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Cross-continental burden of Ebola hemorrhagic fever: A meta-analytical comparison, prevalence, mortality, and risk factors

Maram Alsuhaibani[1], Yassir A. Almofti[1], Mohammed Al-Rasheed[2], Alaa Azhari[3], Mahmoud kandeel[1*]

[1]*Department of Biomedical Sciences, College of Veterinary Medicine, King Faisal University, 31982 Al-Ahsa, Saudi Arabia.*
[2]*Department of Clinical Sciences, College of Veterinary Medicine, King Faisal University, 31982 Al-Ahsa, Saudi Arabia.*
[3]*Faculty of Medicine, University of Khartoum, Khartoum 11111, Sudan.*

Corresponding author: Mahmoud kandeel (*Email: mkandeel@kfu.edu.sa*)

Abstract

Ebola hemorrhagic fever has increasingly spread beyond its traditional epicenters in Africa to other parts of the world, bearing significant implications for various health and non-health populations. This study examines Ebola's prevalence and burden in Africa, Europe, and North America, as well as the risk factors associated with it. A systematic review and meta-analysis were performed following PRISMA guidelines. Literature was searched through PubMed, Google Scholar, and the Cochrane Library, supplemented by manual searches and grey literature from authoritative health organizations. Meta-analysis was conducted using RevMan with a fixed-effects model and 95% confidence intervals (CI). There were 17 outbreaks covered in the included studies. There were 34,527 cases, 17,116 deaths, and an overall case fatality rate (CFR) of 49.57%. Regionally, Africa accounted for 99.96% of the cases and 99.98% of the reported deaths. The meta-analysis showed that the difference in the odds of infected healthcare workers dying from Ebola relative to non-healthcare patients was insignificant [OR=0.66, 95% CI, 0.39-1.12, I2=75%, p=0.12]. There was also no significant difference between the CFR of male and female patients infected by the virus, despite men being at a slightly higher risk of mortality from the infection compared to women [OR=0.88, 95% CI, 0.48-1.62, I2=0%, p=0.69]. This study showed that Africa continues to have the highest number of Ebola cases and deaths while retaining a high CFR. While there is no statistical difference in the odds of death among the non-health population, healthcare workers bear a higher burden of the outbreaks as they have higher odds of dying compared to non-healthcare populations. There is no significant difference in the CFR of male and female patients despite men being more likely to develop infections.

Keywords: Ebola, Filoviridae, Hemorrhagic Fever, Mortality, Virus.

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Transparency: The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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1. Introduction

Ebola virus disease (EVD) or Ebola hemorrhagic fever (EHF) is caused by filoviruses and is associated with high fatality rates [1]. EVD presents a serious public health concern and has steadily developed into a global crisis that requires continuous follow-up [2]. Imported cases of EVD have been reported from both North America and Europe since the disease was first documented in 1976, following outbreaks in Zaire (now the Democratic Republic of the Congo) and Sudan. However, Africa, particularly West and Central Africa, continues to be the most severely impacted regions [3, 4].

According to the World Health Organization [5], the case fatality rate (CFR) of EVD ranges between 25%-90% [6]. The healthcare system is one of the areas that are significantly impacted by EVD outbreaks [7]. Given the highly contagious nature of the disease, healthcare workers face a significant risk of infection and death when managing patients [8]. The risk increases when healthcare workers manage suspected and unconfirmed cases before an outbreak is officially declared. Understanding the impact of the disease on frontline healthcare providers' ability is essential in maintaining adequate personnel to handle outbreaks.

The spread of Ebola beyond its traditional areas of Central and West Africa after the 2014-2016 outbreak [9] illustrates the increased risk of infection in European and American contexts. Comparing the factors that potentially explain differences in the cases, deaths, and CFR is essential in managing the prevalence and burden of the disease. Understanding the prevalence and burden of EVD in Africa, North America, and Europe provides a realistic chance to build a global strategy for preventing outbreaks and managing the disease. Due to the disease's rarity, highly contagious nature, and high CFR, comprehending it only via individual research or case reports might be difficult [10, 11]. Pooled studies and systematic analysis provide an effective way of understanding and managing Ebola [12, 13]. This systematic review and meta-analysis aim to highlight and compare the state of Ebola in Africa, Europe, and North America. The disease's trends, severity, and impact are identified to help in decision-making around managing the problem.

