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Review

Case fatality rate and viral aetiologies of acute respiratory tract infections in HIV positive and negative people in Africa: The VARIAFRICA-HIV systematic review and meta-analysis

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ABSTRACT

Background: To set priorities for efficient control of acute respiratory tract infection (ARTI) in Africa, it is necessary to have accurate estimate of its burden, especially among HIV-infected populations.
Objectives: To compare case fatality rate (CFR) and viral aetiologies of ARTI between HIV-positive and HIV-negative populations in Africa.
Study design: We searched PubMed, EMBASE, Web of Knowledge, Africa Journal Online, and Global Index Medicus to identify studies published from January 2000 to April 2018. Random-effect meta-analysis method was used to assess association (pooled weighted odds ratios (OR) with 95% confidence interval (CI)).
Results: A total of 36 studies (126,526 participants) were included. CFR was significantly higher in patients with HIV than in HIV-negative controls (OR 4.10, 95%CI: 2.63–6.27, I^2: 93.7%). The risk was significantly higher among children ≤5 years (OR 5.51, 95%CI 2.83–10.74) compared to people aged > 5 years (OR 1.48, 95%CI 1.17–1.89); p = 0.0002. There was no difference between children (15 years) and adults and between regions of Africa. There was no difference for viral respiratory aetiologies (Enterovirus, Adenovirus, Bocavirus, Coronavirus, Metapneumovirus, Parainfluenza, Influenza, and Respiratory Syncytial Virus) of ARTI between HIV-positive and HIV-negative people, except for Rhinovirus where being HIV-negative was associated with Rhinovirus (OR 0.70; 95%CI 0.51–0.97, I^2: 63.4%).
Conclusions: This study shows an increased risk of deaths among HIV-infected individuals with ARTI, however with no difference in viral aetiologies compared to HIV-negative individuals in Africa. ARTI deserves more attention from HIV health-care providers for efficient control. Specific strategies are needed for HIV-positive children under 5.

1. Background

Acute respiratory infections represent one of the major public health concerns. Among these respiratory infections, pneumonia causes about 15% (1 million) of infectious and non-infectious deaths of children under 5 every year and represents the leading infectious cause of death worldwide among this age group [1]. In general population, respiratory viruses are responsible for most of the acute respiratory infections and several risk factors including HIV infection, have been associated with severe acute respiratory infections [2–4]. Data from original studies have shown that irrespective of antiretroviral therapy, morbidity and mortality from acute respiratory infections remains higher in HIV positive individuals than HIV negative individuals [5,6]. Evidence suggest that the burden, in term of deaths, of respiratory viral infections like influenza is higher in Africa compared to other regions [7]. This burden can be fuelled by HIV infection in Africa where about 70% of all HIV

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positive individuals resided in 2016 [8]. Estimating the burden of respiratory infections in HIV-positive patients in Africa is therefore crucial for guiding health decision making for efficient control of ARTI in Africa. To date, influenza vaccine is not integrated in the immunization program of almost all African countries [9]. In addition, with the imminent availability of human respiratory syncytial virus vaccines, it is necessary to set priorities for vaccination and management of acute respiratory infections in Africa, and more particularly in people living with HIV.

Although several studies in Africa have contributed to show a greater severity of respiratory infections among HIV positive people [10], there is currently no systematic review with meta-analysis comparing the case fatality rate (CFR) between HIV-positive and -negative individuals with respiratory tract infections at the continent level. Comparing HIV-positive and -negative individuals regarding ARTI would help to know in which direction specific interventions are needed. Any identified difference would help to know in which direction specific strategies are needed for people living with HIV.

Therefore, to the best of our knowledge, we conducted the first systematic review and meta-analysis to investigate whether current data may suggest specific attention to HIV-positive individuals; with the aim for better control and preventive strategies for acute respiratory infections. Specifically, we aimed to compare the proportion of Viral Aetiologies of Acute Respiratory tract Infections in Africa between HIV-positive (VARIAFRICA-HIV) and HIV-negative populations. We also aimed to compare CFR between HIV-positive and HIV-negative populations with acute respiratory tract infections (ARTI).

2. Study design

2.1. Design

This systematic review and meta-analysis was reported following the PRISMA guidelines as illustrated by the checklist (Supplementary Table 1) [11]. The systematic review is registered in PROSPERO, CRD42018088261.

2.2. Eligibility criteria

We considered cross-sectional, case control, and cohort studies including both HIV-positive and HIV-negative populations with ARTI, residing in Africa regardless of age and ethnicity. The primary outcome of interest was case fatality rate and the secondary outcome was proportion of respiratory viral aetiologies of ARTI. Respiratory viruses had to be identified with polymerase chain reaction technique (PCR). Studies conducted during outbreak periods, studies including only HIV positive people or only HIV negative people were excluded.

2.3. Search strategy for identifying relevant studies

We did a comprehensive search on electronic databases among which Medline (through PubMed), Excerpta Medica Database, African Journals Online, Web of Knowledge, and Global Index Medicus. The search strategy was adapted to suit each database as illustrated by the search on PubMed (Supplementary Table 2). We considered studies published from 1st January 2000 until 30 April 2018, without any language restriction. We arbitrary limited to 2000 to have contemporaneous and recent data since the epidemiology of HIV infection was drastically changed in the last years. To supplement the electronic search, references of all relevant studies were also screened for potential consideration.

2.4. Selection of studies for inclusion in the review

Two review authors (SK and AFM) independently screened the titles and abstracts of aggregated citations retrieved from the electronic search, and full texts of potentially eligible articles were further assessed for inclusion. Disagreements were resolved through discussion and unreached consensus was resolved by a third review author (JJB). The Kappa statistics were used to estimate the agreement on study selection between the review authors before discussion [12].

