zoonotic diseases

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Systematic Review

Zoonotic Diseases in Sub-Saharan Africa: A Systematic Review and Meta-Analysis

Jérôme Ateudjieu [1,2,3], Joseph Nelson Siewe Fodjo [3,4,*], Calson Ambomatei [5], Ketina Hirma Tchio-Nighie [1] and Anne-Cecile Zoung Kanyi Bissek [3]

1 Department of Health Research, M.A. SANTE (Meilleur Accès aux Soins de Santé), Yaoundé P.O. Box 3390, Cameroon; jateudjieu@masante-cam.org (J.A.); ktchio@masante-cam.org (K.H.T.-N.)
2 Department of Public Health, Faculty of Medicine and Pharmaceutical Sciences, University of Dschang, Dschang P.O. Box 67, Cameroon
3 Division of Health Operations Research, Ministry of Public Health, No. 8, Rue 3038 quartier du Lac, Yaoundé P.O. Box 3390, Cameroon; annezkbissek@yahoo.fr
4 Global Health Institute, University of Antwerp, Doornstraat 331, 2610 Antwerp, Belgium
5 Health Search Association, Yaoundé P.O. Box 1274, Cameroon; calsonambomatei@healthsearchassociation.net
* Correspondence: josephnelson.siewefodjo@uantwerpen.be

Simple Summary: Zoonotic diseases are those that contaminate humans as a result of direct contact with animals. These are increasingly being reported in the African continent, but synthesized information about their occurrence and the deaths they engender in sub-Saharan Africa (SSA) is scarce. To close this gap, we searched for available information on zoonotic diseases in SSA and compiled the findings into a single report using appropriate statistical techniques. We found that zoonotic diseases had been reported in 26 SSA countries, affecting a total of 28,934 individuals (on average, 54.4 cases for every 1000 persons in the affected zones) and causing 1182 deaths (on average, 345.4 fatalities for every 1000 infected persons). All the SSA sub-regions (West, Central, East, and Southern) were affected. The most contagious zoonotic diseases identified were rickettsiosis, toxoplasmosis, and Q-fever, while the deadliest included Marburg, Ebola, and leptospirosis. These findings are crucial to inform relevant stakeholders on the need to closely monitor zoonotic diseases and prioritize those with the greatest health risks. Furthermore, countries must be adequately prepared to respond adequately to future outbreaks.

Abstract: Frequent animal–human interactions in sub-Saharan Africa (SSA) pose an increased risk for the transmission of zoonotic diseases. While there are sporadic reports of zoonotic diseases outbreaks in SSA, a synthetic overview is necessary to better understand how the sub-region is impacted by these pathologies. We conducted a systematic review of zoonotic diseases studies conducted in SSA between 2000 and 2022. Quantitative reports including case reports/series from countries spanning West, Central, East, and Southern SSA and that provided empirical data on the occurrence of zoonotic diseases in humans with documented evidence of animal origin were eligible for inclusion. The 55 eligible articles provided 82 reports of zoonotic diseases for a total of 28,934 human cases (pooled attack rate: 54.4 per 1000) and 1182 deaths (pooled fatality rate: 345.4 per 1000). Only 31 (37.8%) of the studies were conducted during ongoing outbreaks. We identified the zoonotic diseases in SSA with the highest attack rates (rickettsiosis, toxoplasmosis, Q-fever) and CFR (Marburg, Ebola, leptospirosis), which should be prioritized for surveillance and response preparedness. Addressing the threat of zoonotic diseases in SSA requires the strengthening of health systems and implementation of a one health approach. Importantly, research should be encouraged during ongoing epidemics to fortify immediate response strategies and work toward preventing future outbreaks.

Keywords: zoonotic diseases; sub-Saharan Africa; outbreaks; (re)emerging diseases; One Health

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1. Introduction

Direct or indirect contact between human beings and animals is common in many communities in Sub-Saharan Africa (SSA). Animal husbandry is a major economic activity in this part of the world, as it accounts for approximately 40% of the continent's gross domestic product (ranging from 10% to 80% in different countries) [1]. In addition, residents in rural communities in SSA, particularly those involved in hunting, are likely to encounter wild animals in the forests. One of the consequences of the frequent contacts between humans and animals is the spread of zoonotic diseases, which are infectious diseases transmitted from animals to humans and vice versa [2]. It has been reported that more than 60–75% of human pathogens are of zoonotic origin, including a wide range of bacteria, viruses, protozoa, parasites, fungi, and other pathogens [3,4]. Based on etiology, zoonoses are classified into bacterial zoonoses (such as anthrax, salmonellosis, tuberculosis, Lyme disease, brucellosis, and plague), viral zoonoses (such as rabies, acquired immune deficiency syndrome (AIDS), Ebola, and avian influenza), parasitic zoonoses (such as trichinosis, toxoplasmosis, trematodosis, and echinococcosis), fungal zoonoses (such as ringworm), rickettsial zoonoses (Q-fever), chlamydial zoonoses (psittacosis), mycoplasma zoonoses (*Mycoplasma pneumoniae* infection), protozoal zoonoses, and diseases caused by acellular non-viral pathogenic agents (such as transmissible spongiform encephalopathies and mad cow disease) [5,6]. In some cases, after an initial transmission of the pathogen from an animal to a human, genotypic and/or phenotypic adaptations would enhance the virulence of the pathogen and allow for subsequent human-to-human transmission [7].

