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

Running title: Sex Differences in Morbidity and Mortality of ALRTIs

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Abstract

Context: Biological sex is thought to influence morbidity and mortality patterns in children living in sub-Saharan Africa due to acute lower respiratory tract infections (ALRIs), but little is known about the effect of sex on ALRI.

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

Data Sources, Study Selection, and Data Extraction: We systematically searched electronic databases for publications from 1971 to 2016: PubMed, African Journals Online, and Google scholar for ALRI literature in the African children's population. 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 published peer-reviewed journal articles reporting on incidence, aetiology and/or 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 pneumonia cases reported 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 favour 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).

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

Keywords: Respiratory tract infections, Pneumonia, Respiratory syncytial viruses, Sex Characteristics

1. Background

Lower respiratory tract infections (LRTIs) are common diseases in children worldwide, accounting for high morbidity, high hospital admissions, and high healthcare costs, especially in developing countries (1). In children aged 1-59 months, pneumonia accounted for an estimated 1·071 million (0·977–1·176) deaths which are 14·1% of all-cause mortality; leading diarrhoea (9·9%; 0·751 million, 0·538–1·031), and malaria (7·4%; 0·564 million, 0·432–0·709) among the three most common diseases claiming most lives of children <5 years of age (2). Although global mortality rates among children aged <5 years have been declining, there are marked variations in the magnitude and trends that exist across regions and countries of the world, and mortality rates ranged from 8% to 15% among African children (3-5). Generally, the highest overall mortality rates were from studies of children with either HIV, severe malnutrition, unvaccinated and very severe pneumonia (3, 6, 7).

Recently, sustainable solutions to the problem of high numbers 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 aetiological 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 most LRTI has been suspected of having a potentially higher risk of death and worse morbidity in males than females (13). Despite this assumption, epidemiological data on the evidence of sex differences for LRTI in children in sub-Saharan Africa are strikingly limited. In a review published by Falagas (13) in 2007, of the 52 studies on LRTI included, 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 chances of having severe ALRI were 1.5 (95% CI: 1.0 to 2.3) times higher in males than females, but only one report included was from Africa (14).

2. Objective

To date, no systematic reviews of published literature have assessed the relationship between sex and LRTI in the African children's population. The objective of this review was to systematically assess the quality of available evidence and to present summary estimates of the strength of the association between sex and incidence, aetiologies, and outcomes of LRTI in children using narrative and meta-analysis methods.

3. 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 to 2016. These databases were searched for studies that report data on incidence, aetiologies, and outcomes of LRTI for both male and female children. The terms used and details of the search steps were in Table I and II.

Table I. 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)

Table II: 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

4. Study selection and eligibility criteria

We included published peer-reviewed journal articles reporting data on any of our outcomes of interest, namely incidence, aetiology, and case fatality. The titles and abstracts of the articles 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 incidence, aetiology 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 III) have been fully reviewed and analysed. We limited the articles reviewed to only those studies involving human subjects, written in English, and research conducted in Africa.

Table III: Criteria for inclusion and exclusion of the reviewed studies	
Inclusion criteria	Exclusion criteria
1. Studies on children with an admission diagnosis pneumonia or bronchiolitis, and/or report of the presence of lower chest wall in-drawing in a child with cough and difficulty breathing with increase in the respiratory rate for age	1. Studies which the case definitions are not clearly stated or if it is inconsistently applied
2. Studies which reported data on any of the outcome of interest for both male and female participants	2. No sex-related data were reported on any of the outcomes
3. Studies in children below 15 years	3. Reported data for children with acute upper respiratory infections not necessitating hospital admission
4. Studies with known designs including observational studies (case series, cross-sectional, case-control, cohort) and randomized control trials	4. Methods of data collection and documentation are not reported

We acknowledged the fact that different researchers would have used different case definitions for the LRTI and the outcome. Thus, we defined acute LRTI episode in the health facility setting as "any child with an admission diagnosis of pneumonia or bronchiolitis" as the main manifestations of LRTI in children. In studies conducted outside health facilities, the presence of lower chest wall in-drawing 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).

5. Data extraction

The conduct of this review was carried out following the PRISMA Checklist (16). After iterative 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 (AEO) has extracted data while the second author (LM) has cross-checked all extracted data compiled using Microsoft Excel 2010. To ensure the accuracy of the extracted data, the second author (LM) compared the extracted information with the original data published in the selected complete texts (or in the supporting documents submitted by the authors). Any identified errors have been discussed and corrected, if necessary.

5.1.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 bias related to the analysis (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 risk (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 “signalling” questions in all (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 signalling 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 in relation to 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 were found to have less than moderate overall bias risks were used for data synthesis.

5.2.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, aetiology and case fatality of LRTI in individual studies. Gaps in 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 test for small-study effects, a potential cause of publication bias (22). For studies that have reported on RSV and case fatality, the findings of the study were further summarized using an unadjusted odds ratio with 95% confidence intervals (CI). Statistical analysis was performed using Stata Version 12.1 (StataCorp, Texas USA) and using metan commands to produce forest plots. Statistical analysis was performed using Stata Version 12.1 (StataCorp, Texas USA) and using metan commands to produce forest plots.

