Review Paper:

A Systematic Review and Meta-analysis of Sex Differences in Morbidity and Mortality of Acute Lower Respiratory Tract Infections Among African Children

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ABSTRACT

Context: Although biological sex influences Acute Lower Respiratory Tract Infections (ALRIs) morbidity and mortality patterns in children living in sub-Saharan Africa, the exact mechanism about the effect is unknown.

Objective: We assessed the quality and strength of evidence on the association of sex with incidence, etiology, and outcomes of ALRI in African children.

Data Sources, Study Selection, and Data Extraction: We systematically searched electronic databases for publications from 1971-2016 in PubMed, African Journals Online, and Google scholar for ALRI literature in the African children. We used (pneumonia OR bronchiolitis OR "community-acquired pneumonia" OR CAP OR "hospital-acquired pneumonia" OR "nosocomial pneumonia" OR "ventilator-acquired pneumonia" OR "lung abscess" OR "pleural effusion" OR "empyema thoracis") AND (sex OR gender) AND (Africa OR Sub-Saharan) as search terms. We included the published peer-reviewed journal articles reporting on incidence, etiology, and case fatality. We summarized the findings using narrative and meta-analysis methods.

Results: We included 14 studies with sex-related data; the median (IQR) number of reported pneumonia cases was 148 (87-770) and 114 (56-599) for male and female patients, respectively. Only two studies reported a sex-specific incidence. The odds of sex were in favor of male sex, and the chances of identification of Respiratory Syncytia Virus (RSV) were significantly lower in males than in females (OR=0.60; 95% CI: 0.42, 0.86). Estimates from 9 studies showed that the death rate for males was significantly higher than for females (OR=1.26; 95% CI=1.20–1.33).

Conclusions: Sex-disaggregated data on incidence, etiology, and case fatality of pneumonia are scarcely reported in studies published in Africa. However, males appear to die more often than females, and females more likely to have RSV infection.

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1. Context

Lower respiratory tract infections (LRTIs) are common diseases in children worldwide, accounting for high morbidity, hospital admissions, and healthcare costs, especially in developing countries (1). In children aged 1-59 months, pneumonia accounts for about 1.071 million deaths (range: 0.977–1.176), which comprise 14.1% of all-cause mortality. Pneumonia along with diarrhea (9.9%; 0.751 million death, range: 0.538–1.031), and malaria (7.4%; 0.564 million death, range: 0.432–0.709) are among the three most common diseases claiming most lives of children <5 years of age (2). Although the global mortality rate among children aged <5 years is declining, there are marked variations in the magnitude and trends across regions and countries of the world, and the mortality rates range from 8% to 15% among African children (3-5). Generally, the highest overall mortality rates were reported from studies on children with either HIV, severe malnutrition, unvaccinated, and very severe pneumonia (3, 6, 7).

Recently, sustainable solutions to the high number of child deaths associated with LRTI have been advocated through management (8) and prevention of pneumonia (9, 10). It is, therefore, essential to know the incidence, likely etiological agents, and burden of LRTI mortality in Africa as it relates to demographic risk factors (11, 12). Conventional knowledge maintains that male children develop LRTIs more frequently than females, and are at higher risk of mortality and morbidity (13). Despite these assumptions, epidemiological data on the evidence of sex differences for LRTI in children in sub-Saharan Africa are strikingly limited. In a review of the 52 studies on LRTI, published by Falagas (13) in 2007, only 7 were carried out on children, and none was done in Africa. Even for non-African countries, the association between sex and LRTI has been inconsistently reported. More recently, Jackson's systematic review found that the odds of having severe ALRI was 1.5 (95% CI: 1.0 to 2.3) times higher in males than females, but only one included report was from Africa (14).

2. Objective

To date, no systematic review of published literature has assessed the relationship between sex and LRTI in African children. This review aimed to determine the quality of available evidence systematically and to present summary estimates of the strength of the association of sex with the incidence, etiology, and outcomes of LRTI in children using narrative and meta-analysis methods.

Protocol registration and data sources

The protocol for this systematic review has been approved and registered with PROSPERO (CRD42019122494). We searched for literature on acute lower respiratory infections in African children using (https://www.ncbi.nlm.nih.gov/pubmed/), African Journals Online (www.ajol.info), and Google scholar (https://scholar.google.co.za/) from 1971-2016. These databases were searched for studies that report data on the incidence, etiology, and outcomes of LRTI for both male and female children. The terms used and details of the search steps were presented in Table 1 and Table 2.

Study selection and eligibility criteria

We included the published peer-reviewed journal articles reporting data on any of our outcomes of interest, namely incidence, etiology, and case fatality. The titles and abstracts of the articles that were initially identified have been reviewed, to select studies with objectives or focus on our desired results, for a more detailed examination. The decision to include a study was based on whether the data on the incidence, etiology, and case fatality of acute LRTI were included in the abstract or body of the article. Subsequently, each eligible article was read to identify the relevant individual patient data in full text. Only those studies that met the inclusion criteria (Table 3) were thoroughly reviewed and analyzed. We limited the articles reviewed to only those studies involving human subjects, written in English, and research conducted in Africa.