In the past, emerging zoonotic diseases have included globally devastating diseases such as Ebola virus disease, Middle East respiratory syndrome (MERS), highly pathogenic avian influenza, severe acute respiratory syndrome, and bovine spongiform encephalopathy [4,8]. Between 2020 and 2023, the world was confronted with the COVID-19 pandemic, which was also thought to be a disease of zoonotic origin [9]. Zoonotic diseases such as COVID-19 are not only leading causes of morbidity and mortality but also major causes of significant economic losses [6,10]. More recently, several outbreaks of monkeypox have been reported across several continents [11]. The culprit pathogen, the monkeypox virus, was first identified in 1959 when monkeys shipped from Singapore to a Denmark research facility fell ill [12]; however, the first confirmed human case was in 1970 when the virus was isolated from a child in the Democratic Republic of Congo suspected to have smallpox [13].

From 2012 to 2022, the rate of zoonotic disease outbreak in SSA increased by 63% compared to the preceding decade (2001–2011). From 2001 to 2022, 33% of public health emergencies in this part of the globe were zoonotic disease outbreaks [14]. The death of people and animals (which contribute immensely to the economy), morbidity, and travel restrictions that occur as direct and indirect consequences of zoonotic disease outbreaks impose a heavy burden on the economies and health systems of the nations concerned. Thus, zoonotic diseases need to be monitored closely since they have the potential to become devastating epidemics, and even pandemics. In this paper, we aimed to map zoonotic diseases that have been reported in SSA during the current century and attempt to identify their reservoirs, mortality and/or morbidity. With the often-fragile health systems in Africa, such evidence would contribute to epidemic/pandemic preparedness via updated scientific evidence and will allow the limited resources to be invested in monitoring the priority high-risk zoonoses that show a potential to (re)emerge in future.

2. Methods

We followed the PRISMA 2020 guidelines [15]. These guidelines lay out the internationally approved methods for conducting systematic reviews; the process starts by conducting a systematic search in the target databases using well-defined keywords to retrieve abstracts of potentially eligible publications. After the screening of abstracts based on eligibility criteria, the full papers for the remaining reports must be sought and read in detail to determine whether they comply with the inclusion criteria for the review. At each stage, the reasons for non-inclusion should be noted until the eligible reports are identified

for data extraction and analysis. This study has been registered in PROSPERO (registration number: CRD42023465455).

2.1. Search Strategy

We searched PubMed, Scopus, and Cochrane databases for published literature in French and English indexed until the 21 November 2022. Key search terms included 'zoonosis', 'outbreak', 'emerging', 'reservoir', and 'sub-Saharan Africa' in the titles and abstracts (see Supplementary File S1 for full search strings). We also conducted manual searches and reviewed the reference lists of relevant review articles on this topic to identify additional records that were eligible for inclusion.

2.2. Screening and Data Extraction

Inclusion and exclusion criteria: We included quantitative reports from SSA (including case reports/series) that provided empirical data on the occurrence of zoonotic diseases in humans (with documented evidence of animal origin) and were published as from 1 January 2000. Outbreak data from the World Health Organization (WHO) were also extracted from published literature when available. Since we sought to identify zoonotic diseases that are likely to affect the general human population, we excluded studies reporting infections only in animals without any human cases, and those conducted on specific human populations (for instance, HIV-infected individuals). We equally excluded mathematical modeling studies, systematic reviews, commentaries, and opinion papers/viewpoints. Using the Rayyan online platform [16], two authors (JNSF and CA) independently performed the screening of abstracts for inclusion in this review.

Assessment of reports and extraction of data: Given that the goal of this review was to be as wide and exhaustive as possible in documenting zoonotic outbreaks in SSA since the year 2000, the assessment of reports for quality was not stringent to enable reports that provided some information on the subject at hand to be included. The two authors who performed abstract screening proceeded to select studies eligible for inclusion. In case of conflicting opinions, the opinion of another author (JA) was sought to arrive at a decision to include or reject the study. Relevant crude data were then extracted from the included studies into Microsoft Excel spreadsheets. The main variables of interest included the number of cases of the zoonotic infection reported in the article, firstly among humans and potentially among studied animals; these were used to calculate attack rates of the zoonotic diseases. Furthermore, available mortality data among infected human cases were also obtained from the reports to compute fatality rates. Additional variables of interest included the year and country of study, study setting (conducted during an ongoing outbreak or not), and the reported animal reservoirs for the causal pathogen.

