

The Incidence and Mortality of Yellow Fever in Africa – A Systematic Review and Meta-analysis

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Abstract

Background

Understanding the occurrence of yellow fever epidemics is critical for targeted interventions and control efforts to reduce the burden of disease. We assessed data on the yellow fever incidence and mortality rates in Africa.

Methods

We searched the Cochrane Library, SCOPUS, MEDLINE, CINAHL, PubMed, Embase, Africa-wide and Web of science databases from 1 January 1975 to 30th October 2020. Two authors extracted data from included studies independently and conducted a meta-analysis.

Results

Of 840 studies identified, 12 studies were deemed eligible for inclusion. The incidence of yellow fever per 100,000 population ranged from <1 case in Nigeria, < 3 cases in Uganda, 13 cases in DRC, 27 cases in Kenya, 40 cases in Ethiopia, 46 cases in Gambia, 1,267 cases in Senegal, and 10,350 cases in Ghana. Case fatality rate associated with yellow fever outbreaks ranged from 10% in Ghana to 86% in Nigeria. The mortality rate ranged from 0.1/100,000 in Nigeria to 2,200/100,000 in Ghana.

Conclusion

The yellow fever incidence rate is quite constant; in contrast, the fatality rates vary widely across African countries over the study period. Standardized demographic health surveys and surveillance as well as accurate diagnostic measures are essential for early recognition, treatment and control.

Background

Yellow fever is an acute systemic illness caused by flavivirus transmitted by infected mosquitoes belonging to the *Aedes* and *Haemogogus* species.¹ Most of the yellow fever cases identified in Africa are seen in the unvaccinated population who live in the yellow fever belt. In severe cases, this viral infection causes high fever, bleeding into the skin and death of cells in the liver and kidney.² Currently there is no treatment or cure or drugs for yellow fever but the disease can be prevented through vaccination. A yellow fever vaccine is available and administered to travelers and laboratory workers. Good in-hospital supportive treatment improves survival rate. A diagnosis of yellow fever is difficult to make as the definition for suspected cases is based on similar signs and symptoms to other diseases like malaria, typhoid, dengue fever and other haemorrhagic fevers. Laboratory diagnosis exists, but the availability and lack of diagnostic capacity are major challenges in African countries. Consequently, it is a major public health problem often underreported in Africa. Yellow fever has three modes of transmission cycles (Figure 1).

The first is sylvatic or jungle yellow fever, which happens when monkeys living in the tropical rainforest are infected through mosquitoes bites; when humans visit or work in the jungle, the virus is transmitted from monkeys to humans by mosquitoes.³ The other mosquitoes that do not have the virus become infected as they feed on the faeces of the bitten monkeys, and the cycle continues.³ The second is the intermediate yellow fever (savannah) cycle, which includes the transmission of the virus from mosquitoes to humans living or working in the jungle border areas.³ In this cycle, the virus can be transmitted from monkey to human or from human to human through mosquitoes.³ While the third is urban yellow fever, which includes the transmission of the virus between humans and urban mosquitoes, mainly *Aedes aegypti*.⁴ The virus spreads in the urban environment through humans who were infected through mosquito bites in the forest or savannah. Outbreaks are typically triggered by sylvatic and intermediate forms where the virus is transmitted when humans come into close contact with monkeys.⁴

The case fatality rate of yellow fever is high and there is no known cure for this disease.⁴ In Africa and South America, 200,000 cases of yellow fever are recorded every year of which 90% occur in Africa, causing approximately 30,000 deaths.⁵ However, the burden of yellow fever in Africa contributes to very poor economic growth in Africa. A study by Marycelin Mandu Baba and colleagues⁶ reported that persistent yellow fever outbreaks in Eastern African countries bring about significant adverse socio-economic challenges on the health system and suffering among the people. It is estimated that as many as 610 million people in 32 African countries, including more than 219 million dwelling in urban settings remain at high risk of contracting yellow fever. This is facilitated by an increase in globalisation and volume of trade.⁷

The World Health Organization (WHO) has reported few cases of yellow fever from 1980⁸, until 2016, when an upsurge in cases, to as high as 1040 at highly irregular intervals were recorded compared to cases between 1986 and 1995.⁹ However, it is uncertain whether the recent increase in number of cases is due to increased surveillance or increased disease activity in these countries.

Understanding yellow fever epidemiology as determined by its evolution is important to develop preventative measures such as immunization policies to mitigate yellow fever infection. Yellow fever cases are frequently reported in West Africa than anywhere else in the world, followed by East Africa.⁷ Major epidemics have occurred in West Africa, and epizootic yellow fever occurred for the first time in history in Kenya, East Africa, in 1992–1993.⁷ It was reported that two cases of yellow fever were imported to Europe from West Africa in recent years which had fatal outcomes, suggesting intercontinental transmission.⁷

During the 60th World Health Assembly in May 2007, yellow fever initiative was launched, with the sole aim of supporting special immunization campaigns in 12 West African countries at high risk of yellow fever epidemic (i.e. Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Ghana, Guinea, Liberia, Mali, Nigeria, Senegal, Sierra Leone and Togo).¹⁰ These countries identified target populations for vaccination to increase immunization coverage and consequently prevent outbreaks.¹⁰ Furthermore, WHO in coalition

with other organisations like the United Nations Children's Fund (UNICEF) and Global Alliance for Vaccines and Immunisation (GAVI) have developed a strategy known as 'eliminate yellow fever epidemics (EYE)'¹¹ to counter yellow fever's changing epidemiology i.e. increased risk of urban outbreaks and international spread. The aim of the strategy has been to target the most vulnerable countries, address global risks, build resilience in urban centres and increase preparedness in areas with very high potential for outbreaks and ensure reliable vaccine supply, contain outbreaks rapidly and prevent internal spread.¹¹ In December 2016, cases of yellow fever were detected in Luanda, the capital of Angola, which were previously in the category of low-risk areas for yellow fever. The disease spread rapidly from Luanda to other urban communities in Angola and crossed into the neighbouring country of the Democratic Republic of Congo (DRC).^{12, 13} This observation emphasizes the fact that yellow fever is a neglected tropical disease which needs more public health strategies to contain it coupled with more studies to be conducted in Africa to generate in-depth evidence for effective interventions.

Due to lack of reporting of yellow fever cases in Africa, the overall burden of the disease may potentially be underestimated. The WHO estimated the burden of and associated mortality of yellow fever in Africa to be between 84 000–170 000 severe cases and 29 000–60 000 deaths occurred in 2013.^{9,14} While some estimates of the burden of yellow fever exist in Africa, we could not find a published systematic review and meta-analysis on yellow fever for the entire Africa continent. Thus this review was aimed to quantify and summarize the overall burden of and fatality associated with yellow fever in Africa.

