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# Human Vaccines & Immunotherapeutics

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

--Manuscript Draft--

<b>Manuscript Number:</b>	KHVI-2018-0490R1
<b>Full Title:</b>	The burden of vaccine-preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa: a systematic review and meta-analysis
<b>Article Type:</b>	Research Paper
<b>Manuscript Classifications:</b>	Epidemiology; HIV; Infectious Disease; Pediatrics; Tropical Medicine; Vaccinology
<b>Abstract:</b>	<p>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 &lt;18years 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.</p>
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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 <18years 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.

**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.<sup>1</sup> 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.<sup>2,3</sup> 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.<sup>4</sup> The incidence of HIV infections among children declined in 2014 but there were still 220,000 new infections that year alone.<sup>4</sup> HIV-infected children have an increased risk of developing various vaccine-preventable diseases due to their defective immune systems.<sup>5</sup> 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.<sup>2</sup>

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.<sup>6,7</sup> Coverage of routine vaccinations is still low in some developing countries and not sufficient to meet the Global Vaccine Action Plan (GVAP) targets.<sup>8-10</sup> Some African countries have low or decreasing immunisation coverage over the years with some not achieving  $\geq 90\%$  national coverage for vaccines included in their national immunisation schedule by the World Health Organization (WHO) in 2016.<sup>11</sup> 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.<sup>12</sup>

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).<sup>13</sup> 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.

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90 The gap in knowledge, especially in terms of evidence-based research, on the burden of vaccine-  
91 preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa,  
92 warrants this study.<sup>14</sup> This study completed a systematic review of literature and meta-analysis to  
93 identify the incidence, prevalence and mortality due to various vaccine-preventable diseases  
94 among HIV-infected and HIV-exposed children in sub-Saharan Africa since the advent of HIV in  
95 the 1980s. This study is essential in determining the trend and current burden of vaccine-  
96 preventable disease epidemiology in sub-Saharan Africa.

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## 98 Objectives

### 99 Primary objectives

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

### 109 Secondary objective

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

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## 115 Results

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### 117 Literature search and result

118 Figure 1 shows the study selection process reported in line with PRISMA guidelines. We identified  
119 3430 publications through the search of different databases. We also identified 13 additional

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

### 123 Study characteristics

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

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

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

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**Figure 1: Flow diagram of the selection process**



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**Table 1: Characteristics of the study population**

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2 **Incidence rates**

3 **Tuberculosis:** Nine studies<sup>15,17-20,22,32,35</sup> on TB were pooled to give an overall incidence rate  
4 estimate of 60 (95% CI 30 – 70) per 1,000 child-years at risk for tuberculosis based on a  
5 random-effects model ( $I^2 = 99%$ ; Figure 2). Subgroup analysis established change over time in  
6 incidence rates when comparing studies conducted before and after 2011. The pooled incidence  
7 rates for tuberculosis in those conducted before 2010 was 70 (95% CI -20 - 160) per 1,000  
8 child-years<sup>32,35</sup> and 40 (95% CI 20 - 50) per 1,000 child-years in studies conducted between  
9 2011 and 2018.<sup>15,17-20,22</sup> The heterogeneity of the TB incidence could not be explained by the  
10 subgroup analysis. Kouakoussui et al. reported TB incidence of 0.71 per 100 child/months  
11 before initiation of highly active antiretroviral therapy (HAART) and 0.16 per 100  
12 child/months during HAART treatment among Ivorian HIV-infected children.<sup>60</sup>

13 **Pneumococcal infections:** Incidence of invasive pneumococcal disease among HIV-infected  
14 children aged <1 and 1–4 years was 1022 (95% CI 923–1123) per 100,000 and 198 (95% CI  
15 178–220) per 100,000 respectively in 2008.<sup>89</sup> The incidence of pneumococcus-associated  
16 lower respiratory tract infection among HIV-exposed uninfected children was 109 (95% CI  
17 47–214) per 100,000 and 629 (95% CI 130–1838) per 100,000 among HIV-infected children.<sup>86</sup>  
18 Ásbjörnsdóttir et al. reported the incidence of pneumonia among Kenyan HIV-exposed  
19 uninfected infants to be 900 (95% CI 800–1000) per 1,000 child-years.<sup>81</sup> Nunes et al. reported  
20 the incidence of invasive pneumococcal disease to be 1509 (95% CI 1350 – 1680) per 100,000  
21 during early (HAART) and 742 (95% CI 644 – 851) during established-HAART eras for less  
22 than 18-year old South Africans.<sup>87</sup>

23 **Pertussis:** The incidence of pertussis among Zambian HIV-exposed infants was reported to be  
24 3.7 (95% CI 0.9–10.1) per 1000 person-months<sup>75</sup> while Soofie et al. reported the incidence to  
25 be 2.9 (95% CI 1.8 – 4.5) per 1,000 child-years.<sup>78</sup>

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

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33 **Prevalence**

34 Twenty-one TB prevalence studies were pooled together and reported estimated prevalence of  
 35 16% (95% CI 12 - 19,  $I^2 = 99\%$ ). For studies conducted within the period 1991-2000, the  
 36 prevalence was 13% (95% CI 8 - 18)<sup>40,43</sup>; lower in 2001-2010 with an estimate of 8% (95% CI  
 37 5 - 11,  $I^2 = 96\%$ )<sup>22,33,37,38,51</sup> and recorded the highest prevalence in recent years with 15% (95%  
 38 CI 8 - 22,  $I^2 = 99\%$ )<sup>15,16,18,19,21,23,27,29,31,41,45,46,52,57</sup> (Figure 3). Fourteen prevalence studies on  
 39 hepatitis B (HBV) infection in HIV-infected children were pooled together with an estimate  
 40 prevalence of 5% (95% CI 4 - 7,  $I^2 = 90\%$ ). Studies conducted between 2001 and 2010 had a  
 41 prevalence of 3% (95% CI 2 - 5)<sup>67,68</sup> and 4% (95% CI 3 - 6) between 2011 and 2018<sup>61,63,64,65-  
 42 72,74</sup> (Figure 4).

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

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

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

56 **Trend in incidence and prevalence**

57 We analysed the trend in TB incidence with respect to publication years. The trend was non-  
 58 linear with a downtrend from 2000 to 2010 (at -12.5% per year) and a reduced downward trend  
 59 from 2011 to 2018 (at -1.5 per year) as shown in Figure 5. The trend in HBV prevalence was  
 60 also analysed. The trend was not linear. There was evidence of a downtrend from 2000 to 2010  
 61 (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).

**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**

#### 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% of all TB cases dying from the disease. Subgroup analysis shows the CFR was 18% (95% CI 6 – 24)<sup>47</sup> in the 1991-2000 period, 6% (17 – 38,  $I^2 = 95%$ )<sup>33,35-37,48,49,53,54,56,59</sup> in 2001-2010 and 13% (95% CI 9 – 17,  $I^2 = 96%$ )<sup>15,16,18,20,23-25,30,34,39,44,46,47,50,55,56</sup> 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,  $I^2 = 95%$ ).<sup>81,84,85,90</sup> One study shows that pertussis has CFRs of 13% (95% CI 2 – 38)<sup>78</sup> and for measles the CFR was 1% (95% CI 0 - 4).<sup>76</sup>

#### 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 (Figure 7 and 8). Likewise, studies assessing the CFR of TB demonstrated no significant publication bias Begg's test P = 0.385 (Figure 9).

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

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95 **Figure 8: Funnel plot of studies reporting on the prevalence of hepatitis B virus infection in HIV-infected**  
96 **children**

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99 **Figure 9: Funnel plot of studies reporting on the case-fatality rate of tuberculosis in HIV-infected**  
100 **children**

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## 103 Discussion

104 This study provides a comprehensive overview of the incidence rate, prevalence and case  
105 fatality rates of different vaccine-preventable diseases in HIV-infected and HIV-exposed  
106 children in sub-Saharan African countries. The review shows that TB is the most researched  
107 vaccine-preventable disease in HIV-infected children in various African countries and settings.  
108 This is not surprising because of the relationship between TB and HIV infection with respect  
109 to the high susceptibility of TB in HIV-infected individuals,<sup>91,92</sup> Other vaccine-preventable  
110 diseases like HBV infection, pneumococcal infection, measles, rotavirus gastroenteritis,  
111 pertussis and Hib infections were also studied in several African countries. Important vaccine-  
112 preventable diseases such as poliomyelitis, diphtheria, tetanus and yellow fever had no eligible  
113 studies for inclusion revealing the dearth of incidence and prevalence studies on these diseases.  
114 The pooled incidence, prevalence and CFRs reveal there are still high burdens of several  
115 vaccine-preventable diseases in sub-Saharan Africa.

116

117 According to WHO, the global incidence of TB has been reducing at an average of 2 percent  
118 per year.<sup>91</sup> TB incidence has declined in the African region by 4 percent annually since 2013.<sup>91</sup>  
119 Southern African countries with the highest prevalence and incidence of HIV such as South  
120 Africa, Lesotho, Zimbabwe, Eswatini, Namibia and Zambia had remarkable reductions in TB  
121 incidence.<sup>91</sup> Our study shows that TB incidence reduced over time, however, the event per  
122 child-year is still high when compared with the End TB strategy goals.<sup>93</sup> The World Health  
123 Assembly adopted the resolution known as “*End TB strategy goals*” which is about the global  
124 strategy and targets for tuberculosis prevention, care and control after 2015<sup>93</sup>. In spite of the  
125 reduction in TB incidence among children, there are still cases of high incidence in certain  
126 countries bearing in mind that many countries in African countries are classified as high-  
127 burden.<sup>96</sup> A retrospective cohort study in a very high TB/HIV prevalent region in Nigeria  
128 showed a high incidence rate of 21.2/100 per year among children within six months of ART

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129 enrollment at a period when others were recording much lower incidence.<sup>18</sup> TB prevalence has  
130 fluctuated over time with about 15% of HIV-infected children having the disease at a given  
131 point in time. As of 2017, it was estimated that the global CFR was 16% with many African  
132 countries recording more than 20%.<sup>91</sup> This rate is also far higher than the End TB Strategy  
133 milestone of 10% by 2020.