2.3. Definition of Terms

The attack rate is the proportion of a study population that were reported to have the zoonotic disease in a given study. This was calculated by dividing the number of reported cases of the disease by the total population being studied and expressed per 1000.

Case fatality rate (CFR) refers to the proportion of infected humans that end up dying of the zoonotic disease. It was calculated by dividing the number of reported deaths by the total number of infected cases and expressed per 1000.

2.4. Data Analysis

Extracted data on zoonotic infections and deaths were exported to R version 4.2.2 for analysis. Attack rates and CFRs were considered as proportions and pooled using the 'metaprop' function in the R-package 'meta', which implements the inverse variance method with logit transformation and uses the restricted maximum likelihood estimator to calculate the heterogeneity during pooling. We used random-effect models to calculate the pooled estimates of attack rates and CFR; the Knapp–Hartung adjustment was used to calculate 95% confidence intervals [17]. Subgroup analyses were performed to compare

different zoonotic diseases. For pooled estimates, clustering by study country was used to account for possible intra-country correlations.

3. Results

The literature search (both database and manual) resulted in 590 abstracts. Upon screening, 55 studies were included [18–72] from which 82 reports were extracted for analysis (Figure 1).

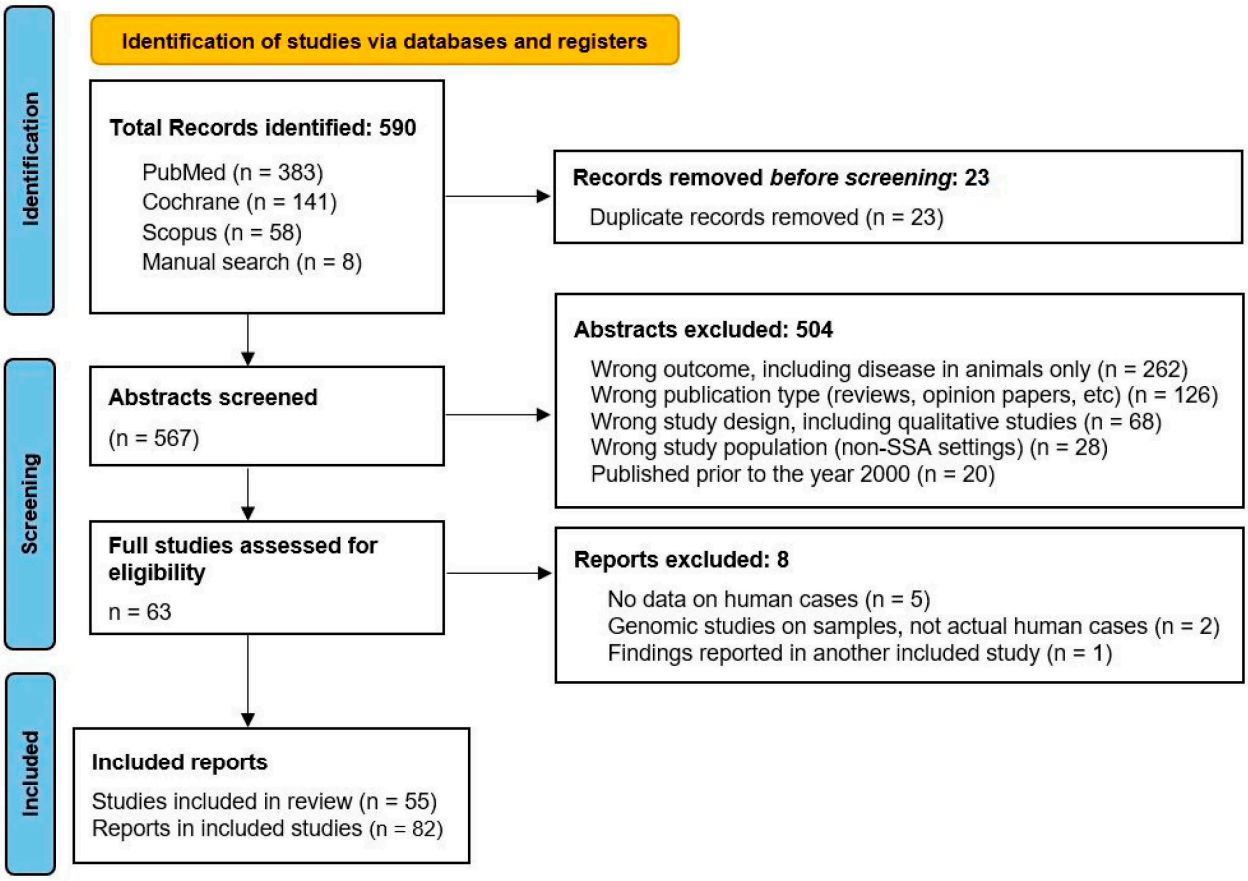

Figure 1. PRISMA flow diagram for the inclusion of eligible studies.