Methods

1.1 Eligibility criteria

In this review, we considered outbreak reports, cross sectional studies and other observational studies (case series, case report, epidemiological surveys, surveillance studies etc) including published and unpublished studies carried out in Africa that reported the incidence, mortality and case fatality rate of yellow fever across all age groups. We included only patients who were considered to have suspected or confirmed cases of yellow fever. Suspected cases were defined as cases that were characterized by acute onset of fever followed by jaundice within two weeks of the onset of the first symptoms¹⁵ and confirmed cases as suspected cases that were laboratory-confirmed or epidemiologically linked to a laboratory-confirmed cases or outbreaks.¹⁵ Probable cases were defined as a suspected case and one of the following: i) epidemiologically link to a confirmed case or an outbreak; ii) positive post-mortem liver histopathology.

We considered probable cases as being confirmed cases when they included any of the following: a probable case and one of the following: i) detection of yellow fever-specific IgM; ii) detection of four-fold increase in yellow fever IgM and/or IgG antibody titres between acute and convalescent serum samples, iii) detection of yellow fever virus-specific neutralizing antibodies.

All the different modes of transmission were considered and both hospital and field patients (population based) were included in this review.

1.2 Search method for identification of studies for inclusion

We exclusively searched the following databases: Cochrane library, MEDLINE, PUBMED, Embase, SCOPUS, CINAHL (EBSCOhost), Africa-wide (EBSCOhost) and Web of science (SCI-EXPANDED) for studies published from 1 January 1975 to 30 October 2020 including unpublished studies. Subject specific search terms “outbreak”, “Burden of disease”, Incidence, Prevalence, Survey, Surveillance, Epidemic, Epidemiology, “yellow fever”, “yellow jack”, “yellow fever vaccines”, vaccination”, seroprevalence, “haemorrhagic fever”, “Jungle fever,” “cross sectional studies”, Africa, individual African country names such as, “North Africa”, “West Africa,” “Central Africa”, “East Africa”, “Southern Africa”, and “Sub-Saharan Africa”, “under developed countries”, “Developing countries”, “low income economy”, were used. Also, regional grouping such as sub-Saharan Africa and West Africa were also used to look for studies indexed under regional names. Medical Subject Heading (Mesh) terms were used in PubMed search.

We searched abstract presentations on yellow fever from medical conferences such as International Society for Infectious Diseases (ISID), and other Global Experts Meetings on Infectious Diseases. We also consulted an expert librarian at Stellenbosch University, South Africa, to improve and sharpen the search strategy (Supplementary Table 1). We identified other eligible studies by searching the reference list of included studies. We also hand searched journals through their websites such as the South African Medical Journal (SAMJ), African Journal of Infectious Diseases, Emerging Infectious Diseases, Southern African Journal of Infectious Diseases, Pan African Medical Journal and Lancet Infectious Diseases Journal.

1.3 Data extraction

Two review authors independently and in duplicate screened titles and abstracts and selected studies for inclusion in this review using the set eligibility criteria. The identified studies were retrieved for full texts and included in the review after re-screening. Any discrepancies were resolved by consensus or by a third reviewer. We independently and in duplicate extracted the data on the following: burden of disease, characteristics of the participants, study setting, study design, date of study, study location. Risk of bias was assessed for each of the included studies using the validated quality appraisal tool developed by Hoy and colleagues (Supplementary Table 3).¹⁶ We assessed each domain as either low or high risk of bias and regarded studies which were unclear as high risk of bias. We scored the overall risk of bias according to the number of high risk of bias parameters per study: low (1-3), moderate (4-6) and high (7-9).

1.4 Data synthesis and management

All included studies focused on incidence, case fatality rate (CFR), and mortality. We calculated incidence by dividing the number of confirmed and suspected cases by the total population in that region and expressed it per 100,000 population. We calculated 95% CI for the incidence using the standard formula for calculating the standard error of a proportion, per 100,000, that is,

$$\sqrt{\frac{p(100000 - p)}{n}}$$

where p = incidence (per 100,000), and n = sample size. We assumed normality of the incidence statistic and used the critical value of 1.96 while calculating the 95% confidence intervals. We calculated CFR by dividing the number of deaths from yellow fever over a defined period of time by the number of individuals diagnosed with yellow fever then multiplied by 100 to yield a proportion. Mortality rate was calculated by dividing the number of deaths by the total population and then multiplied by 100,000.

We performed random-effects meta-analysis due to the variability in incidence estimates from different countries. We assessed heterogeneity using both the Chi-square test ($p < 0.10$ considered significant) and the I-square test statistic ($> 50\%$ considered significant).¹⁷ We investigated sources of heterogeneity through subgroup analysis with respect to the country of study.¹⁶ Heterogeneity was also explored by examining the potential differences in the characteristics of the population such as the settings and other characteristics in the 'Characteristics of included studies' table. We performed meta-analyses using STATA version 15 and displayed results using forest plots. However, due to significant heterogeneity in meta-analyses for incidence rate and CFR, we elected to report results narratively per study per country. The meta-analysis for mortality rate was not possible due to insufficient data; the results for the mortality rate were reported narratively.

Results

2.1 Identification of studies for review

We identified 839 studies from electronic search of five databases. After removing duplicates, we screened the titles and abstracts of 493 published articles and excluded 464 studies. We retrieved the full texts of the remaining 29 studies and excluded 12 of these studies^{1, 7, 12, 18-26} because they either did not report on the yellow fever burden or were from non-African countries. From the 17 studies that reported on yellow fever incidence, we excluded five more studies^{21, 24-27} because they only reported on the evaluation of yellow fever vaccine without reporting data on yellow fever burden. We finally included 12 studies (Figure 2).^{2, 31-41}

2.2 Characteristics of included studies

A summary table of characteristics of the included studies is presented in the appendices (Supplementary Table 2) We categorized studies based on year of assessment, test methods implemented for confirming the diagnosis of yellow fever, and clinical case definition used. The number of studies published each year increased modestly from 1975 to 2018. Although studies originated from eight African countries, three studies were from Nigeria³²⁻³⁴, two studies each from Senegal^{36,37} and Uganda^{38,41} and one study from each of the five countries, Kenya³⁵, Ethiopia³⁹, Ghana³¹, Gambia² and DRC⁴⁰. The majority of studies 'Seven', were from West Africa^{2,31-37} 'Three' studies from East Africa^{35,38,41}, 'One' from North Eastern Africa³⁹ and 'One' studies from Central Africa.⁴⁰ All the three modes of yellow fever transmission considered in this review were reported by at least one study. Eight studies reported that the outbreak was due to sylvatic mode of transmission^{2,32,35-39,41}, two studies reported that it was due to an urban mode of transmission^{33,40} and only one study reported the intermediate mode of transmission.³⁹