134  
135 The pooled HBV infection prevalence among HIV-infected children was 5%, however, a study  
136 done in Rwanda in 2010 revealed a seroprevalence of 16%.<sup>68</sup> Ott et al. showed that sub-Saharan  
137 Africa had the highest HBV burden with West African countries having up to 12% hepatitis B  
138 surface antigen prevalence among children and adolescents in the 1990s.<sup>94</sup> There has been a  
139 reduction within the region largely due to immunisation programmes, however, there is high  
140 endemicity in some areas. A systematic review of HBV prevalence in Nigeria from studies  
141 conducted from 2000 to 2013 shows that HBV infection ranged from 0.5% to 46.8% with the  
142 pooled prevalence estimate for Nigeria being 13.6%.<sup>95</sup>

143  
144 Our finding shows that the seroprevalence of rotavirus gastroenteritis among African HIV-  
145 infected children was 14% although with a small number of included studies. The incidence  
146 and CFR of diarrhoea and pneumonia are much higher in low-income than in high-income  
147 countries and this is reflected in many African and southeast Asian countries having the highest  
148 burden of the diseases.<sup>96</sup> The African region has the highest incidence and total death secondary  
149 to diarrhoea and pneumonia with rotavirus and *Streptococcus pneumoniae* being the  
150 commonest culprits.<sup>96</sup> Studies have shown that there is still a persistently high incidence of  
151 some vaccine-preventable diseases in HIV-infected individuals than non-exposed ones even  
152 after the introduction of highly active antiretroviral therapy.<sup>97</sup> The incidence of pertussis is also  
153 higher in HIV-exposed and infected children, however, this decreases as the number of vaccine  
154 doses uptake increases.<sup>98</sup>

155  
156 Many African countries with high burdens of HIV are critically lagging in terms of  
157 antiretroviral treatment coverage for HIV-infected children.<sup>99</sup> Sub-optimal ART coverage in  
158 children will lead to viral load increase, immunosuppression, etc. and a subsequent high burden  
159 of various vaccine-preventable diseases. Vaccination coverage in many African countries is  
160 still below the expected target.<sup>100</sup> As of 2017, the average coverage of third-dose pentavalent  
161 vaccine was 80% while the first dose of measles vaccine in the Global Alliance for Vaccines

162 and Immunisation (Gavi)-supported countries was 78%.<sup>100</sup> The average coverage of Gavi-  
163 funded vaccines in supported countries progressed from 37% in 2016 to 41% in 2017.

164  
165 . Use of vaccines has been established to be a beneficial healthcare intervention targeted in  
166 protecting children and adolescents from various vaccine-preventable diseases. Low uptake of  
167 vaccines by African children exposes them to more diseases than children in other regions. It  
168 has also been established that HIV-infected children are more susceptible to vaccine-  
169 preventable diseases such as TB, pneumonia, viral hepatitis etc.<sup>101,102</sup> Vaccination is therefore  
170 essential in HIV-infected patients because of the increased risk of developing various infectious  
171 diseases due to their defective immune systems. Studies have also shown that there are poor  
172 immune responses to primary vaccination among HIV-infected children in comparison to HIV-  
173 unexposed and HIV-exposed children. The poor immune response among HIV-infected  
174 children may require booster doses for optimal immunity against vaccine-preventable  
175 diseases.<sup>103,104</sup>

176  
177 This review revealed research inequalities across the African region regarding studies on the  
178 burden of vaccine-preventable diseases among HIV-infected and HIV-exposed children. South  
179 Africa contributed about half of the included articles with Nigeria and Kenya following with  
180 fewer studies. This finding is not different from an earlier study looking at the distribution of  
181 epidemiological studies across Africa.<sup>105</sup> Some of the Eastern and Southern African countries  
182 with high HIV prevalence had at least an article included in this study, however, West African  
183 countries only had publications from Nigeria and Cote d'Ivoire.

184  
185 To the best of our knowledge, this is the first systematic review that addressed the need for  
186 knowing the burden of vaccine-preventable diseases among HIV-infected and HIV-exposed  
187 children in sub-Saharan Africa. Knowledge gap concerning the burden of vaccine-preventable  
188 diseases will impact negatively on the advocacy endeavours targeted at improving vaccination  
189 and vaccine-preventable diseases control efforts in Africa. Healthcare workers and  
190 policymakers need to have a good idea of the burden of different diseases to allocate resources  
191 and facilitate optimal vaccination coverage.

## 192 **Recommendations**

193 This review has shown that TB is one of the most important vaccine-preventable diseases in  
194 Africa with the BCG vaccine conferring protection against severe forms of the disease.

196 However, the same vaccine is contraindicated in immunocompromised children who ironically  
197 are susceptible to the disease.<sup>13</sup> The dilemma of BCG use in HIV-exposed children warrants  
198 the call for newer and safer vaccines against TB especially in HIV-infected children. African  
199 governments and other supporting agencies should ensure that every child has access to routine  
200 childhood vaccines. Issues of under-vaccination and vaccine hesitancy should be adequately  
201 tackled to ensure better vaccine uptake and reduction in the burden of vaccine-preventable  
202 diseases.

203  
204 The research capacity of African clinicians, researchers and health administrators should be  
205 built up for them to conduct basic epidemiological research such as incidence, prevalence,  
206 mortality and CFR among HIV-exposed children in various health facilities and communities.  
207 Researchers should be encouraged to disseminate their findings to their immediate  
208 communities and Departments of Health and to publish their findings in peer-reviewed  
209 journals. Established research groups such as Global Burden of Diseases Network should  
210 include the burden of vaccine-preventable diseases in HIV-exposed and non-exposed children  
211 as part of their regular or annual publications. Other African countries should emulate South  
212 Africa in increasing their research activities and outputs with respect to HIV-exposed children.

213  
214 There is a need to advocate for an equitable share of healthcare budgeting and finance at every  
215 level of governance in African countries. This will help in ensuring that there is a fair share of  
216 resources for preventive and treatment services such as vaccination and antiretroviral therapy  
217 for HIV-exposed children. African countries should, as a matter of urgency, complete the  
218 introduction of newer and important vaccines such as rotavirus vaccine, Hib vaccine and  
219 pneumococcal vaccine. These should be included as part of their current national immunisation  
220 programme schedule.<sup>95</sup> According to WHO, the global coverage for both pneumococcal  
221 vaccine and rotavirus vaccines were as little as 44 percent and 25 percent respectively.<sup>100</sup>  
222 African countries should be supported in developing vaccine procurement budgets,  
223 procurement practices, and capacity development for vaccine planning and advocacy.<sup>106</sup>

### 225 **Study limitations**

226 This study was limited by several factors beyond the reviewers' control. We planned to review  
227 all the vaccine-preventable diseases associated with vaccines included in the national  
228 immunisation programme schedule in sub-Saharan Africa, however, we could not find articles  
229 that met the eligibility criteria for some of the diseases. Secondly, there was high heterogeneity



230 even with sub-group analysis between included studies, which implies the possibility of other  
231 contributory factors associated with the diseases. Some of the studies did not include relevant  
232 information such as antiretroviral coverage, CD4 count, viral load, vaccination status and other  
233 contributory factors. Thirdly, we could not include many studies because the diagnostic criteria  
234 for different vaccine-preventable diseases were not specified and clearly defined.

235  
236 Furthermore, the presence of various limitations did not stop us from making some meaningful  
237 conclusions from this study. This review gives a clearer picture of the burden and trend of TB  
238 and able to have insights about the burden of other diseases as well despite having a small  
239 number of studies included in this review. African investigators should as a matter of priority  
240 have proper diagnostic criteria and documentation for diseases for all HIV-infected and HIV-  
241 exposed children treated at the health facilities across the region. Key parameters such as CD4  
242 counts, vaccination status etc. should be included in future studies.

## 243 244 **Conclusions**

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

## 253 254 255 **Methods and design**

256 This systematic review was developed in line with the Preferred Reporting Items for Systematic  
257 Review and Meta-Analysis (PRISMA) 2015 statement.<sup>107</sup> The review was registered with  
258 PROSPERO (International prospective register of systematic reviews) (CRD42018095341).

### 259 **Inclusion criteria**

260 *Type of participants*: The review included sub-Saharan African children who are HIV-infected  
261 or HIV-exposed and aged <18 years old.

262 Types of outcome:

1 263 We included studies that reported the incidence, prevalence and case-fatality rates (CFR) as  
2 264 outcomes in HIV-infected and HIV-exposed children.

4 265 Primary outcomes

5 266 Prevalence was defined as proportions of all individuals suspected of having specific vaccine-  
6 267 preventable diseases with confirmed laboratory diagnosis or proportions of individuals  
7 268 fulfilling clinical case definition for specific vaccine-preventable diseases. Incidence was  
8 269 defined as the number of new cases of different vaccine-preventable diseases that occur during  
9 270 a given period in the defined population.

15 271 We also determined the trend in the incidence and/or prevalence of vaccine-preventable  
16 272 diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa from 1980 to  
17 273 2018.

22 274 Secondary outcomes

23 275 We included CFRs associated with vaccine-preventable diseases. Case fatality was described  
24 276 as mortality among confirmed or probable cases for a specific vaccine-preventable disease.

27 277 Type of studies: The review included cohort studies, case-control studies, cross-sectional  
28 278 studies and other observational studies. We planned to include studies that involved any of  
29 279 the following vaccine-preventable diseases:

- 33 280 i. Tuberculosis
- 34 281 ii. Poliomyelitis
- 35 282 iii. Hepatitis B virus infection
- 36 283 iv. Rotavirus gastroenteritis
- 37 284 v. Diphtheria
- 38 285 vi. Tetanus
- 39 286 vii. Pertussis
- 40 287 viii. Pneumococcal diseases
- 41 288 ix. Measles
- 42 289 x. Rubella
- 43 290 xi. Yellow fever

54 291 Exclusion criteria

- 55 292 • Intervention studies
- 56 293 • Unclear diagnostic criteria

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### 296 [Search strategy methods for the identification of studies](#)

297 A comprehensive search strategy was developed to identify relevant studies up to August 2018,  
298 regardless of publication status or language. Scopus, Web of Science, MEDLINE via PubMed  
299 and CINAHL were searched for relevant publications. The search process was complemented  
300 by reviewing citations of all identified eligible studies. We also searched relevant World Health  
301 Organization position papers and documents on vaccines. (See Appendix for PubMed search  
302 strategy).

### 303 [Selection of eligible studies](#)

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

### 309 [Data collection process](#)

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

313 The following data were extracted from selected studies:

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

### 320 [Risk of bias in individual studies](#)

321 The risk of bias and quality of the included studies were assessed with the Newcastle-Ottawa  
322 Quality Scale.<sup>108</sup> The criteria assessed included the following (1) selection of participants, (2)  
323 comparability, (3) exposure, and (4) outcome.