The included studies reported human cases of zoonotic diseases from 26 SSA countries, namely Angola, Cameroon, Central African Republic, Republic of Congo, Ivory Coast, Democratic Republic of Congo, Ethiopia, Gabon, Ghana, Kenya, Liberia, Madagascar, Mauritania, Mozambique, Namibia, Niger, Nigeria, Senegal, Sierra Leone, South Africa, South Sudan, Sudan, Tanzania, Uganda, Zambia, and Zimbabwe (Figure 2). The full list of the included reports and their characteristics is presented in the Supplementary Table S1. Kenya had the highest number of published reports documenting zoonotic diseases in humans (13 in total, representing 15.9%% of all 82 included reports); next came South Africa with 9 (11.0%) reports, and Uganda with 7 (8.5%) reports.

Twenty-eight zoonotic diseases were covered by the 82 eligible reports, yielding a cumulative total of 28,934 human infections from 2000 to 2022. Only 31/82 (37.8%) of the studies were conducted during ongoing outbreaks. Monkeypox accounted for the highest number of reports (13), followed by Rift Valley Fever (12) and Ebola (10). Common animal reservoirs that were identified included cattle, rodents, pigs, bats, camels, gorillas, poultry, snakes, and cats (Table 1).

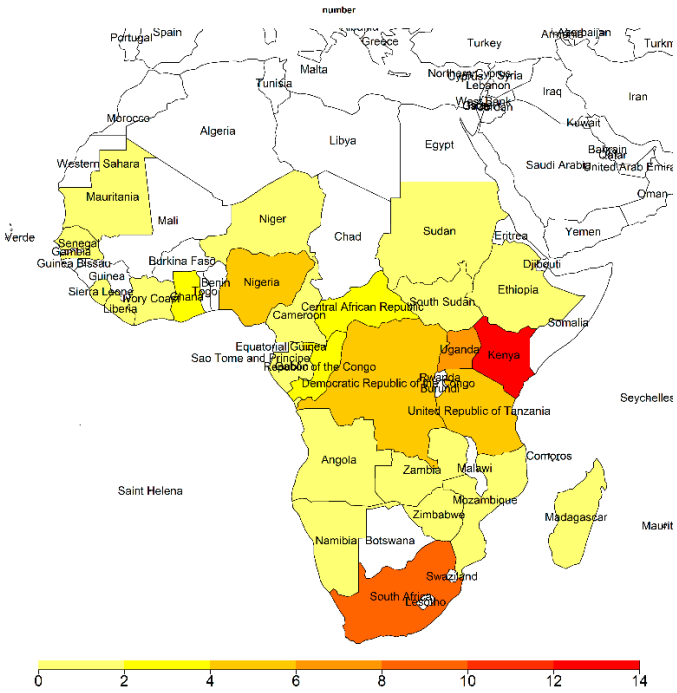

Figure 2. Number of zoonotic disease reports per country in sub-Saharan Africa.

Table 1. Zoonotic diseases reported in sub-Saharan Africa between 2000 and 2022.

Zoonotic Disease (*Countries*)	Number of Reports	Studies Conducted in Outbreak Setting	Total Number of Human Infections Reported	Total Number of Human Deaths Reported	Total Number of Animal Infections	Animal Reservoirs Identified	Identified Risk Factors
Anthrax (*Uganda, Zambia, Zimbabwe*)	3 [18,28,53]	3 (100%)	1911	85		Cattle	Handling raw meat/cattle carcasses
Astrovirus (*Nigeria*)	1 [39]	0 (0.0%)	7				
Bartonellosis (*South Africa*)	1 [66]	0 (0.0%)	7				
Borreliosis (*Zambia*)	1 [62]	0 (0.0%)	1		64		
Brucellosis (*Kenya, South Africa, Tanzania, Uganda*)	8 [22,26,43,49, 54,55,57,66]	1 (12.5%)	630		74	Cattle	Handling raw meat
Cysticercosis (*Nigeria*)	1 [31]	0 (0.0%)	43			Pigs	
Dobrava (*Ghana*)	1 [59]	0 (0.0%)	80			Rodents	
Escherichia. coli (*Uganda*)	1 [41]	0 (0.0%)	6		45	Cattle	
Ebola (*Congo, DRC, Gabon, South Sudan, Uganda*)	10 [27,46]	9 (90.0%)	1249	711		Bats, gorillas, monkeys	Contact with rodents
Echinococcosis (*Mauritania, Sudan*)	2 [21,24]	0 (0.0%)	23		22	Dogs, camels	

