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RESEARCH PAPER

The burden of vaccine-preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa: a systematic review and meta-analysis

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ABSTRACT

There are knowledge gaps regarding evidence-based research on the burden of vaccine-preventable diseases among human immunodeficiency virus (HIV)-infected and HIV-exposed children aged <18 years in sub-Saharan Africa. It is therefore essential to determine the trend and burden of vaccine-preventable diseases. We completed a systematic review and meta-analysis to identify the incidence, prevalence and case-fatality rates (CFR) attributed to various vaccine-preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa. The trends in the prevalence of vaccine-preventable diseases among HIV-infected and HIV-exposed children were also determined. Nine studies on tuberculosis (TB) were pooled to give an overall incidence rate estimate of 60 (95% confidence interval [CI] 30–70) per 1,000 child-years. The incidence of pneumococcal infections varied between 109–1509 per 100,000 while pertussis was between 2.9 and 3.7 per 1000 child-year. Twenty-two TB prevalence studies reported an estimated prevalence of 16%. Fifteen prevalence studies on hepatitis B infection were pooled together with an estimated prevalence of 5%. The pooled prevalence for pneumococcal infections was 2% while rotavirus diarrhoea reported a prevalence of 13%. Twenty-nine studies on TB were pooled to give an overall CFR estimate of 17% while pneumococcal infections in HIV-infected and exposed children were pooled together with a resultant rate of 15%. Some of the vaccine-preventable diseases still have high incidences, prevalence and CFR among HIV-infected and HIV-exposed children. There is also a dearth of research data on the burden of several vaccine-preventable diseases among HIV-infected and exposed children and a need for more studies in this area.

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KEYWORDS
HIV; vaccine-preventable diseases; sub-Saharan Africa; burden

Background

Human immunodeficiency virus (HIV) infection remains a leading public-health challenge and a principal cause of the infectious disease burden in low- and middle-income countries especially in sub-Saharan Africa.[1] This region accounts for the bulk of HIV infection with about 36.7 million people living with the disease an estimated 75% of the global burden.[2,3] It was also estimated that approximately 2.1 million children aged under 15 years were living with HIV with the majority coming from sub-Saharan Africa and about 31% having access to antiretroviral therapy in 2014.[4] The incidence of HIV infections among children declined in 2014 but there were still 220,000 new infections that year alone.[4] HIV-infected children have an increased risk of developing various vaccine-preventable diseases due to their defective immune systems.[5] This makes it crucial to focus on the vaccination of HIV-infected and exposed children. The majority of these children are also residents of low-and-middle-income countries characterised by limited access to HIV diagnosis, treatment and care.[2]

Vaccination against various vaccine-preventable diseases has been proven to be a beneficial and cost-effective public-health measure for protecting children, adolescents and adults from these diseases, thereby reducing the morbidity and mortality attributable to them.[6,7] Coverage of routine vaccinations is still low in some developing countries and not sufficient to meet the Global Vaccine Action Plan (GVAP) targets.[8–10] Some African countries have low or decreasing immunisation coverage over the years with some not achieving ≥ 90% national coverage for vaccines included in their national immunisation schedule by the World Health Organization (WHO) in 2016.[11] Sub-Saharan African countries account for about 34% of the global vaccine-preventable diseases burden, and are also responsible for the highest proportion of under-five mortality from these diseases.[12]

Recently, most developing countries have included routine childhood vaccines such as hepatitis B; Bacillus Calmette–Guérin (BCG); diphtheria, tetanus and pertussis (DTP); *Haemophilus influenzae* type b (Hib); polio; pneumococcal conjugate; measles; rotavirus (RV), rubella and yellow fever vaccines in their national Expanded Programme on Immunisation (EPI).[13] These vaccines also protect against diseases such as tuberculosis, poliomyelitis, rotavirus gastroenteritis, diphtheria, tetanus, pertussis, pneumococcal diseases, hepatitis B infection, rubella, measles and yellow fever.

The gap in knowledge, especially in terms of evidence-based research, on the burden of vaccine-preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa,

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warrants this study.[14] This study completed a systematic review of literature and meta-analysis to identify the incidence, prevalence and mortality due to various vaccine-preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa since the advent of HIV in the 1980s. This study is essential in determining the trend and current burden of vaccine-preventable disease epidemiology in sub-Saharan Africa.

Objectives

Primary objectives

(1) To appraise all available published literature on the incidence and prevalence of vaccine-preventable diseases such as tuberculosis, poliomyelitis, hepatitis B virus infection, rotavirus gastroenteritis, diphtheria, tetanus, pertussis, pneumococcal diseases, measles, rubella and yellow fever among HIV-infected and HIV-exposed children in sub-Saharan Africa.
(2) To determine the trend in the incidence and/or prevalence of vaccine-preventable diseases such as tuberculosis, poliomyelitis, hepatitis B virus infection, rotavirus gastroenteritis, diphtheria, tetanus, pertussis, pneumococcal diseases, measles, rubella and yellow fever among HIV-infected and HIV-exposed children in sub-Saharan Africa from 1980 to 2018.

Secondary objective

(1) To describe the case-fatality rate ascribed to vaccine-preventable diseases such as tuberculosis, poliomyelitis, hepatitis B virus infection, rotavirus gastroenteritis, diphtheria, tetanus, pertussis, pneumococcal diseases, measles, rubella and yellow fever among HIV-infected and HIV-exposed children in sub-Saharan Africa.

Results

Literature search and result

Figure 1 shows the study selection process reported in line with PRISMA guidelines. We identified 3430 publications through the search of different databases. We also identified 13 additional