We acknowledged the fact that different researchers used different case definitions for the LRTI and the outcomes. Thus, we defined acute LRTI episode in the health facility setting as "any child with an admission diagnosis of pneumonia or bronchiolitis" as the primary manifestations of LRTI in children. In studies conducted outside health facilities, the presence of lower chest wall indrawing in children with cough and difficulty breathing at an increased rate of breathing for age was used to define the case, as in the WHO case definition for pneumonia (11, 15).

3. Data Extraction

The conduct of this review was carried out following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (16). After itera-

Table 1. Full search terms and strategy used for systematically reviewing the articles indexed in PubMed

No.	Concepts	Search Terms
1	Lower respiratory tract infections, LRTI and pneumonia	(("bronchiolitis"[MeSH Terms] OR "bronchiolitis"[All Fields]) OR ("pneumonia"[MeSH Terms] OR "pneumonia"[All Fields]) OR "community-acquired pneumonia"[All Fields] OR CAP [All Fields] OR "hospital-acquired pneumonia"[All Fields] OR "nosocomial pneumonia"[All Fields] OR "ventilator-acquired pneumonia"[All Fields] OR "lung abscess"[All Fields] OR "pleural effusion"[All Fields] OR "empyema thoracis"[All Fields])
2	Sex, sex differences, and gender	(("sex"[MeSH Terms] OR "sex"[All Fields]) OR ("sex"[MeSH Terms] OR "sex"[All Fields] OR "gender"[All Fields] OR "gender identity"[MeSH Terms] OR ("gender"[All Fields] AND "identity"[All Fields]) OR "gender identity"[All Fields]))
3	Settings	("africa"[MeSH Terms] OR "africa"[All Fields] OR " sub-Saharan"[MeSH Terms] OR "sub-Saharan"[All Fields])
4	Outcomes	Incidence OR Prevalence OR Aetiology OR etiology OR admission OR "Case fatality" OR Mortality
5	Combination of terms	#1 AND #2 AND #3 AND #4
6	Filters	Humans AND (Language: English) AND (Age: birth-18 years)

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Table 2. Search terms and strategy used for retrieving published articles from Google Scholar and Africa Journal Online

No.	Concepts	Search Terms
1	Population	Child OR Children OR under-5s OR "less than 5 years"
2	Disease	"Lower respiratory tract infections" OR LRTI OR pneumonia
3	Comparison	Sex OR "Sex differences" OR Gender
4	Setting	Africa OR sub-Saharan
5	Combination of terms	#1 AND #2 AND #3

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tive database searches and screenings of all titles and abstracts to identify full-text articles for detailed review, a data abstraction form was developed. One author (Adebola E. Orimadegun) extracted data while the second author (Landon Myer) cross-checked all extracted data compiled using Microsoft Excel 2010. To ensure the accuracy of the extracted data, the second author (Landon Myer) compared the extracted information with the original data published in the selected complete texts (or in the supporting documents submitted

Table 3. Criteria for inclusion and exclusion of the reviewed studies

Inclusion Criteria	Exclusion Criteria
Studies on children with an admission diagnosis of pneumonia or bronchiolitis, and or report of the presence of lower chest wall indrawing in a child with cough and difficulty breathing with an increase in the respiratory rate for age	Studies which the case definitions are not clearly stated or if it is inconsistently applied
Studies which reported data on any of the outcomes of interest for both male and female participants	No sex-related data were reported on any of the outcomes
Studies in children below 15 years	Reported data for children with acute upper respiratory infections not necessitating hospital admission
Studies with known designs, including observational studies (case series, cross-sectional, case-control, cohort) and randomized controlled trials	Methods of data collection and documentation are not reported

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by the authors). Any identified errors were discussed and corrected, if necessary.

Assessment of quality of studies

We assessed the quality of selected studies and potential risk of bias with the Newcastle-Ottawa Scale (17, 18), following the Cochrane Handbook (19). This tool includes 10 items that assess measurement bias, selection bias, and analysis bias-related (all rated as either high, moderate, or low risk) and an overall assessment of the risk of bias rated as either low, moderate, or high (Supplementary file 1). We followed the format of the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACRO-BAT-NRSI) (20) by using 11 "signaling" questions (Supplementary file 1). Each question has a single answer, either yes (low risk of bias), probably yes (moderate risk of bias), no (serious to the critical risk of bias), or insufficient information to assess (unable to allocate the risk of bias). Based on the answers to the signaling questions on external and internal validity, the overall risk of bias was assigned to each study as either "low" (suggesting that the study is comparable to a well-performed randomized trial); "moderate" (suggesting that the study is sound for a non-randomized study; or "high" (indicating the study is too problematic to provide useful evidence concerning sex). If there is not enough information to make a reasonable overall assessment, the study should be assigned "no information" and not used for data synthesis. Only those studies that have less than moderate overall bias risks were used for data synthesis.