Table 1. *Cont.*

Zoonotic Disease (*Countries*)	Number of Reports	Studies Conducted in Outbreak Setting	Total Number of Human Infections Reported	Total Number of Human Deaths Reported	Total Number of Animal Infections	Animal Reservoirs Identified	Identified Risk Factors
Enterocytozoon (*Mozambique*)	1 [51]	0 (0.0%)	9				
HTLV (*Gabon*)	1 [64]	0 (0.0%)	2		2	Gorillas	
Influenza A (*Cameroon, South Africa*)	2 [32,50]	1 (50.0%)	59		64	Poultry, pig	
Lassa virus (*Ghana*)	1 [59]	0 (0.0%)	34		2	Rodents	
Leishmaniasis (*Senegal*)	1 [34]	0 (0.0%)	44		57	Dogs	
Leptospirosis (*Ghana, Kenya, South Africa, Tanzania*)	9 [22,23,26,48, 49,56,59,65,66]	1 (11.1%)	616	1	347	Cattle, rats, rodents	Milking, exposure to contaminated water
Marburg (*Angola, Uganda*)	2 [20,40]	2 (100%)	378	330	31	Bats	
MERSCOV (*Kenya*)	1 [58]	1 (100%)	3		124	Camel	
Monkeypox (*CAR, Cote d'Ivoire, DRC, Liberia, Nigeria, Sierra Leone, Sudan*)	13 [25,30,42,45, 47,61,72]	10 (76.9%)	19,767	15		Unknown (Monkeys?)	Contact with live or dead animals
Pentastomiasis (*DRC*)	2 [67,68]	0 (0.0%)	6			Snakes	Cooking/eating snake meat
Puumala (*Ghana*)	1 [59]	0 (0.0%)	74			Rodents	
Q fever (*South Africa*)	1 [66]	0 (0.0%)	67				Cattle
Rabies (*Ethiopia, Namibia*)	2 [37,69]	0 (0.0%)	2293		1907	Kudus, jackals, dogs, cattle, cats, elands, goats	Animal bites
Rickettsiosis (*South Africa*)	1 [66]	0 (0.0%)	104				Exposure to dogs?
Rift Valley Fever (*Kenya, Madagascar, Mauritania, Niger, South Africa, South Sudan, Uganda*)	12 [26,29,33,35, 36,38,44,60,63, 66,70]	3 (25.0%)	1132	40	191	Cattle, livestock, cow	Milking, handling raw meat, animal birthing/ slaughtering
SIV (*Cameroon*)	1 [71]	0 (0.0%)	179				Exposure to fresh primate blood
Toxoplasmosis (*Ethiopia*)	1 [52]	0 (0.0%)	158			Cats	Exposure to cats
Tuberculosis (*Nigeria*)	1 [19]	0 (0.0%)	52		2	Cattle	
OVERALL	82	31 (37.8%)	28,934	1182	2932		

CAR: Central African Republic; DRC: Democratic Republic of Congo; HTLV: Human T-Lymphotropic Virus; SIV: Simian Immunodeficiency Virus.

3.1. Attack Rate of Zoonotic Diseases in Sub-Saharan Africa

A total of 28,934 infected humans were reported from a pool of 87,319,187 surveyed individuals. The overall pooled attack rate was 54.4 per 1000. The pooled attack rate was highest for rickettsiosis (770.4 per 1000) and lowest for pentastomiasis (1.0 per 1000), as shown in Figure 3. Stratifying the included reports based on the epidemiological setting, the pooled attack rate during ongoing outbreaks was 6.9 per 1000 compared to 97.6 per 1000 outside of outbreaks.

