve1

Abstract

Background: Ebola and Marburg virus diseases are said to occur at a low prevalence, but are very severe diseases with high lethality. The fatality rates reported in different outbreaks ranged from 24–100%. In addition, sero-surveys conducted have shown different seropositivity for both Ebola and Marburg viruses. We aimed to use a meta-analysis approach to estimate the case fatality and seroprevalence rates of these filoviruses, providing vital information for epidemic response and preparedness in countries affected by these diseases.

Methods: Published literature was retrieved through a search of databases. Articles were included if they reported number of deaths, cases, and seropositivity. We further cross-referenced with ministries of health, WHO and CDC databases. The effect size was proportion represented by case fatality rate (CFR) and seroprevalence. Analysis was done using the `metaprop` command in STATA.

Results: The weighted average CFR of Ebola virus disease was estimated to be 65.0% [95% CI (54.0–76.0%), I² = 97.98%] whereas that of Marburg virus disease was 53.8% (26.5–80.0%, I² = 88.6%). The overall seroprevalence of Ebola virus was 8.0% (5.0%–11.0%, I² = 98.7%), whereas that for Marburg virus was 1.2% (0.5–2.0%, I² = 94.8%). The most severe species of ebolavirus was Zaire ebolavirus while Bundibugyo Ebolavirus was the least severe.

Conclusions: The pooled CFR and seroprevalence for Ebola and Marburg viruses were found to be lower than usually reported, with species differences despite high heterogeneity between studies. Countries with an improved health surveillance and epidemic response have lower CFR, thereby indicating need for improving early detection and epidemic response in filovirus outbreaks.

Keywords: Ebola virus disease, Marburg virus disease, Case fatality rate, Meta-analysis, Systematic review, Seroprevalence

Background

Ebola virus disease (EVD) and Marburg virus disease (MVD) are caused by filoviruses in the family Filoviridae and are both associated with high case fatality rates (CFR). The World Health organization (WHO) reports that the CFR of EVD ranges from 25.0 to 90.0% while that of MVD ranges from 24.0 to 88.0% [1]. In the early phases of a major Ebola outbreak in West Africa, CFR was reported to be 70.8% [2]. The CFR of EVD seems to be species dependent with Ebola Zaire and Ebola Sudan species being most pathogenic (with a reported CFR of 100%), while Ebola Bundibugyo appears to have a lower CFR at 34% [3]. A recent study by Lefebvre et al. that used data from WHO database estimated the CFR of EVD to be 65.4% irrespective of the Ebola virus species [4]. A few studies have tried to pool the CFR of EVD and MVD, but did not use the meta-analysis approach [5].

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Although EVD is known to be very severe, there are some species of Ebola virus that cause less serious disease. For example, Taï Forest ebolavirus, formerly known as Côte d’Ivoire ebolavirus, has not been associated with any fatality and the only case ever reported recovered from the disease [6]. While there have been some reports of EVD being associated with a CFR of 100%, this CFR is attributed to only a single case fatality that did not result in transmission of the virus to other individuals [7, 8]. It seems that CFR differs from species to species, however, both Ebola Sudan and Ebola Zaire have shown a CFR of 100% [1]. Also, the CFR of the MVD outbreak that occurred in Uganda in 2014 was reported to be 100%, but again only one person was diagnosed and died from the disease [9]. The largest MVD outbreak was in Angola in 2004 with CFR of 90% [10] and in Democratic Republic of Congo (DRC) in 1998 with CFR of 83% [11].

There is evidence that a substantial proportion of infected humans in Central Africa seem to recover without being detected by the health care system, and apparently healthy individuals have been found to be seropositive for Ebola and Marburg viruses [12–15]. Furthermore, Marburg virus has been found in apparently healthy cave-dwelling fruit bats of species rousettus aegyptiacus, which are believed to be reservoirs for Marburg virus, and responsible for the spill over into human populations [16–19]. Because of the variations in the reported CFR and the presence of seropositive individuals, it is important to determine the severity and prevalence of these viral haemorrhagic fevers. This is important for forecasts and risk analysis especially during outbreaks for epidemic preparedness and response by affected countries. This will help to estimate how many infected people with EVD or MVD are likely to die from the disease during outbreaks. Whereas there are few studies that have estimated CFR of EVD [4, 5], these did not use a meta-analysis approach and no meta-analysis has been performed on CFR of EVD, MVD, seroprevalence of Ebola and Marburg viruses. Therefore, our aim was to determine the overall weighted estimate (effect size) of the CFR and seroprevalence of EVD and MVD using available published literature on outbreak reports, WHO and CDC databases and population based studies for seroprevalence of filoviruses (Marburg and Ebola viruses). We also explored whether CFR and seroprevalence of these filoviruses differs according to virus species and country.