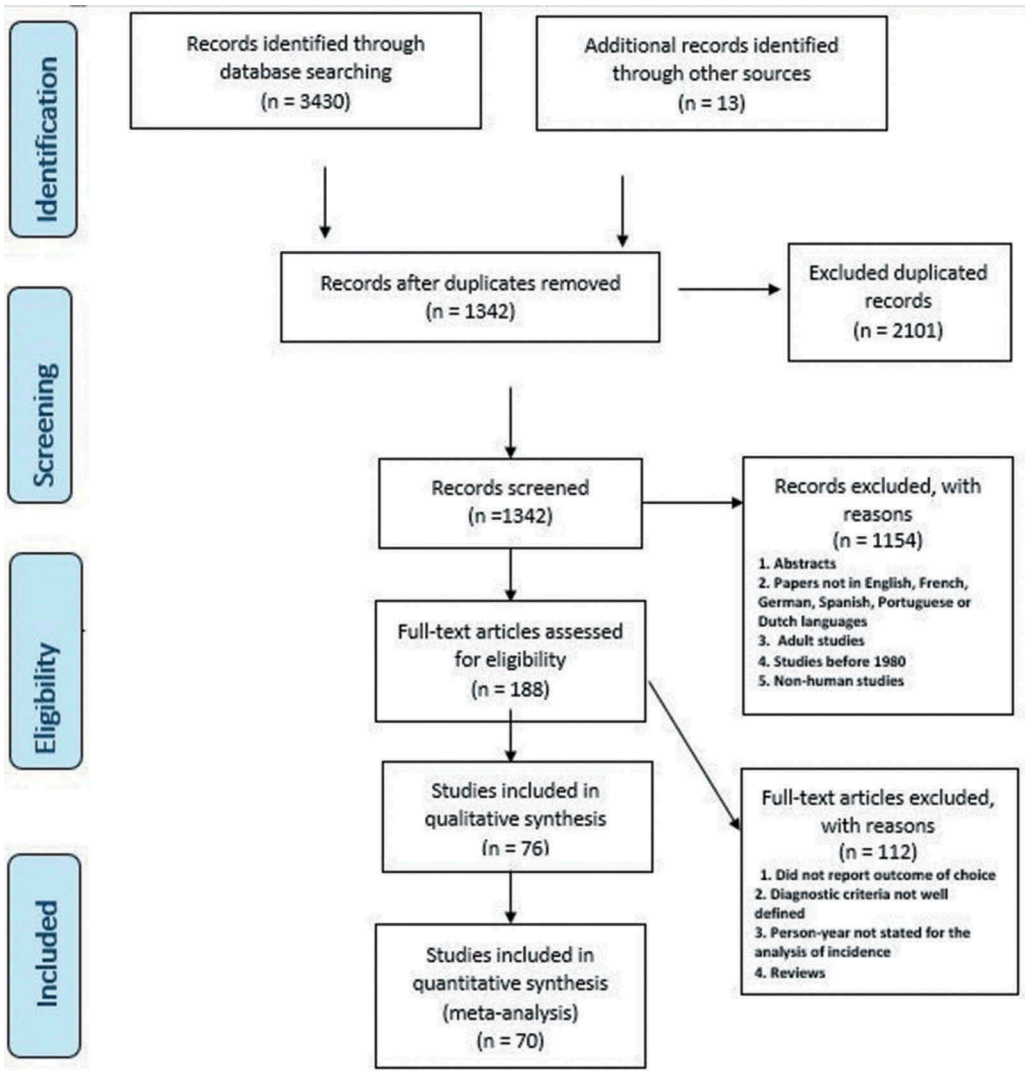

Figure 1. Flow diagram of the selection process.

articles through the screening of reference lists of various related articles. We screened 188 full-text articles and selected 76 articles for inclusion in the review and 70 articles were suitable for the meta-analysis (Figure 1).

Study characteristics

Table 1 provides a summary of the included studies and the vaccine-preventable diseases of interest. The table shows that 45 articles reported on tuberculosis, 14 on hepatitis B virus infection, ten studies focused on pneumococcal infections, two on rotavirus gastroenteritis, three on measles and three on pertussis. The included articles consist of 41 cross-sectional studies, 31 cohort studies, four case-control studies and one time-series analysis.

South Africa had the highest number of published articles with 35 articles, Nigeria produced 10 articles, four were from Kenya, four from Ethiopia and two studies were conducted in multiple countries. The other studies were conducted in Rwanda, Tanzania, Cote d' Ivoire, Uganda, Malawi, Botswana, Zimbabwe, Zambia, Mozambique and Swaziland (Table 1). A total of 46,882 children were included in this review. HIV-infected children were included in 71 studies while two studies had both HIV-infected and HIV-exposed uninfected children, and one study with only HIV-exposed children. The included studies were conducted between 1992 and 2016.

Using the Newcastle-Ottawa Quality Scale for the quality assessment of the eligible studies, 11 articles scored eight points; 15 articles scored seven points; 27 articles scored six points; 15 articles scored five points; seven articles scored four points and two articles scored three points. The characteristics of the eligible studies are summarised in Table 1.

Incidence rates

Tuberculosis

Nine studies[15,17–20,22,32,35] on TB were pooled to give an overall incidence rate estimate of 60 (95% CI 30–70) per 1,000 child-years at risk for tuberculosis based on a random-effects model (I^2= 99%; Figure 2). Subgroup analysis established change over time in incidence rates when comparing studies conducted before and after 2011. The pooled incidence rates for tuberculosis in those conducted before 2010 was 70 (95% CI −20–160) per 1,000 child-years[32,35] and 40 (95% CI 20–50) per 1,000 child-years in studies conducted between 2011 and 2018.[15,17–20,22] The heterogeneity of the TB incidence could not be explained by the subgroup analysis. Kouakoussui et al. reported TB incidence of 0.71 per 100 child/months before initiation of highly active antiretroviral therapy (HAART) and 0.16 per 100 child/months during HAART treatment among Ivorian HIV-infected children.[60]

Pneumococcal infections

Incidence of invasive pneumococcal disease among HIV-infected children aged <1 and 1–4 years was 1022 (95% CI 923–1123) per 100,000 and 198 (95% CI 178–220) per 100,000 respectively in 2008.[89] The incidence of pneumococcus-associated lower respiratory tract infection among HIV-exposed uninfected children was 109 (95% CI 47–214) per 100,000 and 629 (95% CI 130–1838) per 100,000 among HIV-infected children.[86] Ásbjörnsdóttir et al. reported the incidence of pneumonia among Kenyan HIV-exposed uninfected infants to be 900 (95% CI 800–1000) per 1,000 child-years.[81] Nunes et al. reported the incidence of invasive pneumococcal disease to be 1509 (95% CI 1350–1680) per 100,000 during early (HAART) and 742 (95% CI 644–851) during established-HAART eras for less than 18-year old South Africans.[87]

Pertussis

The incidence of pertussis among Zambian HIV-exposed infants was reported to be 3.7 (95% CI 0.9–10.1) per 1000 person-months[75] while Soofie et al. reported the incidence to be 2.9 (95% CI 1.8–4.5) per 1,000 child-years.[78]

Prevalence

Twenty-one TB prevalence studies were pooled together and reported estimated prevalence of 16% (95% CI 12–19, I^2 = 99%). For studies conducted within the period 1991–2000, the prevalence was 13% (95% CI 8–18);[40,43] lower in 2001–2010 with an estimate of 8% (95% CI 5–11, I^2= 96%)[22,33,37,38,51] and recorded the highest prevalence in recent years with 15% (95% CI 8–22, I^2= 99)[15,16,18,19,21,23,27,29,31,41,45,46,52,57] (Figure 3). Fourteen prevalence studies on hepatitis B (HBV) infection in HIV-infected children were pooled together with an estimate prevalence of 5% (95% CI 4–7, I^2= 90%). Studies conducted between 2001 and 2010 had a prevalence of 3% (95% CI 2–5)[67,68] and 4% (95% CI 3–6) between 2011 and 2018[61,63–72,74] (Figure 4).

The pooled prevalence for pneumococcal infections was 2% (95% CI 1–4). There has been a reduction in prevalence from 9% (95% CI 5–14)[83] in 1996 to 1% (95% CI 0–5)[84] in 2001. Pooled prevalence for pertussis was 3% (95% CI 2–4)[14,78] while measles was 6% (95% CI 2–10).[75,76] Two rotavirus diarrhoea prevalence studies were pooled together and reported an estimated prevalence of 13% (95% CI 8–17, I^2= 0%).[79,80]

Trend in incidence and prevalence

We analysed the trend in TB incidence with respect to publication years. The trend was non-linear with a downtrend from 2000 to 2010 (at −12.5% per year) and a reduced downward trend from 2011 to 2018 (at −1.5 per year) as shown in Figure 5. The trend in HBV prevalence was also analysed. The trend was not linear. There was evidence of a downtrend from 2000 to 2010 (at −4.7% per year) and (at −5.3% per year) from 2011 to 2018 as shown in Figure 6. The TB prevalence trend was also non-linear. There was evidence of initial downtrend from 2000 to 2010 (at −3.2% per year) and upward trend from 2011 to 2018 (at +32.7 per year).