Data synthesis and analysis

The data extracted from the included studies regarding sex differences were summarised (Supplementary file 2). Since we anticipated significant clinical and methodological heterogeneity, we narratively summarized the potential effect of sex on the incidence, etiology, and case fatality of LRTI in individual studies. Gaps in the research have also been highlighted. We conducted a meta-analysis to pool data for case-fatality because it is the only outcome with reasonably well-recorded data from studies with a low or moderate risk of bias. We evaluated heterogeneity using the Chi square-based Q statistic (significant for P<0.1) (21). The funnel plot and Egger's test were used to check for small-study effects, a potential cause of publication bias (22). For studies that have reported on Respiratory Syncytia Virus (RSV) and case fatality, the findings of the study were further summarized using an unadjusted odds ratio with a 95% confidence interval (CI). Statistical analysis was performed in Stata v. 12.1 (StataCorp, Texas USA) and using metan commands to produce forest plots.

4. Results

Characteristics of studies, design, and participants

A total of 262 studies with sex-related data were retrieved (Figure 1); 175 reports were screened out due to missing eligibility criteria. There were no sex-related data on any of the outcomes of interest in the full-texts of 73 out of 87 full-text articles assessed for eligibility; these were also excluded from further review. We identified only 14 studies that reported on the incidence, etiology, and or case fatality of LRTI among African children disaggregated by sex. These studies were conducted in the Gambia (23), Kenya (5, 24), Malawi (25), Mali (26), Mozambique (27, 28), Nigeria (29-33), and South Africa (34, 35) (Table 4). However, one Nigeria (33) study was excluded from narrative analysis for the high incidence of LRTI, which was considered an outlier (ranged from 6.1 to 8.1 episodes per child-year an incidence ratio of 1.08 [male=7.2; female=6.7]).

The publication dates for all the 14 studies ranged from 1990 to 2016. We found data on sex differences for case fatality in 9 (26-31, 34), etiology in 3 (23, 34, 35), and incidence of pneumonia in 3 (5, 28, 34) articles. There was no article on bronchiolitis with data on sex differences. All studies focused on LRTI as defined by clinical presentations and or radiological findings.

The study population was children aged less than 5 years in all articles but two studies, including a Nigerian research (30), which extended the participants' age to 110 months and a study from Kenya (5) which included adults, too. Also, most of the studies were health facility-based (n=12/13), and data were prospectively collected in 11 studies (26-31). Nine studies were cross-sectional in design (5, 24, 25, 27-32), 3 were case-control studies (26, 34, 36) and only 2 studies (33, 35) involved follow up of their participants for at least 1 year. Our assessment showed that none of the studies in the review had a very high risk of bias. Four studies (5, 25, 33, 36) were classified as having a moderate risk of bias, while the remaining 10 studies have a low risk of bias.

Sex difference in the incidence of pneumonia

Generally, pneumonia was reported more frequently in males than females in 13 out of 14 studies. Two studies reported the sex-specific incidence of pneumonia. The overall incidence of LRTI was lower in female than