Methods
Procedures for systematic reviews and meta-analysis have been developed to summarize scientific evidence from the literature. This work was done following the guidelines published in the PRISMA statement [20] and MOOSE guidelines for observational studies [21] as follows.

Literature search strategy
A detailed literature search was conducted by the authors in PubMed (as well as Medline), Web of Science and Google Scholar until 5th October 2015. In cases where there was no peer-reviewed publication for a known outbreak, data was retrieved from websites of WHO and CDC. The following key words were used; “ebola”, “ebolavirus”, “viral haemorrhagic fevers”, “marburg virus disease”, “marburg haemorrhagic fever”, “marburg virus outbreak”, “ebola virus disease outbreak”, “marburg virus”, “ebola outbreak”, “seroprevalence of ebola virus”, “seroprevalence of marburg virus” and “risk factors of viral haemorrhagic fevers”. The search included all articles and outbreak reports about EVD and MVD and cross-referencing of primary articles was done to obtain the original articles. Since the number of outbreaks of EVD and MVD are known and few, efforts were made to obtain all information about these outbreaks from WHO and CDC websites and Ministries of health of respective countries.

Study selection criteria
Studies were included in the meta-analysis if they reported the total number of cases and total number of deaths from the outbreak of EVD or MVD. Also studies that were reporting CFR and sero-prevalence in percentages were included. Studies or reports that did not include total number of deaths or cases were excluded as well as studies that did not report original data (Fig. 1). We also excluded studies that reported outbreaks of Ebola species that are not pathogenic to humans and those species that have not caused mortality in humans. In cases where there were multiple publications, we used the one with the most complete data or the most recent one. In cases where there was controversy on the number of cases and deaths between studies, we cross-referenced with the respective ministries of health, WHO or CDC databases to reconcile these discrepancies. Seroprevalence studies included were only those that were population based and comprised apparently healthy individuals. We excluded articles that reported sero-prevalence during outbreaks or in sick individuals.

Data extraction
LN compiled a list of articles and discrepancies were discussed and resolved by consensus between FM, CK and JL. We used a standardized data extraction form and the following information was extracted for each qualifying study and outbreak report: i) author; ii) Country; iii) number of cases; iv) number of deaths; v) CFR (if reported); vi) month and year of outbreak; vii) year of publication viii)
and species involved. For population-based seroprevalence studies, the following additional information was retrieved: i) sample size and ii) number of seropositive samples.

Statistical analysis
Data were collected in a Microsoft Excel® spreadsheet and outcome measures were calculated. CFR was calculated as number of deaths divided by reported cases whereas seroprevalence was calculated as number of individuals seropositive divided by total sample size in each study. Our effect size (ES), the principal summary measure, was the proportion represented by CFR and seroprevalence. We used the newly developed metaprop command [22] for performing meta-analysis of binomial data in STATA (StataCorp, College Station, TX, USA). The metaprop command was preferred to metan command because it implements procedures that are specific to binomial data and is appropriate for dealing with proportions close to or at the margins and also uses the Freeman-Tukey double arcsine transformations to stabilize the variances [22]. The meta-analysis of CFR was stratified by country and species where possible.

The following parameters were estimated: Cochran’s Q indicating differences in true ESs, an estimate of the true variance of ESs between studies (our estimate of τ²) and Higgins I² which is an estimate of what proportion of the observed variance that reflects real differences in ES. If I² is close to 0, then almost all the observed variation is spurious, and there is nothing to explain. If I² is large, then reasons for the observed variance should be evaluated [23, 24]. Sensitivity analysis was done by excluding studies that reported very few numbers or zero deaths or no seropositives. A meta-regression procedure was done to assess if factors such as species, country, year and month of outbreak influence CFR of both EVD and MVD using the traditional logit-transformation: Logit (prevalence) = ln [prevalence/ (1 – prevalence)] Variance (logit) = 1/ (np) + 1/[n (1 – p)] [25]. The Beggs’s and Egger’s tests were used in combination with a funnel plot to assess potential publication bias and visualised using funnel plots [24, 26].