6. Results

6.1. 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 incidence, aetiology, and/or case fatality of LRTI among African children disaggregated by sex. These came from the Gambia (23), Kenya (5, 24), Malawi (25), Mali (26), Mozambique (27, 28), Nigeria (29-33) and South Africa (34, 35) (Table IV). However, one Nigeria (33) study was excluded from narrative analysis for the incidence of LRTI, because the estimated

incidence estimate was considered to be 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 nine (26-31, 34), aetiology in three (23, 34, 35) and incidence of pneumonia in three (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.

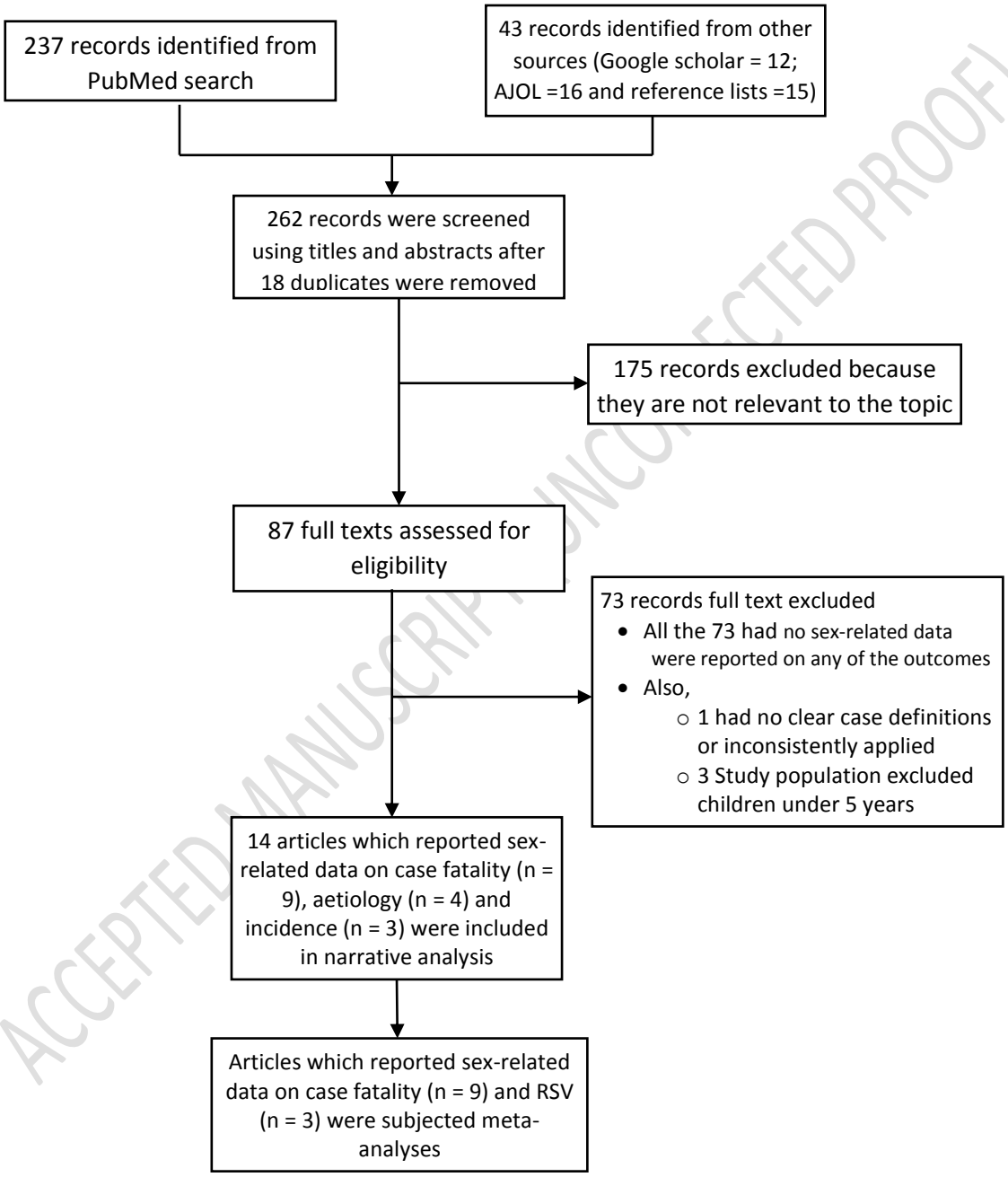

Figure 1: Flow diagram for the selection of studies

Table IV: Characteristics of studies included in the review

Study	Year	Country	Sample size	Design	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	Aetiology
Johnson (32)	1992	Nigeria	103	Prospective, cross-sectional and hospital-based	3-19 months	Aetiology
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	2weeks – 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, cohort of infants from birth	Birth – 12months	Aetiology/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	Nested case-control study in a cohort infant from birth	Birth – 12months	Case fatality Aetiology

*With data disaggregated by sex NB: Zar and Le Roux are the same cohorts

The study population was children aged less than 5 years in all but two studies including a Nigerian study (30) which extended participants' age to 110 months and a Kenya study (5) which also included adults. Also, most of the studies were health facility-based (n=12/13) and data were prospectively collected in 11 studies (26-36), 9 studies were cross-sectional in design (5, 24, 25, 27-32), 3 were case-control studies (26, 34, 36) and only two studies (33, 35) involved follow up of participants for at least a year, respectively. Our assessment showed that none of the studies included in the review has 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.