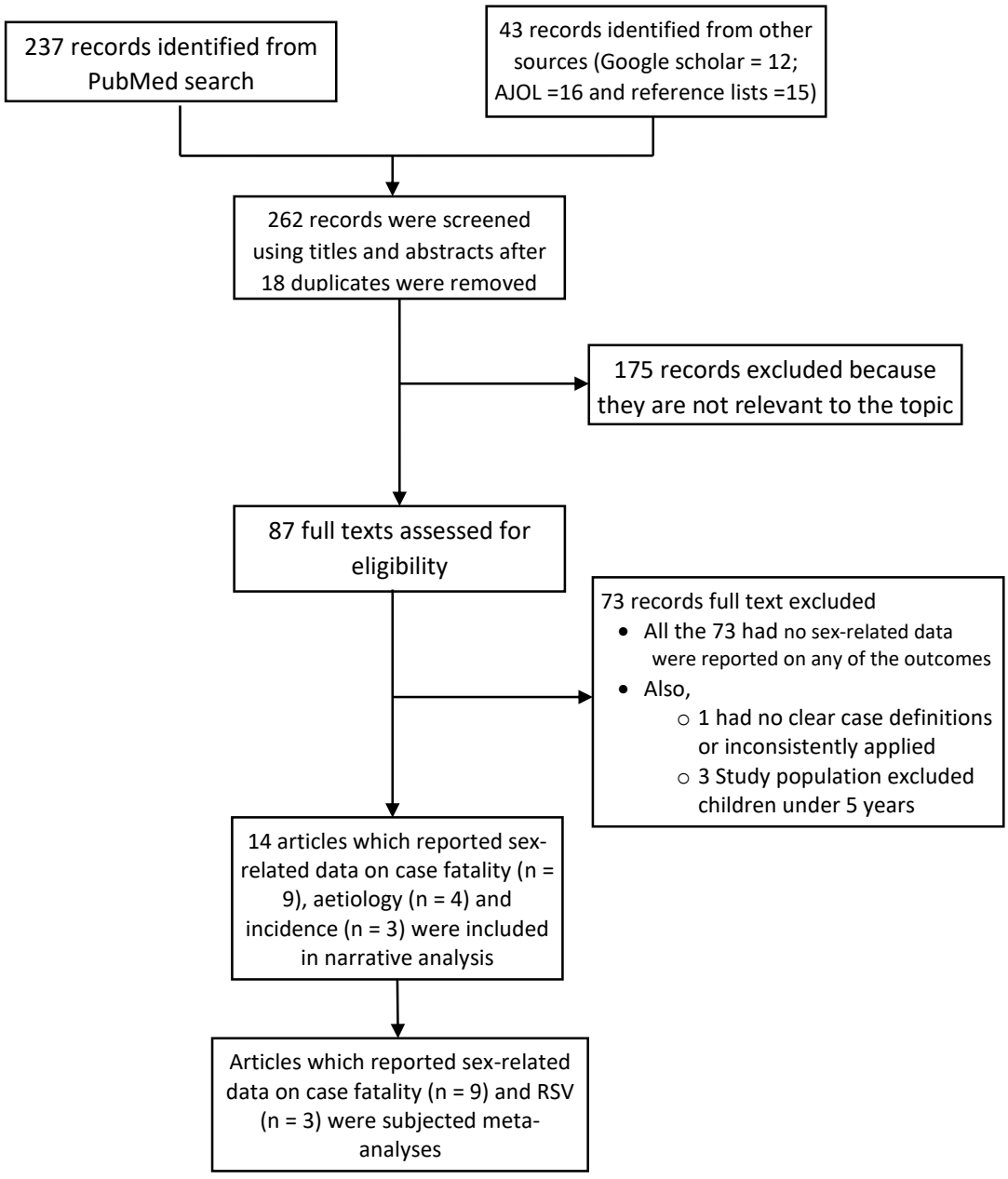

Figure 1. Flow diagram for the selection of studies

male children in South Africa, with an incidence ratio of 0.49 (35). The Kenya study reported the incidence (per 100000 person-years) of pneumonia for children aged 0-4 years 5-9 years and 10-14 years as female/male rate ratio of 0.84 (95% CI; 0.75-0.95), 0.98 (95% CI; 0.64-1.52), and 1.51 (95% CI; 0.81-2.88), respectively. The authors reported a lower risk of pneumonia in female than male children younger than 5 years (RR=0.84, 95% CI; 0.75-0.95). These two studies used either clinical or WHO case definitions of LRTI. It was, however, difficult to pool the incidence data for the two studies because the participants' ages varied widely with apparent high heterogeneity. Also, the numbers of male and female children were not presented in the report from Kenya.

Sex differences in etiology of LRTI in children

Out of the 14 studies, 4 studies (28.6%) were reviewed, investigated, and presented sex-related data on the etiology of LRTI (23, 27, 32, 34). In microbiology-

Table 4. Characteristics of studies included in the review

Study	Year	Country	Sample Size	Study Design	Study Population	Outcomes*
Oyejide (33)	1990	Nigeria	861	Longitudinal, community-based	0-59 months	Incidence
Forge (36)	1991	The Gambia	90	Prospective, case-control, and hospital-based	Infants <12 months	Etiology
Johnson (32)	1992	Nigeria	103	Prospective, cross-sectional, and hospital-based	3-19 months	Etiology
Tornheim (5)	2007	Kenya	2466	Retrospective, cross-sectional, and hospital-based	0->65 years	Incidence
Johnson (31)	2008	Nigeria	323	Prospective, cross-sectional, and hospital-based	2 weeks-59 months	Case fatality
Sigauque (28)	2009	Mozambique	757	Prospective, cross-sectional, and hospital-based	0-23 months	Case fatality
Ayieko (24)	2012	Kenya	3372	Retrospective, cross-sectional, and hospital-based	6 to 23 months	Case fatality
AbdulKarim (30)	2013	Nigeria	167	Prospective, cross-sectional and hospital-based	1-110 months	Case fatality
Bénet (26)	2015	Mali	118	Prospective, case–control, and hospital-based	5-55 months	Case fatality
Abdulkadir (29)	2015	Nigeria	200	Prospective, cross-sectional, and hospital-based	2 and 59 months	Case fatality
le Roux (35)	2015	South Africa	141	Prospective, a cohort of infants from birth	Birth-12 months	Etiology/Incidence
Lazzerini (25)	2016	Malawi	102708	Retrospective, cross-sectional, and hospital-based	2-59 months	Case fatality
Bassat (27)	2016	Mozambique	825	Prospective, cross-sectional, and hospital-based	0-59 months	Case fatality
Zar (34)	2016	South Africa	314	A nested case-control study in a cohort infant from birth	Birth – 12 months	Case fatality Etiology

*With data disaggregated by sex.