Results
Literature search result
Results from the literature search are illustrated in Fig. 1. The literature search yielded 7551 articles. Of these, 4898 were excluded as duplicates. After reviewing the titles and the abstract, only 153 articles were retrieved for detailed evaluation. After full evaluation of retrieved publications, 72 articles were included in this study. Of those included in the study, 23 reported outbreaks of EVD (Table 1) [3, 8, 27–41, 7, 42, 43], 12 reported outbreaks of MVD (Table 2) [10, 11, 42, 44–51], 26 reported seroprevalence of Ebola virus (Table 3) [8, 12–14, 28, 31, 52–54, 29, 55–70] and 11 reported sero-prevalence of Marburg virus (Table 4) [14, 15, 57, 61–64, 67, 71–73]. Most of the sero-prevalence studies reported both Marburg and Ebola viruses.

Two more outbreaks have occurred without human mortalities namely Ebola Reston [74, 75] and another caused by Tai Forest virus [6]. Zaire ebolavirus species was responsible for most of the outbreaks with 14/23 (60.9%) [8, 28, 30–32, 34–36, 39, 40, 41, 37, 76] followed by Sudan ebolavirus with 30.3% (7/23) outbreaks [27, 29, 38, 7, 42, 77] and lastly Bundibugyo ebolavirus 8.7% (2/23) [3, 42]. Most articles reported DRC [7/23] [8, 28, 32, 39, 40, 42, 76] and Uganda (5/23) [3, 33, 7, 42] as countries most affected by EVD outbreaks. Other countries reported include Gabon (4/23) [31, 34, 36, 78], Republic of Congo (3/23) [35, 37, 41], South Sudan (3/23) [27, 29, 38] and multiple countries in West Africa associated with the recent single outbreak [79–82]. Interestingly, most of the EVD outbreaks
Table 1: Summary of the studies included in a systematic review and meta-analysis describing case fatality rate for Ebola virus disease in Africa

| Author and Year of Publication | Deaths | Cases | Country       | Year and month of outbreak       |
|-------------------------------|--------|-------|---------------|----------------------------------|
|WHO International Study Team, 1978 [27] | 151    | 284   | South Sudan   | 1976, June–November               |
|International Commission, 1978 [28] | 280    | 318   | DRC           | 1976, Sept–Oct                    |
|Heymann et al., 1980 [8] | 1      | 1     | DRC           | 1977, June                        |
|Baron et al., 1983 [29] | 22     | 34    | South Sudan   | 1979, June–Oct                    |
|Amblard et al., 1997 [30] | 30     | 49    | Gabon         | 1994, November                    |
|Khan et al., 1999 [32] | 255    | 315   | DRC           | 1995, May                         |
|Georges et al., 1999 [31] | 21     | 31    | Gabon         | 1996, May                         |
|Milleliri et al., 2004 [34] | 45     | 60    | Gabon         | 1996, May                         |
|Okware et al., 2002 [33] | 224    | 425   | Uganda        | 2000, October                     |
|Nkoghe et al., 2005 [36] | 97     | 124   | Gabon         | 2000, December                    |
|Rouquet et al. (2005) [37] | 128    | 143   | ROC           | 2003, December                    |
|Boumandouki et al., 2005 [35] | 29     | 35    | ROC           | 2003, Oct–Dec                    |
|Onyango et al., 2007 [38] | 7      | 17    | South Sudan   | 2004, April–June                  |
|Nkoghe et al., 2011 [41] | 10     | 12    | ROC           | 2005, April–May                   |
|Leroy et al., 2009 [39] | 186    | 264   | DRC           | 2007, May and November            |
|Wamala et al., 2010 [3] | 39     | 116   | Uganda        | 2007, August                      |
|Grard et al., 2011 [40] | 15     | 32    | DRC           | 2008, Jan                         |
|Shoemaker et al., 2012 [7] | 1      | 1     | Uganda        | 2011, May                         |
|Albariño et al., 2013 [42] | 4      | 11    | Uganda        | 2012, July                        |
|Albariño et al., 2013 [42] | 3      | 6     | Uganda        | 2012, Nov                         |
|Albariño et al., 2013 [42] | 13     | 36    | DRC           | 2012, August                      |
|Maganga et al., 2014 [43] | 49     | 69    | DRC           | 2014, July                        |
|WHO, 2016 [79, 90] | 11323  | 28646 | West Africa   | March, 2014                       |