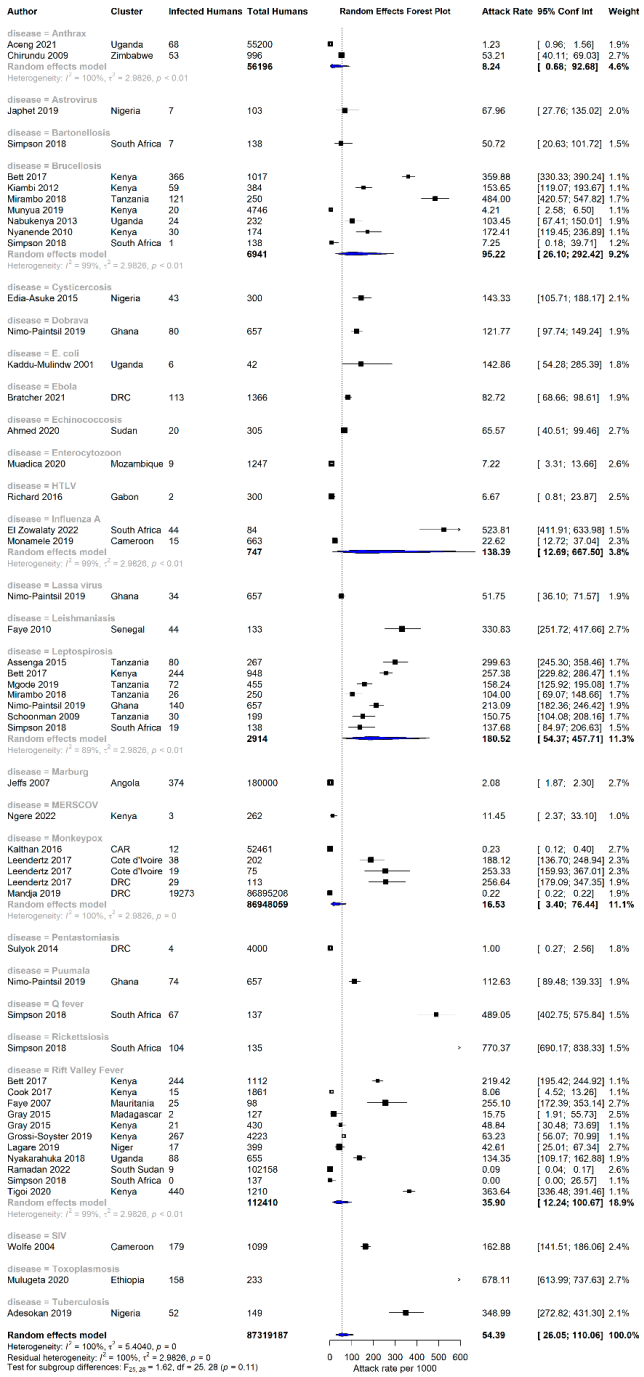

Figure 3. Pooled attack rates of the included zoonotic diseases [18–72]. The black square dots represent point attack rates for each study, with the confidence intervals shown as horizontal black lines. The blue diamond-shaped items represent pooled attack rates for each zoonotic disease. The overall pooled attack rate is indicated by the vertical dotted line. The studies mentioned in the figure are fully referenced in the Supplementary Table S1.

3.2. Case Fatality Rates of Zoonotic Diseases in Africa

Overall, 1182 deaths were reported from zoonotic diseases in the study sites. The pooled CFR for zoonotic diseases was 345.4 per 1000. However, for individual diseases, CFRs ranged from 55.0 per 1000 (for anthrax) to 802.1 per 1000 (for Marburg), as shown in Figure 4. Stratifying the included reports based on the epidemiological setting, the pooled CFR during ongoing outbreaks was 338.6 per 1000 compared to 364.8 per 1000 outside of outbreaks (only two studies outside outbreaks documented deaths).