Ten of the studies^{2,31-34,36-41} were reported from hospital and field-based surveillance studies while two studies^{35,38} were only in-hospital-based surveillance studies. Nine studies^{2,31-34,36,37,39,41} included participants of all ages while four studies reported the disease in specific age groups such as from 10-70 years³⁵, 3 months -83 years³⁸, 3-64 years⁴¹ and 10-72 years⁴⁰, respectively. Nine of the included studies^{2,31,34-39,41} were conducted in rural areas, two^{33,40} in urban areas and one³⁹ in mixed rural/urban setting. The population was reported in all the studies to live on subsistence farming, growing several crops and rearing livestock as well. Most of the people practice domestic water storage except for one of the studies³⁷ that reported that the people practice less livestock rearing and less domestic water storage while one of the studies⁴⁰ did not report on any of the above. Rainy season and increased breeding sites were reported in all the studies to be a risk factor for yellow fever epidemic as these can increase the mosquito population. However, two studies^{36,41} did not attribute the outbreak to the rains but reported that the people were in contact with the forest after returning from the Internally Displaced Persons camps, having to clean their homes when they returned after two years and the multiple natural breeding sites for mosquitoes, respectively, led to the outbreak. All the included studies also reported that yellow fever was confirmed using viral serology by doing ELISA and identifying IgM to yellow fever virus, and virus isolation. Some of the studies for instance^{33,35} reported that histopathology on liver specimens were done. One study,³¹ reported that test for antibody neutralization was not done.

The duration of the outbreak lasted for 11 months in Ethiopia³⁹ followed by Gambia which lasted for 8 months.² Outbreaks in DRC⁴⁰, Kenya³⁵, and Nigeria³² lasted for 7, 6 and 5 months, respectively. One of the studies reported from Nigeria³³ recorded that the outbreak lasted for 4 months. One study from Senegal³⁶ reported 2 months while the other study from Senegal³⁷ reported only one month. The other studies reported that the outbreak lasted for 3 months^{33,36,37}, while the study done in Ghana did not report the duration of the outbreak.³¹

2.3 Assessment of risk of bias of included studies.

We evaluated all the studies in ten different domains using the risk of bias tool¹⁶ and our summary assessment was low risk of bias for ten studies (83.33%)^{2, 32-39, 41} and moderate risk of bias for 2 studies (16.67%) (Supplementary Table 3).

2.4 Incidence of Yellow Fever

Meta-analysis of yellow fever incidence estimates from different studies and countries resulted in significant heterogeneity ($I^2=99.4\%$, $P<0.001$, Figure 3) and therefore we report narrative results per study. The two studies from Uganda found very low incidence of less than 3 and 13 cases per 100,000 population respectively, Kenya <30 cases per 100,000, Ethiopian 40 cases per 100,000, In Gambia < 50 cases per 100,000, Nigeria the incidence ranged from <1 to over 80 cases per 100,000 population. The two studies in Senegal found incidence rates of approximately 1,300 and 5,900 cases per 100,000 population while Ghana found the highest incidence which ranged between 320 to over 10,000 cases per 100,000 population (Figure 3).

2.5 Case Fatality Rate

Meta-analysis of CFR (in %) resulted in significant heterogeneity ($I^2=95.6\%$, $P<0.001$, Figure 3) and therefore we report results narratively per study. The only study from DRC had the lowest CFR of just over 10%. The Ethiopian study found a CFR of slightly over 30%, the two studies from Uganda found CFRs of just over 30% each, while the one study from Gambia found a CFR of less than 30%. The CFRs in different regions of Ghana ranged from just over 16% in Volta Region to almost 40% in Brong Ahafo. The two Senegal studies found high CFRs of 28% and 42%, while the Kenyan study found a higher CFR of over 60%. Lastly, the Nigerian studies found varying CFRs from 11% to 85% (Figure 4).

2.6 Mortality Rate

We could not perform meta-analysis of mortality rate because the population sizes were not reported by most included studies. The results also differed widely such that a meta-analysis would likely result in high heterogeneity. We therefore reported the results narratively for each study. The two studies from Senegal had high mortality rates ranging from over 500 to almost 1,700 deaths per 100,000. The Ethiopian and Kenyan single studies had low mortality rates of 12 and 17 deaths per 100,000 population. In Uganda, the mortality rates were even lower, ranging from less than 1 to 4 deaths per 100,000 population. In Gambia, it was 12 deaths per 100,000 population. In Ghana, the mortality rate ranged from just over 50 in Volta Region to over 2,200 deaths per 100,000 population in the Eastern Region. The one study in DRC found a low mortality rate of 1 death per 100,000 population. Lastly, the studies from Nigeria found mortality rates ranging from 0.2 deaths per 100,000 population in Kwara State to more than 44 deaths per 100,000 population in South Eastern Nigeria.

Discussion

We carried out this systematic review with the objective of estimating the incidence and associated mortality of yellow fever in Africa. We found 12 studies from 8 countries in Africa, showing that studies are scarce in yellow fever-endemic African countries. We found in studies in Nigeria³²⁻³⁴ Uganda^{38, 41} Senegal^{36, 37} Kenya³⁵, Ethiopia³⁹, Gambia², Ghana³¹ and Democratic Republic of Congo⁴⁰. 'Eight' studies were undertaken more than twenty years ago, and only 'Four' studies were recent. This shows there is scarcity of data, thereby making the true estimation of yellow fever incidence difficult in Africa. However, data found shows that yellow fever is a disease of the East and West African countries. Ten studies were hospital and field-based surveillance and the remaining two studies were based on hospital-initiated surveillance system. We found that incidence of yellow fever varies in different countries. The incidence of yellow fever was highest in Senegal ^{36, 37} (1300 – 5900/100000 followed by 320/100000 in Ghana³⁰ and lowest in Uganda with a range of 3 -13/100000 ^{38, 41}. The reason for this increase could be due to an improved surveillance reporting system. Case fatality rate was highest (60%) in Kenya and ranged from 11% to 85% in Nigeria while DRC had the lowest case fatality rate of over 10%.^{33, 35, 40} Finally, mortality rate was highest in Senegal ^{36, 37} 500 – 1700 deaths/100000, Uganda^{38, 41} had a low mortality rate of less than 1 to 4 deaths /100000 while Nigeria ranged from 0.2 to 44 deaths /100000 ^{32, 33, 34}. These findings could also be as a result of better surveillance system and global awareness now compared to what we had previously. Some studies report that a combination of some factors like socioeconomic, demographic and ecological circumstances favoured the high incidence of yellow fever in Africa.⁴² Other authors have indicated that Africa monkey are resistant to the yellow fever virus and if they become infected they usually do not die but rather become immune and humans become accidentally infected during their short forest activities. ⁴² Usually African population are at a higher risk of the disease because of very low immunity. This is due to low vaccination coverage and also linked to their daily activities and occupation such as farming, deforestation, and cattle grazing, which bring them in close proximity to the forest where the vectors live.