Case-fatality rates

Twenty-nine studies on TB were pooled to give an overall CFR estimate of 17% (95% CI: 13–20, I^2 = 95%) which translates to 17%

Table 1. Characteristics of the study population.

First author and year	Study period	Study design	Country	Sample size	VPD	Outcomes	HIV status	Quality scores
Abuogi 2013[15]	2009–2010	Cohort	Kenya	689	Tuberculosis	C, I, P	HI	7
Adams 2014[16]	2006–2012	Cross-sectional	Tanzania	1193	Tuberculosis	C, P	HI	4
Alemu 2016[17]	2009–2014	Cohort	Ethiopia	645	Tuberculosis	I	HI	6
Anigilaje 2016[18]	2010–2013	Cohort	Nigeria	368	Tuberculosis	P	HI	8
Auld 2014[19]	2004–2008	Cohort	Cote d' Ivoire	2110	Tuberculosis	I, P	HI	8
Bakeera 2011[20]	2003–2006	Cohort	Uganda	1806	Tuberculosis	I, C	HI	8
Bonnet 2018[21]	2012–2014	Cohort	Uganda	113	Tuberculosis	C	HI	7
Braitstein 2009[22]	2001–2007	Cohort	Kenya	6,535	Tuberculosis	I, P	HI	8
Buck 2013[23]	2010	Cohort	Malawi	4874	Tuberculosis	C, P	HI	8
Carlucci 2017[24]	2012–2014	Cohort	Multiple	386	Tuberculosis	C	HI	8
Cavanaugh 2012[25]	2006–2007	Cross-sectional	Kenya	323	Tuberculosis	C	HI	6
Chaya 2016[26]	2006–2011	Cross-sectional	South Africa	47	Tuberculosis	I	HI	6
Cruz 2015[27]	NR	Cohort	Botswana	100	Tuberculosis	P	HI	6
Dangor 2013[28]	2005–2009	Time-series analysis	South Africa	1985	Tuberculosis	I	HI	7
De Maayar 2011[29]	NR	Cross-sectional	South Africa	58	Tuberculosis	P	HI	7
Ebonyi 2016[30]	2005–2013	Cohort	Nigeria	260	Tuberculosis	C	HI	8
Ebonyi 2016b[31]	2005–2012	Cohort	Nigeria	876	Tuberculosis	P	HI	8
Elenga 2005[32]	2000–2003	Cohort	Cote d' Ivoire	282	Tuberculosis	I	HI	8
Ferrand 2010[33]	2007–2008	Cross-sectional	Zimbabwe	139	Tuberculosis	P	HI	7
Hall 2017[34]	2005–2008	Cohort	South Africa	224	Tuberculosis	C	HI	8
Hesseling 2009a[35]	2004–2006	Cross-sectional	South Africa	3321	Tuberculosis	C	HI	6
Hesseling 2005[36]	1992–2000	Cohort	South Africa	93	Tuberculosis	C	HI	8
Hesseling 2006[37]	2002–2005	Cohort	South Africa	108	Tuberculosis	C, P	HI	7
Hesseling 2009b[38]	2004–2006	Cross-sectional	South Africa	3321	Tuberculosis	I, P	HI	7
Hicks 2014[39]	2009–2010	Cohort	South Africa	64	Tuberculosis	C	HI	6
Jeena 2000[40]	1995–1998	Cross-sectional	South Africa	27	Tuberculosis	P	HI	5
Kasambira 2011[41]	2006–2009	Cross-sectional	South Africa	270	Tuberculosis	P	HI	6
Madhi 2000b[42]	1996–1997	Cross-sectional	South Africa	67	Tuberculosis	C	HI	5
Meyers 2000[43]	1996	Cross-sectional	South Africa	144	Tuberculosis	P	HI	5
Mwangwa 2017[44]	2012–2013	Cohort	Multiple	17	Tuberculosis	C	HI	7
Obiagwu 2013[45]	2010	Cross-sectional	Nigeria	22	Tuberculosis, Measles	P	HI	6
Okechukwu 2011[46]	2007–2008	Cross-sectional	Nigeria	210	Tuberculosis	C, P	HI	6
Osman 2017[47]	2005–2012	Cohort	South Africa	3143	Tuberculosis	C	HI	6
Padayatchi 2006[48]	1993–2002	Cross-sectional	South Africa	6	Tuberculosis	C	HI	5
Palme 2002[49]	1995–1997	Cohort	Ethiopia	58	Tuberculosis	C	HI	6
Patel 2013[50]	2007–2009	Cohort	Congo DRC	31	Tuberculosis	C	HI	7
Robinson 2007[51]	1999–2001	Case-control	South Africa	47	Tuberculosis	P	HI	6
Rose 2012[52]	2008–2010	Cohort	Tanzania	54	Tuberculosis	P	HI	6
Schaaf 2007[53]	2003–2005	Cross-sectional	South Africa	133	Tuberculosis	C	HI	5
Soeters 2005[54]	2000–2001	Cross-sectional	South Africa	43	Tuberculosis	C	HI	4
Walters 2014[55]	2003–2010	Cohort	South Africa	494	Tuberculosis	C	HI	6
Walters 2008[56]	2003–2005	Cross-sectional	South Africa	137	Tuberculosis	C	HI	6
Westerlund 2014[57]	2003–2008	Cohort	Ethiopia	138	Tuberculosis	P	HI	7
Wiseman 2011[58]	2004–2006	Cross-sectional	South Africa	52	Tuberculosis	C	HI	5
Yotebieng 2010[59]	2004–2008	Cohort	South Africa	573	Tuberculosis	C	HI	6
Kouakoussui 2004[60]	2003	Cohort	Cote d'Ivoire	270	Tuberculosis	I	HI	7
Abera 2014[61]	2014	Cross-sectional	Ethiopia	253	HBV infection	P	HI	6
Ashir 2009[62]	2007	Case-control	Nigeria	284	HBV infection	P	HI	5
Beghin 2017[63]	2014	Cross-sectional	South Africa	183	HBV infection	P	HI	6
Chotun 2015[64]	2011–2012	Cross-sectional	South Africa	1000	HBV infection	P	HE	6
Uleanya 2016[65]	NR	Cross-sectional	Nigeria	140	HBV infection	P	HI	4
Dziuban 2013[66]	2009–2011	Cross-sectional	Swaziland	500	HBV infection	P	HI	3
Ikpeme 2013[67]	2010–2011	Cross-sectional	Nigeria	166	HBV infection	P	HI	4
Jooste 2016[68]	2015–2016	Cohort	South Africa	625	HBV infection	P	HI	7
Muro 2013[69]	2006–2008	Cross-sectional	Tanzania	157	HBV infection	P	HI	5
Mutwa 2013[70]	2010	Cohort	Rwanda	88	HBV infection	P	HI	7
Nwolisa 2013[71]	2010	Cross-sectional	Nigeria	139	HBV infection	P	HI	4
Sadoh 2011[72]	NR	Cross-sectional	Nigeria	155	HBV infection	P	HI	5
Telatela 2007[73]	2006	Cross-sectional	Tanzania	167	HBV infection	P	HI	4
Varo 2016[74]	2008–2010	Cross-sectional	Malawi	91	HBV infection	P	HI	3
Moss 2002[75]	1998–2000	Cross-sectional	Zambia	93	Measles	P	HI	6
Wirth 2015[76]	2009–2010	Case-control	Botswana	189	Measles	C	HI	5
du Plessis 2018[14]	2013–2015	Cross-sectional	South Africa	300	Pertussis	P	HI	6
Gill 2016[77]	2015	Cohort	Zambia	347	Pertussis	I	HI	7
Soofie 2016[78]	2015	Cross-sectional	South Africa	599	Pertussis	C, I, P	HE	5
Johnson 2000[79]	1996–1997	Cross-sectional	South Africa	31	Rotavirus gastroenteritis	P	HI	6
Moyo 2014[80]	2010–2011	Case-control	Tanzania	26	Rotavirus gastroenteritis	P	HI	5
Asbjörnsdóttir 2013[81]	1999–2002	Cohort	Kenya	388	Pneumococcal infection	C,I	HI	6
Nathoo 1996[82]	1993–1994	Cohort	Zimbabwe	168	Pneumococcal infection	P	HI	7
Zar 2001[83]	1998	Cross-sectional	South Africa	151	Pneumococcal infection	P	HI	6
Jones 1998[84]	1996	Cross-sectional	South Africa	25	Pneumococcal infection	C	HI	5
Roca 2010[85]	2004–2006	Cross-sectional	Mozambique	54	Pneumococcal infection	C	HI	6
Cohen 2016[86]	2009–2013	Cross-sectional	South Africa	211	Pneumococcal infection	I	HEU,HI	4
Nunes 2011[87]	2003–2008	Cross-sectional	South Africa	938	Pneumococcal infection	I	HI	6
von Mollendorf 2017a[88]	2009–2013	Cross-sectional	South Africa	495	Pneumococcal infection	C, I	HI	5
von Gottberg 2013[89]	2003–2008	Cross-sectional	South Africa	1749	Pneumococcal infection	I	HI	5
Nyasulu 2011[90]	2003–2005	Cross-sectional	South Africa	1124	Pneumococcal infection	C	HI	6