2. Materials and Methods

2.1. Search Strategy

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A search was conducted on PubMed, Google Scholar, and Cochrane Library databases. Additionally, manual and reference list searches were used to identify articles and grey literature reports on the prevalence and burden of Ebola in Africa, Europe, and North America. Grey literature from reputable organizations was included in the search. The published literature was considered for inclusion if it reported EVD cases, the number of deaths, and CFR. The findings were also cross-referenced with the ministries of health, the CDC, and the WHO whenever such data were available.

2.2. Inclusion and Exclusion Criteria

Any report published from the first outbreak in 1976 until January 2025 was eligible for inclusion. The reports had to describe confirmed or probable Ebola cases based on the definition of the disease provided by the WHO. There were no restrictions on the nature of publication, study design, and populations, provided they were within the three regions (Africa, Europe, and North America). Reports focusing on Ebola cases outside the three regions were also excluded. Suspected and unconfirmed Ebola cases were also excluded. The other excluded articles include abstract-only sources, studies with overlapping data, and non-human studies and reports.

2.3. Data Extraction

The data extraction was performed by the researcher who was involved in collecting and summarizing data on the articles. Demographic information, as well as other characteristics such as the country/continent, nature of the infection, strain, time of report, and number of patients, were also collected. The case fatality rate (CFR) and seropositive survivors are also documented, with data indicating subcategories depending on male and female CFR. The infection and death data were further subdivided based on whether the patients were healthcare professionals or non-healthcare personnel.

2.4. Quality Assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the included articles.

2.5. Statistical Analysis

Quantitative data, such as the totals and events, were pooled together and analyzed in the meta-analysis. A fixed effects model and a confidence interval (CI) of 95% were applied to the analysis. The level of heterogeneity between the included studies was determined using the I^2 statistic. I^2 <50% was interpreted as low heterogeneity, 75% <I^2>50% as moderate heterogeneity, and I2 > 75% as high heterogeneity. The study used the Review Manager Version 5.4 (RevMan 5.4) as the analysis software. Forest plots of the pooled studies were generated from the software.

3. Results

3.1. Study Selection

A total of 576 studies were searched in the databases. The manual search and reference list search yielded another 218 sources. Of these studies, 346 were excluded for being duplicates. Upon title and abstract screening, an additional 216 articles were excluded. The researcher could not retrieve 74 articles. After full-text screening, 26 articles remained for systematic review and meta-analysis. Figure 1 is the PRISMA flowchart illustrating the search, selection, and screening process and outcome.