From the studies that we included in this review, the outbreaks that occurred were due to sylvatic mode of transmission which involves the virus passed on between non-human primates (e.g., monkeys) and mosquito species found in the forest canopy.^{31-34, 37-39, 41} Yellow fever is endemic in the sylvatic settings in Africa predominantly in East and West Africa. The sylvatic mode of transmission gives a more regular epidemic pattern as opposed to urban transmission which often gives a periodic and more unpredictable outbreak. This information is ideal as it would help policy makers focus the strategies on how best to fight the regular clustering of yellow fever epidemic. Some of these strategies would include using an integrated mosquito management (IMM) ⁴³ program steps such as: i) surveillance: this will help detect the different mosquito species in a given area and with this data, they are able to effectively time larvicide and adulticide activities; ii) public education: this includes educating the general public on how to control mosquito breeding sites at their backyard; iii) larval and adult mosquito control: inspecting sources of standing water looking for mosquito larval so as to eliminate them before they become adults that can transmit the virus while the adult mosquitoes are treated using pesticides. We also noticed that yellow fever is endemic with the outbreaks occurring during rainy season. It is known that rainy season

increases the breeding sites and the mosquito population which transmit the disease. Hence heavy and prolonged rainfall result in high vector population due a favorable breeding environment for mosquitoes due to heavy rainfall during rainy season. This provides adequate ground to support continued circulation of the virus especially in the sylvatic cycle.

Previously, prevention of this disease was done through vector control which was very effective in reducing the occurrence of the disease. However, smaller outbreaks occur due to changes in the distribution of the disease and currently, vaccination strategies such as routine infant immunization, mass vaccination campaigns and vaccination of travelers going to yellow fever endemic regions are used to protect people against these outbreaks. Yellow fever vaccine called 17D is known for preventing the disease and just a single dose of the vaccine confers immunity and lifelong protection. The vaccine provides effective immunity within 10 days for 80 -100% of people vaccinated, and within 30 days for more than 99% of people vaccinated.⁴ Most African countries where yellow fever is endemic have included yellow fever vaccine in the Expanded Programme on Immunization schedule for new-born babies. Most of the yellow fever cases identified in Africa are seen in the unvaccinated population who live in the yellow fever belt. Some countries have sustained epidemics across multiple years like Ghana (1977–83), Guinea (2000–2005), Nigeria (1986–1994) and Congo (2011-2013).⁴⁵ Looking at previous data on yellow fever over a period of 25 years in Africa, showed that yellow fever has been persistent in West and Central Africa.⁴⁵ In East Africa, yellow fever has mostly been in Kenya ⁴⁵ However cases were also reported in Uganda and Ethiopia. The estimated annual provincial incidence in 32 African countries known to be endemic for yellow fever varied from 0.7% to 10% ⁴⁵ which is low compared to the overall incidence rates found by this systematic review. A recent study reported that in 2018 there were approximately 109,000 (95% CI 67,000 -173,000) severe infections and 51,000 (95%CI (31,000 - 82,000) deaths due attributed to yellow fever in DRC and Amazon region.⁴⁶

In addition, the highest burden was seen in the DRC due to a high force of infection and low vaccination coverage.⁴⁶ Both the incidence and fatality rates found in this study are high compared to our findings. The review has shown that yellow fever incidence seems to have been pretty constant throughout African countries over the inclusion period of the review. However three of the studies included showed high incidence rates.^{31, 36, 37} In contrast, the fatality rates varied widely across African countries over the same period of the review. Since most of the studies were conducted between 1984 and 1998, moderately high vaccination coverage rates across much of western and central Africa in the 1970s were the result of mass preventive campaigns in the 1940s to the 1960s,^{47, 48} which reduced the number of outbreaks⁴⁷. Coverage declined between 1960 and 2000 in most areas due to limited vaccination activity, the birth of new unvaccinated cohorts, a steady decline in the proportion of older covered cohorts through mortality ⁴⁷ and vaccine stock shortages, which have been frequently reported in the African region.¹¹ Past public health successes led to a lax in maintaining local yellow fever vaccination coverage leading to waning herd immunity and an eventual re-emergence of large outbreaks in West Africa in the 2000s. ^{48, 49}

In fact, yellow fever may not easily be eliminated due to the presence of non-human wildlife reservoirs that sustain the sylvatic transmission cycle of the virus in non-urban settings, however the risk of a yellow fever outbreak can be eliminated if successful vector control, vaccination and surveillance of the disease are implemented and maintained.⁴⁸ The joint effort by the WHO, the UNICEF, the Global Alliance for Vaccinations and Immunization (GAVI) and yellow fever virus (YFV) endemic countries created the Yellow Fever Initiative (YFI) in 2006⁵⁰, which focused primarily on widespread yellow fever vaccination initiatives and the implementation of childhood immunization vaccine. In the context of an emergency preparedness effort, this initiative has created an opportunity for global stock of yellow fever vaccines.^{13, 51} The 17D yellow fever vaccine is effective, safe, affordable, readily available, and can prevent the disease with just a single dose being sufficient enough to confer sustained immunity and lifelong protection.

The review has limitations the main one being paucity of yellow fever incidence/prevalence data from different African countries. The incidence estimates from the different studies were significantly heterogeneous and there were not enough data from the studies to determine the sources of this heterogeneity, but could have been due to the different geographical nature in Africa, seasons, settings (rural or urban), different populations, statistical methods and regional differences. Studies included in this review were fewer hence limiting the scope of to generate a more accurate estimates of the burden of yellow fever in African regions. Secondly most of the included studies were predominantly from East-West Africa, hence understanding the burden of yellow fever in other regions is restricted.

The risk of bias assessment showed that 83% of studies showed to have a low risk of bias, however included studies might not have been representative of a larger population. Furthermore, in most of the included studies, the number of confirmed and suspected cases were not clearly distinguished. As such this limits generalizability of the incidence and case fatality rate estimates to a larger African population.