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NB: Zar and Le Roux are the same cohorts.

based studies, the leading reported bacterial cause was Streptococcus pneumonia, identified in two studies (27, 32). Streptococcus pneumonia accounted for 4.5% of 557 and 6.1% of 380 pneumonia cases in males and females, respectively. Other reported bacterial pathogens were Haemophilus influenzae type B in two studies (32, 34) (male=37/247 [10.9%]; female=1/276 [0.4%]), and Staphylococcus aureus in one study (32) (male=7/55 [12.7%]; female=7/48 [14.6%]). Sex disaggregated results on rhinovirus and Pneumocystis jirovecii were presented by two (27, 34) studies out of the four studies, while only one study (34) reported sex distribution for the influenza virus, parainfluenza, and bocavirus as pathogens. Influenza virus, parainfluenza, and bocavirus were identified more frequently in male than female infants, male constitutes over 60% children from whom isolates were obtained. Bassat and Lanaspa (27) identified rhinovirus as the dominant pathogen in both male (n=125/497; 25.2%) and female (n=69/328; 21.0%) children followed by adenovirus (male 68/497; female 34/328), Pneumocystis jirovecii (male 28/497; female 29/328) and Streptococcus pneumonia (male 24/497; female 22/328).

RSV was the most frequently reported viral cause of pneumonia for both males (n=79/745, 10.6%) and females (n=70/599, 11.7%) children. It was identified in three studies from The Gambia (23), Nigeria (32) and South Africa (34). These parts of the sex-related data on etiologic agents were subjected to meta-analysis, and the pooled sex effect (with 95% CI and the P-value) and heterogeneity test were as presented in Table 5 and Figure 2. Only the study from Mozambique (27) has the 95% confidence interval for the odds ratio crossing the "line of no difference", while others showed a significant odds ratio in favor of male children. Overall, the effect of sex averaged for all the three studies was in favor of the male sex, i.e., odds of identifying RSV was significantly lower in male than female children (OR=0.60; 95% CI: 0.42, 0.86).

Sex differences in mortality among children with LRTI

We identified 9 studies from Nigeria (n=3), Mozambique (n=2), Kenya (n=1), Mali (n=1), Malawi (n=1), and

Table 5. Summary statistics of Forrest plot for three studies included in the meta-analysis for the effect of sex on RSV as an etiologic agent for LRTI

First Author	Year	Country	No. of Cases		OR	95% CI		Weight (%)
			Male	Female		Lower	Upper	
Forge (36)	1991	The Gambia	51	39	0.48	0.17	1.30	15.07
Bassat (27)	2016	Mozambique	497	328	0.96	0.53	1.72	30.53
Zar (34)	2016	South Africa	208	106	0.44	0.26	0.74	54.40
Pooled OR					0.60	0.42	0.86	

Heterogeneity Chi-squared=3.97 (df=2), P=0.137.

Test of OR=1 : z=2.75 , P=0.006.

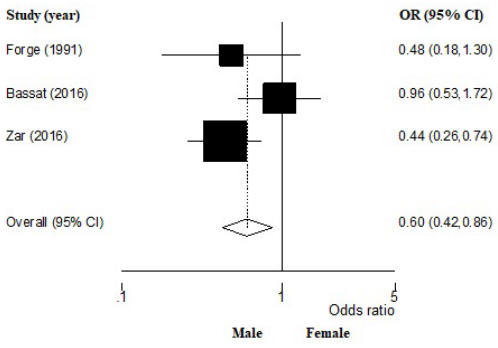

Figure 2. Forest plots for meta-analysis odds ratio estimates for the effect of sex on RSV as a cause of LRTI among African children

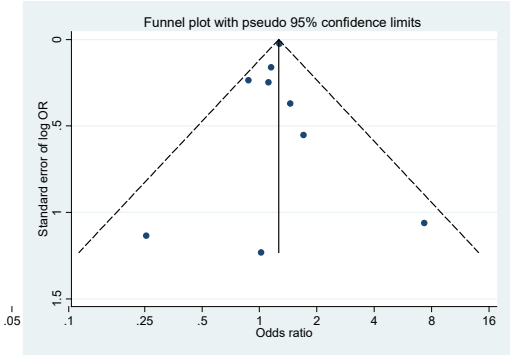

Figure 3. Funnel plot, using data from 9 studies of case fatality in childhood pneumonia

South Africa (1) with sex-related data on case fatality (Table 6). The distribution of the included publications in the funnel plots (Figure 3) shows symmetrical scattered points on either side of the overall effect line. This observation was supported by the results of the Egger's test (P>0.05), suggesting no remarkable publication biases. The meta-analysis odds ratio estimates for the effect of sex on case fatality with statistical tests for heterogeneity are shown in Figure 4. The pooled estimate indicates that the odds of fatality were significantly higher for male than female children (OR=1.26; 95% CI: 1.20-1.33).