6.2. Sex difference in the incidence of pneumonia

Generally, pneumonia was reported more frequently in males than females in 13 of 14 studies. Two studies reported the sex-specific incidence of pneumonia. The overall incidence of LRTI was lower in female than male children in South Africa, incidence ratio was 0.49 (35); the Kenya study reported incidence (per 100,000 person-years) of pneumonia for children aged with female/male rate ratio of 0.84 (95% CI 0.75-0.95) for 0-4 years; 0.98 (95% CI 0.64-1.52) 5-9 years and 1.51 (95% CI 0.81-2.88) for 10-14 years. The authors reported that there was a lower risk of pneumonia in female than male children less than 5years (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 pull the incidence data for the two studies because the participants' ages varied widely and there was apparent high heterogeneity. Also, the numbers of male and female children were not presented in the report from Kenya.

6.3. Sex differences in aetiology of LRTI in children

Four (28.6%) studies (23, 27, 32, 34) out of the 14 studies reviewed investigated and presented sex-related data on aetiology of LRTI. In microbiology-based studies, the leading bacterial cause reported is Streptococcus pneumoniae, were identified in two studies (27, 32). Streptococcus pneumoniae accounted for 4.5% of 557 and 6.1% of 380 pneumonia cases in males and females, respectively. Other bacterial pathogens reported 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 jiroveci were presented by two (27, 34) out the four studies while only a 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, Lanaspa (27), identified rhinovirus as the dominant pathogen in both male (n = 125/497; 25.2%) and female (n = 69/328; 21.0%) followed by adenovirus (male 68/497; female 34/328), Pneumocystis jirovecii (male 28/497; female 29/328) and Streptococcus pneumoniae (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, were identified in three studies from The Gambia (23), Nigeria (32) and South Africa (34). These parts of the sex-related data on aetiologic agents were subjected to meta-analysis and the pooled sex effect (with 95% CI and p-value) and heterogeneity test were as presented in Table V 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 favour of male children. Overall, the effect of sex averaged for all the three studies was in favour of the male sex, that is odds of identifying RSV was significantly lower in male than female children (OR=0.60; 95% CI: 0.42, 0.86).

Table V: Summary statistics of Forrest plot for three studies included in the meta-analysis for the effect of sex on RSV as aetiologic 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 (d.f. = 2) p = 0.137
Test of OR=1 : z= 2.75 p = 0.006

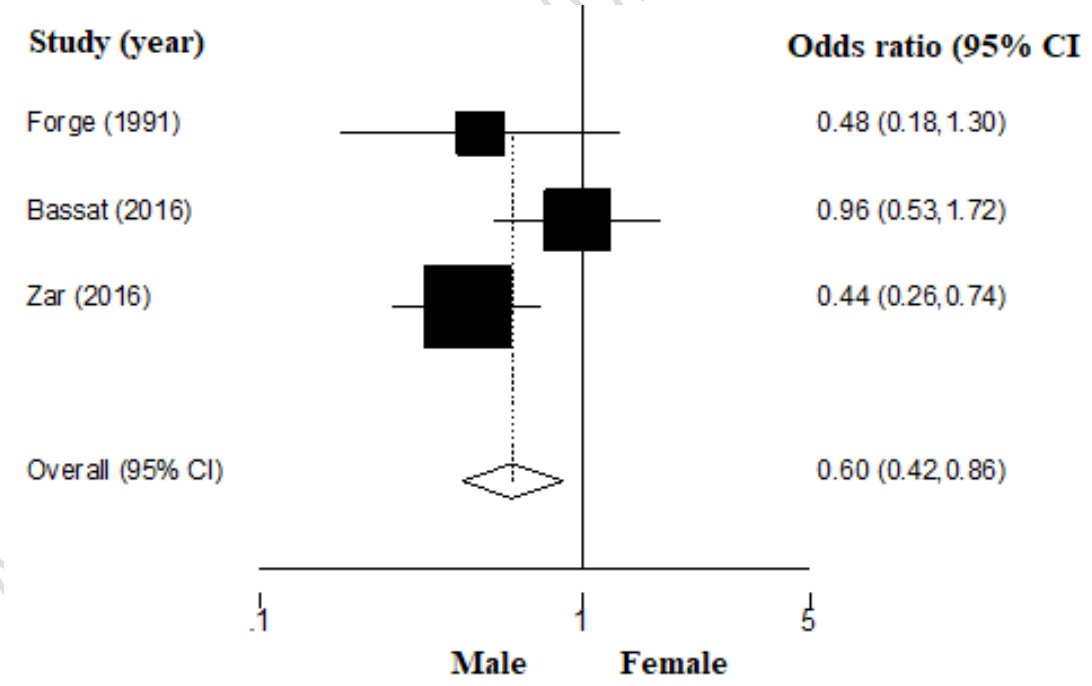

Figure 2: Forrest plots for meta-analysis odds ratio estimates for the effect of sex on RSV as a cause of LRTI among African children

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 South Africa (1) with sex-related data on case fatality (Table VI). 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 test (p>0.05) suggesting that there might not have been remarkable publication biases. The meta-analysis odds ratio estimates for the effect of sex on case fatality with statistical tests for heterogeneity are as 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).