Conclusions

This systematic review identified twelve observational studies assessing yellow fever incidence and fatality rates in Africa. Data shows that yellow fever incidence rate is quite constant across African countries with high incidence rates reported in three studies of the 12 studies. The case fatality rates for yellow fever varied widely across Africa. However the lack of reliable epidemiological data on yellow fever in Africa compromises the public health priority that could give rise to yellow fever infection.

For that reason it is essential to provide standardized demographic health surveys as a *population surveillance* strategy to track the burden of yellow fever as well as accurate diagnostic measures for early recognition and treatment of yellow fever. Knowing that yellow fever usually re-emerges in rural areas, rural facilities should be enforced in yellow fever prevention, management and reporting approach. Timely and accurate diagnosis of yellow fever could avoid untoward case fatality rates and minimize under-reporting. Accurate yellow fever data is substantial for good public health policy and guide planning of vaccine volumes and delivery system. In addition public health control strategy should focus

on strengthening yellow fever prevention including incorporating yellow fever immunization schedules in African endemic countries and mandatory reporting of cases in primary, secondary and tertiary levels. Future research should focus on evaluating yellow fever immunogenicity in children.

Declarations

Authors contribution: AN, PN, EZS developed the protocol. AN and EZS screened, selected studies and extracted data for this review. AM performed data and results interpretation. AN, PN drafted the manuscript. JLT critically reviewed the manuscript and wrote other sections of the review. All authors read and approved the final manuscript.

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References

1. Kwallah AO, Inoue S, Thairu-Muigai AW, et al. Sero-prevalence of yellow fever virus in selected health facilities in Western Kenya from 2010 to 2012. *Japanese Journal of Infectious Diseases*. 2014; 68(3): 230–4.
2. Monath TP, Craven RB, Adjukiewicz A, et al. Yellow fever in the Gambia, 1978–1979: epidemiologic aspects with observations on the occurrence of orungo virus infections. *The American journal of tropical medicine and hygiene*. 1980; 29(5): 912-928.
3. *Transmission of Yellow Fever Virus*. Atlanta: Centers for Disease Control and Prevention; 2019
4. WHO (2016). Fractional dose yellow fever vaccine as a dose-sparing option for outbreak response: WHO Secretariat information paper (No. WHO/YF/SAGE/16.1). Geneva: World Health Organization; 2016.
5. Mutebi J.P and Barrett A.D The epidemiology of yellow fever in Africa. *Microbes and infection*. 2002; 4(14):1459-1468.
6. Baba MM and Ikusemoran M. Is the absence or intermittent YF vaccination the major contributor to its persistent outbreaks in eastern Africa?. *Biochemical and biophysical research communications*. 2017; 492(4): 548-557.

7. Gubler DJ. The global emergence/resurgence of arboviral diseases as public health problems. 2002, Archives of medical research. 2002; 33(4): 330-342.
8. Legesse M, Endale A, Erku W, et al. Community knowledge, attitudes and practices on Yellow fever in South Omo area, Southern Ethiopia. PLoS Negl Trop Dis. 2018;12(4):e0006409.
9. Marlow MA, de Feliciano Pambasange MAC, Francisco C, et al. Notes from the field: knowledge, attitudes, and practices regarding yellow fever vaccination among men during an outbreak—Luanda, Angola, 2016. MMWR. Morbidity and Mortality Weekly Report. 2017; 66(4): p.117.
10. Monath TP, Nichols R, Archambault WT, et al. Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III multicenter, double-blind clinical trial. Am J Trop Med Hyg. 2002; 66(5):533–41.
11. Eliminate yellow fever epidemics (EYE): a global strategy, 2017–2026. Geneva: World Health Organization; 2018
12. Kraemer M U, Faria N R, Reiner JRC, et al. Spread of yellow fever virus outbreak in Angola and the Democratic Republic of the Congo 2015–16: a modelling study. The Lancet infectious diseases. 2017; 17(3): 330-338.
13. Bifani AM, Ong EZ, de Alwis R. Vaccination and Therapeutics: Responding to the Changing Epidemiology of Yellow Fever. Curr Treat Options Infect Dis. 2020; 12:349-360.
14. Yellow fever. Geneva: World Health Organization; 2019
15. Ingelbeen B, Weregemere NA, Noel H, et al. Urban yellow fever outbreak—Democratic Republic of the Congo, 2016: Towards more rapid case detection. PLOS Negl. Trop. Dis. 2018; 12(12): e0007029.
16. Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. Journal of Clinical Epidemiology. 2012; 65(9): 934-939
17. Schroll JB, Moustgaard R, Gøtzsche PC. Dealing with substantial heterogeneity in Cochrane reviews. Cross-sectional study. BMC medical research methodology. 2011; 11: 22.
18. Tsai TF, Lazuick JS, Ngah RW, et al. Investigation of a possible yellow fever epidemic and serosurvey for flavivirus infections in northern Cameroon, 1984. Bulletin of the World Health Organization. 1987; 65(6): 855–60.
19. Onyango CO, Grobbelaar AA, Gibson GVF, et al. Yellow Fever Outbreak, Southern Sudan, 2003. Emerging infectious diseases. 2004; 10(9):1668.
20. Ellis BR and Barrett AD. The enigma of yellow fever in East Africa. Reviews in medical virology. 2008; 18(5): 331-346.
21. Wiysonge CS, Nomo E, Mawo J, et al. Yellow fever control in Cameroon: Where are we now and where are we going? BMC medicine. 2008; 6(1): 3.
22. Farnon EC, Gould LH, Griffith KS, et al. Household-Based Sero-Epidemiologic Survey after a Yellow Fever Epidemic, Sudan, 2005. The American journal of tropical medicine and hygiene. 2010; 82(6): 1146–52.