Table 6. Summary statistics of forest plot for eight studies included in the meta-analysis for the effect of sex on case fatality among African children

First Author	Year	Country	No. of Cases		OR	95% CI		Weight (%)
			Male	Female		Lower	Upper	
Johnson (31)	2008	Nigeria	177	146	1.45	0.70	2.99	0.42
Sigauque (28)	2009	Mozambique	440	317	1.12	0.69	1.81	1.06
Ayieko (24)	2012	Kenya	1762	1443	1.15	0.84	1.58	2.47
AbdulKarim (30)	2013	Nigeria	100	67	7.33	0.92	58.70	0.04
Abdulkadir (29)	2015	Nigeria	119	81	1.71	0.58	5.04	0.18
Bénet (26)	2015	Mali	57	61	0.25	0.03	2.35	0.13
Zar (34)	2016	South Africa	208	106	1.02	0.09	11.37	0.04
Bassat (27)	2016	Mozambique	497	328	0.87	0.55	1.39	1.30
Lazzerini (25)	2016	Malawi	46138	56570	1.27	1.20	1.34	94.4
Poled OR					1.26	1.20	1.33	

Heterogeneity Chi-squared=8.29 (df=8), P=0.406.

Test of OR=1: Chi-squared=91.00 (df=1), P<0.001.

I-squared=5.7% (Calculated based on DerSimonial-Laird method).

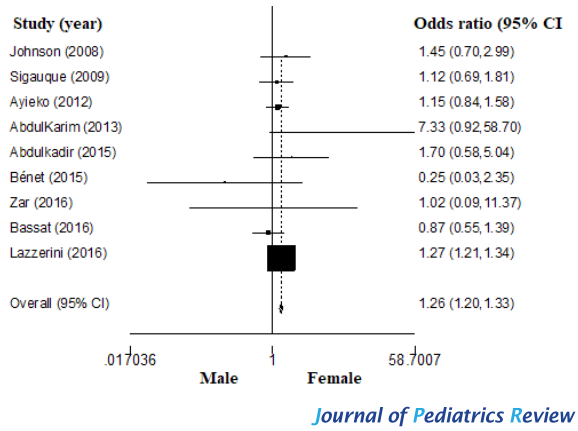

Figure 4. Forrest plots for meta-analysis odds ratio estimates for the effect of sex on case fatality among African children

5. Discussion

This novel review synthesizes published studies from African countries on sex differences in incidence, etiology, and case fatality of LRTI in children. We observed that despite the increasing evidence that gender is an essential factor which influences the diseases and response to treatments (13, 37, 38), data on sex-related differences in incidence, etiology, and outcomes of LRTI are scarce. We found only two studies (5, 35) that reported the incidence of pneumonia between males and females, and they both reported a higher rate for male than female children. There were inconsistencies in the reports of pathogens identified in children with LRTI so that RSV was the leading cause in the three studies that disaggregated etiologic agents by sex. Our summary statistics indicated that the odds of RSV infection was significantly higher in female than male children. We further observed that only 9 studies reported an association between sex and case fatality and the overall estimate revealed that the odds of death was higher in male children (OR=1.26; 95% CI 1.20-1.33).

To our knowledge, our study is the first comprehensive attempt to systematically assess the effect of sex on the incidence, etiology, and mortality of ALRI in children of the African population. Excess pneumonia found among males compared with females has been previously described (39, 40). However, it remains unclear whether sex differences in pneumonia incidence is due to variability in susceptibility between boys and girls or to selection bias from preferential care-seeking. The incidence reported for male children (0.36 episodes per child-year) in the South Africa study is considerably higher than the estimated rate (0.33 episodes per child-year) for African children aged less than 5 years (41), and more recent estimate is 0.22 episodes per child-year (interquartile range: 0.11-0.51) for all low and middle–income countries (LMIC) derived from 35 community-based studies published between 1990 and 2012 (42). The considerable variation in the incidence between the studies selected for our review was most probably due to the distinct study designs and or real differences in the prevalence of pneumonia in the various study settings. For instance, the Nigeria study (33) had an error in respect of the application of case definition and that affected the computation of incidence that the study estimate of 6.1-8.1 episodes per child-year was remarkably higher than any rate ever reported.

The difficulties associated with pooling data for estimation of the incidence of pneumonia have been highlighted (42). These problems included the scarcity of longitudinal studies in LMIC, the necessity of conducting such studies over a full calendar year, active and frequent screening of a large number of children, as well as the correctness of application of case definition by the assessor (42). All of these issues limited our ability to pool data in this review. Similarly, we were unable to combine sex-related data on the etiology of pneumonia in children, given the heterogeneity of the data (41).