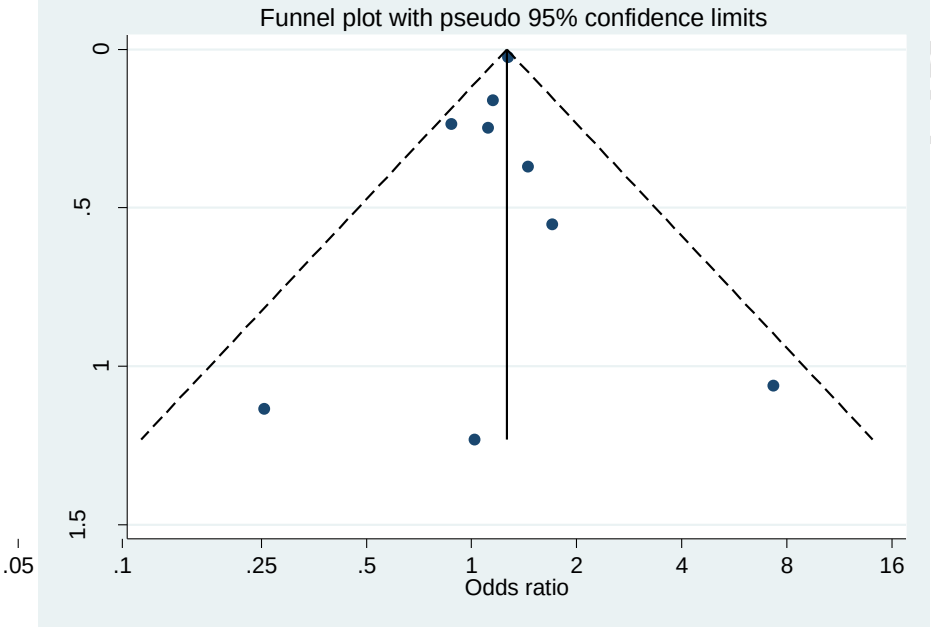

Figure 3: Funnel plot, using data from 9 studies of case fatality in childhood pneumonia

Table VI: Summary statistics of Forrest plot for 8 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		%
			Male	Female		Lower	Upper	Weight
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 (d.f. = 8) p = 0.406

Test of OR=1: chi-squared = 91.00 (d.f. = 1) p <0.001
I-squared = 5.7% (Calculated based on DerSimonial-Laird method)

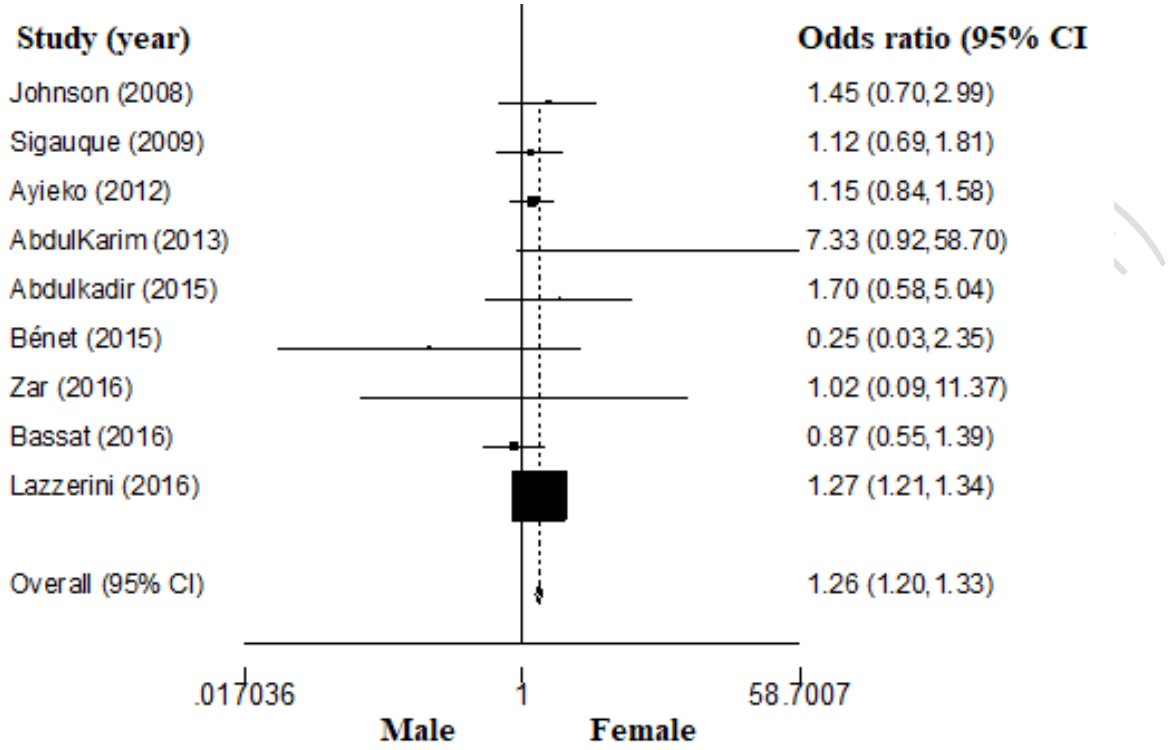

Figure 4: Forrest plots for meta-analysis odds ratio estimates for the effect of sex on case fatality among African children