2.5. Data extraction and management

Data were extracted independently by two review authors (SK and AFM) and double checked by a third review author (JJB) for accuracy. In case of missing data in an article, the authors of this article were contacted to request the unreported details. Data extracted included:

- Description of the article: name of the first author, year of publication;
- Study characteristics: study design, sampling method, timing of data collection, period of participants' recruitment, setting, location (country and regions according to United Nations Statistical Division);
- Participants' characteristics: clinical presentation, types of sample used for viral detection, mean/median age, age group, and proportion of males.
- Proportions of respiratory viral aetiologies of ARTI and case fatality rate in both HIV positive and HIV negative groups or enough data to compute these estimates.

2.6. Risk of bias assessment

The methodological quality of the studies was assessed using Newcastle Ottawa Scale [13]. Scoring questions on a scale of 0 (no) and 1 (yes) was assigned to each item to have a total score for each article. According to the total score obtained, each article was classified as high risk (0–3 points), moderate risk (4–6 points), and low risk of bias (7–9 points). The assessment was done by two review authors (SK and JJB) and discrepancies were resolved through discussion and consensus. The kappa statistics were used to investigate the agreement between the review authors before discussion [12].

2.7. Data synthesis and analysis

We did data meta-analyses using the package '*meta*' (version 4.9-2) of R (version 3.5.1, The R Foundation for Statistical Computing). Random-effect meta-analysis by Mantel-Haenszel (MH) method was used to assess the association between HIV infection and case fatality rate or viral aetiologies, and reported as pooled weighted odds ratios (OR) with both 95% confidence and 95% prediction intervals [14]. Symmetry of counter-enhanced funnel plots (for outcome with 10 studies or more) and Harbord test were used to assess reporting and publication bias [15]. Consideration of significant publication bias was at a threshold of $p < 0.10$. Heterogeneity across studies was assessed by χ^2 on Cochran's Q test, and reported as I^2 statistics [16]. In case of substantial heterogeneity ($I^2 > 50\%$) [17], we did subgroup-analysis (people aged $\leq$ 5 years versus $>$ 5 years, adults ($>$ 15 years) versus children, and UNSD regions) to investigate possible sources of residual heterogeneity.

3. Results

3.1. Study selection and characteristics

Initially, we identified 1721 records. Finally, 36 full texts were retained for the review and included in the meta-analysis [18–53] (Fig. 1). The inter-rater agreement for study selection was high ($\kappa = 0.74$). Of the 36 included studies, 18 (50%) low risk of bias, 18 (50%) moderate risk of bias, none had high risk of bias. In total, 126,526 participants were included. Data were from nine countries. No

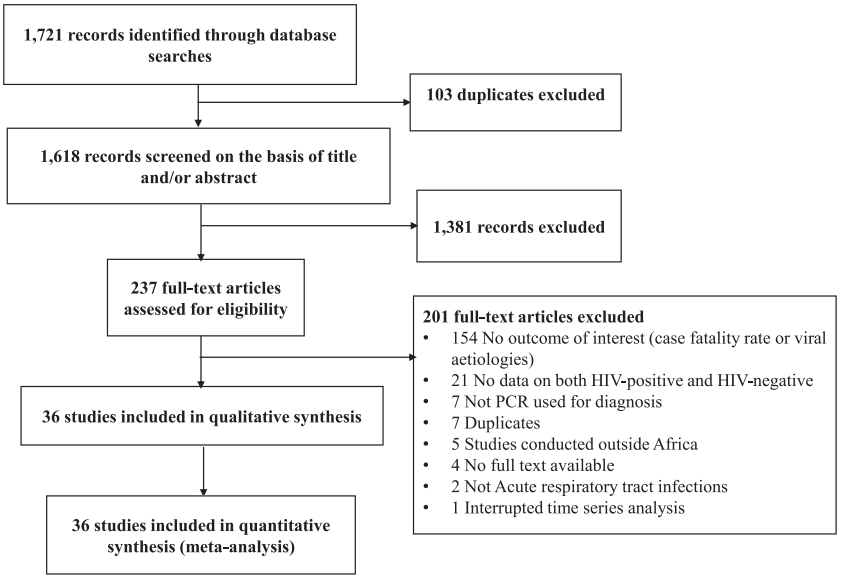

Fig. 1. Flow diagram of study selection.

data were from western and northern Africa. One study was from central Africa, 14 from eastern Africa, and 21 from southern Africa. Characteristics of included studies are presented in the Supplementary Table 3 and detailed in the Supplementary Table 4.

3.2. Case fatality rate

In total, 60,224 participants were included in the analysis for case fatality rate. Case fatality rate was significantly higher among HIV-positive (1514/18159, 8.3%) than HIV-negative people (1555/38996, 4.0%) (pooled OR 4.10, 95% CI 2.63–6.27, I^2: 93.7%, 25 studies; Fig. 2). There was most probably missing data on the bottom left-hand-side of the counter-enhanced funnel plot (Supplementary Fig. 1), as confirmed by the Harbord test (p = 0.0009; Supplementary Table 5). However, since the majority of this area contains regions of high statistical significance, this reduces the plausibility that publication bias is the underlying cause of this funnel asymmetry. However, after adjustment with Trim-and-Fill method (Supplementary Fig. 2), the pooled OR was 1.28 (95%CI 0.84–1.95, 43 (18 added) studies, I^2 = 95.7%) (Supplementary Table 6). The sensitivity analysis including only low risk of bias studies yielded a finding close to that of crude analysis: pooled OR 4.33, 95% CI 2.02–9.29, 11 studies.