324

## 325 Data synthesis

1 326 OOA summarised the incidence and prevalence of various vaccine-preventable diseases.  
2  
3 327 Where possible, incidence and prevalence data from each of the included studies were  
4  
5 328 combined by random effects meta-analysis in accordance with the Mantel-Haenszel method.  
6

7 329 Heterogeneity was evaluated using the Chi-squared test of homogeneity (significant for  $P <$   
8  
9 330 0.1) and quantified using the I-squared statistic (>50% substantial heterogeneity).<sup>109</sup> Subgroup  
10  
11 331 analyses were conducted in cases with substantial heterogeneity. Subgroup analysis was  
12  
13 332 conducted using the following variables: period of study (1991- 2000, 2001-2010 and 2011 –  
14  
15 333 2018). We also used funnel plot regression to assess publication bias. STATA software version  
16  
17 334 14.0 (STATA Corporation, College Station, TX, USA) was used to do all calculations, the  
18  
19 335 meta-analysis and generate forest plots.<sup>110</sup>  
20

## 21 336 Additional analyses: Trend analysis

22 337 We examined time trends in the incidence and prevalence of vaccine-preventable diseases  
23  
24 338 estimates using Poisson regression models with the prevalence estimates as the outcome  
25  
26 339 variable and the calendar year of the publication as the predictor. This method allows for  
27  
28 340 estimation of time trends across individual calendar years to obtain average annual percentage  
29  
30 341 change (AAPC), if the rate of change is at a constant rate of the previous year.<sup>111</sup> The Poisson  
31  
32 342 regression procedure fits a model of the following form:

$$33 \log(\textit{prevalence}_y) = b_0 + b_1y + \log(\textit{sample size}) \quad (1)$$

34  
35 343  
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37 344 where ‘cases’ equal prevalence estimates reported per year, log is the natural log,  $b_0$  is the  
38  
39 345 intercept,  $b_1$  is the trend,  $y$  is the year – given as 0, 1, 2, ... 18 (year 0 is 1970, year 1 is 1971,  
40  
41 346 and so on to 2014), and log of ‘sample size’ was entered as the offset. The AAPC was calculated  
42  
43 347 using the following formula:

$$44 \textit{AAPC} = (e^{b_1} - 1) \times 100 \quad (2)$$

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## 51 350 Abbreviations

52 351 BCG: Bacillus Calmette–Guérin

53 352 DTP: Diphtheria, tetanus and pertussis

54 353 EPI: Expanded Programme on Immunisation

55 354 GVAP: Global Vaccine Action Plan  
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355 Hib: *Haemophilus influenzae* type b  
1 356 HIV: Human immunodeficiency virus  
2  
3 357 PCV: Pneumococcal conjugate vaccine  
4  
5 358 PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis  
6  
7 359 RV: Rotavirus  
8  
9 360 WHO: World Health Organization

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11 361

## 362 Authors' contributions

14 363 OOA developed the protocol, search strategy, the data analysis and manuscript preparation.  
15  
16 364 OOA and AA did the screening, study selection and data extraction. OAU and CSW guided  
17  
18 365 the development of this study. All authors were involved in the results interpretation, revision  
19  
20 366 and approval of the final manuscript.

21  
22 367

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34  
35 373 those of the National Health Service, National Institute for Health.

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## 40 375 Disclosure of potential conflicts of interest

41 376 No potential conflicts of interest were disclosed.

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## Appendix

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1 The burden of vaccine-preventable diseases among HIV-  
2 infected and HIV-exposed children in sub-Saharan Africa: a  
3 systematic review and meta-analysis  
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5

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32 **Abstract**

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

52 **Keywords:** HIV; vaccine-preventable diseases; sub-Saharan Africa; burden

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## 60 Background

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

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

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

90 The gap in knowledge, especially in terms of evidence-based research, on the burden of vaccine-  
91 preventable diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa,  
92 warrants this study.<sup>14</sup> This study completed a systematic review of literature and meta-analysis to  
93 identify the incidence, prevalence and mortality due to various vaccine-preventable diseases  
94 among HIV-infected and HIV-exposed children in sub-Saharan Africa since the advent of HIV in  
95 the 1980s. This study is essential in determining the trend and current burden of vaccine-  
96 preventable disease epidemiology in sub-Saharan Africa.

97

## 98 Objectives

### 99 Primary objectives

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

### 109 Secondary objective

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

114

## 115 Results

116

### 117 Literature search and result

118 Figure 1 shows the study selection process reported in line with PRISMA guidelines. We identified  
119 3430 publications through the search of different databases. We also identified 13 additional

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

### 123 **Study characteristics**

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

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

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

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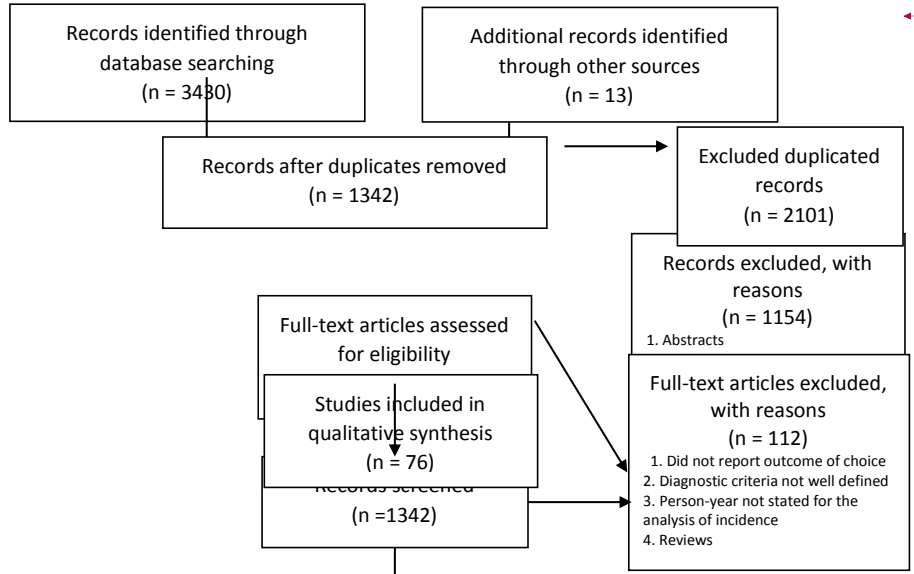
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Identification  
Eligibility



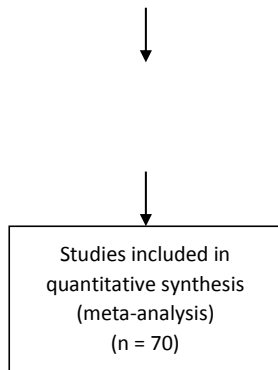
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Figure 1: Flow diagram of the selection process

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**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 <sup>35</sup>	2009–2010	Cohort	Kenya	689	Tuberculosis	C, I, P	HI	7
Adams 2014 <sup>36</sup>	2006–2012	Cross-sectional	Tanzania	1193	Tuberculosis	C, P	HI	4
Alemu 2016 <sup>37</sup>	2009–2014	Cohort	Ethiopia	645	Tuberculosis	I	HI	6
Anigilaje 2016 <sup>38</sup>	2010–2013	Cohort	Nigeria	368	Tuberculosis	P	HI	8
Atid 2014 <sup>39</sup>	2004–2008	Cohort	Cote d'Ivoire	2110	Tuberculosis	I, P	HI	8
Bakeera 2011 <sup>40</sup>	2003–2006	Cohort	Uganda	1806	Tuberculosis	I, C	HI	8
Bonnet 2018 <sup>24</sup>	2012–2014	Cohort	Uganda	113	Tuberculosis	C	HI	7
Braitstein 2009 <sup>22</sup>	2001–2007	Cohort	Kenya	6,535	Tuberculosis	I, P	HI	8
Buck 2013 <sup>23</sup>	2010	Cohort	Malawi	4874	Tuberculosis	C, P	HI	8
Carlucci 2017 <sup>24</sup>	2012–2014	Cohort	Multiple	386	Tuberculosis	C	HI	8
Cavanaugh 2012 <sup>25</sup>	2006–2007	Cross-sectional	Kenya	323	Tuberculosis	C	HI	6
Chaya 2016 <sup>26</sup>	2006–2011	Cross-sectional	South Africa	47	Tuberculosis	I	HI	6
Cruz 2015 <sup>27</sup>	NR	Cohort	Botswana	100	Tuberculosis	P	HI	6
Dangor 2013 <sup>28</sup>	2005–2009	Time-series analysis	South Africa	1985	Tuberculosis	I	HI	7
De Maayar 2011 <sup>29</sup>	NR	Cross-sectional	South Africa	58	Tuberculosis	P	HI	7
Ebonyi 2016 <sup>30</sup>	2005–2013	Cohort	Nigeria	260	Tuberculosis	C	HI	8
Ebonyi 2016b <sup>31</sup>	2005–2012	Cohort	Nigeria	876	Tuberculosis	P	HI	8
Elenga 2005 <sup>32</sup>	2000–2003	Cohort	Cote d'Ivoire	282	Tuberculosis	I	HI	8
Ferrand 2010 <sup>33</sup>	2007–2008	Cross-sectional	Zimbabwe	139	Tuberculosis	P	HI	7
Hall 2017 <sup>24</sup>	2005–2008	Cohort	South Africa	224	Tuberculosis	C	HI	8
Hesseling 2009a <sup>25</sup>	2004–2006	Cross-sectional	South Africa	3321	Tuberculosis	C	HI	6
Hesseling 2005 <sup>26</sup>	1992–2000	Cohort	South Africa	93	Tuberculosis	C	HI	8
Hesseling 2006 <sup>27</sup>	2002–2005	Cohort	South Africa	108	Tuberculosis	C, P	HI	7
Hesseling 2009b <sup>28</sup>	2004–2006	Cross-sectional	South Africa	3321	Tuberculosis	I, P	HI	7
Hicks 2014 <sup>39</sup>	2009–2010	Cohort	South Africa	64	Tuberculosis	C	HI	6
Jeena 2000 <sup>40</sup>	1995–1998	Cross-sectional	South Africa	27	Tuberculosis	P	HI	5
Kasambira 2011 <sup>41</sup>	2006–2009	Cross-sectional	South Africa	270	Tuberculosis	P	HI	6
Madhi 2000b <sup>42</sup>	1996–1997	Cross-sectional	South Africa	67	Tuberculosis	C	HI	5
Meyers 2000 <sup>43</sup>	1996	Cross-sectional	South Africa	144	Tuberculosis	P	HI	5