NR- Not recorded; C- Case-fatality rate; I – Incidence; P – Prevalence; Hib- Haemophilus influenzae type b; HI- HIV-infected; HE- HIV-exposed; HEU – HIV-exposed uninfected; VPD – vaccine–preventable diseases.

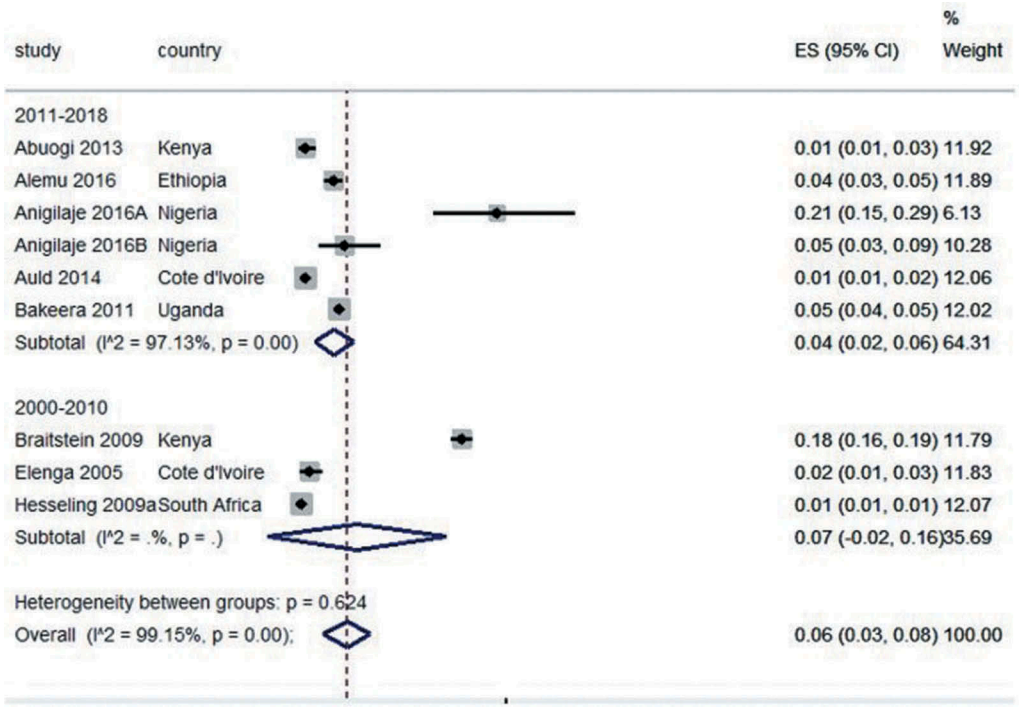

Figure 2. Forest plot of studies with data on incidence rates of tuberculosis in HIV-exposed children.

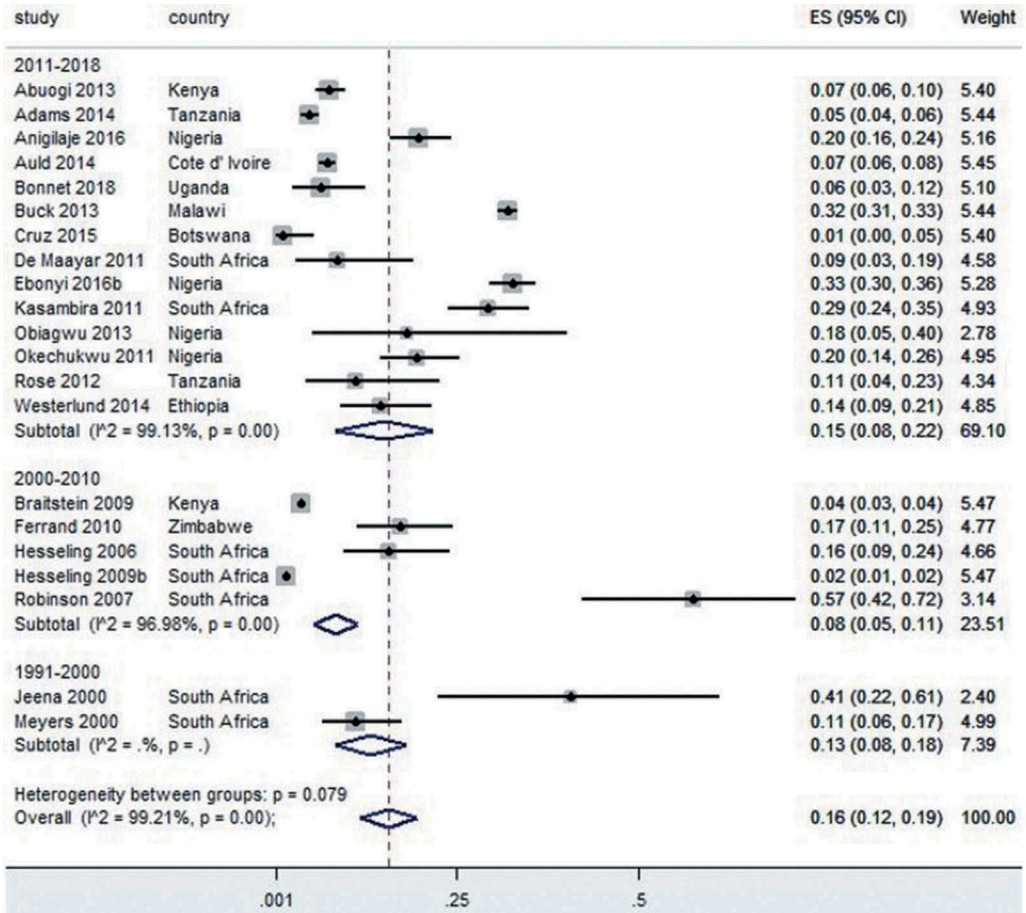

Figure 3. Forest plot of studies with data on the prevalence of tuberculosis in HIV-infected children.