DRC Democratic Republic of Congo, ROC Republic of Congo

Table 2: Summary of studies included in a systematic review and meta-analysis describing case fatality rate for Marburg virus from searched literature globally

| Author and Year of Publication | Deaths | Cases | Country               | Year & Month of outbreak |
|-------------------------------|--------|-------|-----------------------|--------------------------|
|Siegert, 1972 [44, 45] | 7      | 31    | Germany and Yugoslavia| 1967, August              |
|Gear et al., 1975 [91] | 1      | 3     | Johannesburg, South Africa| 1975, February            |
|Smith et al., 1982 [92] | 1      | 2     | Kenya                 | 1980, January             |
|Johnson et al., 1996 [49] | 1      | 1     | Kenya                 | 1987, August              |
|Nikiforov et al., 1994 [48] | 1      | 1     | Russia                | 1990                     |
|Bausch et al., 2006 [11] | 128    | 154   | DRC                   | 1998, October             |
|Towner et al., 2006 [10] | 227    | 252   | Angola                | 2004, October             |
|Adjemian et al., 2011 [51] | 1      | 4     | Uganda                | 2007, June                |
|Centers for Disease & Prevention, 2009 [50] | 0   | 1     | USA from Uganda       | 2008, January             |
|Timen et al., 2009 [93] | 1      | 1     | Netherlands from Uganda| 2008, July                |
|Albarino et al., 2013 [42, 94] | 13   | 36    | DRC                   | 2012, August              |
|WHO, 2015 [95] | 1      | 1     | Uganda                | 2014, October             |

DRC Democratic Republic of Congo
### Table 3
Summary of studies included in a systematic review and meta-analysis describing sero-prevalence of Ebola virus from literature

| Author and Year of Publication | Sample size | Seropositive | Country       |
|--------------------------------|-------------|--------------|---------------|
| Van der Groen and Pattyn 1979  | 251         | 43           | DRC           |
| Saluzzo, Gonzalez et al. 1980  | 499         | 17           | CAR           |
| Bouree & Bergmann, 1983        | 1517        | 147          | Cameroon      |
| Johnson et al., 1983           | 741         | 8            | Kenya         |
| Van der Waals, Pomeroy et al.  | 225         | 30           | Liberia       |
| Meunier et al., 1987           | 1528        | 319          | CAR           |
| Paix et al., 1988              | 375         | 4            | Cameroon      |
| Tomori, Fabiyi et al. 1988     | 1,677       | 30           | Nigeria       |
| Gonzalez et al., 1989          | 5070        | 629          | Central Africa|
| Mathiot, Fontenille et al. 1989| 381         | 17           | Madagascar    |
| Johnson, Gonzalez et al. 1993a | 427         | 75           | CAR           |
| Johnson, Gonzalez et al. 1993b| 4295        | 914          | CAR           |
| Busico et al., 1999            | 575         | 24           | DRC           |
| Nakounne, Selekon et al. 2000  | 1762        | 104          | CAR           |
| Heffernan et al., 2005         | 979         | 14           | Gabon         |
| Allela et al., 2005            | 439         | 64           | Gabon         |
| Lahm, Kombila et al. 2007      | 1147        | 14           | Gabon         |
| Becquart et al., 2010          | 4349        | 665          | DRC           |
| Heymann et al., 1980           | 1096        | 79           | DRC           |
| Burke et al., 1978             | 984         | 38           | DRC           |
| Baron et al., 1983             | 106         | 23           | Sudan         |
| Georges et al., 1999           | 441         | 58           | Gabon         |
| Becker, Feldmann et al. 1992   | 1288        | 11           | Germany       |
| Gonzalez, Nakoune et al. 2000  | 1331        | 71           | CAR           |
| Bertherat, Renaut et al. 1999  | 236         | 24           | Gabon         |
| Nikoghe, Padilla et al. 2011   | 4349        | 667          | DRC           |