Mwangwa 2017 <sup>44</sup>	2012–2013	Cohort	Multiple	17	Tuberculosis	C	HI	7
Obiagwu 2013 <sup>45</sup>	2010	Cross-sectional	Nigeria	22	Tuberculosis, Measles	P	HI	6
Okechukwu 2011 <sup>46</sup>	2007–2008	Cross-sectional	Nigeria	210	Tuberculosis	C, P	HI	6
Osman 2017 <sup>47</sup>	2005–2012	Cohort	South Africa	3143	Tuberculosis	C	HI	6
Padayatchi 2006 <sup>48</sup>	1993–2002	Cross-sectional	South Africa	6	Tuberculosis	C	HI	5
Palme 2002 <sup>49</sup>	1995–1997	Cohort	Ethiopia	58	Tuberculosis	C	HI	6
Patel 2013 <sup>50</sup>	2007–2009	Cohort	Congo DRC	31	Tuberculosis	C	HI	7
Robinson 2007 <sup>51</sup>	1999–2001	Case-control	South Africa	47	Tuberculosis	P	HI	6
Rose 2012 <sup>52</sup>	2008–2010	Cohort	Tanzania	54	Tuberculosis	P	HI	6
Schaaf 2007 <sup>53</sup>	2003–2005	Cross-sectional	South Africa	133	Tuberculosis	C	HI	5
Soeters 2005 <sup>54</sup>	2000–2001	Cross-sectional	South Africa	43	Tuberculosis	C	HI	4
Walters 2014 <sup>55</sup>	2003–2010	Cohort	South Africa	494	Tuberculosis	C	HI	6
Walters 2005 <sup>56</sup>	2003–2005	Cross-sectional	South Africa	137	Tuberculosis	C	HI	6
Westerlund 2014 <sup>57</sup>	2003–2008	Cohort	Ethiopia	138	Tuberculosis	P	HI	7
Wiseman 2011 <sup>58</sup>	2004–2006	Cross-sectional	South Africa	52	Tuberculosis	C	HI	5
Yotebieng 2010 <sup>59</sup>	2004–2008	Cohort	South Africa	573	Tuberculosis	C	HI	6
Kouakoussui 2004 <sup>60</sup>	2003	Cohort	Cote d'Ivoire	270	Tuberculosis	I	HI	7
Abera 2014 <sup>61</sup>	2014	Cross-sectional	Ethiopia	253	HBV infection	P	HI	6
Ashir 2009 <sup>62</sup>	2007	Case-control	Nigeria	284	HBV infection	P	HI	5
Beghin 2017 <sup>63</sup>	2014	Cross-sectional	South Africa	183	HBV infection	P	HI	6
Chotun 2015 <sup>64</sup>	2011–2012	Cross-sectional	South Africa	1000	HBV infection	P	HE	6
Uleanya 2016 <sup>65</sup>	NR	Cross-sectional	Nigeria	140	HBV infection	P	HI	4
Dziuban 2013 <sup>66</sup>	2009–2011	Cross-sectional	Swaziland	500	HBV infection	P	HI	3
Ikpeme 2013 <sup>67</sup>	2010–2011	Cross-sectional	Nigeria	166	HBV infection	P	HI	4
Jooste 2016 <sup>68</sup>	2015–2016	Cohort	South Africa	625	HBV infection	P	HI	7
Muro 2013 <sup>69</sup>	2006–2008	Cross-sectional	Tanzania	157	HBV infection	P	HI	5
Mutwa 2013 <sup>70</sup>	2010	Cohort	Rwanda	88	HBV infection	P	HI	7
Nwolisa 2013 <sup>71</sup>	2010	Cross-sectional	Nigeria	139	HBV infection	P	HI	4
Sadoh 2011 <sup>72</sup>	NR	Cross-sectional	Nigeria	155	HBV infection	P	HI	5
Telatela 2007 <sup>73</sup>	2006	Cross-sectional	Tanzania	167	HBV infection	P	HI	4
Varo 2016 <sup>74</sup>	2008–2010	Cross-sectional	Malawi	91	HBV infection	P	HI	3
Moss 2002 <sup>75</sup>	1998–2000	Cross-sectional	Zambia	93	Measles	P	HI	6
Wirth 2015 <sup>76</sup>	2009–2010	Case-control	Botswana	189	Measles	C	HI	5
du Plessis 2018 <sup>14</sup>	2013–2015	Cross-sectional	South Africa	300	Pertussis	-P	HI	6

Gill 2016 <sup>77</sup>	2015	Cohort	Zambia	347	Pertussis	I	HI	7
Seofie 2016 <sup>78</sup>	2015	Cross-sectional	South Africa	599	Pertussis	C, I, P	HE	5
Johnson 2000 <sup>79</sup>	1996-1997	Cross-sectional	South Africa	31	Rotavirus gastroenteritis	P	HI	6
Moyo 2014 <sup>80</sup>	2010-2011	Case-control	Tanzania	26	Rotavirus gastroenteritis	P	HI	5
Asbjörnsdóttir 2013 <sup>81</sup>	1999-2002	Cohort	Kenya	388	Pneumococcal infection	C, I	HI	6
Nathoo 1996 <sup>82</sup>	1993-1994	Cohort	Zimbabwe	168	Pneumococcal infection	P	HI	7
Zar 2001 <sup>83</sup>	1998	Cross-sectional	South Africa	151	Pneumococcal infection	P	HI	6
Jones 1998 <sup>84</sup>	1996	Cross-sectional	South Africa	25	Pneumococcal infection	C	HI	5
Roca 2010 <sup>85</sup>	2004-2006	Cross-sectional	Mozambique	54	Pneumococcal infection	C	HI	6
Cohen 2016 <sup>86</sup>	2009-2013	Cross-sectional	South Africa	211	Pneumococcal infection	I	HEU, HI	4
Nunes 2011 <sup>87</sup>	2003-2008	Cross-sectional	South Africa	938	Pneumococcal infection	I	HI	6
von Mollendorf 2017a <sup>88</sup>	2009-2013	Cross-sectional	South Africa	495	Pneumococcal infection	C, I	HI	5
von Gottberg 2013 <sup>89</sup>	2003-2008	Cross-sectional	South Africa	1749	Pneumococcal infection	I	HI	5
Nyasulu 2011 <sup>90</sup>	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.

1

## 2 **Incidence rates**

3 **Tuberculosis:** Nine studies<sup>15,17-20,22,32,35</sup> on TB were pooled to give an overall incidence rate  
4 estimate of 60 (95% CI 30 – 70) per 1,000 child-years at risk for tuberculosis based on a  
5 random-effects model ( $I^2 = 99%$ ; Figure 2). Subgroup analysis established change over time in  
6 incidence rates when comparing studies conducted before and after 2011. The pooled incidence  
7 rates for tuberculosis in those conducted before 2010 was 70 (95% CI -20 - 160) per 1,000  
8 child-years<sup>32,35</sup> and 40 (95% CI 20 - 50) per 1,000 child-years in studies conducted between  
9 2011 and 2018.<sup>15,17-20,22</sup> The heterogeneity of the TB incidence could not be explained by the  
10 subgroup analysis. Kouakoussui et al. reported TB incidence of 0.71 per 100 child/months  
11 before initiation of highly active antiretroviral therapy (HAART) and 0.16 per 100  
12 child/months during HAART treatment among Ivorian HIV-infected children.<sup>60</sup>

13 **Pneumococcal infections:** Incidence of invasive pneumococcal disease among HIV-infected  
14 children aged <1 and 1–4 years was 1022 (95% CI 923–1123) per 100,000 and 198 (95% CI  
15 178–220) per 100,000 respectively in 2008.<sup>89</sup> The incidence of pneumococcus-associated  
16 lower respiratory tract infection among HIV-exposed uninfected children was 109 (95% CI  
17 47–214) per 100,000 and 629 (95% CI 130–1838) per 100,000 among HIV-infected children.<sup>86</sup>  
18 Ásbjörnsdóttir et al. reported the incidence of pneumonia among Kenyan HIV-exposed  
19 uninfected infants to be 900 (95% CI 800–1000) per 1,000 child-years.<sup>81</sup> Nunes et al. reported  
20 the incidence of invasive pneumococcal disease to be 1509 (95% CI 1350 – 1680) per 100,000  
21 during early (HAART) and 742 (95% CI 644 – 851) during established-HAART eras for less  
22 than 18-year old South Africans.<sup>87</sup>

23 **Pertussis:** The incidence of pertussis among Zambian HIV-exposed infants was reported to be  
24 3.7 (95% CI 0.9–10.1) per 1000 person-months<sup>75</sup> while Soofie et al. reported the incidence to  
25 be 2.9 (95% CI 1.8 – 4.5) per 1,000 child-years.<sup>78</sup>

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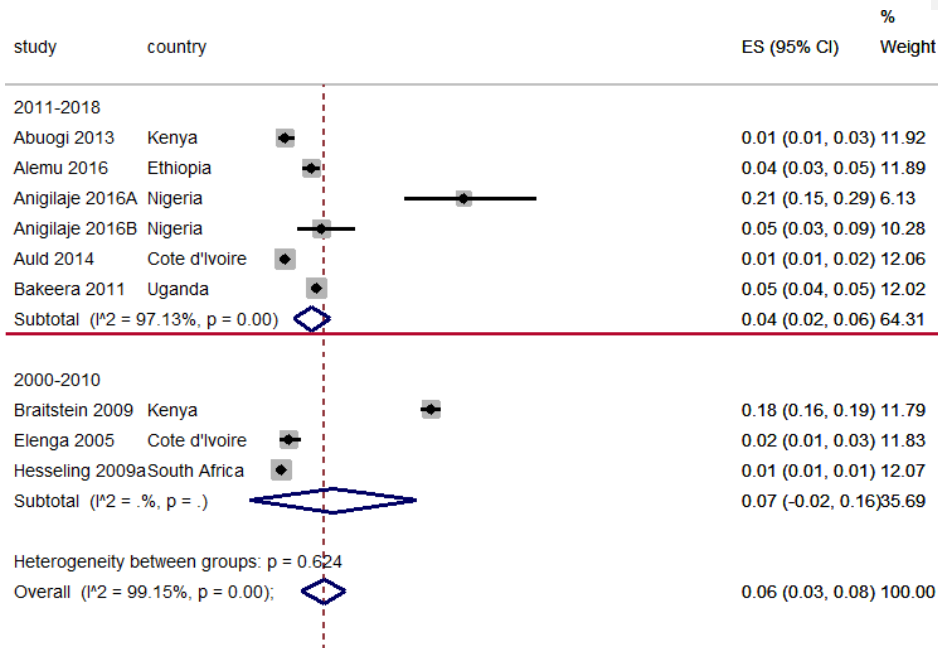
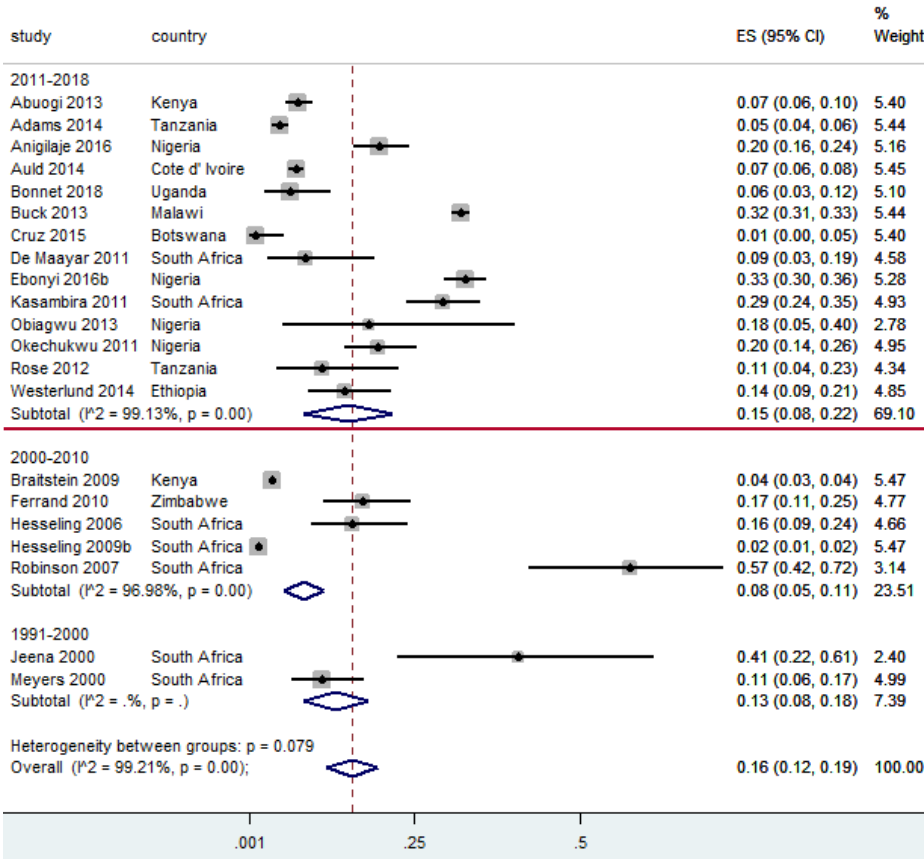