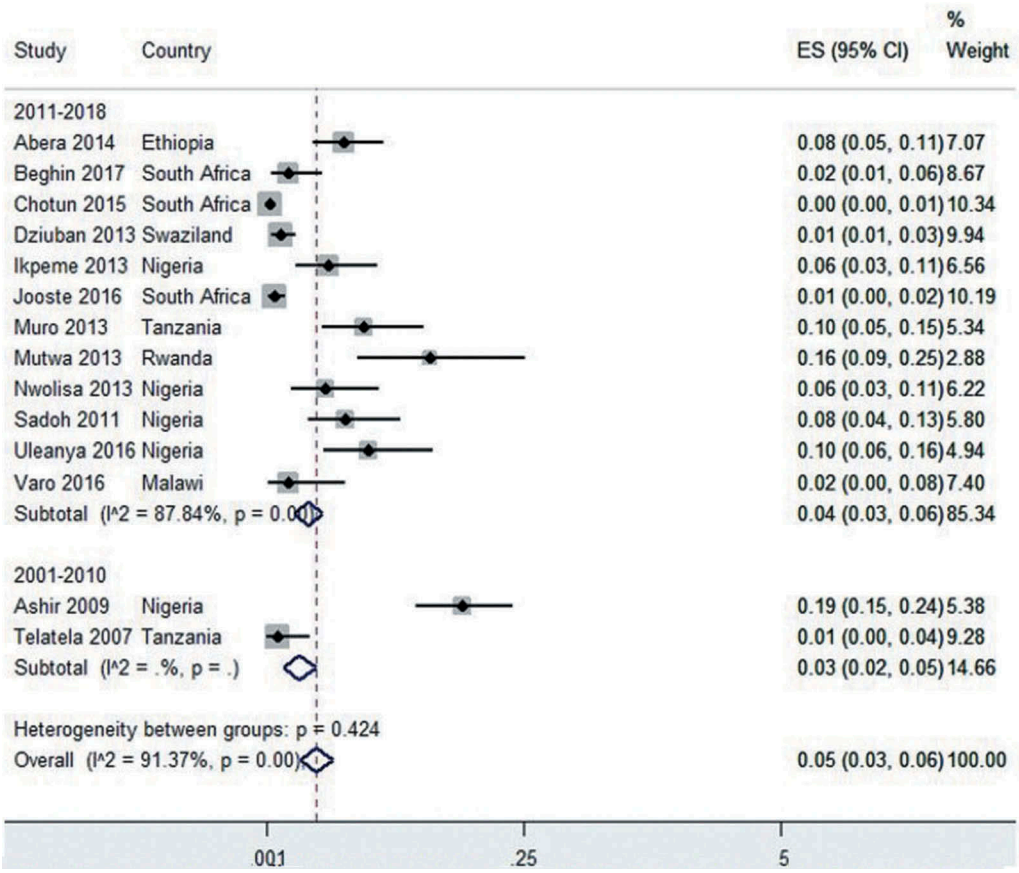

Figure 4. Forest plot of studies with data on the prevalence of hepatitis B virus infection in HIV-infected and HIV-exposed children.

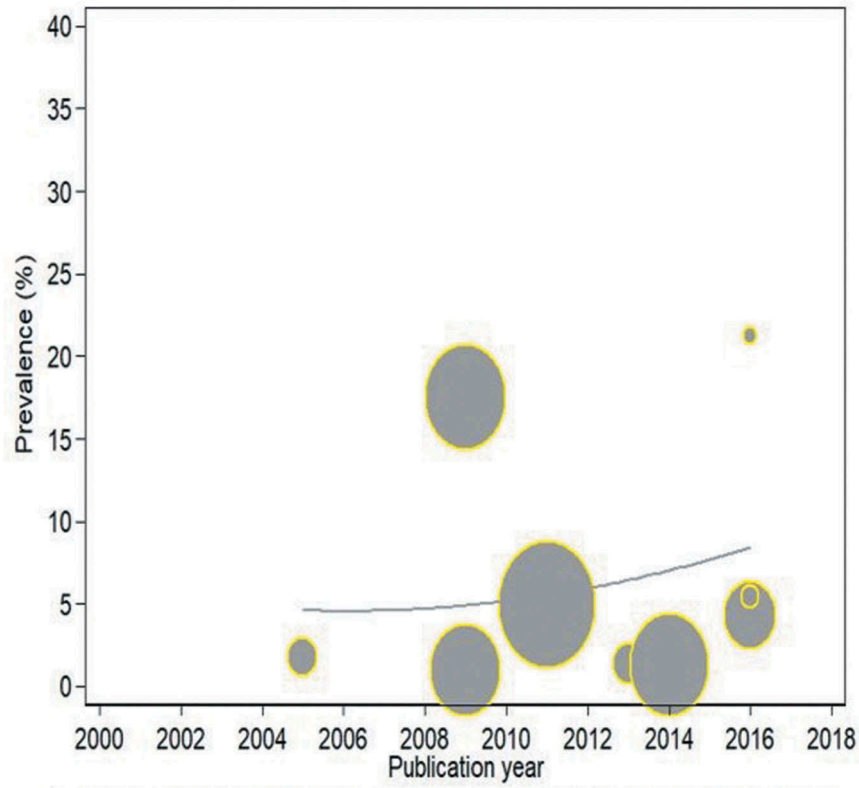

Figure 5. Trends in the incidence of tuberculosis in HIV-infected and exposed children with respect to publication years.

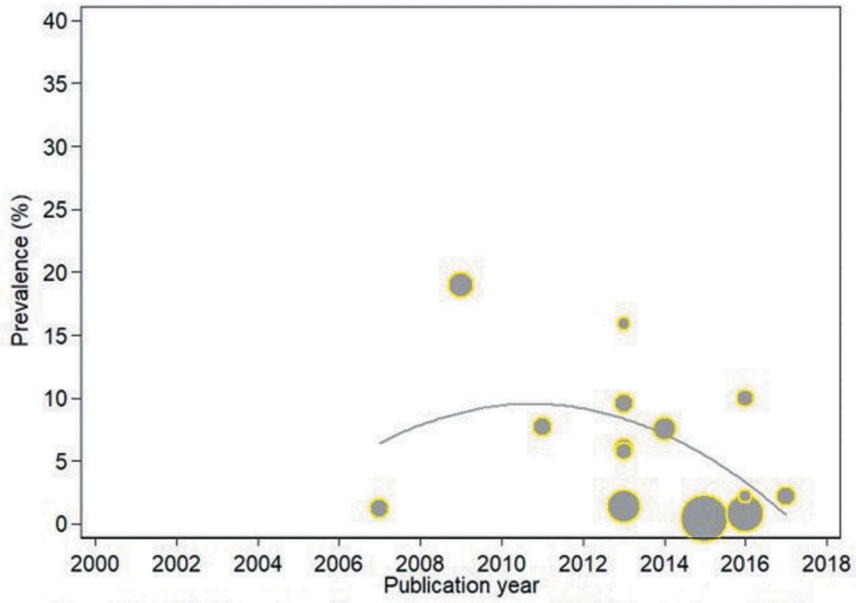

Figure 6. Trends in the prevalence of hepatitis B virus infection in HIV-infected and exposed children with respect to publication years.