23. Attoh-Touré H, Dagnan, NS, Tagliante-Saracino J. Resurgence of yellow fever epidemics in Côte-d'Ivoire. *Bulletin de la Société de Pathologie Exotique*. 2010; 103(5): 323-326.
24. Green A. Yellow fever continues to spread in Angola Health workers in Angola warn that although the number of newly confirmed cases of yellow. *Lancet*. 2015; 387(10037): 2493.
25. Grobbelaar AA, Weyer J, Moolla N, et al. (2016) Resurgence of Yellow Fever in Angola, 2015 – 2016. *Emerging Infectious Diseases*. 2016; 22(10): 1854
26. Nishino K, Yactayo S, Garcia E, et al. Yellow fever urban outbreak in Angola and the risk of extension Flambée urbaine de fièvre jaune en Angola et risque d' extension. *Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire*. 2016; 91(14):186-190.
27. Markoff L. (2013). Yellow fever outbreak in Sudan. *New England Journal of Medicine* 368(8), 689-691.
28. Nogodalla MA. Yellow fever outbreak investigation and response, Darfur State, Sudan, September-November 2012. *International Journal of Infectious Diseases*. 2014; 21: 259.
29. Rachas A, Nakouné E, Bouscaillou J, et al. Timeliness of yellow fever surveillance, Central African Republic. *Emerging infectious diseases*. 2014; 20(6): 1004.
30. Tsegaye MM, Beyene B, Ayele W, et al. Sero-prevalence of yellow fever and related Flavi viruses in Ethiopia: a public health perspective. *BMC public health*. 2018; 18(1): 1011.
31. Agadzi VK, Boatman BA, Appawu MA, et al. Yellow fever in Ghana, 1977-80. *Bulletin of the World Health Organization*. 1984; 62(4): 577.
32. De Cock KM, Nasidi, A, Enriquez J, et al. Epidemic yellow fever in eastern Nigeria, 1986. *The Lancet*. 1988; 331(8586): 630-633.
33. Nasidi A, Monath TP, DeCock K, et al. Urban yellow fever epidemic in western Nigeria, 1987. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1989; 83(3): 401-406.
34. Yellow fever: Investigation of an epidemic in Imo State. *Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire*. 1995; 70(15):107-110.
35. Sanders EJ, Marfin AA, Tukei PM, et al. First recorded outbreak of yellow fever in Kenya, 1992-1993. I. Epidemiologic investigations. *The American journal of tropical medicine and hygiene*. 1998; 59(4): 644-649.
36. Thonnon J, Fontenille D, Tall A, et al (1998) Re-emergence of yellow fever in Senegal in 1995. *Am J Trop Med Hyg*. 1998; 59(1): 108–14.
37. Thonnon J, Spiegel A, Diallo M, et al. Yellow fever outbreak in Kaffrine, Senegal, 1996: epidemiological and entomological findings. *Tropical Medicine and International Health*. 1998; 3(11): 872-877.
38. Wamala JF, Malimbo M, Okot CL, et al. Epidemiological and laboratory characterization of a yellow fever outbreak in northern Uganda, October 2010–January 2011. *International Journal of Infectious Diseases*. 2012; 16(7): e536-e542.

39. Lilay A, Asamene N, Bekele A, et al. Reemergence of yellow fever in Ethiopia after 50 years, 2013: epidemiological and entomological investigations. *BMC infectious diseases*. 2017; 17(1): 1-6.
40. Otshudiema JO, Ndakala NG, Mawanda EK, et al. Yellow Fever Outbreak -Kongo Central Province, Democratic Republic of the Congo, August 2016. *MMWR Morb Mortal Wkly Rep*. 2017; 66(12): 335–8.
41. Kwagonza L, Masiira B, Kyobe-bosa H, et al (2018) Outbreak of yellow fever in central and southwestern Uganda, February – May 2016. *BMC infectious diseases*. 2018; 18(1): 548.
42. Chippaux JP and Chippaux A. Yellow fever in Africa and the Americas: a historical and epidemiological perspective. *Journal of Venomous Animals and Toxins including Tropical Diseases*. 2018; 24(1):1-14.
43. Detection and investigation of serious adverse events following yellow fever vaccination, Guidance from an informal consultation of experts, 18–19 November 2008. Geneva: World Health Organization; 2008
44. Pezzoli L. Deployments from the oral cholera vaccine stockpile, 2013–2017. *Wkly Epidemiol Rec*. 2017, 92(32): 437-42
45. Garske T, Van Kerkhove MD, Yactayo S, et al. Yellow Fever in Africa: estimating the burden of disease and impact of mass vaccination from outbreak and serological data. *PLoS medicine* 2014;11(5): e1001638.
46. Gaythorpe KAM, Hamlet ATP, Jean K, et al (2020) The global burden of yellow fever. *Medrxiv*. 2020; <https://doi.org/10.1101/2020.10.14.20212472>
47. Durieux C. Mass yellow fever vaccination in French Africa south of the Sahara. *Yellow Fever Vaccination, Monograph Series*. 1956; 30:115-21.
48. Shearer FM, Moyes CL, Pigott DM, et al Global yellow fever vaccination coverage from 1970 to 2016: an adjusted retrospective analysis. *The Lancet infectious diseases*. 2017; 17(11): 1209-17.
49. Rogers DJ, Wilson AJ, Hay SI, Graham AJ. The global distribution of yellow fever and dengue. *Advances in parasitology*. 2006; 62:181-220.
50. Yellow fever initiative: providing an opportunity of a lifetime. Geneva: World Health Organization; 2010
51. WHO . International coordination group on vaccine provision for yellow fever: report of the annual meeting. Geneva: World Health Organization, 12 September 2019; 2020.