Figure 2: Forest plot of studies with data on incidence rates of tuberculosis in HIV-exposed children

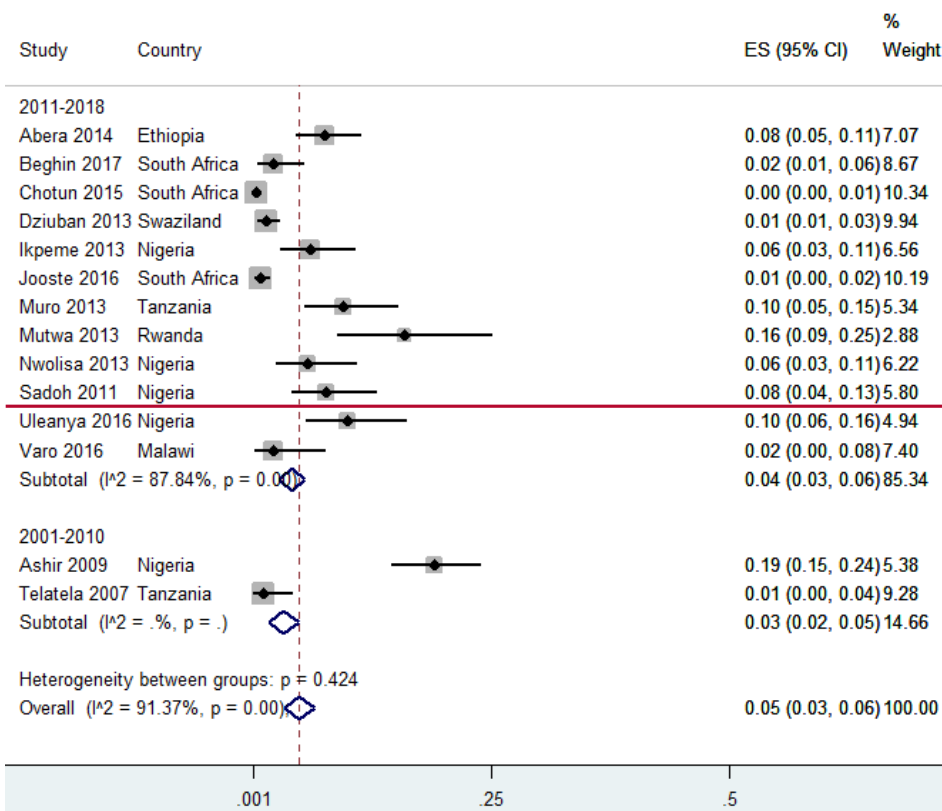
### Prevalence

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)<sup>40,43</sup>; lower in 2001-2010 with an estimate of 8% (95% CI 5 - 11,  $I^2 = 96\%$ )<sup>22,33,37,38,51</sup> and recorded the highest prevalence in recent years with 15% (95% CI 8 - 22,  $I^2 = 99\%$ )<sup>15,16,18,19,21,23,27,29,31,41,45,46,52,57</sup> (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)<sup>67,68</sup> and 4% (95% CI 3 - 6) between 2011 and 2018<sup>61,63,64,65-72,74</sup> (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)<sup>83</sup> in 1996 to 1% (95% CI 0 - 5)<sup>84</sup> in 2001. Pooled prevalence for pertussis was 3% (95% CI 2 - 4)<sup>14,78</sup> while measles was 6% (95% CI 2 - 10).<sup>75,76</sup> Two rotavirus diarrhoea prevalence studies were pooled together and reported an estimated prevalence of 13% (95% CI 8 - 17,  $I^2 = 0\%$ ).<sup>79,80</sup>



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



52

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

55

56 **Trend in incidence and prevalence**

57 We analysed the trend in TB incidence with respect to publication years. The trend was non-  
 58 linear with a downtrend from 2000 to 2010 (at -12.5% per year) and a reduced downward trend  
 59 from 2011 to 2018 (at -1.5 per year) as shown in Figure 5. The trend in HBV prevalence was  
 60 also analysed. The trend was not linear. There was evidence of a downtrend from 2000 to 2010  
 61 (at -4.7% per year) and (at -5.3% per year) from 2011 to 2018 as shown in Figure 6. The TB  
 62 prevalence trend was also non-linear. There was evidence of initial downtrend from 2000 to  
 63 2010 (at -3.2% per year) and upward trend from 2011 to 2018 (at +32.7 per year).



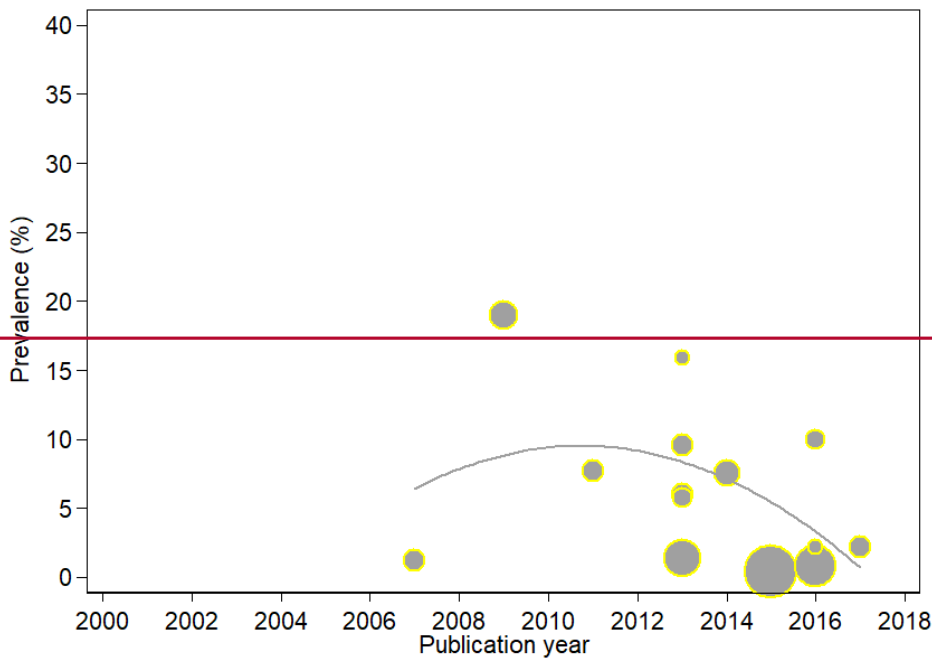
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65 **Figure 5: Trends in the incidence of tuberculosis in HIV-infected and exposed children with respect to**  
 66 **publication years**

67

68

69



70

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

73

74 **Case-fatality rates**

75 Twenty-nine studies on TB were pooled to give an overall CFR estimate of 17% (95% CI: 13  
 76 - 20,  $I^2 = 95\%$ ) which translates to 17% of all TB cases dying from the disease. Subgroup  
 77 analysis shows the CFR was 18% (95% CI 6 – 24)<sup>47</sup> in the 1991-2000 period, 6% (17 – 38,  $I^2$   
 78 = 95%)<sup>33,35-37,48,49,53,54,56,59</sup> in 2001-2010 and 13% (95% CI 9 – 17,  $I^2 = 96\%$ )<sup>15,16,18,20,23-  
 79 25,30,34,39,44,46,47,50,55,56</sup> in 2011 – 2018. Four studies were pooled for pneumococcal infections  
 80 CFRs in HIV-infected and exposed children with a resultant rate of 15% (95% CI 4 – 26,  $I^2 =$   
 81 95%).<sup>81,84,85,90</sup> One study shows that pertussis has CFRs of 13% (95% CI 2 – 38)<sup>78</sup> and for  
 82 measles the CFR was 1% (95% CI 0 - 4).<sup>76</sup>

83

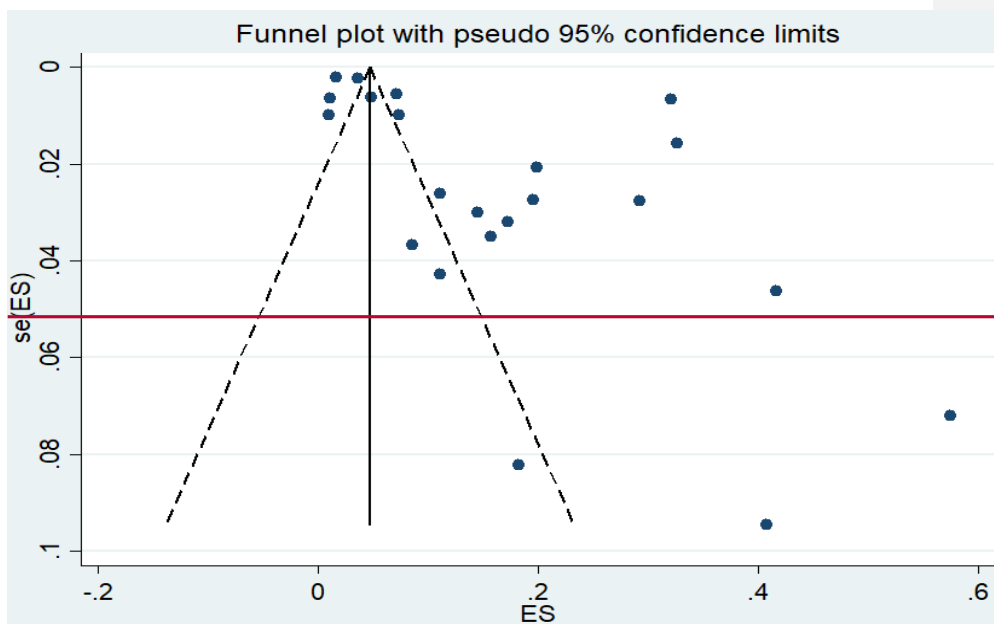
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85 **Publication bias assessment**

86 Funnel-plot analyses of studies reporting on the prevalence of TB revealed nil significant  
87 publication bias, with the P value for the Begg's test being 0.185 while the studies assessing  
88 the prevalence of HBV infection showed significant Begg's test with P value of 0.001 (Figure  
89 7 and 8). Likewise, studies assessing the CFR of TB demonstrated no significant publication  
90 bias Begg's test P = 0.385 (Figure 9).