	HIV Positive		HIV Negative			Odds Ratio	Odds Ratio
Study	Events	Total	Events	Total	Weight	MH, Random, 95% CI	MH, Random, 95% CI
Cohen, 2015 [1]	3	78	7	591	3.4%	3.61 [0.99; 13.14]	
Cohen, 2015 [2]	352	4642	87	1660	4.8%	1.48 [1.16; 1.88]	
Cohen, 2015 [3]	47	695	46	5240	4.7%	8.18 [5.42; 12.36]	
Cohen, 2015 [4]	22	419	13	620	4.4%	2.55 [1.28; 5.06]	
Cohen, 2016	27	207	44	2281	4.6%	7.66 [4.65; 12.62]	
Graham, 2011	18	134	4	130	3.8%	4.46 [1.55; 12.89]	
Hellferscee, 2017	8	107	5	434	3.7%	6.67 [2.23; 19.93]	
Hooli, 2016	18	152	50	1999	4.5%	5.31 [3.03; 9.30]	
Jeena, 2006	4	106	6	358	3.5%	2.38 [0.70; 8.08]	
Jeena, 2007	3	82	2	284	2.9%	4.97 [0.96; 25.70]	
Kelly, 2015	2	20	12	217	3.2%	2.22 [0.53; 9.37]	
Lazzerini, 2016	579	9061	1024	19370	4.9%	1.22 [1.10; 1.36]	
Madhi, 2000 [1]	72	548	13	617	4.5%	6.81 [3.76; 12.33]	
Madhi, 2000 [2]	59	433	12	497	4.5%	6.17 [3.30; 11.52]	
Madhi, 2007	2	45	0	154	1.4%	17.76 [0.84; 376.84]	
Majozi, 2017	12	65	43	273	4.4%	1.24 [0.62; 2.48]	
Moyes, 2017	21	218	5	53	3.9%	0.96 [0.36; 2.58]	
Ngari, 2017	17	85	51	2035	4.5%	9.84 [5.44; 17.82]	
Nunes, 2014	92	517	9	943	4.4%	21.38 [10.86; 42.11]	
Scott, 2000	14	117	11	113	4.2%	1.25 [0.55; 2.84]	
Sigaúque, 2009	13	49	3	146	3.5%	15.16 [4.43; 51.91]	
Srinivasan, 2012	7	55	12	256	4.0%	3.02 [1.16; 7.87]	
Sutcliffe, 2016	82	111	84	582	4.6%	16.50 [10.21; 26.65]	
Yone, 2012	9	62	4	44	3.6%	1.60 [0.48; 5.27]	
Zar, 2001	31	151	8	99	4.2%	2.81 [1.26; 6.29]	
Total (95% CI)	**1514**	**18159**	**1555**	**38996**	**100.0%**	**4.07 [2.64; 6.27]**	
Prediction interval						**[0.49; 33.79]**	

Heterogeneity: Tau^2 = 0.9989; Chi^2 = 380.38, df = 24 (P < 0.0001); I^2 = 93.7% [91.8%; 95.1%]

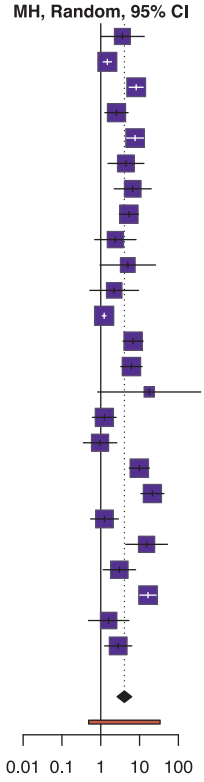

Fig. 2. Comparison of case fatality rate between HIV-positive and HIV-negative populations with acute respiratory tract infections in Africa.

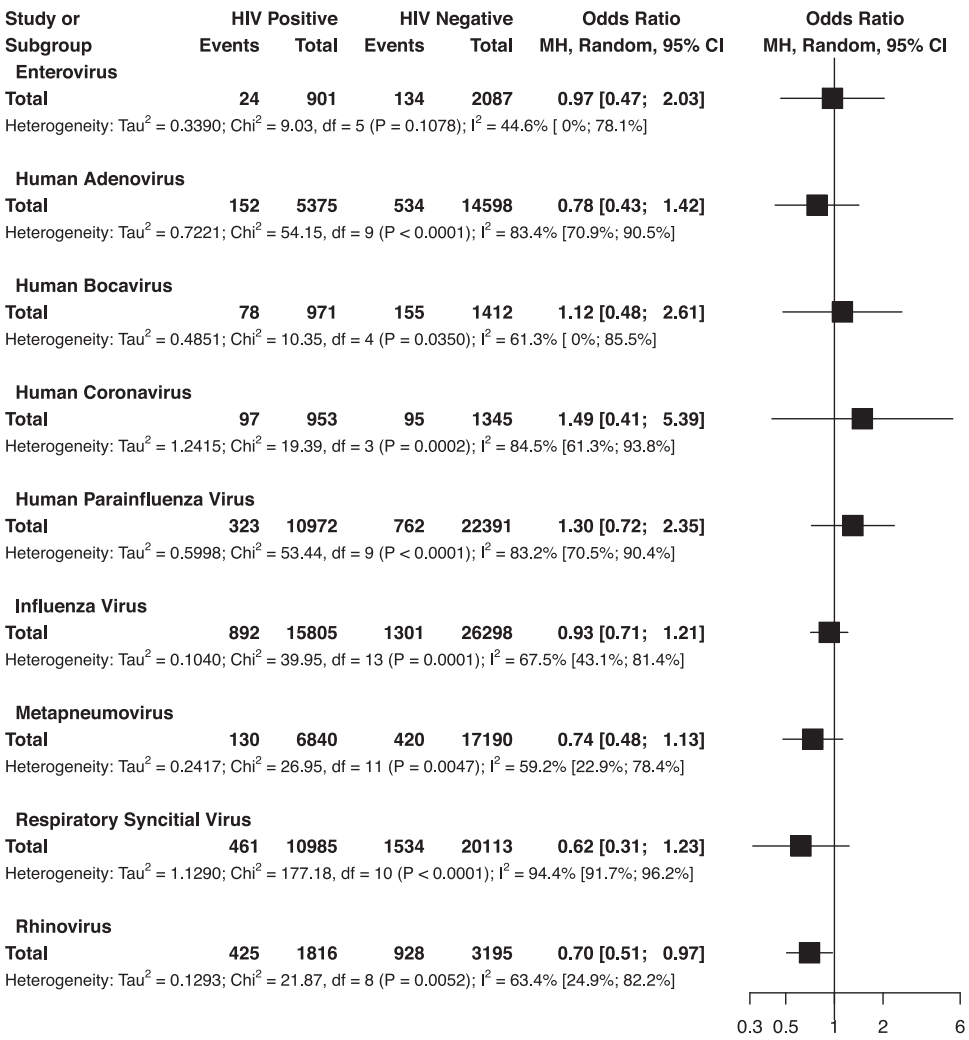

Fig. 3. Comparison of viral aetiologies of acute respiratory tract infections between HIV-positive and HIV-negative populations with in Africa.