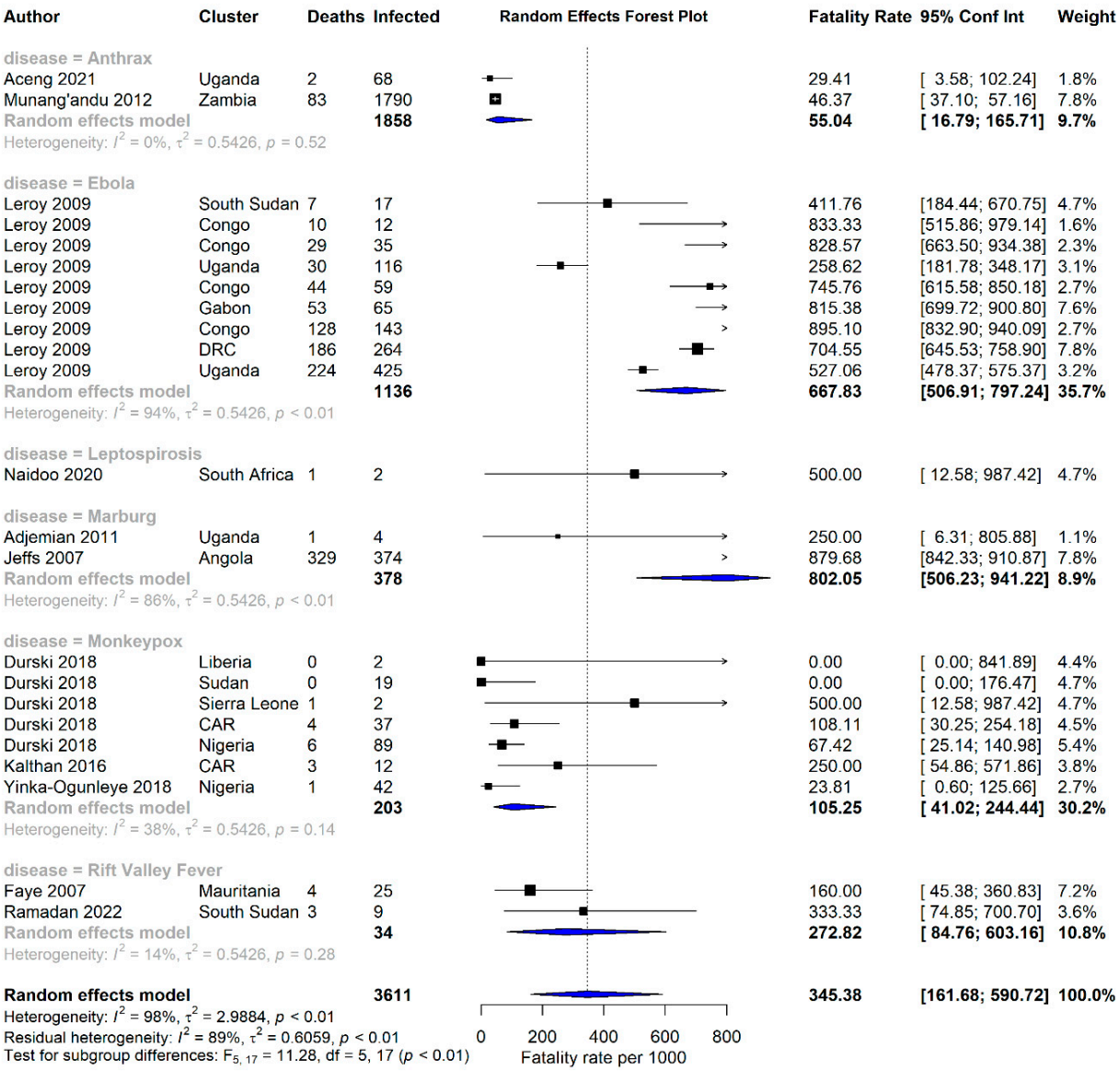

Figure 4. Pooled case fatality rates for the included zoonotic diseases [18–72]. The black square dots represent point fatality rates for each study, with the confidence intervals shown as horizontal black lines. The blue diamond-shaped items represent pooled fatality rates for each zoonotic disease. The overall pooled fatality rate is indicated by the vertical dotted line. The studies mentioned in the figure are fully referenced in the Supplementary Table S1.

4. Discussion

In this review, we aimed to document the occurrence of zoonotic diseases in SSA as per reports from the year 2000 onward. After a systematic search, we identified 28 zoonotic diseases in the 82 eligible reports, with a total of 28,934 documented human infections. These numbers highlight the fact that zoonotic diseases are common and could potentially

increase in magnitude in this part of the globe, owing to the frequent human–animal contact [73]. It is likely that the documented cases under-report the real situation in these countries, especially considering that COVID-19 cases are not included in these numbers as none of the screened reports clearly linked it to an animal origin. Health systems must therefore be prepared to respond quickly during outbreaks of existing and emerging zoonotic diseases. The emergence of high-consequence infectious diseases of (potential) zoonotic origin such as Ebola and COVID-19 [74,75], together with the sustained burden of other zoonotic diseases such as rabies [76], has highlighted the need for health systems in SSA to be strengthened in their one health approach to appropriately monitor, prevent, and address zoonotic diseases. Thus, implementing multisectoral action plans and response teams is critical [77]. Only 31 (37.8%) of the studies were conducted during ongoing outbreaks. While disease outbreaks may be accompanied by certain difficulties to conduct research [78], it is important to collect real-time data as early as possible during the emergency response. This would provide a wealth of information to improve the ongoing response and ameliorate preparedness toward future public health emergencies. The recent COVID-19 pandemic, which engendered devastating effects on life and livelihood, underpinned the utmost importance of data to improve response especially when the pathogenesis and modes of transmission of the disease are not fully understood [79]. We found that the three most reported zoonotic diseases were monkeypox, Rift Valley Fever, and Ebola viral disease. These pathologies have all been reported to be deadly in humans. The estimated CFR for monkeypox ranged from 0 to 11% during the 2022 outbreak [80]; meanwhile, that of Rift Valley fever during an outbreak in Mauritania in 2022 was reported to be as high as 49% [81]. As for Ebola virus disease, the CFR has been reported to range from 20% to 90%, depending on the species [82]. Considering the pooled CFR for each disease in our review, it suggests that zoonotic diseases kill at least one in every twenty infected persons (for anthrax), with a peak fatality of four in five infected persons for Marburg disease. These findings depict the significant threat represented by zoonotic diseases and should serve as a wake-up call to the health systems in place in SSA [83]. Common animal reservoirs that were identified included cattle, rodents, pigs, bats, camels, gorillas, poultry, snakes, and cats. All these (and others) are animals that are frequently in contact with human beings, either as food, pets, and domestic animals kept for commercial purposes, or encountered during human activities like hunting and hiking. Additionally, the abundance of human-commensal species, such as rats, is increasing alongside urbanization and deforestation, further raising the opportunity for humans to acquire zoonotic diseases [84]. With globalization having eased human movements from one part of the world to another, investing in the control of zoonotic diseases in SSA is fast becoming a global health concern as they can easily be introduced into hitherto non-endemic sites in the developed world [85]. Given the wide geographical distribution of the identified animal reservoirs for zoonotic diseases in SSA, adequate epidemiological surveillance measures should be put in place to ensure optimal surveillance and response preparedness [86]. In that regard, platforms like ZOVER [87] can be particularly useful in understanding the landscape of zoonotic diseases and vectors across the globe. Another looming threat for zoonotic outbreaks is the misuse of antimicrobials in animals, which fosters the development of resistances and eventually leading to human infections via a food web or otherwise [88]. Here again, a one health approach would be necessary to control antimicrobial use in animals and the environment at large.