7. DISCUSSION

This novel review synthesizes published studies from African countries on sex differences in incidence, aetiology and case fatality of LRTI in children. We observed that despite the increasing evidence that an individual's sex is an important factor which influences the diseases and response to treatments (13, 37, 38), data on sex-related differences in incidence, aetiology, and outcomes of LRTI were scarce. We found only two studies (5, 35) that reported the incidence of pneumonia between males and females and they both reported a higher incidence for male thank children. There were inconsistencies in the reports of pathogens identifies in children with LRTI and RSV was the leading cause in the three studies that disaggregated aetiologic agents by sex. Our summary statistics indicated that the odds of RSV infection were 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 than female 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 incidence, aetiology, 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 considerably higher than the estimated incidence (0.33 episodes per child-year) for African children aged less than 5 years (41) and more recent estimate (0.22 episodes/child–year; interquartile range: 0.11–0.51) for all low and middle–income countries (LMIC) derived from 35 community–based studies published between1990 and 2012 (42). The large variation in incidence between the studies selected for our review was most probably due to the distinct study designs and/or real differences in the incidence 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. The estimate, 6.1 to 8.1 episodes per child-year, in that study was remarkably higher than any incidence ever reported.

The difficulties associated with pooling data for estimation of the incidence of pneumonia have been highlighted (42). These include the scarcity of longitudinal studies in LMIC, the need to be conducted such study over full calendar years, active and frequent screening of a large number of children as well as the correctness of application of case definition by the assessor (42), and these issues limited our ability to pool data here. Similarly, we were unable to combine sex-related data on aetiologies of pneumonia in children given the heterogeneity of the data (41).

In our review, bacterial and viral aetiologies of pneumonia were inconsistently reported for male and female children. The leading bacterial and viral causes for pneumonia found in our review agree with previous reports (43-46). However, it is not clear in literature why the predisposition to some pathogen have sex preference. Generally, in Africa, there is the need to conduct more studies on aetiology pneumonia with a focus on segregating data by sex in children. Such studies will help define the new distribution of pneumonia-causing aetiologies in both sexes and these may likely 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 aetiologies (47). Therefore, interpreting the results of studies on the aetiologies 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 synthesis evidence and ensure transparency in our report, to 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 language, synthesis, 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 as 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 a single study substantially influenced the overall estimate of the

odds of deaths, but a repeat analysis without the study had no major 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 need to be considered seriously by clinical researchers and physicians and that the needs of children with pneumonia may demand to pay attention to sex differences.

8. Conclusions

In conclusion, there is a relative paucity of sex-disaggregated data on incidence, aetiology and case fatality of pneumonia in studies published from Africa, males seem to die more frequently than females. Compared to males, females 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.

Conflict of Interest Disclosure: None

Authors' Contribution: AEO and LM conceptualised and developed the original idea, wrote study the protocol, abstracted and analysed data and wrote the manuscript. AAA contributed significantly to the assessment of study quality, drafting of the manuscript and critical revision of the manuscript for important intellectual content.

References

1. G. B. D. Mortality Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1459-544. [Doi:10.1016/S0140-6736(16)31012-1]
2. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012;379(9832):2151-61. [Doi:10.1016/S0140-6736(12)60560-1]
3. O'Callaghan-Gordo C, Bassat Q, Morais L, Diez-Padrisa N, Machevo S, Nhampossa T, et al. Etiology and epidemiology of viral pneumonia among hospitalized children in rural Mozambique: a malaria endemic area with high prevalence of human immunodeficiency virus. Pediatr Infect Dis J. 2011;30(1):39-44. [Doi:10.1097/INF.0b013e3181f232fe]

4. Hussey G, Hitchcock J, Schaaf H, Coetzee G, Hanslo D, van Schalkwyk E, et al. Epidemiology of invasive Haemophilus influenzae infections in Cape Town, South Africa. Ann Trop Paediatr. 1994;14(2):97-103
5. Tornheim JA, Manya AS, Oyando N, Kabaka S, Breiman RF, Feikin DR. The epidemiology of hospitalized pneumonia in rural Kenya: the potential of surveillance data in setting public health priorities. Int J Infect Dis. 2007;11(6):536-43. [Doi:10.1016/j.ijid.2007.03.006]
6. Campbell JD, Kotloff KL, Sow SO, Tapia M, Keita MM, Keita T, et al. Invasive pneumococcal infections among hospitalized children in Bamako, Mali. Pediatr Infect Dis J. 2004;23(7):642-9. [Doi:00006454-200407000-00010 [pii]]
7. Nantanda R, Hildenwall H, Peterson S, Kaddu-Mulindwa D, Kalyesubula I, Tumwine JK. Bacterial aetiology and outcome in children with severe pneumonia in Uganda. Ann Trop Paediatr. 2008;28(4):253-60. [Doi:10.1179/146532808X375404]
8. Saffar MJ, Rezai MS. Management of Lower Respiratory Tract Illnesses in Developing Countries: A Narrative Review. Journal of Pediatrics Review. 2014;2(2):47-56
9. Kirkwood BR, Gove S, Rogers S, Lob-Levyt J, Arthur P, Campbell H. Potential interventions for the prevention of childhood pneumonia in developing countries: a systematic review. Bull World Health Organ. 1995;73(6):793-8
10. Victora CG, Kirkwood BR, Ashworth A, Black RE, Rogers S, Sazawal S, et al. Potential interventions for the prevention of childhood pneumonia in developing countries: improving nutrition. Am J Clin Nutr. 1999;70(3):309-20
11. WHO. Recommendations for management of common childhood conditions, Evidence for technical update of pocket book recommendations. Geneva: World Health Organization; 2012.
12. Falade AG, Ayede AI. Epidemiology, aetiology and management of childhood acute community-acquired pneumonia in developing countries--a review. Afr J Med Med Sci. 2011;40(4):293-308
13. Falagas ME, Mourtzoukou EG, Vardakas KZ. Sex differences in the incidence and severity of respiratory tract infections. Respir Med. 2007;101(9):1845-63. [Doi:10.1016/j.rmed.2007.04.011]
14. Jackson S, Mathews KH, Pulanic D, Falconer R, Rudan I, Campbell H, et al. Risk factors for severe acute lower respiratory infections in children: a systematic review and meta-analysis. Croat Med J. 2013;54(2):110-21
15. WHO. Technical bases for the WHO recommendations on the management of pneumonia in children at first-level health facilities. Geneva: World Health Organization; 1991.
16. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1. [Doi:10.1186/2046-4053-4-1]
17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European Journal of Epidemiology. 2010;25(9):603-5. [Doi:10.1007/s10654-010-9491-z]

18. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: h ttp. ohri ca/programs/clinical_epidemiology/oxford asp (accessed June 2014). 2011
19. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, ; 2011 Available from www.handbook.cochrane.org.
20. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. [Doi:10.1136/bmj.i4919]
21. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58. [Doi:10.1002/sim.1186]
22. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L, Moreno SG. Assessing publication bias in meta-analyses in the presence of between-study heterogeneity. Journal of the Royal Statistical Society: Series A (Statistics in Society). 2010;173(3):575-91. [Doi:10.1111/j.1467-985X.2009.00629.x]
23. Forgie IM, O'Neill KP, Lloyd-Evans N, Leinonen M, Campbell H, Whittle HC, et al. Etiology of acute lower respiratory tract infections in Gambian children: I. Acute lower respiratory tract infections in infants presenting at the hospital. Pediatr Infect Dis J. 1991;10(1):33-41. [Doi:10.1097/00006454-199101000-00008]
24. Ayieko P, Okiro EA, Edwards T, Nyamai R, English M. Variations in mortality in children admitted with pneumonia to Kenyan hospitals. PLoS One. 2012;7(11):e47622. [Doi:10.1371/journal.pone.0047622]
25. Lazzerini M, Seward N, Lufesi N, Banda R, Sinyeka S, Masache G, et al. Mortality and its risk factors in Malawian children admitted to hospital with clinical pneumonia, 2001-12: a retrospective observational study. Lancet Glob Health. 2016;4(1):e57-68. [Doi:10.1016/S2214-109X(15)00215-6]
26. Benet T, Sylla M, Messaoudi M, Sanchez Picot V, Telles JN, Diakite AA, et al. Etiology and Factors Associated with Pneumonia in Children under 5 Years of Age in Mali: A Prospective Case-Control Study. PLoS One. 2015;10(12):e0145447. [Doi:10.1371/journal.pone.0145447]
27. Bassat Q, Lanaspa M, Machevo S, O'Callaghan-Gordo C, Madrid L, Nhampossa T, et al. Hypoxaemia in Mozambican children <5 years of age admitted to hospital with clinical severe pneumonia: clinical features and performance of predictor models. Trop Med Int Health. 2016;21(9):1147-56. [Doi:10.1111/tmi.12738]
28. Sigauque B, Roca A, Bassat Q, Morais L, Quinto L, Berenguera A, et al. Severe pneumonia in Mozambican young children: clinical and radiological characteristics and risk factors. J Trop Pediatr. 2009;55(6):379-87. [Doi:10.1093/tropej/fmp030]
29. Abdulkadir MB, Ibraheem RM, Gobir AA, Johnson WBR. Hypoxaemia as a measure of disease severity in young hospitalised Nigerian children with pneumonia: A cross-sectional study. South African Journal of Child Health. 2015;9(2):53-6
30. Abdulkarim A, Ibraheem R, Adegboye A, Johnson W, Adeboye M. Childhood pneumonia at the University of Ilorin Teaching Hospital, Ilorin Nigeria. Nigerian Journal of Paediatrics. 2013;40(3):284-9