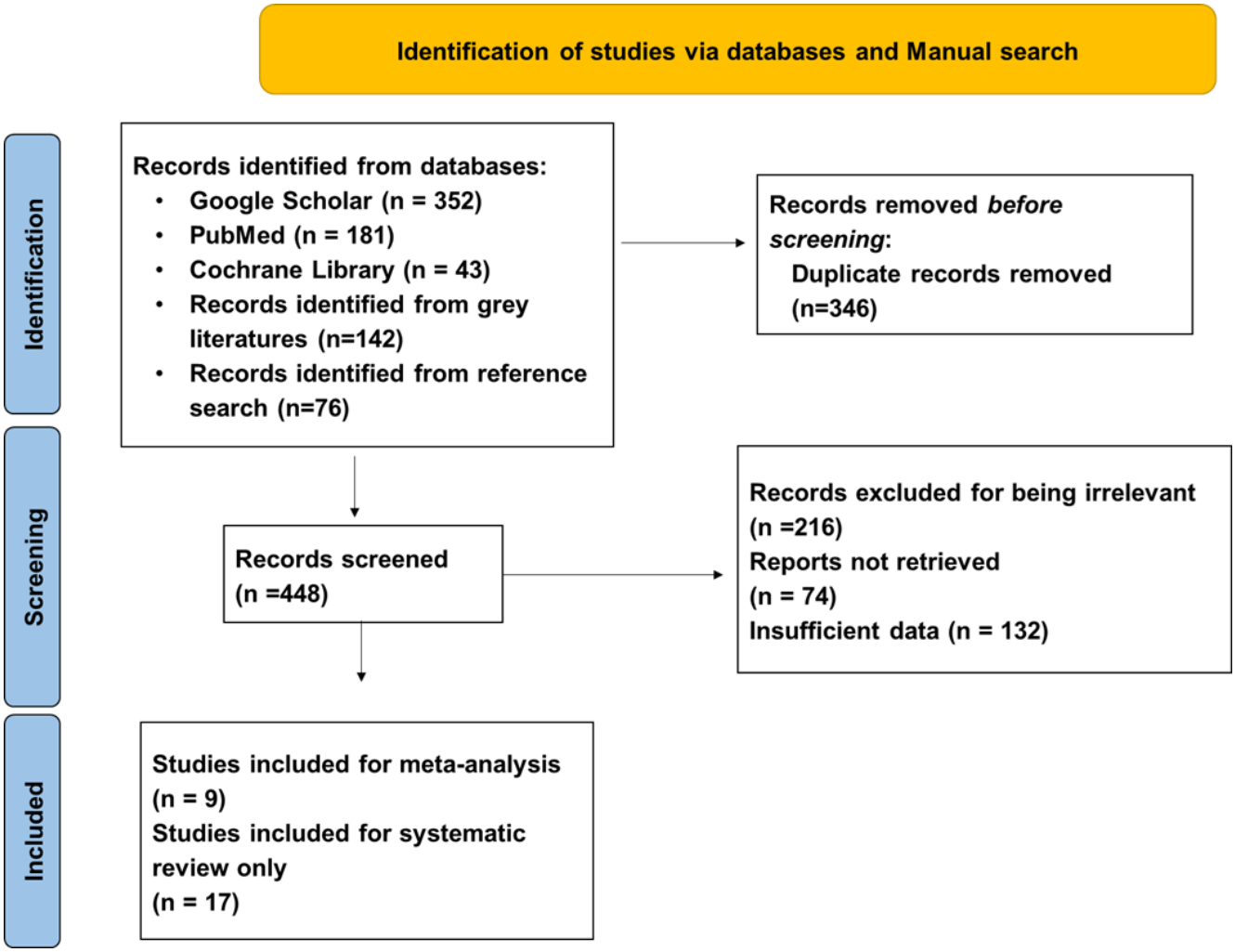

Figure 1.
PRISMA Flow Chart illustrating the systematic review process. This flowchart outlines the step-by-step progression of study selection, screening, and inclusion, as per the PRISMA guidelines.

Table 1.
Characteristics of the included studies, including the study design, publication date, number of cases, number of deaths, location and species of virus.

Author	Design	Publication Date	Cases (n)	Deaths (n)	Country	Month/Year of Outbreak	Virus species	Reference
WHO	Report	1978	284	151	Sudan	Jun-Nov/1976	Sudan ebolavirus	Ebola Haemorrhagic Fever in Sudan [14]
Bell et al.	Report	2016	28649	13325	Guinea, Liberia, Sierra Leone, USA Senegal, Nigeria, Mali	Mar/2014 - Apr/2016	Zaire ebolavirus, Côte d'Ivoire ebolavirus (CIEBOV)	Bell [15]
Shoemaker	Case report	2012	1	1	Uganda	2011	Sudan ebolavirus	Shoemaker et al. [16]
Wamala et al.	Retrospective study	2011	116	39	Uganda	2007-2008	Bundibugyo ebolavirus	Wamala et al. [17]
Jahrling et al.	Report	1990	4	0	USA	1989	Reston ebolavirus	Jahrling et al. [18]
Le Guenno et al.	Case report	1995	1	0	Cote D'Ivoire	1994	Taï Forest ebolavirus	Le Guenno et al. [19]
Emond et al.	Case study	1977	1	0	UK	1976	Zaire ebolavirus	Emond et al. [20]
International Commission	Report	1978	318	280	Zaire	Sep-Oct/1976		Burke et al. [21]
Khan et al.	Retrospective study	1999	315	254	DRC	1995		Khan et al. [22]
WHO	Report	2003	65	53	Gabon	2001-2002		World Health Organization [23]
Milleliri et al.	Retrospective study	2004	51	31	Gabon	1994		Milleliri et al. [24]
Borisevich et al.	Review	2006	2	2	Russia	2004, 1996		Borisevich et al. [25]
Leroy et al.	Retrospective study	2009	260	186	DRC	May-Nov/2007		Leroy et al. [10]
WHO	Review	2009	32	15	DRC	2008-2009		WHO [26]
Georges et al.	Retrospective study	1999	91	66	Gabon	1996-1997		Georges et al. [27]
Albarino et al	Retrospective study	2013	68	24	DRC, Uganda	Aug/2012-Nov/2012		Albarino et al. [28]
Maganga et al.	Retrospective study	2014	69	49	DRC	Jul-Oct/2014		Maganga et al. [29]
WHO	Case report	2014	1	0	Spain	2014		WHO [30]
WHO	Case report	2015	1	0	Italy	2014-2016		WHO [31]
Nsio et al.	Retrospective study	2020	8	4	DRC	2017		Nsio et al. [11]
Wadoum et al.	Retrospective study	2021	3470	2287	DRC	2018-2020		Wadom et al. [32]
WHO	Report	2021	12	6	DRC	Feb-May/2021		WHO [33]
WHO	Report	2021	11	9	DRC	Oct-Dec/2021		WHO [33]
WHO	Report	2022	130	55	DRC	2020		WHO [33]
Okware et al.	Retrospective study	2002	425	224	Uganda	200-2001	Sudan ebolavirus	Okware et al. [34]
ECDC	Review	2022	142	55	Uganda	Sep/2022-Jan/2023		ECDC [35]