The overall pooled attack rate for zoonotic diseases in SSA was 54.4 per 1000, with extremes of 1.0 per 1000 (pentastomiasis) and 770.4 per 1000 (rickettsiosis). These numbers indicate that many of these diseases are highly transmissible from animals to humans, and subsequent human-to-human transmission has been reported for some of them [7]. Zoonoses therefore constitute a major public health concern with a substantial impact on the global economy and sustainability [89]. The transmission of animal pathogens to humans (a phenomenon known as zoonotic spillover) is increasingly being reported and should be addressed with much urgency to mitigate the damage caused by these diseases [90–92].

In a report dated March 2023 [93], it was suggested that the risk of pathogen spillover can be reduced by stopping the clearing and degradation of tropical and subtropical forests, improving the health and economic security of communities residing in emerging disease hotspots, enhancing biosecurity in animal husbandry, shutting down or strictly regulating wildlife markets and trade, and expanding pathogen surveillance. Furthermore, since we have succeeded in identifying the zoonoses in SSA with the highest CFR (Marburg, Ebola, leptospirosis) and attack rates (rickettsiosis, toxoplasmosis, Q-fever), these should be prioritized for investigations into the various factors (biological, social, cultural, and environmental) that contribute to their spread as this will help attenuate the negative impact of these diseases on human life.

It is worth mentioning a few limitations that must be considered when interpreting our study findings. First, the studies we included differed widely in terms of methodology and population. This high heterogeneity made it difficult to draw certain solid conclusions. Therefore, more precise information can be obtained by conducting site-specific studies for the identified zoonotic diseases using a uniform study design to ease comparisons. Second, only 37.8% of the studies we included were conducted during ongoing outbreaks, which implies that our overall conclusions can hardly be directly applied to real-life active epidemics settings for the different zoonotic diseases. Nevertheless, stratification of the extracted data found that attack/fatality rates were generally lower during outbreaks since more people are routinely screened as part of the epidemic response, and this inflates the denominator compared to non-outbreak settings whereby only suspected cases are tested. Third, the risk of bias was also high for many of the included studies since they were mostly cross-sectional investigations. Therefore, we recommend that more cohort studies (including continuous surveillance) to corroborate our findings and explore other relevant aspects in the epidemiology of zoonotic diseases. Owing to limited research capacity and under-reporting, we acknowledge that the geographical locations, timings and frequency of zoonotic diseases laid out in this review may not reflect the full extent of these diseases in the SSA setting. Also, as we were dealing with data from studies and not surveillance data, the presented findings provide only limited insight into some epidemiological aspects of the reported zoonoses, particularly their exact geographical distribution and transmission dynamics. True zoonoses mapping should result from a surveillance system that integrates continuous detection and investigation of clinical human cases, animal cases, and the circulation of the strains involved. To achieve better detection, understanding, and anticipation of zoonoses-related epidemics and pandemics, we suggest setting up surveillance of cases in at-risk populations and instituting genomic surveillance to appreciate the transmission patterns and spread of zoonoses between regions or communities as well as its determinants of transmission. This necessitates a multisectoral approach involving clinicians, public health experts, animal health-related actors, and global collaboration [7]. Crucially, capacity building and networking across different countries, laboratories, and relevant agencies would facilitate the surveillance and proactiveness vis-à-vis zoonotic diseases. It is in this light that a quadripartite agreement was signed between the Food and Agriculture Organization (FAO), the World Organization for Animal Health, the UN Environment Program (UNEP) and the World Health Organization (WHO) in 2022 to strengthen cooperation to sustainably balance and optimize the health of humans, animals, plants, and the environment by leveraging on one health approaches [94].

5. Conclusions

In conclusion, (re)emerging zoonotic diseases are increasingly being reported in SSA. Having identified the priority zoonotic diseases from the published studies conducted in SSA, emphasis should now be laid on addressing the associated factors (including animal reservoirs) using a one health approach. Importantly, outbreak preparedness needs to be strengthened and contextually adapted to the local landscape of zoonotic outbreaks in this part of the world.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/zoonoticdis3040021/s1. File S1: Search strings for the retrieval of relevant literature; Table S1: Characteristics of the included studies (55 publications containing a total of 82 reports)

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