**Note:** DRC Democratic Republic of Congo, ROC Republic of Congo, CAR Central African Republic

### Table 4
Summary of studies included in a systematic review and meta-analysis describing sero-prevalence of Marburg disease from published literature

| Author and Year of Publication | Sample size | Seropositive | Country          |
|--------------------------------|-------------|--------------|------------------|
| Van der Waals, Pomeroy et al.  | 225         | 3            | Liberia          |
| Gonzalez, Josse et al. 1989    | 5070        | 20           | Central African countries |
| Johnson, Ocheng et al. 1983    | 1899        | 8            | Kenya            |
| Mathiot, Fontenille et al. 1989| 384         | 0            | Madagascar       |
| Becker, Feldmann et al. 1992   | 1288        | 34           | Germany          |
| Johnson, Gonzalez et al. 199a  | 427         | 5            | CAR              |
| Johnson, Gonzalez et al. 1993b| 4295        | 137          | CAR              |
| Gonzalez, Nakoune et al. 2000  | 1340        | 33           | CAR              |
| Nakounne, Selekon et al. 2000  | 1762        | 35           | CAR              |
| Bausch, Borchert et al. 2003   | 912         | 15           | DRC              |
| Borchert, Mulangu et al. 2006  | 300         | 0            | DRC              |

**Note:** DRC Democratic Republic of Congo, CAR Central African Republic
occurred during months of May, June and July and no outbreaks were reported in the month of February.

Meta-analysis and meta-regression of CFR and seroprevalence of EVD

The weighted CFR of EVD from 23 outbreaks was 65% (95% CI: 54–76%) (Fig. 2). There was a substantial between-study variance indicating heterogeneity in the overall CFR of EVD, $I^2 = 97.98%$. On stratification by Ebola virus species, the CFR for *Sudan ebolavirus* was 53%, *Bundibugyo ebolavirus* was 34%, whereas that of *Zaire ebolavirus* was 75%. From the meta-regression, the CFR for *Zaire ebolavirus* was higher compared to other Ebola species ($\beta = 0.006$, Coefficient = 0.19, 95% CI = 0.063 - 0.588). In sub-analysis analysis by country, the highest CFR for EVD was observed in Republic of Congo (89.0%, 84.0–93.0%) whereas the lowest was found in Uganda (43.0%, 27.0–61.0%) (Fig. 3). However, the large West African EVD outbreak that affected multiple countries had an even lower CFR at 40% (39–40%). The pooled ES for Ebola virus seroprevalence was 8% [5–11%] with substantial between-study variance ($I^2 = 98.7%$) (Fig. 4).

Meta-analysis and meta-regression of CFR and seroprevalence of MVD

The MVD CFR was lower than that of EVD (61%) (Fig. 5). There was no significant difference between CFR of MVD and different variables in the meta-regression model ($P = 0.637$). The pooled seroprevalence of Marburg virus was lower than that of Ebola virus at 1.2% (0.5–2%) (Fig. 6).

Publication bias

In the funnel plots, asymmetry was evident which gives rise to suspected publication bias (Fig. 7). Egger's test
**Fig. 3** Forest plot showing stratified meta-analysis of CFR of Ebola virus disease by country estimated by the random effects model (I^2 = Higgins statistic, ES = Effect size, CI = Confidence Interval, DRC = Democratic Republic of Congo, ROC = Republic of Congo)
was significant for studies reporting CFR and seroprevalence of EVD and MVD ($P = 0.001$, $P < 0.001$, $p = 0.032$, and 0.046 respectively). However, the Begg’s bias test was not significant for studies reporting CFR of EVD and MVD ($p = 0.091$ and $p = 0.293$ respectively), seroprevalence of MVD ($p = 0.95$), but was significant for studies reporting seroprevalence of EVD ($p = 0.007$).

**Discussion**

Our findings show that the overall pooled CFR of EVD of 65% was lower than the previously reported CFR of 90% [83]. This indicates, despite substantial heterogeneity, that more than half of the individuals who contract EVD are more likely to die. Although this CFR appears to be high, it is lower than the exaggerated figure of 90%. This high CFR tends to cause fear and panic in the general public and hence interferes with response mechanisms [84]. The CFR in our study is similar to that reported by Lefebvre *et al.* [4], who reported a CFR of 65% in a study done using WHO database on EVD outbreaks. Although there have been cases of EVD and MVD with 100% CFR [8, 7], these were isolated single cases that should not be generalized by scientific community to consider Ebola and Marburg viruses as highly virulent diseases with CFR of up to 90%. There have been reports with a higher CFR than our maximum of 76% [28, 35, 37, 41], but these either happened long time ago [28] where there was little knowledge about the disease or happened in very remote places where health care delivery systems are not robust.