3.2. Study Characteristics

The studies and reports included in this work were from sixteen countries. Africa had the largest representation of 11 countries: DRC, Uganda, Gabon, Sudan, Guinea, Liberia, Sierra Leone, Senegal, Nigeria, Mali, and Côte d'Ivoire (Table 1). The European countries identified in the search are the UK, Russia, Italy, and Spain. The US was the sole representative of North America. There were 17 outbreaks covered in the included studies. There were 34,527 cases, 17,116 deaths, and an overall CFR of 49.57%. Regionally, Africa had 99.96% of the cases and 99.98% of the reported deaths. North America had 8 cases from two outbreaks with the lowest regional CRF (12.5%), while Europe had the smallest number of cases (5) and CFR of 40%. DRC (formerly Zaire) has the largest number of cases (4,661) and deaths (3,158, CFR = 67.75%). Other leading countries were Uganda (716 cases, 330 deaths, CFR=46.09%), Sudan (284 cases, 151 deaths, CFR=53.17%), and Gabon (207 cases, 150 deaths, CFR=72.46%). Russia had the highest CFR (100%), with two of its cases ending with fatalities. The other countries with CRF above 50% are Gabon (72.46%), DRC (67.75%), and Sudan (53.17%). Other than Russia, the other European countries did not report deaths across the four pandemics they experienced. Based on the study design, 10 of the included studies were retrospective research studies, and the remaining were case reports (12) and reviews (3). The most common viral species that contributed to 19 outbreaks is the Zaire ebolavirus. Sudan ebolavirus (4), Taï Forest ebolavirus (1), Reston ebolavirus (1), and Bundibugyo ebolavirus (1) were also reported. The distribution of cases among different genders and the healthcare providers' contribution to the estimated cases are provided in Table 2. Cumulative data on the distribution of outbreaks, cases, and deaths based on regions and countries are provided in Table 3. The Newcastle-Ottawa Scale was used to assess the included articles. The results of the assessment are provided in Table 4. Studies were regarded to be of excellent quality if they had a score of 7 or higher across the board.

Table 2.
Distribution of outbreaks, cases, deaths, CFR based on gender, healthcare workers or non-healthcare workers.

Author	Date	Cases (n)	Deaths (n)	CFR	Male CFR	Female CFR	Seropositive Survivors	Healthcare Worker Cases (Deaths)	Non-Healthcare Worker Cases (Deaths)
Emond, et al. [20]	1977	1	0	0.00%	0/1	0/0	1	1(0)	0(0)
Burke, et al. [21]	1978	318	280	88.05%	N/A	N/A	38	17(11)	301(269)
WHO [26]	1978	284	151	53.17%	N/A	N/A	133	N/A	N/A
Jahrling, et al. [18]	1990	4	0	25.00%	N/A	N/A	4	N/A	N/A
Le Guenno, et al. [19]	1995	1	0	0.00%	N/A	N/A	1	N/A	N/A
Khan, et al. [22]	1999	315	254	80.63%	N/A	N/A	61	80	235
Georges, et al. [27]	1999	91	66	72.53%	N/A	N/A	25	N/A	N/A
Okware, et al. [34]	2002	425	224	52.71%	N/A	N/A	201	31(17)	394(207)
WHO [30]	2003	65	53	81.54%	N/A	N/A	12	N/A	N/A
Milleliri, et al. [24]	2004	51	31	60.78%	N/A	N/A	20	N/A	N/A
Borisevich, et al. [25]	2006	2	2	100.00%	N/A	N/A	0	N/A	N/A
Leroy, et al. [10]	2009	260	186	71.54%	N/A	N/A	74	N/A	N/A
WHO [6]	2009	32	15	46.88%	N/A	N/A	17	N/A	N/A
Wamala, et al. [17]	2011	116	39	33.62%	23/65	16/51	77	14(0)	102(39)
Shoemaker, et al. [16]	2012	1	1	100.00%	0/0	1-Jan	0	0(0)	1-Jan
Albarino, et al. [28]	2013	68	24	35.29%	N/A	N/A	44	N/A	N/A
Maganga, et al. [29]	2014	69	49	71.01%	21/33	28/36	20	8(8)	61(41)
WHO [31]	2015	1	0	0.00%	1-Jan	0/0	1	1(0)	0(0)