31. Johnson AW, Osinusi K, Aderele WI, Gbadero DA, Olaleye OD, Adeyemi-Doro FA. Etiologic agents and outcome determinants of community-acquired pneumonia in urban children: a hospital-based study. J Natl Med Assoc. 2008;100(4):370-85
32. Johnson WB, Aderele WI, Gbadero DA. Host factors and acute lower respiratory infections in pre-school children. J Trop Pediatr. 1992;38(3):132-6
33. Oyejide C, Osinusi K. Acute respiratory tract infection in children in Idikan community, Ibadan, Nigeria: severity, risk factors, and frequency of occurrence. Review of Infectious Diseases. 1990;12(Supplement 8):S1042-SI046
34. Zar HJ, Barnett W, Stadler A, Gardner-Lubbe S, Myer L, Nicol MP. Aetiology of childhood pneumonia in a well vaccinated South African birth cohort: a nested case-control study of the Drakenstein Child Health Study. Lancet Respir Med. 2016;4(6):463-72. [Doi:10.1016/S2213-2600(16)00096-5]
35. le Roux DM, Myer L, Nicol MP, Zar HJ. Incidence and severity of childhood pneumonia in the first year of life in a South African birth cohort: the Drakenstein Child Health Study. Lancet Glob Health. 2015;3(2):e95-e103. [Doi:10.1016/S2214-109X(14)70360-2]
36. Forgie IM, O'Neill KP, Lloyd-Evans N, Leinonen M, Campbell H, Whittle HC, et al. Etiology of acute lower respiratory tract infections in Gambian children: II. Acute lower respiratory tract infection in children ages one to nine years presenting at the hospital. Pediatr Infect Dis J. 1991;10(1):42-7. [Doi:10.1097/00006454-199101000-00009]
37. Legato MJ, Johnson PA, Manson JE. Consideration of Sex Differences in Medicine to Improve Health Care and Patient Outcomes. JAMA. 2016;316(18):1865-6. [Doi:10.1001/jama.2016.13995]
38. Legato MJ. Gender-specific medicine in the genomic era. Clin Sci (Lond). 2016;130(1):1-7. [Doi:10.1042/CS20150551]
39. Selwyn BJ. The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries. Coordinated Data Group of BOSTID Researchers. Review of Infectious Diseases. 1990;12 Suppl 8:S870-88
40. Henrickson KJ, Hoover S, Kehl KS, Hua W. National disease burden of respiratory viruses detected in children by polymerase chain reaction. Pediatr Infect Dis J. 2004;23(1 Suppl):S11-8. [Doi:10.1097/01.inf.0000108188.37237.48]
41. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ. 2008;86(5):408-16
42. Rudan I, O'Brien KL, Nair H, Liu L, Theodoratou E, Qazi S, et al. Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. J Glob Health. 2013;3(1):010401. [Doi:10.7189/jogh.03.010401]
43. Shann F. Etiology of severe pneumonia in children in developing countries. Pediatr Infect Dis. 1986;5(2):247-52
44. Sinaniotis CA. Viral pneumoniae in children: incidence and aetiology. Paediatr Respir Rev. 2004;5 Suppl A:S197-200
45. Weber MW, Mulholland EK, Greenwood BM. Respiratory syncytial virus infection in tropical and developing countries. Trop Med Int Health. 1998;3(4):268-80

46. Cardinale F, Cappiello AR, Mastrototaro MF, Pignatelli M, Esposito S. Community-acquired pneumonia in children. Early Hum Dev. 2013;89 Suppl 3:S49-52. [Doi:10.1016/j.earlhumdev.2013.07.023]
47. Chen K, Jia R, Li L, Yang C, Shi Y. The aetiology of community associated pneumonia in children in Nanjing, China and aetiological patterns associated with age and season. BMC Public Health. 2015;15:113. [Doi:10.1186/s12889-015-1422-1]
48. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. Clin Infect Dis. 2011;52 Suppl 4:S296-304. [Doi:10.1093/cid/cir045]

Supplementary file 1: Assessment of Risk of Bias for Nine Studies Included in the Review

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)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	LOW
Oyejide (1990)	Yes	Yes	Yes*	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
Forgie (1991)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Probably Yes	Yes	MODERATE
Johnson (2008)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
Sigauque (2009)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
Ayieko (2012)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
AbdulKarim (2015)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
le Roux (2015)	Yes	Yes	Yes*	Yes	NA	Yes	Yes	Yes	Yes	Yes	LOW
Bénet (2015)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	LOW
Abdulkadir (2015)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
Lazzerini (2016)	Yes	Yes	Probably Yes	Probably Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
Johnson (1992)	Yes	Yes	No	Yes	NA	Yes	Probably Yes	Yes	Yes	Yes	MODERATE
Bassat (2016)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE
Tornheim (2007)	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	MODERATE

* Some form of census undertaken NA – Not applicable

Supplementary file 2: Data extracted from the included studies

Numbe	Author	Year	Journal	Design	Aim	setting	Pneumonia	bronchiolitis	Age group	Incidence study	evalence stu	etiology stu	CFR reporte
1	Oyejide	1990	Reviews of	Longitudina	Determine	Nigeria	Yes	No	<5 years	Yes	No	No	No
2	Forge	1991	Pediatric in	Prospective	To investig	The Gambi	Yes	No	<12 months	No	No	Yes	No
3	Johnson	1992	Journal of T	Prospective	To study ba	Nigeria	Yes	Yes	<5 years	No	No	Yes	No
4	Johnson	2008	Journal Of	Prospective	To determi	Nigeria	Yes	No	<5 years	No	No	No	Yes
5	Sigauque	2009	Journal of T	prospective	To assess f	Southern M	Yes	No	0–23 months	No	No	No	Yes
6	Aiyeko	2012	PLoS One	Retrospecti	To analyse	Kenya	Yes	No	<5 years	No	No	No	Yes
7	AbdulKari	2013	Nigeria Jou	Prospective	To investig	Ilorin, Nige	Yes	No	1-110 month	No	No	No	Yes
8	Abdulkadi	2015	South Afric	Prospective	To determi	Ilorin, Nige	Yes	No	2-59 months	No	No	No	Yes
9	Bénet	2015	PLOS One	Prospective	To assess t	Mali	Yes	No	<5 years	No	No	No	Yes
10	le Roux	2015	Lancet Glol	Prospective	To assess t	South Afric	Yes	No	<12 months	Yes	No	No	No
11	Bassat	2016	Tropical M	Prospective	To study cli	Mozambiqu	Yes	No	<2years	No	No	Yes	Yes
12	Zar	2016	Lancet Res	Nested cas	To investig	South Afric	Yes	No	3-19 months	No	No	Yes	Yes
13	Lazzerini	2016	Lancet Glol	Retrospecti	To describe	Hospitals, I	Yes	No	<5 years	No	No	No	Yes
14	Tornheim	2007	Int J. Infect	Retrospecti	To characte	Kenya	Yes	No	0- >65 year	Yes	No	No	No