The high CFR of EVD in Republic of Congo (89%) compared to Uganda (43%) may be due partly, differences in health care system and response mechanisms to outbreaks, but also the severity of the species of Ebola virus involved. For example, Uganda has developed a robust surveillance system for detecting these viral haemorrhagic fevers and epidemic response is started within hours of a positive diagnosis at a CDC supported laboratory in the country [85]. The well-established disease surveillance system and organised health care

| Study                          | ES (95% CI)       |
|-------------------------------|-------------------|
| Van der Groen and Pattyn(1979)| 0.17 (0.13, 0.22) |
| Saluzzo, Gonzalez et al(1980) | 0.03 (0.02, 0.05) |
| Bouree & Bergmann(1983)       | 0.10 (0.08, 0.11) |
| Johnson et al(1983)           | 0.01 (0.01, 0.02) |
| Van der Waals et al(1986)     | 0.13 (0.10, 0.18) |
| Meunier et al( 1987)          | 0.21 (0.19, 0.23) |
| Paix et al(1988)              | 0.01 (0.00, 0.03) |
| Tomori, Fabiyi et al(1988)    | 0.02 (0.01, 0.03) |
| Gonzalez et al(1989)          | 0.12 (0.12, 0.13) |
| Mathiot et al(1989)           | 0.04 (0.03, 0.07) |
| Johnson et al(1993a)          | 0.18 (0.14, 0.21) |
| Johnson et al(1993b)          | 0.21 (0.20, 0.23) |
| Busico et al(1999)            | 0.04 (0.03, 0.06) |
| Nakounne et al(2000)          | 0.06 (0.05, 0.07) |
| Heffernan et al(2005)         | 0.01 (0.01, 0.02) |
| Allela et al(2005)            | 0.15 (0.12, 0.18) |
| Lahm et al(2007)              | 0.01 (0.01, 0.02) |
| Becquart et al(2010)          | 0.15 (0.14, 0.16) |
| Heymann et al(1980)           | 0.07 (0.06, 0.09) |
| Burke et al(1978)             | 0.04 (0.03, 0.05) |
| Baron et al(1983)             | 0.22 (0.15, 0.30) |
| Georges et al(1999)           | 0.13 (0.10, 0.17) |
| Becker et al(1992)            | 0.01 (0.00, 0.02) |
| Gonzalez et al(2000)          | 0.05 (0.04, 0.07) |
| Bertherat et al(1999)         | 0.10 (0.07, 0.15) |
| Nkoghe et al(2011)            | 0.15 (0.14, 0.16) |
| Overall ($I^2 = 98.85\%, p = 0.00$) | 0.08 (0.05, 0.11) |

![Forest plot for the meta-analysis of sero-prevalence studies of Ebola virus ($I^2$ = Higgins statistic, ES = Effect size, CI = Confidence Interval)](image)
**Fig. 5** Forest plot for a meta-analysis of CFR of Marburg virus disease estimated using a random effects model ($I^2$ = Higgins statistic, ES = Effect size, CI = Confidence Interval)

**Fig. 6** Meta-analysis of seroprevalence of Marburg virus estimated using a random effects model ($I^2$ = Higgins statistic, ES = Effect size, CI = Confidence Interval)
delivery in endemic areas might explain the lower CFR for EVD observed in Uganda. But it is also important to note that Uganda has been affected by the less pathogenic species of Ebola virus (Sudan ebolavirus and Bundibugyo ebolavirus) as compared to DRC and West African countries that have experienced Zaire ebolavirus. Also, it is important to look at the denominators and numerators when interpreting the CFR. In this analysis, we see that CFR of EVD in a large outbreak in West Africa that affected multiple countries is at CFR of 40% using WHO data, but this alone would be misleading if the real numbers of deaths and cases were not looked at. As of 30th March 2016, there were 11323 deaths and 28646 cases due to EVD from all countries affected by that outbreak.