In our review, bacterial and viral etiologies of pneumonia were inconsistently reported for male and female children. The leading bacterial and viral causes for pneumonia found in our review agreed with previous reports (43-46). However, literature does not explain why the predisposition to some pathogen has sex preference. Generally, in Africa, there is the need to conduct more studies on the etiology of pneumonia with sex-specific data in children. Such reviews will help define the new distribution of pneumonia-causing etiologies in both sexes that may have important implications for empirical diagnosis and treatments. It is necessary to note that determining the cause of pneumonia in children is often challenging due to difficulties in obtaining direct lung samples. The expectorant easily gets contaminated by oropharyngeal organisms, but the patient's age and probably the child's sex can help narrow the list of probable etiology (47). Therefore, interpreting the results of studies on the etiologies of pneumonia requires an understanding of the limitations imposed by methods of identification and socio-demographic peculiarities of the affected population (48).

In this review, we adopted known methods to select studies and synthesize evidence and ensure transparency in our report. These techniques allow readers to focus on the merits of decisions made in compiling the information presented. Although this systematic review draws primarily from evidence published in

journals written in English, synthesizing and pooling of evidence cover studies from a large number of countries across sub-Saharan Africa, including Francophone settings in West Africa. Therefore, our inferences could still be considered generalizable to the broader sub-Saharan context.

There are three limitations to interpreting the findings of this review. First, there was considerable variability in the sample size of the studies, ranging from 90 (36) to 102708 (25). This is reflected in the wide confidence intervals for some of the reported odds ratio estimates included in the meta-analysis, and one study from Malawi contributed 94.4% of the variation. It appears that one research substantially influenced the overall estimate of the odds of deaths, but a repeated analysis without that study had no significant impact on the assessment for publication bias. Second, there are flaws in some of the data presented in a few studies (35). For example, a direct comparison of incidence rates in two studies that reported sex-related data was difficult because of variation in definitions of LRTI incidence. Finally, we were unable to verify response rates and whether non-participants were different from participants in terms of socio-demographic characteristics in all the observational studies. Despite these concerns, our review shows that sex-related differences should be considered seriously by clinical researchers and physicians in working with children with pneumonia.

6. Conclusions

There is little sex-specific data on the incidence, etiology, and case fatality of pneumonia in studies published from Africa. It seems that male patients die more frequently than females. However, female patients seem to suffer more commonly from RSV infection. Clinicians should be aware of these differences and take them under consideration when managing children with LRTIs. Also, researchers should be encouraged to include and report on sex differences as separately defined variables in LRTI studies. This review shows clearly that male children carry a considerable burden of pneumonia morbidity and mortality in Africa, making them a group that would benefit significantly from existing and newer preventive interventions.

Ethical Considerations

Compliance with ethical guidelines

The protocol for this systematic review has been approved and registered with PROSPERO (CRD42019122494).

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Authors contributions

Adebola E. Orimadegun and Landon Myer conceptualized and developed the original idea, prepared the study protocol, abstracted and analyzed data, and wrote the manuscript. Adedayo A. Adepoju contributed significantly to the assessment of study quality, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Supplementary file 1

First Author (Year of Publication)	Risk of Bias Item										Overall risk of study bias in comparing male and female
	Signalling Questions for External Validity				Signalling Questions for Internal Validity						
	Was the study's target population a close representation of the population in relation to age and sex?	Was the sampling frame a true or close representation of the target population?	Was some form of random selection used to select the sample OR was a census undertaken?	Was the likelihood of non-response bias minimal?	Were data collected directly from the subjects?	Was an acceptable case definition used in the study?	Was the study instrument that measured the parameter of interest shown to have reliability and validity?	Was the same mode of data collection used for all subjects?	Was the length of the shortest prevalence period for the parameter of interest appropriate?	Were the numerators and denominators for the parameter of interest appropriate?	
Zar (2016) (34)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	LOW
Oyejide (1990) (33)	Yes	Yes	Yes*	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
Forgie (1991) (23) (36)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Probably Yes	Yes	MODERATE
Johnson (2008) (31)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
Sigauque (2009) (28)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
Ayieko (2012) (24)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
AbdulKarim (2015) (30)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
le Roux (2015) (35)	Yes	Yes	Yes*	Yes	NA	Yes	Yes	Yes	Yes	Yes	LOW
Bénet (2015) (26)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	LOW
Abdulkadir (2015) (29)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
Lazzerini (2016) (25)	Yes	Yes	Probably Yes	Probably Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
Johnson (1992) (32)	Yes	Yes	No	Yes	NA	Yes	Probably Yes	Yes	Yes	Yes	MODERATE
Bassat (2016) (27)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
Tornheim (2007) (5)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE

* Some form of census undertaken

NA – Not applicable

Supplementary file 2 note on the assessment

This tool is designed to assess the risk of bias in non-randomized observational studies. Please read the additional notes for each item when initially using the tool. Note: If there is insufficient information in the article to permit a judgment for a particular item, please answer No (High risk) for that particular item.