of all TB cases dying from the disease. Subgroup analysis shows the CFR was 18% (95% CI 6–24)[47] in the 1991–2000 period, 6% (17–38, I^2 = 95%)[33,35–37,48,49,53,54,56,59] in 2001–2010 and 13% (95% CI 9–17, I^2 = 96%)[15,16,18,20,23–25,30,34,39,44,46,47,50,55,56] in 2011–2018. Four studies were pooled for pneumococcal infections CFRs in HIV-infected and exposed children with a resultant rate of 15% (95% CI 4–26, I^2= 95%).[81,84,85,90] One study shows that pertussis has CFRs of 13% (95% CI 2–38)[78] and for measles the CFR was 1% (95% CI 0–4).[76]

Publication bias assessment

Funnel-plot analyses of studies reporting on the prevalence of TB revealed nil significant publication bias, with the P value for the Begg's test being 0.185 while the studies assessing the prevalence of HBV infection showed significant Begg's test with P value of 0.001 (Figures 7 and 8). Likewise, studies assessing the CFR of TB demonstrated no significant publication bias Begg's test P = 0.385 (Figure 9).

Discussion

This study provides a comprehensive overview of the incidence rate, prevalence and case fatality rates of different vaccine-preventable diseases in HIV-infected and HIV-exposed children in sub-Saharan African countries. The review shows that TB is the most researched vaccine-preventable disease in HIV-infected children in various African countries and settings. This is not surprising because of the relationship between TB and HIV infection with respect to the high susceptibility of TB in HIV-infected individuals,[11,91] Other vaccine-preventable diseases like HBV infection, pneumococcal infection, measles, rotavirus

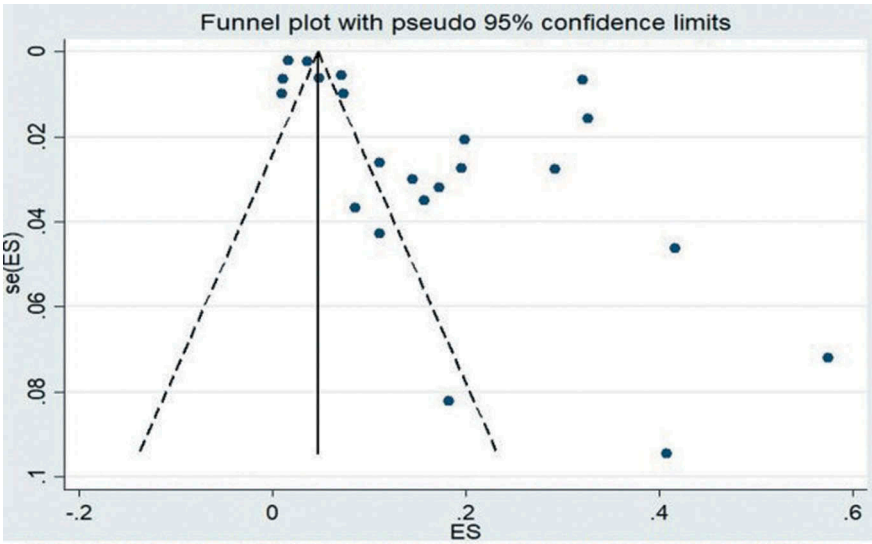

Figure 7. Funnel plot of studies reporting on the prevalence of tuberculosis in HIV-infected children.

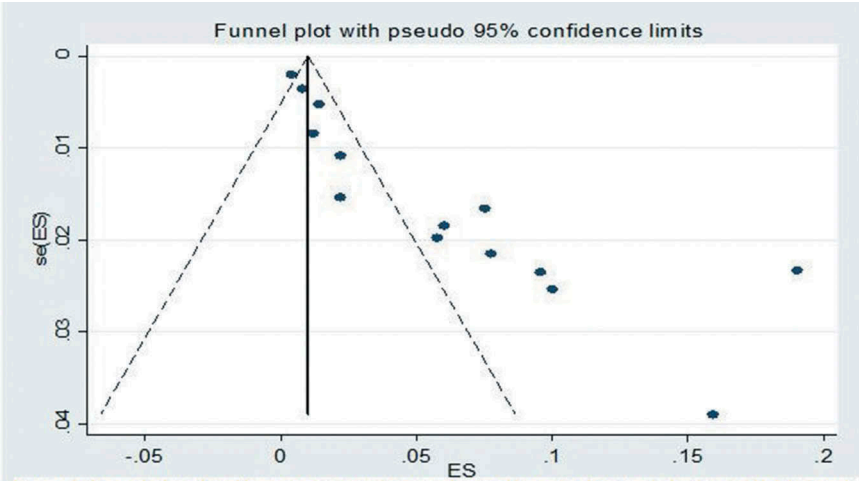

Figure 8. Funnel plot of studies reporting on the prevalence of hepatitis B virus infection in HIV-infected children.

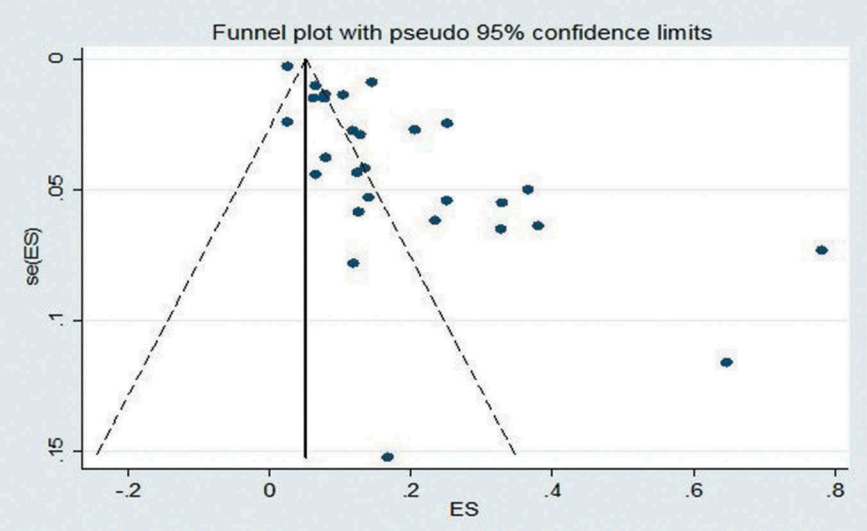

Figure 9. Funnel plot of studies reporting on the case-fatality rate of tuberculosis in HIV-infected children.

gastroenteritis, pertussis and Hib infections were also studied in several African countries. Important vaccine-preventable diseases such as poliomyelitis, diphtheria, tetanus and yellow fever had no eligible studies for inclusion revealing the dearth of incidence and prevalence studies on these diseases. The pooled incidence, prevalence and CFRs reveal there are still high burdens of several vaccine-preventable diseases in sub-Saharan Africa.