Another significant finding of our study was the variation in the severity and CFR among the pathogenic species of Ebola virus. Zaire ebolavirus (CFR, 75%) was found to be the most severe followed by Sudan ebolavirus (CFR, 53%), while Bundibugyo ebolavirus (CFR, 34%) was the least severe species. This finding is supported by McCormick et al., who described differences in severity and filovirus dynamics [86, 87]. The reasons for severity of Zaire ebolavirus are unclear, thus there is a need for further research to determine whether genetic differences are responsible for the variation in pathogenesis of these species. There was also heterogeneity within Zaire ebolavirus outbreaks (P < 0.001) meaning that these outbreaks, although caused by the same species are not always similar. The heterogeneity could further be explained by differences in outbreak investigation designs or approaches, location of the outbreak and data collection methods. This is further supported by the strains that have been found within Ebola Zaire species [40]. There was less heterogeneity in outbreak reports for Bundibugyo ebolavirus and Sudan ebolavirus probably due to few outbreaks that have been caused by these species. However, the meta-regression did not show any influence on CFR of EVD by country of outbreak (p = 0.249). This is probably due to low power given the few number of outbreaks that we have had globally.
With the Metaprop command for meta-analysis of marginal proportions [22], it was possible to estimate the 95% confidence intervals for MVD as 61% (32–88%). The CI was very wide because of the few outbreaks and the number of cases involved in MVD outbreaks as compared to EVD outbreaks. Dropping studies with 100% or 0% CFR for MVD, the CFR reduced from 61 to 53%. With few outbreaks of Marburg virus in different countries, there is a high variation that would impact the estimation of CFR for MVD, but this was not significant from the meta-regression ($p = 0.913$).

We found that apparently healthy individuals in central African countries, that are endemic for viral haemorrhagic fevers, had a 5 and 1% chance of having antibodies against Ebola and Marburg viruses, respectively. This finding suggests that some individuals who get infected with filoviruses make a full recovery without severe complications and being documented by healthcare systems. Although the sero-prevalence is low, it is important that these seropositive individuals are detected early enough because of greater mortality and socio-economic implications associated with these infections. Because serological tests have been reported to have low specificity and there is a lot of cross-reactivity of filoviruses with other viral haemorrhagic fevers [88], this finding should be interpreted with caution. It is important that specific and more accurate tests are developed to accurately measure antibody response against filoviruses and progress in this direction has been made due to the recently approved rapid diagnostic test for Ebola virus by WHO [89].

The limitation of our ES estimates was the heterogeneity that was observed between studies. Efforts to identify sources of heterogeneity were made, and many unmeasured factors could have influenced CFR during outbreaks. These reports had data that were collected using different methods and hence combining them to produce one effect was likely to produce high heterogeneity. Sensitivity analysis by dropping single cases with 100% mortality did not have substantial impact on the result. Funnel plots and Beggs tests suggested that publication bias might have been present, meaning that studies with negative results about Ebola and Marburg viruses are less likely to be published hence affecting the estimate of sero-prevalence and CFR for EVD and MVD.

The fact that laboratory tests for Ebola and Marburg viruses are expensive, used only in specific laboratories and that serological tests are not specific might influence the publication of studies done with these tests.

**Conclusions**

The CFR for Ebola and Marburg viruses is still moderately high but not as high as has been reported in the media and other publications. The CFR of EVD and MVD is higher in countries with poor disease surveillance systems. This calls for an improved surveillance system that will enhance early detection and response to these filovirus outbreaks to avoid a pandemic. The presence of seropositive individuals in apparently healthy populations indicate that cases go undetected by the health care system in affected countries; further calling for robust surveillance for Ebola and Marburg viruses.

**Abbreviations**

CDC: Centres for disease control and prevention USA; CFR: Case fatality rate; CI: Confidence interval; DRC: Democratic Republic of Congo; EVD: Ebola virus disease; MVD: Marburg virus disease; ROC: Republic of Congo; WHO: World Health Organization

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**Availability of data and materials**

The dataset supporting the findings in this meta-analysis is included in the article from Tables 1, 2, 3 and 4.

**Authors’ contributions**

Conceived and designed the protocol: LN, ES, CK. Execution of search strategy and sifting: LN, JL, BM, MF, RK. Manuscript preparation: LN, CK, RK, BM, MF, JL and ES. All authors read and approved the final manuscript.

**Authors’ information**

LN is an Epidemiologist with a background in Veterinary Medicine. He has been working as a zoonotic disease Epidemiologist especially focussing of Ebola and Marburg virus outbreaks in Uganda for the last five years. He is currently pursuing a PhD in Epidemiology of Ebola and Marburg viruses in Uganda at the Norwegian University of Life Sciences, Oslo, Norway.

**Competing interests**

The authors declare that they have no competing interests.

**Consent for publication**

Not applicable.

**Ethics approval and consent to participate**

Not applicable.

**Author details**

1Norwegian University of Life Sciences, Oslo, Norway. 2Makerere University, Kampala, Uganda. 3Norwegian Medicines Agency, Oslo, Norway. 4Ulm University, Ulm, Germany. 5Uganda Virus Research Institute, Entebbe, Uganda.

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