91

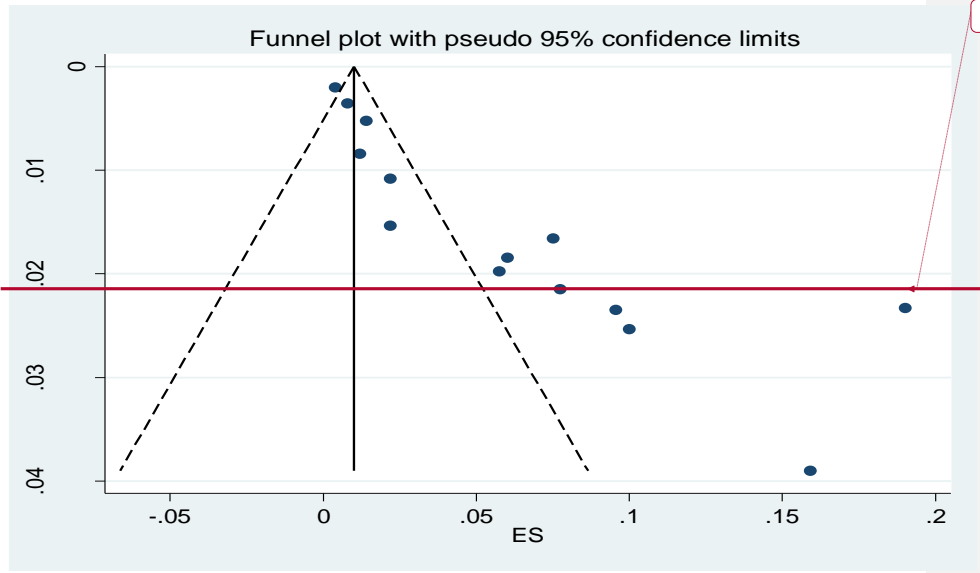


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93 **Figure 7: Funnel plot of studies reporting on the prevalence of tuberculosis in HIV-infected children**

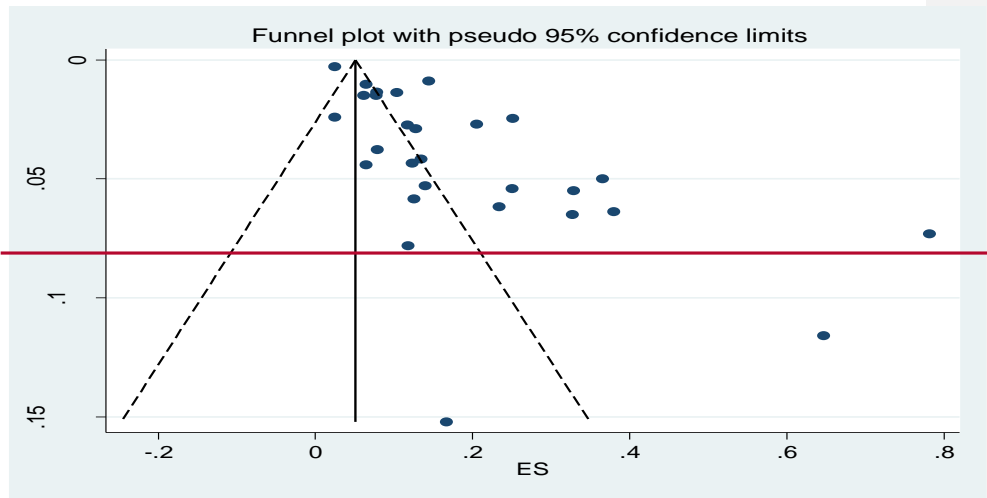
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95  
96 **Figure 8: Funnel plot of studies reporting on the prevalence of hepatitis B virus infection in HIV-infected**  
97 **children**

98



99  
100 **Figure 9: Funnel plot of studies reporting on the case-fatality rate of tuberculosis in HIV-infected**  
101 **children**

102  
103

## 104 Discussion

105 This study provides a comprehensive overview of the incidence rate, prevalence and case  
106 fatality rates of different vaccine-preventable diseases in HIV-infected and HIV-exposed  
107 children in sub-Saharan African countries. The review shows that TB is the most researched  
108 vaccine-preventable disease in HIV-infected children in various African countries and settings.  
109 This is not surprising because of the relationship between TB and HIV infection with respect  
110 to the high susceptibility of TB in HIV-infected individuals.<sup>91,92</sup> Other vaccine-preventable  
111 diseases like HBV infection, pneumococcal infection, measles, rotavirus gastroenteritis,  
112 pertussis and Hib infections were also studied in several African countries. Important vaccine-  
113 preventable diseases such as poliomyelitis, diphtheria, tetanus and yellow fever had no eligible  
114 studies for inclusion revealing the dearth of incidence and prevalence studies on these diseases.  
115 The pooled incidence, prevalence and CFRs reveal there are still high burdens of several  
116 vaccine-preventable diseases in sub-Saharan Africa.

117  
118 According to WHO, the global incidence of TB has been reducing at an average of 2 percent  
119 per year.<sup>91</sup> TB incidence has declined in the African region by 4 percent annually since 2013.<sup>91</sup>  
120 Southern African countries with the highest prevalence and incidence of HIV such as South  
121 Africa, Lesotho, Zimbabwe, Eswatini, Namibia and Zambia had remarkable reductions in TB  
122 incidence.<sup>91</sup> Our study shows that TB incidence reduced over time, however, the event per  
123 child-year is still high when compared with the End TB strategy goals.<sup>93</sup> The World Health  
124 Assembly adopted the resolution known as “*End TB strategy goals*” which is about the global  
125 strategy and targets for tuberculosis prevention, care and control after 2015<sup>93</sup>. In spite of the  
126 reduction in TB incidence among children, there are still cases of high incidence in certain  
127 countries bearing in mind that many countries in African countries are classified as high-  
128 burden.<sup>96</sup> A retrospective cohort study in a very high TB/HIV prevalent region in Nigeria  
129 showed a high incidence rate of 21.2/100 per year among children within six months of ART  
130 enrollment at a period when others were recording much lower incidence.<sup>18</sup> TB prevalence has  
131 fluctuated over time with about 15% of HIV-infected children having the disease at a given  
132 point in time. As of 2017, it was estimated that the global CFR was 16% with many African  
133 countries recording more than 20%.<sup>91</sup> This rate is also far higher than the End TB Strategy  
134 milestone of 10% by 2020.

135  
136 The pooled HBV infection prevalence among HIV-infected children was 5%, however, a study  
137 done in Rwanda in 2010 revealed a seroprevalence of 16%.<sup>68</sup> Ott et al. showed that sub-Saharan

138 Africa had the highest HBV burden with West African countries having up to 12% hepatitis B  
139 surface antigen prevalence among children and adolescents in the 1990s.<sup>94</sup> There has been a  
140 reduction within the region largely due to immunisation programmes, however, there is high  
141 endemicity in some areas. A systematic review of HBV prevalence in Nigeria from studies  
142 conducted from 2000 to 2013 shows that HBV infection ranged from 0.5% to 46.8% with the  
143 pooled prevalence estimate for Nigeria being 13.6%.<sup>95</sup>

144  
145 Our finding shows that the seroprevalence of rotavirus gastroenteritis among African HIV-  
146 infected children was 14% although with a small number of included studies. The incidence  
147 and CFR of diarrhoea and pneumonia are much higher in low-income than in high-income  
148 countries and this is reflected in many African and southeast Asian countries having the highest  
149 burden of the diseases.<sup>96</sup> The African region has the highest incidence and total death secondary  
150 to diarrhoea and pneumonia with rotavirus and *Streptococcus pneumoniae* being the  
151 commonest culprits.<sup>96</sup> Studies have shown that there is still a persistently high incidence of  
152 some vaccine-preventable diseases in HIV-infected individuals than non-exposed ones even  
153 after the introduction of highly active antiretroviral therapy.<sup>97</sup> The incidence of pertussis is also  
154 higher in HIV-exposed and infected children, however, this decreases as the number of vaccine  
155 doses uptake increases.<sup>98</sup>

156  
157 Many African countries with high burdens of HIV are critically lagging in terms of  
158 antiretroviral treatment coverage for HIV-infected children.<sup>99</sup> Sub-optimal ART coverage in  
159 children will lead to viral load increase, immunosuppression, etc. and a subsequent high burden  
160 of various vaccine-preventable diseases. Vaccination coverage in many African countries is  
161 still below the expected target.<sup>100</sup> As of 2017, the average coverage of third-dose pentavalent  
162 vaccine was 80% while the first dose of measles vaccine in the Global Alliance for Vaccines  
163 and Immunisation (Gavi)-supported countries was 78%.<sup>100</sup> The average coverage of Gavi-  
164 funded vaccines in supported countries progressed from 37% in 2016 to 41% in 2017.

165  
166 Low uptake of vaccines by African children exposes them to more diseases than children in  
167 other regions. Use of vaccines has been established to be a beneficial healthcare intervention  
168 targeted in protecting children and adolescents from various vaccine-preventable diseases. Low  
169 uptake of vaccines by African children exposes them to more diseases than children in other  
170 regions. It has also been established that HIV-infected children are more susceptible to  
171 vaccine-preventable diseases such as TB, pneumonia, viral hepatitis etc.<sup>101,102</sup> Vaccination is

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172 therefore essential in HIV-infected patients because of the increased risk of developing various  
173 infectious diseases due to their defective immune systems. Studies have also shown that there  
174 are poor immune responses to primary vaccination among HIV-infected children in comparison  
175 to HIV-unexposed and HIV-exposed children. The poor immune response among HIV-  
176 infected children may require booster doses for optimal immunity against vaccine-preventable  
177 diseases.<sup>103,104</sup>

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178  
179 This review revealed research inequalities across the African region regarding studies on the  
180 burden of vaccine-preventable diseases among HIV-infected and HIV-exposed children. South  
181 Africa contributed about half of the included articles with Nigeria and Kenya following with  
182 fewer studies. This finding is not different from an earlier study looking at the distribution of  
183 epidemiological studies across Africa.<sup>105</sup> Some of the Eastern and Southern African countries  
184 with high HIV prevalence had at least an article included in this study, however, West African  
185 countries only had publications from Nigeria and Cote d'Ivoire.

186  
187 To the best of our knowledge, this is the first systematic review that addressed the need for  
188 knowing the burden of vaccine-preventable diseases among HIV-infected and HIV-exposed  
189 children in sub-Saharan Africa. Knowledge gap concerning the burden of vaccine-preventable  
190 diseases will impact negatively on the advocacy endeavours targeted at improving vaccination  
191 and vaccine-preventable diseases control efforts in Africa. Healthcare workers and  
192 policymakers need to have a good idea of the burden of different diseases to allocate resources  
193 and facilitate optimal vaccination coverage.

#### 194 195 **Recommendations**

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

205

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

215  
216 There is a need to advocate for an equitable share of healthcare budgeting and finance at every  
217 level of governance in African countries. This will help in ensuring that there is a fair share of  
218 resources for preventive and treatment services such as vaccination and antiretroviral therapy  
219 for HIV-exposed children. African countries should, as a matter of urgency, complete the  
220 introduction of newer and important vaccines such as rotavirus vaccine, Hib vaccine and  
221 pneumococcal vaccine. These should be included as part of their current national immunisation  
222 programme schedule.<sup>95</sup> According to WHO, the global coverage for both pneumococcal  
223 vaccine and rotavirus vaccines were as little as 44 percent and 25 percent respectively.<sup>100</sup>  
224 African countries should be supported in developing vaccine procurement budgets,  
225 procurement practices, and capacity development for vaccine planning and advocacy.<sup>106</sup>

226  
227 **Study limitations**  
228 This study was limited by several factors beyond the reviewers' control. We planned to review  
229 all the vaccine-preventable diseases associated with vaccines included in the national  
230 immunisation programme schedule in sub-Saharan Africa, however, we could not find articles  
231 that met the eligibility criteria for some of the diseases. Secondly, there was high heterogeneity  
232 even with sub-group analysis between included studies, which implies the possibility of other  
233 contributory factors associated with the diseases. Some of the studies did not include relevant  
234 information such as antiretroviral coverage, CD4 count, viral load, vaccination status and other  
235 contributory factors. Thirdly, we could not include many studies because the diagnostic criteria  
236 for different vaccine-preventable diseases were not specified and clearly defined.