Risk of Bias Item	Criteria for Answers (Please Circle One Option)	Additional Notes and Examples
	External Validity	
1. Was the study's target population a close representation of the population of interest in relation to relevant variables, e.g. age, and sex?	Yes (Low risk): The study's target population was a close representation of the national population. Probably yes (moderate risk of bias) No (High risk): The study's target population was clearly NOT representative of the national population	The target population refers to the group of people or entities to which the results of the study will be generalized. Examples: The study was conducted in one province only, and it is not clear if this was representative of the national population. The answer is: No (High risk). The study was undertaken in one village only and it is clear this was not representative of the national population. The answer is: No (High risk).
2. Was the sampling frame a true or close representation of the target population?	Yes (Low risk): The sampling frame was a true or close representation of the target population. Probably yes (moderate risk of bias) No (High risk): The sampling frame was NOT a true or close representation of the target population	The sampling frame is a list of the sampling units in the target population and the study sample is drawn from this list. Examples: The sampling frame was a list of almost every individual within the target population. The answer is: Yes (Low risk). The cluster sampling method was used and the sample of clusters/villages was drawn from a list of all villages in the target population. The answer is: Yes (Low risk). The sampling frame was a list of just one particular ethnic group within the overall target population, which comprised many groups. The answer is: No (High risk).
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	Yes (Low risk): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling). Probably yes (moderate risk of bias) No (High risk): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	A census collects information from every unit in the sampling frame. In a survey, only part of the sampling frame is sampled. In these instances, random selection of the sample helps minimize study bias. Examples:
4. Was the likelihood of non-response bias minimal?	Yes (Low risk): The response rate for the study was >/=75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non- responders Probably yes (moderate risk of bias) No (High risk): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders.	Examples: The response rate was 68%; however, the researchers did an analysis and found no significant difference between responders and non-responders in terms of age, sex, occupation and socio- economic status. The answer is: Yes (Low risk). The response rate was 65% and the researchers did NOT carry out an analysis to compare relevant demographic characteristics between responders and non-responders. The answer is: No (High risk).
	Internal Validity	
5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes (Low risk): All data were collected directly from the subjects. Probably yes (moderate risk of bias) No (High risk): In some instances, data were collected from a proxy.	A proxy is a representative of the subject. Examples: All eligible subjects in the household were interviewed separately. The answer is: Yes (Low risk). A representative of the household was interviewed and questioned about the presence of low back pain in each household member. The answer is: No (High risk).
6. Was an acceptable case definition used in the study?	Yes (Low risk): An acceptable case definition was used. Probably yes (moderate risk of bias) No (High risk): An acceptable case definition was NOT used.	

Internal Validity		
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes (Low risk): The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc. No (High risk): The study instrument had NOT been shown to have reliability or validity	The authors used the COPCORD questionnaire, which had previously been validated. They also tested the inter-rater reliability of the questionnaire. The answer is: Yes (Low risk). The authors developed their own questionnaire and did not test this for validity or reliability. The answer is: No (High risk).
8. Was the same mode of data collection used for all subjects?	Yes (Low risk): The same mode of data collection was used for all subjects. No (High risk): The same mode of data collection was NOT used for all subjects	The mode of data collection is the method used for collecting information from the subjects. The most common modes are face-to- face interviews, telephone interviews and self-administered questionnaires. Examples: All eligible subjects had a face-to-face interview. The answer is: Yes (Low risk). Some subjects were interviewed over the telephone and some filled in postal questionnaires. The answer is: No (High risk).
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes (Low risk): The shortest prevalence period for the parameter of interest was appropriate (e.g. point prevalence, one-week prevalence, one-year prevalence). Probably yes (moderate risk of bias) No (High risk): The shortest prevalence period for the parameter of interest was not appropriate (e.g. lifetime prevalence)	The prevalence period is the period that the subject is asked about e.g. "Have you experienced low back pain over the previous year?" In this example, the prevalence period is one year. The longer the prevalence period, the greater the likelihood of the subject forgetting if they experienced the symptom of interest (e.g. low back pain). Examples: Subjects were asked about pain over the past week. The answer is: Yes (Low risk). Subjects were only asked about pain over the past three years. The answer is: No (High risk).
10. Were the numerators and denominators for the parameter of interest appropriate?	Yes (Low risk): The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain). No (High risk): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	There may be errors in the calculation and/or reporting of the numerator and/or denominator. Examples: There were no errors in the reporting of the numerator(s) AND denominator(s) for the prevalence of low back pain. The answer is: Yes (Low risk). In reporting the overall prevalence of low back pain (in both men and women), the authors accidentally used the population of women as the denominator rather than the combined population. The answer is: No (High risk).
11. Summary item on the overall risk of study bias		
Low risk of Bias: Further research is very unlikely to change our confidence in the estimate. Moderate Risk of Bias: Further research is likely to have an important impact on our confidence in the estimate and may change the estimate. High risk of Bias: Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.		