In subgroup analysis, the strength of the association between HIV-infection and CFR was significantly higher among children ≤ 5 years (pooled OR 5.51, 95%CI 2.83–10.74) compared to people aged > 5 years (pooled OR 1.48, 95%CI 1.17–1.89), p = 0.0002 (Supplementary Fig. 3). There was no difference between children (< 15 years) and adults (Supplementary Figure 4) and between regions (Supplementary Figure 5).

3.3. Viral aetiologies of acute respiratory tract infections

In total, 76,174 participants were included in the analysis for viral aetiologies. There was no difference for all the viral respiratory aetiologies (Enterovirus, Human Adenovirus, Human Bocavirus, Human Coronavirus, Human Parainfluenza Virus, Influenza Virus, Human Metapneumovirus, and Respiratory Syncytial Virus) of ARTI between HIV positive and HIV negative people, except for Rhinovirus where HIV-positive persons were less likely to be infected with Rhinovirus than HIV-negative (pooled OR 0.70; 95%CI 0.51-0.97) (Fig. 3). The figure with detailed studies is in the Appendix (Supplementary Figure 6).

Funnel plots for Human Adenovirus, Respiratory Syncytial Virus, Human Parainfluenza Virus, Influenza Virus, and Human Metapneumovirus were presented in Supplementary Figures 7–11, respectively. There was no publication bias for all viruses except for Human Parainfluenza Virus and Human Metapneumovirus (Supplementary Table 5). For both viruses with significant publication bias, there was most probably missing data on the bottom left-hand-side of the counter-enhanced funnel plot reducing the plausibility that publication bias is the underlying cause of this funnel asymmetry. After adjustment with Trim-and-Fill method, HIV positive individuals were less likely to be infected by Human Parainfluenza virus (OR: 0.52; 95%CI: 0.31-0.87; I^2 = 86.4%) and Human Metapneumovirus (OR: 0.46; 95%CI 0.29-0.73, 19; I^2 = 69.2%) (Supplementary Table 5).

In subgroup analysis, there was no difference between children and adults for all respiratory viruses (Supplementary Table 6). The association of HIV infection with the following respiratory viral infections was different between people aged > 5 years and those aged ≤5 years: Human Adenovirus (≤5 years: OR 1.00 [95%CI 0.61–1.64] vs > 5 years: OR 3.91 [95%CI 2.01–7.61]; p = 0.0013), Respiratory Syncytial Virus (≤5 years: OR 0.62 [95%CI 0.31–1.26] vs > 5 years: OR 4.30 [95%CI 2.09–8.87]; p = 0.0002), Human Parainfluenza Virus (≤5 years: OR 1.38 [95%CI 0.73–1.26] vs > 5 years: OR 4.30 [95%CI 2.09–8.87]; p = 0.0002), and Human Metapneumovirus (≤5 years: OR 0.46 [95%CI 0.35-0.60] vs > 5 years: OR 3.00 [95%CI 1.27–7.04]; p < 0.0001) (Supplementary Table 6). The association of HIV infection with the following respiratory viral infections was different between different regions: Respiratory Syncytial Virus (Eastern region: OR 1.50 [95%CI 0.58–3.89] vs Southern: OR 0.40 [95%CI 0.18-0.90]; p = 0.039) and Human Parainfluenza Virus (Eastern region: OR 4.01 [95%CI 2.23–7.24] vs Southern: OR 0.69 [95%CI 0.50-0.96]; p < 0.0001), and Human Metapneumovirus (Eastern region: OR 1.50 [95%CI 0.53–4.22] vs Southern: OR 0.48 [95%CI 0.38-0.61];

p = 0.037) (Supplementary Table 6).

4. Discussion

To the very best of our knowledge this is the first systematic review and meta-analysis to compare the CFR between HIV-positive and -negative people with ARTI in Africa and also to investigate the association between HIV infection and viral aetiologies of ARTI in Africa. Key findings of this review include higher rate of mortality in HIV positive people compared to HIV negative with the burden higher among those aged < 5 years. Another key finding is that in general there was no difference in the viral aetiologies of ARTI between HIV positive and HIV negative people, except for Rhinovirus which was less associated with HIV infection.

As for other communicable and for non-communicable diseases, HIV positive individuals with ARTI have a higher risk of death compared to HIV negative individuals. The explanation lies globally in the immune response and on how work antiretroviral therapy. Immune response in HIV positive patients with ARI may include low levels of antibodies, low level of CD4 + T cell, and other potential immunological dysfunctions that may promote increased mortality in this group of patients [54–56]. The specific pathogenesis that may explain the association between HIV infection and the increased risk of death in patients with acute respiratory infections is not well understood. Unlike our review, studies conducted outside Africa suggested that the presence of HIV infection did not influence the clinical outcomes of people with ARTI [57–60]. This difference can be explained by the fact that people living with HIV in Africa compared to developed countries can experience more limited access to healthcare for advanced HIV disease, malnutrition, parasitic diseases, and low antiretroviral treatment coverage [57,58,60]. Therefore, in an African context, the higher risk of death in people with HIV can not only be explained by HIV infection itself. We found an increased risk of death among children < 5 years. This finding is close to that of general population of children. Indeed, ARTI have a disproportionate effect on children younger than 5 years with increased risk of death and disability-adjusted life-years [61]. The increased mortality among this population may be related to the immaturity of their immune response compared to adults, especially in the case of HIV infection [61]. In addition, evidence support that the adherence to antiretroviral therapy is lower in children compared to adults [62,63]. As antiretroviral therapy is a key component to curb the mortality in HIV positive people, children under five with suboptimal observance to antiretroviral therapy, in addition to a weak immune response in the case of ARTI, can therefore present higher risk of death compared to adults.