237  
238 Furthermore, the presence of various limitations did not stop us from making some meaningful  
239 conclusions from this study. This review gives a clearer picture of the burden and trend of TB

240 and able to have insights about the burden of other diseases as well despite having a small  
241 number of studies included in this review. African investigators should as a matter of priority  
242 have proper diagnostic criteria and documentation for diseases for all HIV-infected and HIV-  
243 exposed children treated at the health facilities across the region. Key parameters such as CD4  
244 counts, vaccination status etc. should be included in future studies.

## 247 Conclusions

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

## 259 Methods and design

260 This systematic review was developed in line with the Preferred Reporting Items for Systematic  
261 Review and Meta-Analysis (PRISMA) 2015 statement.<sup>1073</sup> The review was registered with  
262 PROSPERO (International prospective register of systematic reviews) (CRD42018095341).

### 263 Inclusion criteria

264 Type of participants: The review included sub-Saharan African children who are HIV-infected  
265 or HIV-exposed and aged <18 years old.

### 266 Types of outcome:

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

### 269 Primary outcomes

270 Prevalence was defined as proportions of all individuals suspected of having specific vaccine-  
271 preventable diseases with confirmed laboratory diagnosis or proportions of individuals  
272 fulfilling clinical case definition for specific vaccine-preventable diseases. Incidence was

273 defined as the number of new cases of different vaccine-preventable diseases that occur during  
274 a given period in the defined population.

275 We also determined the trend in the incidence and/or prevalence of vaccine-preventable  
276 diseases among HIV-infected and HIV-exposed children in sub-Saharan Africa from 1980 to  
277 2018.

#### 278 Secondary outcomes

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

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

- 284 i. Tuberculosis
- 285 ii. Poliomyelitis
- 286 iii. Hepatitis B virus infection
- 287 iv. Rotavirus gastroenteritis
- 288 v. Diphtheria
- 289 vi. Tetanus
- 290 vii. Pertussis
- 291 viii. Pneumococcal diseases
- 292 ix. Measles
- 293 x. Rubella
- 294 xi. Yellow fever

295

#### 296 Exclusion criteria

- 297 • Intervention studies
- 298 • Unclear diagnostic criteria

299

#### 300 Search strategy methods for the identification of studies

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



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

#### 307 Selection of eligible studies

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

#### 313 Data collection process

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

317 The following data were extracted from selected studies:

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

#### 324 Risk of bias in individual studies

325 The risk of bias and quality of the included studies were assessed with the Newcastle-Ottawa  
326 Quality Scale.<sup>1084</sup> The criteria assessed included the following (1) selection of participants,  
327 (2) comparability, (3) exposure, and (4) outcome.

328

#### 329 Data synthesis

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

333 Heterogeneity was evaluated using the Chi-squared test of homogeneity (significant for  $P <$   
334  $0.1$ ) and quantified using the I-squared statistic ( $>50\%$  substantial heterogeneity).<sup>1095</sup> Subgroup  
335 analyses were conducted in cases with substantial heterogeneity. Subgroup analysis was

336 conducted using the following variables: period of study (1991- 2000, 2001-2010 and 2011 –  
337 2018). We also used funnel plot regression to assess publication bias. STATA software version  
338 14.0 (STATA Corporation, College Station, TX, USA) was used to do all calculations, the  
339 meta-analysis and generate forest plots.<sup>11096</sup>

#### 340 **Additional analyses: Trend analysis**

341 We examined time trends in the incidence and prevalence of vaccine-preventable diseases  
342 estimates using Poisson regression models with the prevalence estimates as the outcome  
343 variable and the calendar year of the publication as the predictor. This method allows for  
344 estimation of time trends across individual calendar years to obtain average annual percentage  
345 change (AAPC), ~~assuming that~~if the rate of change is at a constant rate of the previous year.  
346 <sup>11097</sup> The Poisson regression procedure fits a model of the following form:

$$347 \log(\text{prevalence}_y) = b_0 + b_1y + \log(\text{sample size}) \quad (1)$$

348 where ‘cases’ equal prevalence estimates reported per year, log is the natural log,  $b_0$  is the  
349 intercept,  $b_1$  is the trend,  $y$  is the year – given as 0, 1, 2, ... 18 (year 0 is 1970, year 1 is 1971,  
350 and so on to 2014), and log of ‘sample size’ was entered as the offset. The AAPC was calculated  
351 using the following formula:

$$352 \text{AAPC} = (e^{b_1} - 1) \times 100 \quad (2)$$

353

#### 354 **Abbreviations**

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

365

366 **Authors' contributions**

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

371

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378

379 **Disclosure of potential conflicts of interest**

380 No potential conflicts of interest were disclosed.

381

382

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## Appendix

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### Search strategy - PubMed

Search	Add to builder	Query	Items found
<a href="#">#6</a>	<a href="#">Add</a>	Search (((#1) AND #2) AND #3) AND #4) AND #5 Sort by: Best Match	<a href="#">1364</a>
<a href="#">#4</a>	<a href="#">Add</a>	Search (newborn* OR bab* OR infan* OR child* OR adolescen* OR teen*) Sort by: Best Match	<a href="#">3843580</a>
<a href="#">#2</a>	<a href="#">Add</a>	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	<a href="#">707401</a>
<a href="#">#5</a>	<a href="#">Add</a>	Search (incidence OR prevalence OR mortality) Sort by: Best Match	<a href="#">3171459</a>
<a href="#">#3</a>	<a href="#">Add</a>	Search ("HIV infected" OR "HIV exposed" OR "HIV infected" OR "HIV exposed" OR "HIV positive" OR "HIV exposed uninfected") Sort by: Best Match	<a href="#">74539</a>
<a href="#">#1</a>	<a href="#">Add</a>	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	<a href="#">558013</a>

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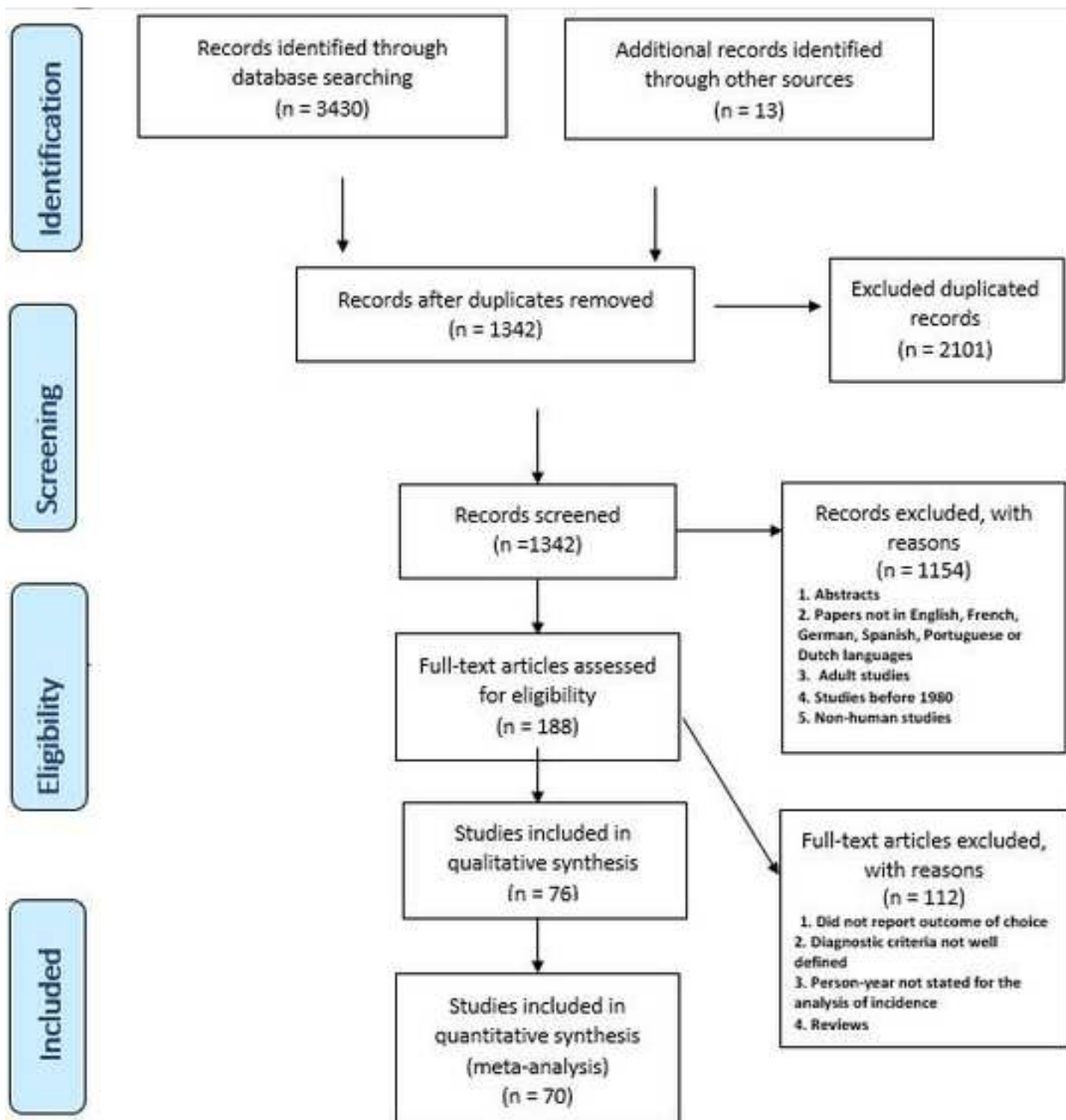