Bell [15]	2016	28649	13325	46.51%	N/A	N/A	15324	N/A	N/A
WHO [6]	2017	1	0	0.00%	0/0	1-Jan	1	1(0)	0(0)
[11]	2020	8	4	50.00%	6-Mar	2-Jan	4	0(0)	8(4)
Wadoum, et al. [32]	2021	3470	2287	65.91%	N/A	N/A	1183	171	3299
WHO [33]	2021	12	6	50.00%	N/A	N/A	6	N/A	N/A
WHO [33]	2021	11	9	81.82%	N/A	N/A	2	N/A	N/A
WHO [33]	2022	130	55	42.31%	N/A	N/A	75	N/A	N/A
ECDC [35]	2022	142	55	38.73%	N/A	N/A	87	N/A	N/A

Table 3.
Distribution of outbreaks, cases, and deaths based on regions and countries.

Region & Country	Years of Outbreak	Cases (n)	Deaths (n)	CFR
Africa				
DRC	1976, 1995, 2007, 2008-2009, 2012, 2014, 2017, 2018-2020, 2020, 2021	4661	3158	67.75%
Uganda	2000-2001, 2007-2008, 2011, 2012, 2022	716	330	46.09%
Gabon	1994, 1996-1997, 2001-2002	207	150	72.46%
Sudan	1976	284	151	53.17%
Others (Guinea, Liberia, Sierra Leone, Senegal, Nigeria, Mali, Cote D'Ivore)	1994, 2014-2016	28646	13324	46.51%
Total		**34514**	**17113**	**49.58%**
Europe				
UK	1976	1	0	0.00%
Spain	2014	1	0	0.00%
Italy	2014-2016	1	0	0.00%
Russia	1996, 2004	2	2	100.00%
Total		**5**	**2**	**40.00%**
North America				
USA	1989, 2014-2016	8	1	12.50%

Table 4.
Quality of Studies. Studies were regarded to be of excellent quality if they had a score of 7 or higher across the board.

Study	Publication Year	Selection	Comparability	Outcome	Quality Assessment
Burke, et al. [21]	2011	4	2	3	Good
WHO [26]	2019	4	1	2	Good
Bell [15]	2020	4	1	3	Good
Maganga, et al. [29]	2014	4	4	4	Good
Albarino, et al. [28]	2013	4	1	2	Good
Shoemaker, et al. [16]	2004	4	2	2	Good
Wamala, et al. [17]	2018	4	4	4	Good
Leroy, et al. [10]	2022	4	1	2	Good
Jahrling, et al. [18]	2015	4	1	3	Good
Emond, et al. [20]	1977	4	2	3	Good
WHO [30]	2017	4	1	2	Good
Borisevich, et al. [25]	2006	4	1	2	Good
WHO [31]	2015	4	2	3	Good
Le Guenno, et al. [19]	1995	4	1	2	Good
WHO [6]	2009	4	1	2	Good
Khan, et al. [22]	1999	4	1	2	Good
Nsio, et al. [11]	2020	4	3	4	Good
Wadoum, et al. [32]	2021	4	1	2	Good
WHO [33]	2022	4	1	2	Good
WHO [33]	2021	4	1	2	Good
WHO [33]	2021	4	1	2	Good