The lack of difference in the respiratory virus for ARTI between HIV-positive and negative individuals suggests that the difference in the germs leading to ARTI may come from others such as bacteria and fungi including tuberculosis and *pneumocystis jirovecii* [64–67]. Indeed, HIV-positive and negative individuals live in the same ecosystems and can therefore be contaminated in the community through air transmission with same microorganisms. In the strategies for curbing the burden of disease related to ARTI, efforts to control respiratory viral infection in terms of viral aetiologies should be the same between HIV positive and negative individuals.

Our findings demonstrated that ARTI deserves more attention from HIV health-care providers, researchers, policy makers, and stakeholders for improved detection, overall proper management, and efficient control of ARTI in people with HIV in Africa, especially for children under 5. Although strategies to curb the burden of ARTI coordinated by the WHO made some advances from 1980 to 1990 toward reducing childhood mortality from LRTI, the HIV epidemic had reduced the efforts made so far [68]. The reduction of morbidity and mortality of ARTI in Africa should not only focus on HIV infection and also requires a multifaceted approach that includes addressing risk factors like smoking, second hand smoking, indoor pollution, undernutrition especially among children under five years old [69]. Strategies to curb the burden among HIV positive individuals can include using viral and conjugate bacterial vaccines to reduce colonization and consequently the microbiological load in the environment of HIV positive individuals [70]. When indicated among HIV-positive individuals, healthcare providers should adhere to guidelines for chemoprophylaxis with cotrimoxazole to prevent among others, respiratory infections among people living with HIV [71,72]. To improve the immunity of HIV positive individuals, routine micronutrient supplements, especially multivitamins can be used. Multivitamins have shown to have benefit in reducing the prevalence of ARTI in HIV positive people [73]. One of the most important point to curb the burden of ARTI is to early initiate antiretroviral treatment among all HIV positive people regardless of CD4 cells count and age as recommended by World Health Organization (WHO) [74]. Antiretroviral treatment has been shown to reduce the frequency of most opportunistic infections and significantly reduce HIV-related mortality, including among people with respiratory tract infections [57–60]. However, implementing this WHO guidelines remain challenging in Africa, a continent with poor human and financial resources and weak healthcare infrastructures [75]. Surveillance for antimicrobial resistance resulting from repeated and prophylactic antibiotic use among HIV positive individuals and its clinical impact should be investigated in future studies. Research are also needed to investigate the effectiveness of vaccine for respiratory pathogens among HIV positive individuals.

This review should be interpreted in consideration of certain limitations. First and common to most reviews of this type, we found a high heterogeneity between studies explained by age groups. However, we were unable to investigate other sources due to inconsistency in reporting of covariates throughout included studies. Second, the various UNSD sub-regions in Africa were not proportionally represented in the review, which may hinder the translatability of our findings to the entire continent. Third, all included studies were observational, which could lead to bias because of unmeasured confounders between HIV positive and negative. Nonetheless and to the best of our knowledge, this is the first systematic review and meta-analysis which has given a clear and accurate estimate of CFR among HIV positive individuals with ARTI compared to HIV-negative with ARTI. It is also the first to investigate association between HIV infection and specific respiratory viral aetiology of ARTI. We searched the biggest electronic databases and used rigorous methodological and statistical procedures to generate our estimates. All studies were assessed as having low to moderate risk of bias in their methodological quality, suggesting that we can be confident in the quality of these estimates. Indeed, the sensitivity analysis including only low risk of bias studies yielded an estimate close to that of crude analysis in CFR analysis. We also considered only studies using polymerase chain reaction as diagnostic method of viral aetiologies of ARTI.

This systematic review and meta-analysis shows an increased risk of deaths among HIV-positive individuals with ARTI compared to HIV negative with ARTI control counterparts, especially among children < 5 years. However, there is no difference in viral aetiologies of ARTI infections between HIV positive and HIV negative individuals in Africa. As such, ARTI deserves more attention from HIV health-care providers, researchers, policy makers, and stakeholders for overall proper management, and efficient control of ARTI in people with HIV in Africa. Specific strategies are needed for HIV-positive children under 5.

Data sharing and data accessibility

All data generated or analysed during this study are included in this published article and its supplementary information files.

Authors' contributions

Conception: SK, JJB, RN. Design: SK, JJB, ET, MSN, RN. Literature

search: JJB. Selection of studies: SK, AFM, JJB. Full texts search: SK. Data extraction: SK, AFM, JJB. Data synthesis and analysis: JJB, SK. Data interpretation: JJB, SK, MSN, ET. Manuscript drafting: SK, JJB. Manuscript editing and revision: SK, JJB, AFM, FBNS, PAN, MSN, ST, ET, RN. Manuscript final version approval: SK, JJB, AFM, FBNS, PTN, MSN, ST, ET, RN. Guarantor of the review: RN.

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Ethical approval

Not required.

Declaration of Competing Interest

The authors declare that they have no competing interests.

CRediT authorship contribution statement

Sebastien Kenmoe: Conceptualization, Data curation, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Jean Joel Bigna:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Abdou Fatawou Modiyingi:** Data curation, Writing - review & editing. **Marie S. Ndangang:** Writing - review & editing. **Paul Alain Ngoupo:** Writing - review & editing. **Fredy Brice N. Simo:** Writing - review & editing. **Serges Tchatchouang:** Writing - review & editing. **Elvis Temfack:** Data curation, Methodology, Writing - review & editing. **Richard Njouom:** Conceptualization, Methodology, Project administration, Supervision, Validation, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcv.2019.06.006.