According to WHO, the global incidence of TB has been reducing at an average of 2 percent per year.[11] TB incidence has declined in the African region by 4 percent annually since 2013.[11] Southern African countries with the highest prevalence and incidence of HIV such as South Africa, Lesotho, Zimbabwe, Eswatini, Namibia and Zambia had remarkable reductions in TB incidence.[11] Our study shows that TB incidence reduced over time, however, the event per child-year is still high when compared with the End TB strategy goals.[92] The World Health Assembly adopted the resolution known as "*End TB strategy goals*" which is about the global strategy and targets for tuberculosis prevention, care and control after 2015.[92] In spite of the reduction in TB incidence among children, there are still cases of high incidence in certain countries bearing in mind that many countries in African countries are classified as high-burden.[93] A retrospective cohort study in a very high TB/HIV prevalent region in Nigeria showed a high incidence rate of 21.2/100 per year among children within six months of ART enrollment at a period when others were recording much lower incidence.[18] TB prevalence has fluctuated over time with about 15% of HIV-infected children having the disease at a given point in time. As of 2017, it was estimated that the global CFR was 16% with many African countries recording more than 20%.[11] This rate is also far higher than the End TB Strategy milestone of 10% by 2020.

The pooled HBV infection prevalence among HIV-infected children was 5%, however, a study done in Rwanda in 2010 revealed a seroprevalence of 16%.[68] Ott et al. showed that sub-Saharan Africa had the highest HBV burden with West African countries having up to 12% hepatitis B surface antigen prevalence among children and adolescents in the 1990s.[94] There has

been a reduction within the region largely due to immunisation programmes, however, there is high endemicity in some areas. A systematic review of HBV prevalence in Nigeria from studies conducted from 2000 to 2013 shows that HBV infection ranged from 0.5% to 46.8% with the pooled prevalence estimate for Nigeria being 13.6%.[95]

Our finding shows that the seroprevalence of rotavirus gastroenteritis among African HIV-infected children was 14% although with a small number of included studies. The incidence and CFR of diarrhoea and pneumonia are much higher in low-income than in high-income countries and this is reflected in many African and southeast Asian countries having the highest burden of the diseases.[93] The African region has the highest incidence and total death secondary to diarrhoea and pneumonia with rotavirus and *Streptococcus pneumoniae* being the commonest culprits.[93] Studies have shown that there is still a persistently high incidence of some vaccine-preventable diseases in HIV-infected individuals than non-exposed ones even after the introduction of highly active antiretroviral therapy.[96] The incidence of pertussis is also higher in HIV-exposed and infected children, however, this decreases as the number of vaccine doses uptake increases.[97]

Many African countries with high burdens of HIV are critically lagging in terms of antiretroviral treatment coverage for HIV-infected children.[98] Sub-optimal ART coverage in children will lead to viral load increase, immunosuppression, etc. and a subsequent high burden of various vaccine-preventable diseases. Vaccination coverage in many African countries is still below the expected target.[99] As of 2017, the average coverage of third-dose pentavalent vaccine was 80% while the first dose of measles vaccine in the Global Alliance for Vaccines and Immunisation (Gavi)-supported countries was 78%.[99] The average coverage of Gavi-funded vaccines in supported countries progressed from 37% in 2016 to 41% in 2017.

Use of vaccines has been established to be a beneficial healthcare intervention targeted in protecting children and adolescents from various vaccine-preventable diseases. Low uptake of vaccines by African children exposes them to more diseases than children in other regions. It has also been established that HIV-infected children are more susceptible to vaccine-preventable diseases such as TB, pneumonia, viral hepatitis etc.[100,101] Vaccination is therefore essential in HIV-infected patients because of the increased risk of developing various infectious diseases due to their defective immune systems. Studies have also shown that there are poor immune responses to primary vaccination among HIV-infected children in comparison to HIV-unexposed and HIV-exposed children. The poor immune response among HIV-infected children may require booster doses for optimal immunity against vaccine-preventable diseases.[102,103]

This review revealed research inequalities across the African region regarding studies on the burden of vaccine-preventable diseases among HIV-infected and HIV-exposed children. South Africa contributed about half of the included articles with Nigeria and Kenya following with fewer studies. This finding is not different from an earlier study looking at the distribution of epidemiological studies across Africa.[104] Some of the Eastern and Southern African countries with high HIV prevalence had at least an article included in this study, however, West African countries only had publications from Nigeria and Cote d'Ivoire.

To the best of our knowledge, this is the first systematic review that addressed the need for knowing the burden of vaccine-preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa. Knowledge gap concerning the burden of vaccine-preventable diseases will impact negatively on the advocacy endeavours targeted at improving vaccination and vaccine-preventable diseases control efforts in Africa. Healthcare workers and policymakers need to have a good idea of the burden of different diseases to allocate resources and facilitate optimal vaccination coverage.

Recommendations

This review has shown that TB is one of the most important vaccine-preventable diseases in Africa with the BCG vaccine conferring protection against severe forms of the disease. However, the same vaccine is contraindicated in immunocompromised children who ironically are susceptible to the disease.[13] The dilemma of BCG use in HIV-exposed children warrants the call for newer and safer vaccines against TB especially in HIV-infected children. African governments and other supporting agencies should ensure that every child has access to routine childhood vaccines. Issues of undervaccination and vaccine hesitancy should be adequately tackled to ensure better vaccine uptake and reduction in the burden of vaccine-preventable diseases.

The research capacity of African clinicians, researchers and health administrators should be built up for them to conduct basic epidemiological research such as incidence, prevalence, mortality and CFR among HIV-exposed children in various health facilities and communities. Researchers should be encouraged to disseminate their findings to their immediate communities and Departments of Health, and to publish their findings in peer-reviewed journals. Established research groups such as Global Burden of Diseases Network should include the burden of vaccine-preventable diseases in HIV-exposed and non-exposed children as part of their regular or annual publications. Other African countries should emulate South Africa in increasing their research activities and outputs with respect to HIV-exposed children.

There is a need to advocate for an equitable share of healthcare budgeting and finance at every level of governance in African countries. This will help in ensuring that there is a fair share of resources for preventive and treatment services such as vaccination and antiretroviral therapy for HIV-exposed children. African countries should, as a matter of urgency, complete the introduction of newer and important vaccines such as rotavirus vaccine, Hib vaccine and pneumococcal vaccine. These should be included as part of their current national immunisation programme schedule.[95] According to WHO, the global coverage for both pneumococcal vaccine and rotavirus vaccines were as little as 44 percent and 25 percent respectively.[99] African countries should be supported in developing vaccine procurement budgets, procurement practices, and capacity development for vaccine planning and advocacy.[105]

Study limitations

This study was limited by several factors beyond the reviewers' control. We planned to review all the vaccine-preventable diseases associated with vaccines included in the national immunisation programme schedule in sub-Saharan Africa, however, we could not find articles that met the eligibility criteria for some of the diseases. Secondly, there was high heterogeneity even with sub-group analysis between included studies, which implies the possibility of other contributory factors associated with the diseases. Some of the studies did not include relevant information such as antiretroviral coverage, CD4 count, viral load, vaccination status and other contributory factors. Thirdly, we could not include many studies because the diagnostic criteria for different vaccine-preventable diseases were not specified and clearly defined.

Furthermore, the presence of various limitations did not stop us from making some meaningful conclusions from this study. This review gives a clearer picture of the burden and trend of TB and able to have insights about the burden of other diseases as well despite having a small number of studies included in this review. African investigators should as a matter of priority have proper diagnostic criteria and documentation for diseases for all HIV-infected and HIV-exposed children treated at the health facilities across the region. Key parameters such as CD4 counts, vaccination status etc. should be included in future studies.