World Health Organization [23]	2003	4	1	2	Good
Georges, et al. [27]	1999	4	1	2	Good
Milleliri, et al. [24]	2004	4	1	2	Good
Okware, et al. [34]	2002	4	3	2	Good
ECDC [35]	2022	4	1	2	Good

3.3. Prevalence of Ebola

The prevalence of Ebola is examined by considering the distribution of the disease in the countries within the three regions from 1976 to 2022. Zaire reported the largest proportion of Ebola cases throughout the years under review, accounting for 13.50% of the reported cases and 18.45% of the mortality (Table 3). Uganda is the second country that contributed 2.07% of cases and 1.93% of deaths in the reviewed period. The other countries contributed below 1% as Africa led the way with 99.96% of the cases and 99.98% of the deaths.

Except for Wamala et al. [17], the studies that examined the infection and death of healthcare workers in Africa reported a high CFR of healthcare workers (>50%) [21, 29, 34]. In all instances, the infections were due to contact with infected patients while providing care. The reports on infection of healthcare workers outside Africa were treated with no deaths reported. The infections outside Africa were due to contact with the imported patient and in the labs.

3.4. Comparison of Deaths Based on Gender

The differences in the CFR of the male and female patients were also examined. While the findings on gender differences were limited, the infections were more likely to be reported among men than women [11, 17]. A meta-analysis was performed to determine the difference in the CFR of the patients based on their gender. There was no significant difference between the CFR of the male and female patients infected by the virus, despite men being at a slightly higher risk of mortality from the infection compared to women [OR=0.88, 95% CI, 0.48-1.62, I^2=0%, p=0.69] (Figure 2).

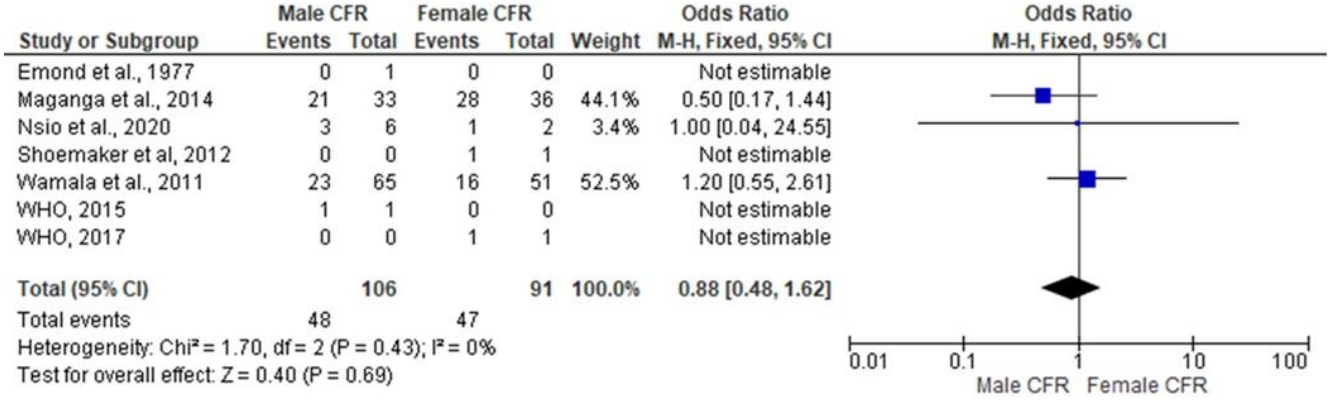

Figure 2.
Forest plot of the odds of death among positive male patients versus positive female patients.

3.5. Comparison of Deaths in Healthcare Workers and Non-Healthcare Populations

A meta-analysis was performed to compare the odds of death after infection among the healthcare and non-healthcare populations. Healthcare workers were more likely to die after infection than non-healthcare workers. However, the difference in the odds of infected healthcare workers dying relative to the non-healthcare patients dying was insignificant [OR=0.66, 95% CI, 0.39-1.12, I^2=75%, p=0.12] (Figure 3).