Figures

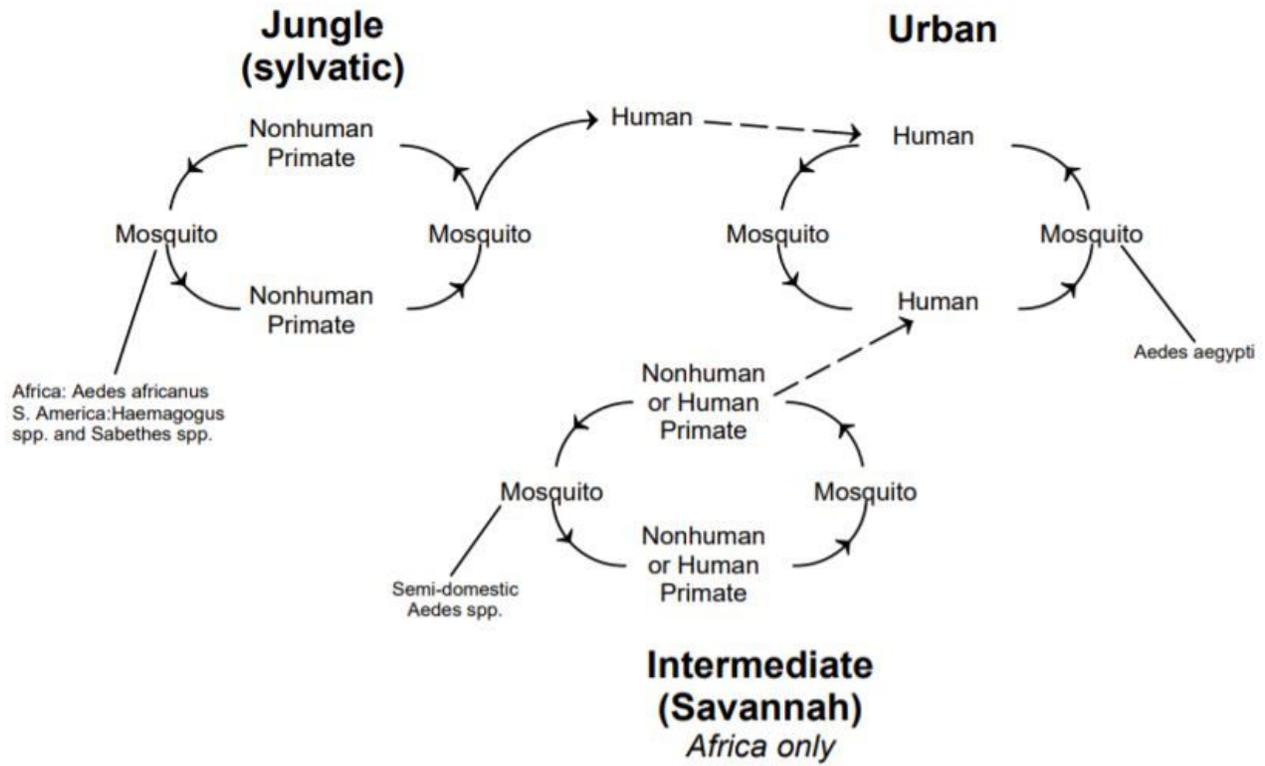


Figure 1

Transmission cycle of yellow fever virus

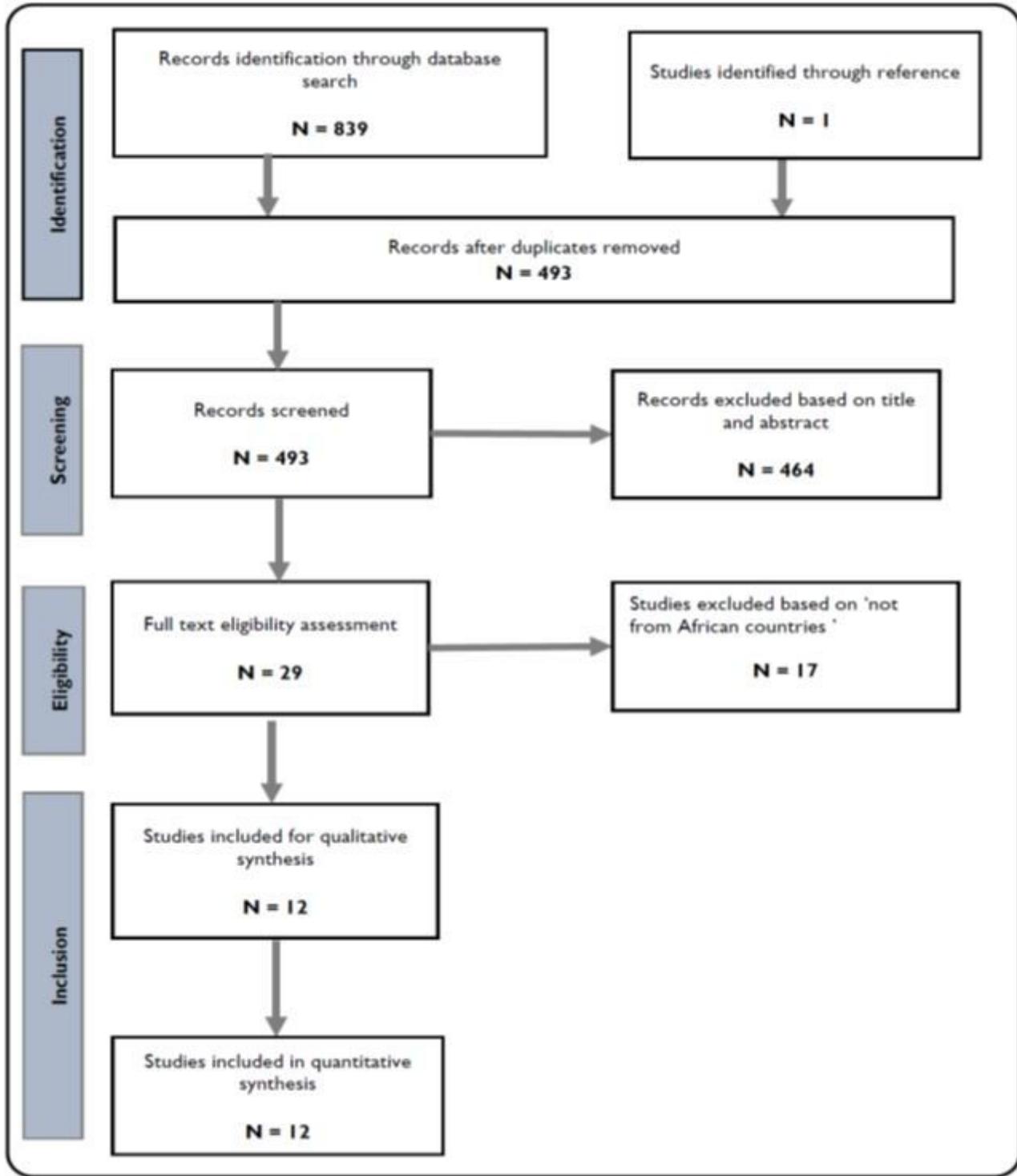


Figure 2

PRISMA flow diagram showing results of studies on yellow fever in Africa.