Conclusions

This systematic review and meta-analysis provide an all-inclusive analysis of the incidence rates, prevalence and CFR of various vaccine-preventable diseases. This study shows that some vaccine-preventable diseases still have high incidence, prevalence and CFRs in HIV-infected and HIV-exposed children. There was also the dearth of research activities on vaccine-preventable disease studies concerning HIV-infected and HIV-exposed uninfected children in many African countries. The findings are useful in advocating for a more equitable share of healthcare financing especially for preventive services such as vaccination of both HIV-exposed and non-exposed children to reduce the burden of vaccine-preventable diseases.

Methods and design

This systematic review was developed in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2015 statement.[106] The review was registered with PROSPERO (International prospective register of systematic reviews) (CRD42018095341).

Inclusion criteria

Type of participants

The review included sub-Saharan African children who are HIV-infected or HIV-exposed and aged <18 years old.

Types of outcome

We included studies that reported the incidence, prevalence and case-fatality rates (CFR) as outcomes in HIV-infected and HIV-exposed children.

Primary outcomes

Prevalence was defined as proportions of all individuals suspected of having specific vaccine-preventable diseases with confirmed laboratory diagnosis or proportions of individuals fulfilling clinical case definition for specific vaccine-preventable diseases. Incidence was defined as the number of new cases of different vaccine-preventable diseases that occur during a given period in the defined population.

We also determined the trend in the incidence and/or prevalence of vaccine-preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa from 1980 to 2018.

Secondary outcomes

We included CFRs associated with vaccine-preventable diseases. Case fatality was described as mortality among confirmed or probable cases for a specific vaccine-preventable disease.

Type of studies

The review included cohort studies, case-control studies, cross-sectional studies and other observational studies. We planned to include studies that involved any of the following vaccine-preventable diseases:

(i) Tuberculosis
(ii) Poliomyelitis
(iii) Hepatitis B virus infection
(iv) Rotavirus gastroenteritis
(v) Diphtheria
(vi) Tetanus
(vii) Pertussis
(viii) Pneumococcal diseases
(ix) Measles
(x) Rubella
(xi) Yellow fever

Exclusion criteria

- Intervention studies
- Unclear diagnostic criteria

Search strategy methods for the identification of studies

A comprehensive search strategy was developed to identify relevant studies up to August 2018, regardless of publication status or language. Scopus, Web of Science, MEDLINE via PubMed and CINAHL were searched for relevant publications. The search process was complemented by reviewing citations of all identified eligible studies. We also searched relevant World

Health Organization position papers and documents on vaccines. (See Appendix for PubMed search strategy).

Selection of eligible studies

Two of the authors, (OOA and AA) screened the search results using the abstract titles. They also independently went through the full text of potential studies to assess whether they met the required inclusion criteria. Non-human studies, reviews, intervention studies, letters, commentaries and editorials were excluded. Studies not written in English, French, German, Spanish, Portuguese or Dutch were excluded. We resolved disagreements by consensus.

Data collection process

The two authors then extracted data from text, tables and figures. The data were recorded on a standardised form. We planned to contact authors of included studies in case of unclear or missing data.

The following data were extracted from selected studies:

- Study characteristics including period and design.
- Vaccine-preventable diseases patient characteristics such as age and HIV status.
- Prevalence or incidence of vaccine-preventable diseases: confirmed cases and cases meeting the clinical definition.
- Diagnostic methods: laboratory methods and clinical case definitions.
- Death attributed to vaccine-preventable diseases.

Risk of bias in individual studies

The risk of bias and quality of the included studies were assessed with the Newcastle-Ottawa Quality Scale.[107] The criteria assessed included the following (1) selection of participants, (2) comparability, (3) exposure, and (4) outcome.

Data synthesis

OOA summarised the incidence and prevalence of various vaccine-preventable diseases. Where possible, incidence and prevalence data from each of the included studies were combined by random effects meta-analysis in accordance with the Mantel-Haenszel method.

Heterogeneity was evaluated using the Chi-squared test of homogeneity (significant for $P < 0.1$) and quantified using the I-squared statistic (>50% substantial heterogeneity).[108] Subgroup analyses were conducted in cases with substantial heterogeneity. Subgroup analysis was conducted using the following variables: period of study (1991–2000, 2001–2010 and 2011–2018). We also used funnel plot regression to assess publication bias. STATA software version 14.0 (STATA Corporation, College Station, TX, USA) was used to do all calculations, the meta-analysis and generate forest plots.[109]

Additional analyses: trend analysis

We examined time trends in the incidence and prevalence of vaccine-preventable diseases estimates using Poisson regression models with the prevalence estimates as the outcome variable and the calendar year of the publication as the predictor. This method allows for estimation of time trends across individual calendar years to obtain average annual percentage change (AAPC), if the rate of change is at a constant rate of the previous year.[110] The Poisson regression procedure fits a model of the following form:

$$\log\left(prevalence_y\right) = b_0 + b_1 y + \log(sample\,size) \qquad (1)$$

where *'cases'* equal prevalence estimates reported per year, log is the natural log, *b0* is the intercept, *b1* is the trend, *y* is the year – given as 0, 1, 2, … 18 (year 0 is 1970, year 1 is 1971, and so on to 2014), and log of 'sample size' was entered as the offset. The AAPC was calculated using the following formula:

$$AAPC = \left(e^{b_1} - 1\right) \times 100 \qquad (2)$$

Authors' contributions

OOA developed the protocol, search strategy, the data analysis and manuscript preparation. OOA and AA did the screening, study selection and data extraction. OAU and CSW guided the development of this study. All authors were involved in the results interpretation, revision and approval of the final manuscript.

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Abbreviations

BCG	Bacillus Calmette–Guérin
DTP	Diphtheria, tetanus and pertussis
EPI	Expanded Programme on Immunisation
GVAP	Global Vaccine Action Plan
Hib	*Haemophilus influenzae* type b
HIV	Human immunodeficiency virus
PCV	Pneumococcal conjugate vaccine
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
RV	Rotavirus
WHO	World Health Organization

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Appendix

Search strategy – PubMed

Search	Add to builder	Query	Items found
#6	Add	Search ((((#1) AND #2) AND #3) AND #4) AND #5 Sort by: Best Match	1364
#4	Add	Search (newborn* OR bab* OR infan* OR child* OR adolescen* OR teen*) Sort by: Best Match	3843580
#2	Add	Search (tuberculosis OR TB OR poliomyelitis OR polio OR rotavirus OR diphtheria OR tetanus OR pertussis OR pneumococcal OR pneumonia OR measles OR "yellow fever" OR "Hepatitis B" OR "Haemophilus influenza" OR "Hemophilus influenza" OR influenza) Sort by: Best Match	707401
#5	Add	Search (incidence OR prevalence OR mortality) Sort by: Best Match	3171459
#3	Add	Search ("HIV infected" OR "HIV exposed" OR "HIV-infected" OR "HIV-exposed" OR "HIV positive" OR "HIV exposed uninfected") Sort by: Best Match	74539
#1	Add	Search (Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR Cameroon OR "Cape Verde" OR "Central African Republic" OR Chad OR Congo OR "Democratic Republic of Congo" OR DRC OR Djibouti OR "Equatorial Guinea" OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR "Guinea Bissau" OR Guinea OR "Ivory Coast" OR "Cote d'Ivoire" OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR "Republic of the Congo" OR Reunion OR Rwanda OR Senegal OR Seychelles OR "Sierra Leone" OR "Sao Tome and Principe" OR Somalia OR "South Africa" OR "South Sudan" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR Zambia OR Zimbabwe OR Africa OR "sub Saharan Africa") Sort by: Best Match	558013