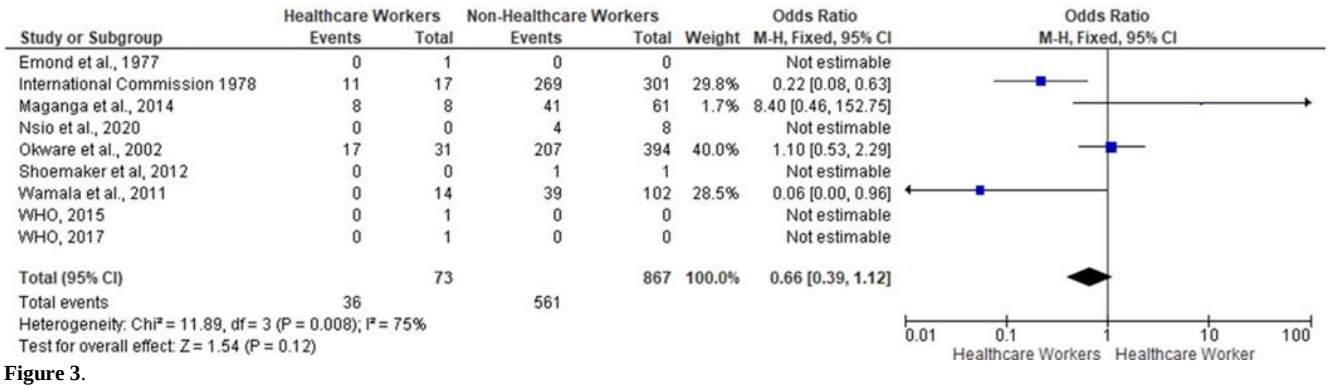

Figure 3.
Forest plot of the odds of death among infected healthcare workers compared to non-healthcare patients.

4. Discussion

This study highlights the severity and prevalence of Ebola since the first outbreak in 1976. The findings show that Ebola remains highly prevalent in Africa, with Central and Western Africa accounting for most cases. East Africa (Uganda and Sudan) is the other area that has reported a high number of cases and deaths. The cumulative case fatality rate (CFR) of 49.93% is another legitimate concern, as the disease is increasingly being reported outside Africa. This study demonstrates that infected healthcare workers in Africa have a higher risk of death. These findings illustrate the significant burden of the disease and the implications of managing the prevalence of Ebola.

The meta-analysis showed a higher risk of casualty among the infected healthcare providers. While there is no statistical difference with the non-healthcare population, the finding is a concern as the healthcare workers provide the first line of defense during outbreaks. The current study demonstrates that healthcare providers in African countries face a high risk of infection and death from the infection. The likelihood of these healthcare workers operating in isolated or remote areas, which takes some time before the results of suspected cases are confirmed, further increases the risk. In their study,

Wamala et al. [17] reported a cluster of 9 cases and six deaths that resulted from a mother-daughter nurse pair involved in handling the remains of a diseased, infected patient before barrier nursing and supervised burials were in place [17].

There is a disparity in how cases in Europe and North America have been managed to avoid the transmission of infection from healthcare personnel and reduce deaths. Aside from the two laboratory workers who died in Russia [25], the healthcare professionals who were identified as potentially infected were isolated and provided with care before severe outcomes were presented [31]. Improvements in managing healthcare staff during pandemics are critical in increasing the resilience and capacity of the healthcare systems and improving the quality of care received by patients.

According to Wamala et al. [17], the efforts by organizations such as the Africa CDC in training and vaccinating healthcare workers, as well as the provision of contact tracing and surveillance, laboratory services, and cross-border surveillance, have been critical in managing recent outbreaks [32]. There are still substantial barriers to eliminating Africa's disproportionate share of Ebola's global prevalence and burden. Difficulties, such as inaccessibility to some regions during hostilities in DRC, where the disease's epicenter was located, complicated the second-largest epidemic in history, which occurred between 2018 and 2020 [32]. These unique aspects must be considered when alleviating the burden of an underserved healthcare system attempting to deal with this highly contagious disease.

Because of the stigma surrounding the illness, vital facts like the rate of infection among caregivers cannot be determined from the available information. It is challenging to offer information that indicates the prevalence and effect of the disorder due to a lack of data on gender, population subgroups, and the origin of infection. Because the expansion factor cannot be calculated without longitudinal monitoring data, it will be difficult, if not impossible, to draw reliable conclusions and forecast the disease's future prevalence.

5. Conclusions

According to the present findings, Africa continues to have the highest case fatality rate (CFR) and the highest number of Ebola-related deaths. While there is no statistical difference in the odds of death among the non-healthcare population, healthcare workers bear a higher burden of the outbreaks as they have higher odds of dying compared to the non-healthcare populations. There is no significant difference in the CFR of male and female patients despite men being more likely to develop infections.

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