Supplementary file 2: Data extracted from the included studies continue…

incidence in male	dence in fer	revalence in ma	evalence in fem	crude association	adjusted association	total_LRTI	al_bronchio	al_pneumo	otal_contro	
7.	6.	NR	NR	NR	NR	860	NR	860	NR	
NR	NR	NR	NR	NR	NR	90	NR	90		43
NR	NR	NR	NR	NR	NR	103	14	89	NR	
NR	NR	NR	NR	NR	NR	323	NR	323	NR	
NR	NR	NR	NR	M/F, OR =0.83 (0.51–1.33)	NR	757	NR	757		4081
NR	NR	NR	NR	0.89 (0.74–1.12)	0.87 (0.64–1.19)	3205	NR	3205	NR	
NR	NR	NR	NR	NR	NR	167	NR	167	NR	
NR	NR	NR	NR	NR	NR	200	NR	200	NR	
NR	NR	NR	NR	M/F only Chi square	NR	118	NR	118		98
NR	NR	NR	NR	incide M/F 2·02 (1·40–2·96)	NR	697	NR	697	NR	
NR	NR	NR	NR	NR	NR	834	NR	834	NR	
NR	NR	NR	NR	NR	NR	314	NR	314	NR	
NR	NR	NR	NR	F/M, OR = 1.37 (1.29 – 1.47)	F/M, OR = 1.38 (1.25 - 1.52)	110617	NR	110617	NR	
NR	NR	NR	NR	incide M/F 0.84 (0.75–0.95)	NR	1078	NR	1078	NR	

Supplementary file 2: Data extracted from the included studies continue…

male_cases	ale_cases_t	nale_control	e_controls	ile_pneumo	ale_pneum	ale_bronch	male_bronch	s_pneum_	s_pneum_f	h_bronch_	n_bronch_fer	detella_m	rdetell_fem	mophiluB_r
487	374	NR	NR	487	374	NR	NR	NR	NR	NR	NR	NR	NR	NR
51	39	18	25	51	39	NR	NR	NR	NR	NR	NR	NR	NR	NR
55	48	NR	NR	55	48	NR	NR	NR	NR	NR	NR	NR	NR	NR
177	146	NR	NR	177	146	NR	NR	22	13	NR	NR	NR	NR	NR
440	317	2164	1917	440	317	NR	NR	46	30	NR	NR	NR	NR	NR
1762	1443	NR	NR	1762	1443	NR	NR	97	90	NR	NR	NR	NR	NR
100	67	NR	NR	100	67	NR	NR	10	1	NR	NR	NR	NR	NR
119	81	NR	NR	119	81	NR	NR	12	5	NR	NR	NR	NR	NR
57	61	36	62	57	61	NR	NR	1	4	NR	NR	NR	NR	NR
372	325	NR	NR	97	44	NR	NR	NR	NR	NR	NR	NR	NR	NR
502	332	NR	NR	502	332	NR	NR	47	35	NR	NR	NR	NR	NR
192	92	228	190	192	228	NR	NR	2	1	NR	NR	NR	NR	NR
49639	60978	NR	NR	46138	56570	NR	NR	3400	3333	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Supplementary file 2: Data extracted from the included studies continue…

mophilB_fe	rcoplasma_m	oplasm_fe	nphyloco_m	phyloc_fem	nfluenza_m	fluenza_fe	reptococ_m	eptoco_fem	oraxella_m	araxella_fem	RSV_male	RSV_female	fluenza_ma	luenza_fem
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	9	12	NR	NR
NR	NR	NR	7	7	1	0	1	1	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	24	22	NR	NR	29	20	NR	NR
NR	NR	NR	NR	NR	26	1	NR	NR	NR	NR	41	38	26	14
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Supplementary file 2: Data extracted from the included studies continue…

rainflue_m	rainflu_fem	enovirus_m	enoviru_fem	etapn_mal	etapn_fem	cavirus_m	cavirus_fem	ytomeg_ma	tomeg_fem	ronavir_m	onavir_fem	terovir_m	terovir_fem	hinovir_mal
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	68	34	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	125
36	16	48	29	NR	NR	33	16	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Supplementary file 2: Data extracted from the included studies continue…

inovir_fem	eumocys_m	umocys_fem	ther_orgma	her_orgfem	bordetell2	bordetell3	haemophil2	haemophil3	mycoplasm	mycoplasm	staphyloc2	staphyloc3	h2	h3
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
69	28	29	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Supplementary file 2: Data extracted from the included studies continue…

streptoco2	streptoco3	moraxella2	moraxella3	respirato2	respirato3	infl2	infl3	parainflu2	parainflu3	adenoviru2	adenoviru3	netapneum	netapneum	bocavirus2
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Supplementary file 2: Data extracted from the included studies continue…

bocavirus3	cytomegal2	cytomegal3	coronavir2	coronavir3	enterovir2	enterovir3	rhinoviru2	rhinoviru3	neumocys	pneumocys	others2	others3
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
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