References

[1] L. Liu, S. Oza, D. Hogan, J. Perin, I. Rudan, J.E. Lawn, et al., Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis, Lancet 385 (2015) 430–440.
[2] C. Figueiredo-Mello, P. Naucler, M.D. Negra, A.S. Levin, Prospective etiological investigation of community-acquired pulmonary infections in hospitalized people living with HIV, Medicine 96 (2017) e5778.
[3] A. Muller, D. Klinkenberg, J. Vehreschild, O. Cornely, R.L. Tillmann, C. Franzen, et al., Low prevalence of human metapneumovirus and human bocavirus in adult immunocompromised high risk patients suspected to suffer from Pneumocystis pneumonia, J. Infect. 58 (2009) 227–231.
[4] J. Garbino, S. Inoubli, E. Mossdorf, R. Weber, M. Tamm, P. Soccal, et al., Respiratory viruses in HIV-infected patients with suspected respiratory opportunistic infection, AIDS 22 (2008) 701–705.
[5] P. Gona, R.B. Van Dyke, P.L. Williams, W.M. Dankner, M.C. Chernoff, S.A. Nachman, et al., Incidence of opportunistic and other infections in HIV-infected children in the HAART era, Jama 296 (2006) 292–300.
[6] S. Madhi, N. Ramasamy, K. Petersen, A. Madhi, K. Klugman, Severe lower respiratory tract infections associated with human parainfluenza viruses 1-3 in children infected and noninfected with HIV type 1, Eur. J. Clin. Microbiol. Infect. Dis. 21 (2002) 499–505.
[7] A.D. Iuliano, K.M. Roguski, H.H. Chang, D.J. Muscatello, R. Palekar, S. Tempia, et al., Estimates of global seasonal influenza-associated respiratory mortality: a modelling study, Lancet 391 (2018) 1285–1300.
[8] UNAIDS, Global HIV & AIDS Statistics - 2018 Fact Sheet, UNAIDS, 2018.
[9] J. Duque, M.L. McMorrow, A.L. Cohen, Influenza vaccines and influenza antiviral drugs in Africa: are they available and do guidelines for their use exist? BMC Public Health 14 (2014) 41.
[10] S.A. Madhi, M. Venter, A. Madhi, K. Petersen, K.P. Klugman, Differing manifestations of respiratory syncytial virus-associated severe lower respiratory tract infections in human immunodeficiency virus type 1-infected and uninfected children, Pediatr. Infect. Dis. J. 20 (2001) 164–170.
[11] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, J. Clin. Epidemiol. 62 (2009) 1006–1012.
[12] M.L. McHugh, Interrater reliability: the kappa statistic, Biochem. Med. (Zagreb) 22 (2012) 276–282.
[13] G.A. Wells, B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, et al., The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, The Ottawa Hospital, 2018.
[14] R. DerSimonian, N. Laird, Meta-analysis in clinical trials revisited, Contemp. Clin. Trials 45 (2015) 139–145.
[15] M. Egger, G. Davey Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, Bmj. 315 (1997) 629–634.
[16] J.P. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Stat. Med. 21 (2002) 1539–1558.
[17] W.G. Cochran, The combination of estimates from different experiments, Biometrics 10 (1954) 101–129.
[18] A.A. Annamalay, S. Abbott, C. Sikazwe, S.K. Khoo, J. Bizzintino, G. Zhang, et al., Respiratory viruses in young South African children with acute lower respiratory infections and interactions with HIV, J. Clin. Virol. 81 (2016) 58–63.
[19] A.A. Annamalay, M. Lanaspa, S.K. Khoo, L. Madrid, S. Acácio, G. Zhang, et al., Rhinovirus species and clinical features in children hospitalised with pneumonia from Mozambique, Trop. Med. Int. Health 21 (2016) 1171–1180.
[20] A.L. Cohen, P.K. Sahr, F. Treurnicht, S. Walaza, M.J. Groome, K. Kahn, et al., Parainfluenza virus infection among human immunodeficiency virus (HIV)-infected and HIV-uninfected children and adults hospitalized for severe acute respiratory illness in South Africa, 2009-2014, Open Forum Infect. Dis. 2 (2015) 1–9.
[21] C. Cohen, S. Walaza, J. Moyes, M. Groome, S. Tempia, M. Pretorius, et al., Epidemiology of Severe Acute Respiratory Illness (SARI) among adults and children aged ≥5 years in a high HIV-prevalence setting, 2009-2012, PLoS One 10 (2015).
[22] C. Cohen, S. Walaza, J. Moyes, M. Groome, S. Tempia, M. Pretorius, et al., Epidemiology of viral-associated acute lower respiratory tract infection among children < 5 years of age in a high HIV prevalence setting, South Africa, 2009-2012, Pediatr. Infect. Dis. J. 34 (2015) 66–72.
[23] C. Cohen, J. Moyes, S. Tempia, M. Groome, S. Walaza, M. Pretorius, et al., Mortality amongst patients with influenza-associated severe acute respiratory illness, South Africa, 2009-2013, PLoS One 10 (2015).
[24] C. Cohen, J. Moyes, S. Tempia, M. Groome, S. Walaza, M. Pretorius, et al., Epidemiology of acute lower respiratory tract infection in HIV exposed uninfected infants, Pediatrics 137 (2016).
[25] S.M. Graham, L. Mankhambo, A. Phiri, S. Kaunda, T. Chikaonda, M. Mukaka, et al., Impact of human immunodeficiency virus infection on the etiology and outcome of severe pneumonia in malawian children, Pediatr. Infect. Dis. J. 30 (2011) 33–38.
[26] O. Hellferscee, F.K. Treurnicht, S. Tempia, E. Variava, H. Dawood, K. Kahn, et al., Enterovirus D68 and other enterovirus serotypes identified in South African patients with severe acute respiratory illness, 2009–2011, Influenza Other Respir. Viruses 11 (2017) 211–219.
[27] S. Hooli, T. Colbourn, N. Lufesi, A. Costello, B. Nambiar, S. Thammasitboon, et al., Predicting hospitalised paediatric pneumonia mortality risk: An external validation of RISC and mRISC, and local tool development (RISC-Malawi) from Malawi, PLoS One 11 (2016).
[28] P. Jeena, D.M. Thea, W.B. MacLeod, N. Chisaka, M.P. Fox, H.M. Coovadia, et al., Failure of standard antimicrobial therapy in children aged 3-59 months with mild or asymptomatic HIV infection and severe pneumonia, Bull. World Health Organ. 84 (2006) 269–275.
[29] M.S. Kelly, K.E. Wirth, A.P. Steenhoff, C.K. Cunningham, T. Arscott-Mills, S.C. Boiditswe, et al., Treatment failures and excess mortality among HIV-exposed, uninfected children with pneumonia, J. Pediatric Infect. Dis. Soc. 4 (2015) e117–e126.
[30] S.A. Madhi, K. Petersen, A. Madhi, M. Khoosal, K.P. Klugman, Increased disease burden and antibiotic resistance of bacteria causing severe community-acquired lower respiratory tract infections in human immunodeficiency virus type 1-infected children, Clin. Infect. Dis. 31 (2000) 170–176.
[31] S.A. Madhi, B. Schoub, K. Simmank, N. Blackburn, K.P. Klugman, Increased burden of respiratory viral associated severe lower respiratory tract infections in children infected with human immunodeficiency virus type-1, J. Pediatr. 137 (2000) 78–84.
[32] S.A. Madhi, H. Ludewick, L. Kuwanda, N. Van Niekerk, C. Cutland, T. Little, et al., Pneumococcal coinfection with human metapneumovirus, J. Infect. Dis. 193 (2006) 1236–1243.
[33] S.A. Madhi, H. Ludewick, L. Kuwanda, N. Van Niekerk, C. Cutland, K.P. Klugman, Seasonality, incidence, and repeat human metapneumovirus lower respiratory tract infections in an area with a high prevalence of human immunodeficiency virus type-1 infection, Pediatr. Infect. Dis. J. 26 (2007) 693–699.
[34] N.P. Majozi, N. Nkwanyana, S. Thula, A. Coutsoudis, Association between HIV and proven viral lower respiratory tract infection in paediatric intensive care unit patients at Inkosi Albert Luthuli Central Hospital, Durban, South Africa, SAJCH South Afr. J. Child Health 11 (2017) 154–158.
[35] J. Moyes, C. Cohen, M. Pretorius, M. Groome, A. Von Gottberg, N. Wolter, et al., Epidemiology of respiratory syncytial virus-associated acute lower respiratory tract infection hospitalizations among HIV-infected and HIV-uninfected South African children, 2010-2011, J. Infect. Dis. 208 (2013) S217–S226.