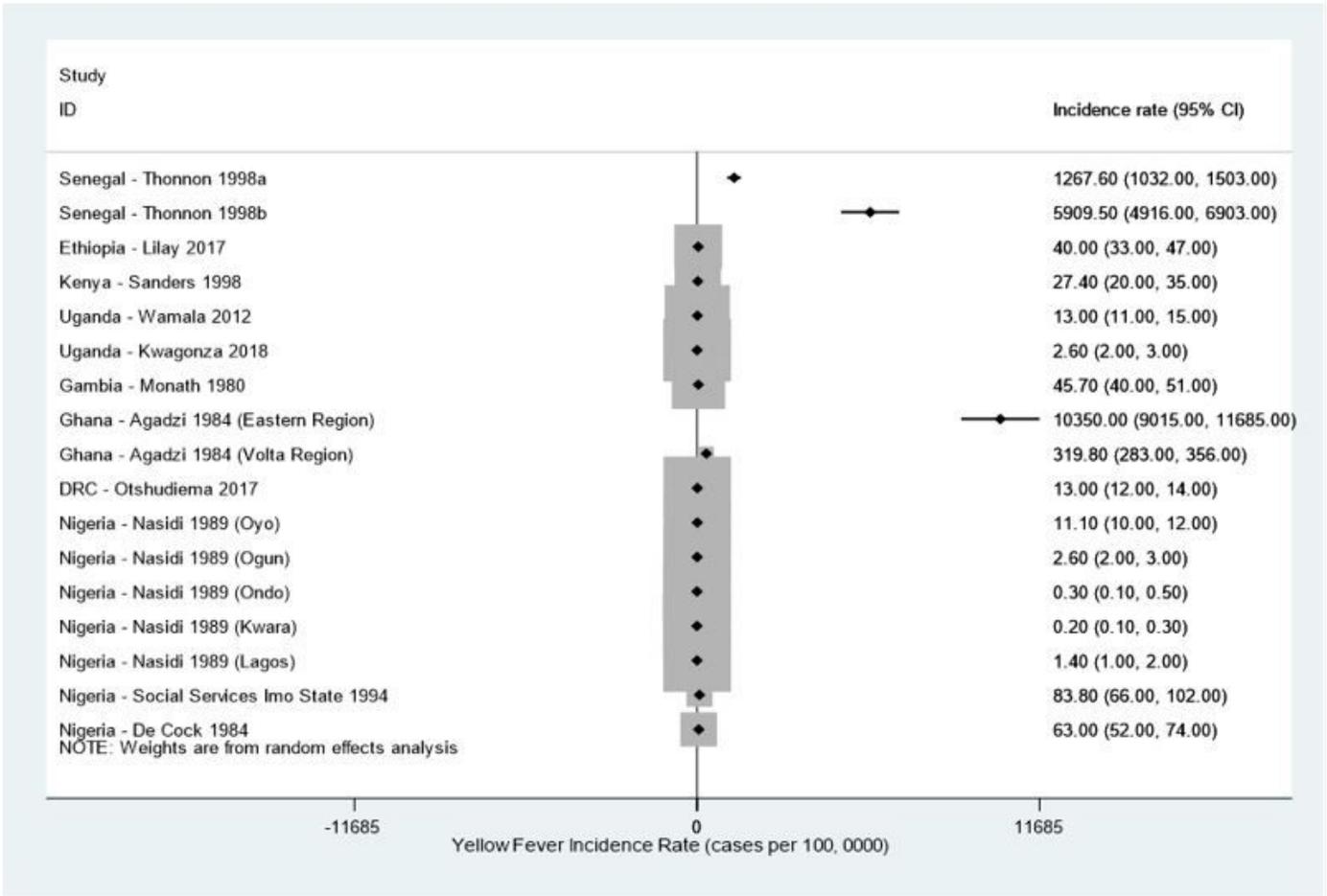


Figure 3

Forest plot showing incidence rates (cases per 100,000) of yellow fever in Africa.

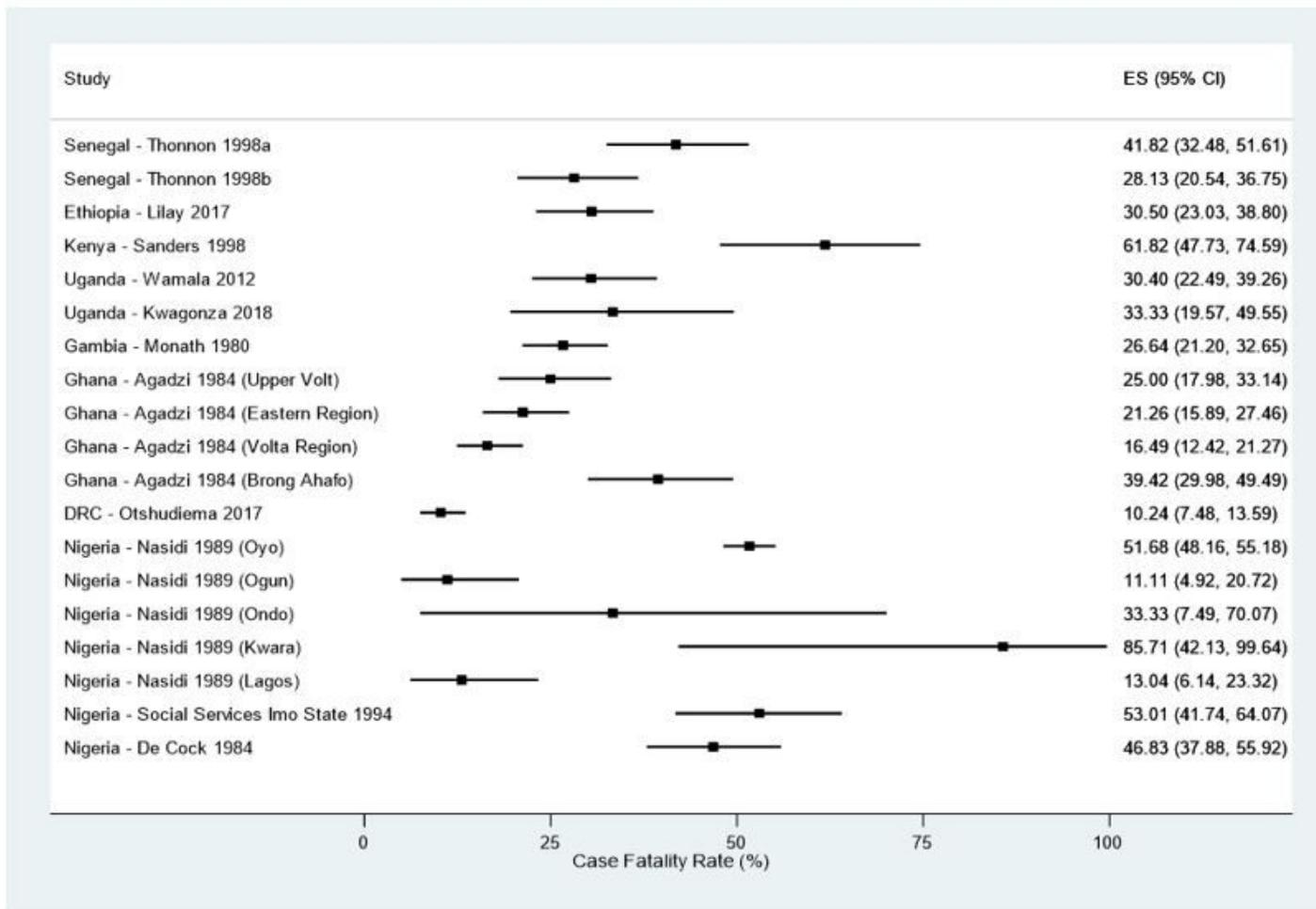


Figure 4

Forest plot showing case fatality rates associated with yellow fever outbreaks in Africa.

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