[36] J. Moyes, S. Walaza, M. Pretorius, M. Groome, A. von Gottberg, N. Wolter, et al., Respiratory syncytial virus in adults with severe acute respiratory illness in a high HIV prevalence setting, J. Infect. 75 (2017) 346–355.
[37] M.M. Ngari, G. Fegan, M.K. Mwangome, M.J. Ngama, N. Mturi, J.A.G. Scott, et al., Mortality after inpatient treatment for severe pneumonia in children: a cohort study, Paediatr. Perinat. Epidemiol. 31 (2017) 233–242.
[38] M.C. Nunes, Z. Kuschner, Z. Rabede, R. Madimabe, N. Van Niekerk, J. Moloi, et al., Clinical epidemiology of bocavirus, rhinovirus, two polyomaviruses and four coronaviruses in HIV-infected and HIV-uninfected South African children, PLoS One 9 (2014).
[39] I. Peterson, N. Bar-Zeev, N. Kennedy, A. Ho, L. Newberry, M.A.S. Joaquin, et al., Respiratory virus-associated severe acute respiratory illness and viral clustering in malawian children in a setting with a high prevalence of HIV infection, malaria, and malnutrition, J. Infect. Dis. 214 (2016) 1700–1711.
[40] J.A.G. Scott, A.J. Hall, C. Muyodi, B. Lowe, M. Ross, B. Chohan, et al., Aetiology, outcome, and risk factors for mortality among adults with acute pneumonia in Kenya, Lancet 355 (2000) 1225–1230.
[41] B. Sigaúque, A. Roca, Q. Bassat, L. Morais, L. Quintó, A. Berenguera, et al., Severe pneumonia in Mozambican young children: clinical and radiological characteristics and risk factors, J. Trop. Pediatr. 55 (2009) 379–387.
[42] M.G. Srinivasan, G. Ndeezi, C. Katureebe Mboijana, S. Kiguli, G.S. Bimenya, V. Nankabirwa, et al., Zinc adjunct therapy reduces case fatality in severe childhood pneumonia: a randomized double blind placebo-controlled trial, BMC Med. 14 (2012).
[43] C.G. Sutcliffe, D.M. Thea, P. Seidenberg, J. Chipeta, L. Mwyanayanda, S.W. Somwe, et al., A clinical guidance tool to improve the care of children hospitalized with severe pneumonia in Lusaka, Zambia, BMC Pediatr. 16 (2016).
[44] S. Tempia, S. Walaza, J. Moyes, A.L. Cohen, C. von Mollendorf, M.L. McMorrow, et al., Attributable fraction of influenza virus detection to mild and severe respiratory illnesses in HIV-Infected and HIV-uninfected patients, South Africa, 2012–2016, Emerging Infect. Dis. 23 (2017) 1124–1132.
[45] M. Venter, R. Lassaunière, T.L. Kresfelder, Y. Westerberg, A. Visser, Contribution of common and recently described respiratory viruses to annual hospitalizations in children in South Africa, J. Med. Virol. 83 (2011) 1458–1468.
[46] E.W.P. Yone, A.D. Balkissou, A.P. Kengne, C. Kuaban, Influence of HIV infection on the clinical presentation and outcome of adults with acute community-acquired pneumonia in Yaounde, Cameroon: a retrospective hospital-based study, BMC Pulm. Med. 12 (2012).
[47] H.J. Zar, D. Hanslo, E. Tannenbaum, M. Klein, A. Argent, B. Eley, et al., Aetiology and outcome of pneumonia in human immunodeficiency virus-infected children hospitalized in South Africa, Acta Paediatr. Int. J. Paediatr. 90 (2001) 119–125.
[48] R.M. Zash, R.L. Shapiro, J. Leidner, C. Wester, A.J. McAdam, R.L. Hodinka, et al., The aetiology of diarrhoea, pneumonia and respiratory colonization of HIV-exposed infants randomized to breast- or formula-feeding, Paediatr. Int. Child Health 36 (2016) 189–197.
[49] P.M. Jeena, A.K. Minkara, P. Corr, F. Bassa, L.M. McNally, H.M. Coovadia, et al., Impact of HIV-1 status on the radiological presentation and clinical outcome of children with WHO defined community-acquired severe pneumonia, Arch. Dis. Child. 92 (2007) 976–979.
[50] M. Lazzerini, N. Seward, N. Lufesi, R. Banda, S. Sinyeka, G. Masache, 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 4 (2016) e57–e68.
[51] D.R. Feikin, M.K. Njenga, G. Bigogo, B. Aura, G. Aol, A. Audi, et al., Etiology and Incidence of viral and bacterial acute respiratory illness among older children and adults in rural western Kenya, 2007-2010, PLoS One 7 (2012) e43656.
[52] A. Ho, S.J. Aston, H. Jary, T. Mitchell, M. Alaerts, M. Menyere, et al., Impact of human immunodeficiency virus on the burden and severity of influenza illness in malawian adults: a prospective cohort and parallel case-control study, Clin. Infect. Dis. 66 (2018) 865–876.
[53] B.O. Nyawanda, J.A. Mott, H.N. Njuguna, L. Mayieka, S. Khagayi, R. Onkoba, et al., Evaluation of case definitions to detect respiratory syncytial virus infection in hospitalized children below 5 years in Rural Western Kenya, 2009-2013, BMC Infect. Dis. 16 (2016) 218.
[54] M. Perreau, Y. Levy, G. Pantaleo, Immune response to HIV, Curr. Opin. HIV AIDS 8 (2013) 333–340.
[55] B. Walker, A. McMichael, The T-cell response to HIV, Cold Spring Harb. Perspect. Med. 2 (2012).
[56] L.A. Chakrabarti, V. Simon, Immune mechanisms of HIV control, Curr. Opin. Immunol. 22 (2010) 488–496.
[57] M. Malinis, J. Myers, J. Bordon, P. Peyrani, R. Kapoor, R. Nakamatzu, et al., Clinical outcomes of HIV-infected patients hospitalized with bacterial community-acquired pneumonia, Int. J. Infect. Dis. 14 (2010) e22–e27.
[58] L.A. Barakat, M. Juthani-Mehta, H. Allore, M. Trentalange, J. Tate, D. Rimland, et al., Comparing clinical outcomes in HIV-infected and uninfected older men hospitalized with community-acquired pneumonia, HIV Med. 16 (2015) 421–430.
[59] D. Christensen, C. Feldman, P. Rossi, T. Marrie, F. Blasi, C. Luna, et al., HIV infection does not influence clinical outcomes in hospitalized patients with bacterial community-acquired pneumonia: results from the CAPO international cohort study, Clin. Infect. Dis. 41 (2005) 554–556.
[60] C. Cilloniz, C. Garcia-Vidal, A. Moreno, J.M. Miro, A. Torres, Community-acquired bacterial pneumonia in adult HIV-infected patients, Expert Rev. Anti. Ther. 16 (2018) 579–588.
[61] Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet Infectious diseases. 2017;17:1133-1161.
[62] H. Castro, A. Judd, D.M. Gibb, K. Butler, R.K. Lodwick, A. van Sighem, et al., Risk of triple-class virological failure in children with HIV: a retrospective cohort study, Lancet 377 (2011) 1580–1587.
[63] WHO, HIV/AIDS: Key Facts, WHO, 2018.
[64] K. Crothers, B.W. Thompson, K. Burkhardt, A. Morris, S.C. Flores, P.T. Diaz, et al., HIV-associated lung infections and complications in the era of combination antiretroviral therapy, Proc. Am. Thorac. Soc. 8 (2011) 275–281.
[65] N. Benito, A. Moreno, J.M. Miro, A. Torres, Pulmonary infections in HIV-infected patients: an update in the 21st century, Eur. Respir. J. 39 (2012) 730–745.
[66] J.L. Davis, M. Fei, L. Huang, Respiratory infection complicating HIV infection, Curr. Opin. Infect. Dis. 21 (2008) 184–190.
[67] C. Feldman, R. Anderson, Bacterial respiratory infections complicating human immunodeficiency virus, Semin. Respir. Crit. Care Med. 37 (2016) 214–229.
[68] S. Sazawal, R.E. Black, Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials, Lancet Infect. Dis. 3 (2003) 547–556.
[69] S.A. Madhi, K.P. Klugman, et al., Acute respiratory infections, in: D.T. Jamison, R.G. Feachem, M.W. Makgoba, E.R. Bos, F.K. Baingana, K.J. Hofman (Eds.), Disease and Mortality in Sub-Saharan Africa, The International Bank for Reconstruction and Development/The World Bank, Washington (DC), 2006.
[70] P. Jeena, The role of HIV infection in acute respiratory infections among children in sub-Saharan Africa, Int. J. Tuberc. Lung Dis. 9 (2005) 708–715.
[71] A.B. Suthar, M.A. Vitoria, J.M. Nagata, X. Anglaret, D. Mbori-Ngacha, O. Sued, et al., Co-trimoxazole prophylaxis in adults, including pregnant women, with HIV: a systematic review and meta-analysis, Lancet HIV 2 (2015) e137–e150.
[72] WHO, Co-trimoxazole Prophylaxis for Malaria and Bacterial Infections in People With HIV, WHO, 2014.
[73] W.W. Fawzi, G.I. Msamanga, D. Spiegelman, R. Wei, S. Kapiga, E. Villamor, et al., A randomized trial of multivitamin supplements and HIV disease progression and mortality, N. Engl. J. Med. 351 (2004) 23–32.
[74] WHO, Guideline on When to Start Antiretroviral Therapy and on Pre-exposure Prophylaxis for HIV, WHO, 2015.
[75] J.J. Bigna, C.S. Plottel, S. Koulla-Shiro, Challenges in initiating antiretroviral therapy for all HIV-infected people regardless of CD4 cell count, Infect. Dis. Poverty 5 (2016) 85.