Figure 1: Flow diagram of the selection process



Figure 2

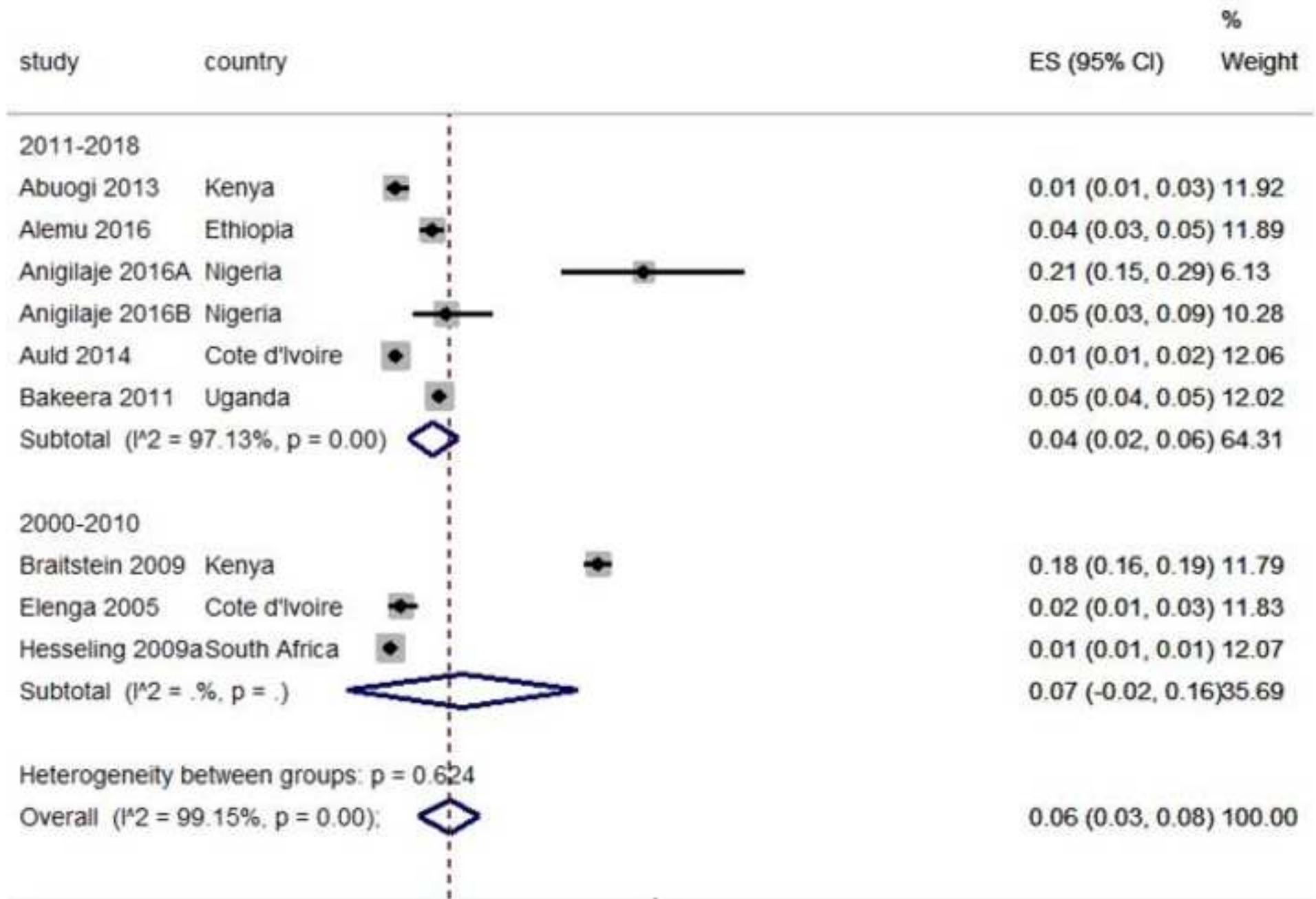


Figure 2: Forest plot of studies with data on incidence rates of tuberculosis in HIV-exposed children

Figure 3

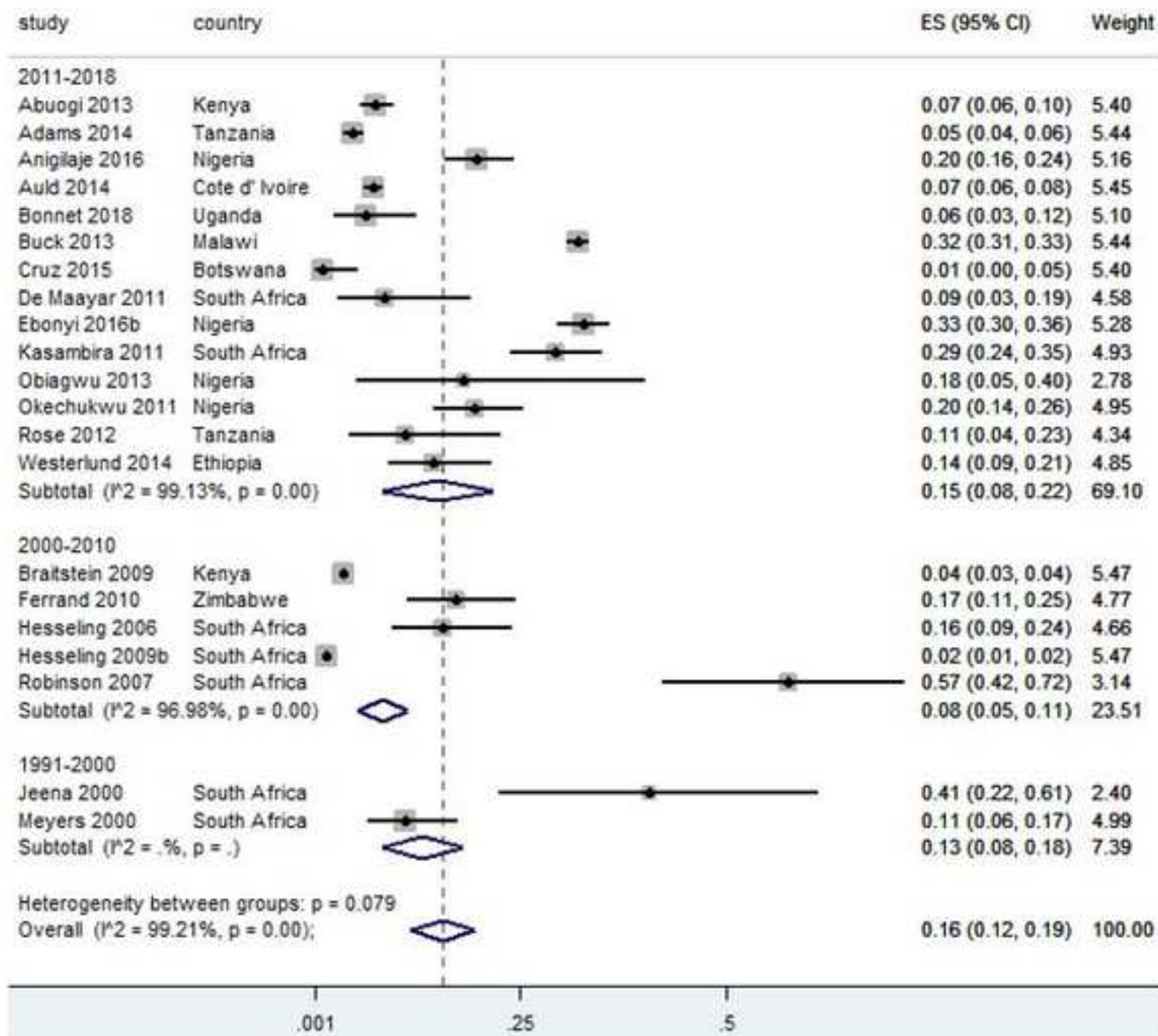


Figure 3: Forest plot of studies with data on the prevalence of tuberculosis in HIV-infected children

Figure 4

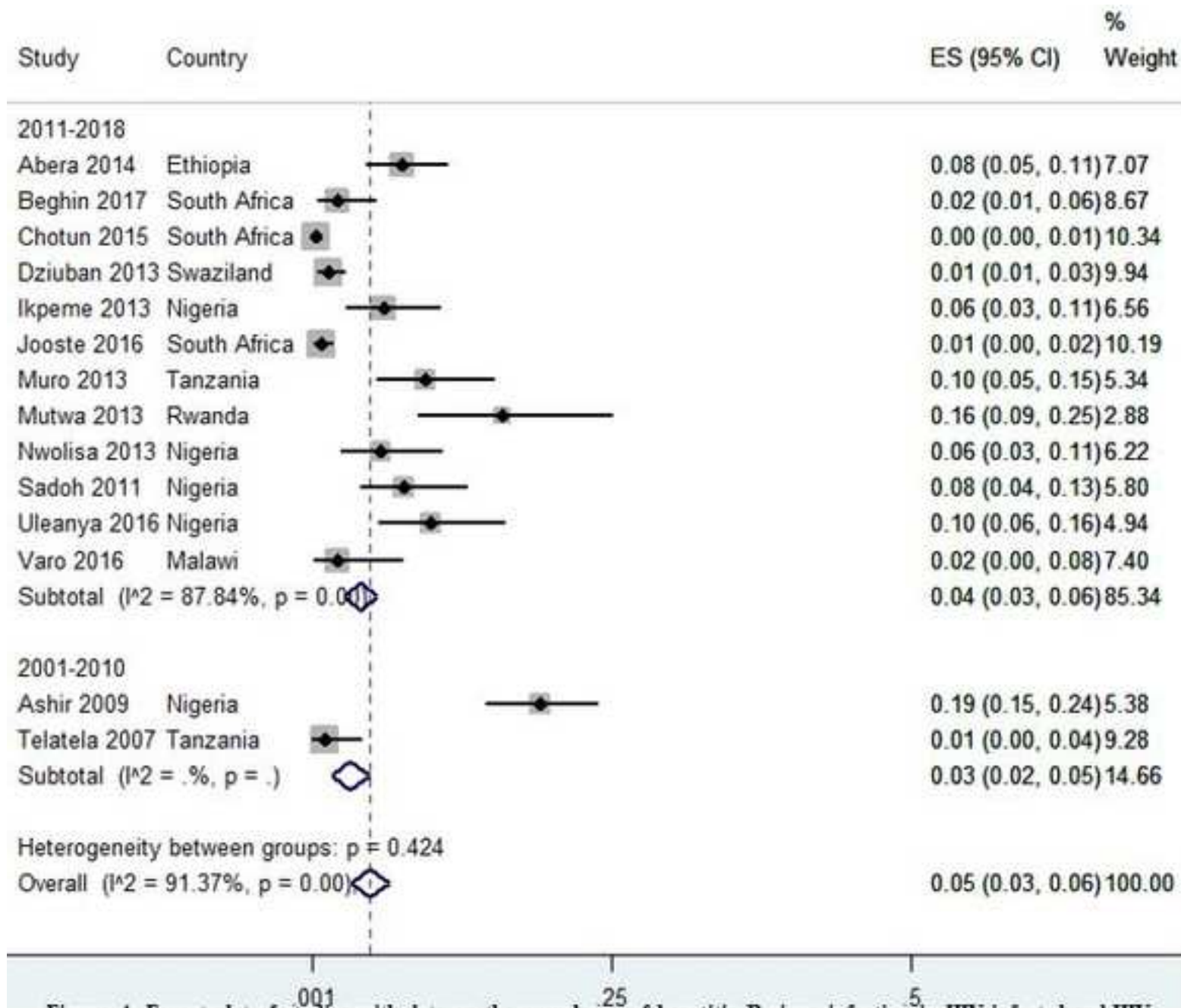


Figure 4: Forest plot of studies with data on the prevalence of hepatitis B virus infection in HIV-infected and HIV-exposed children

Figure 5

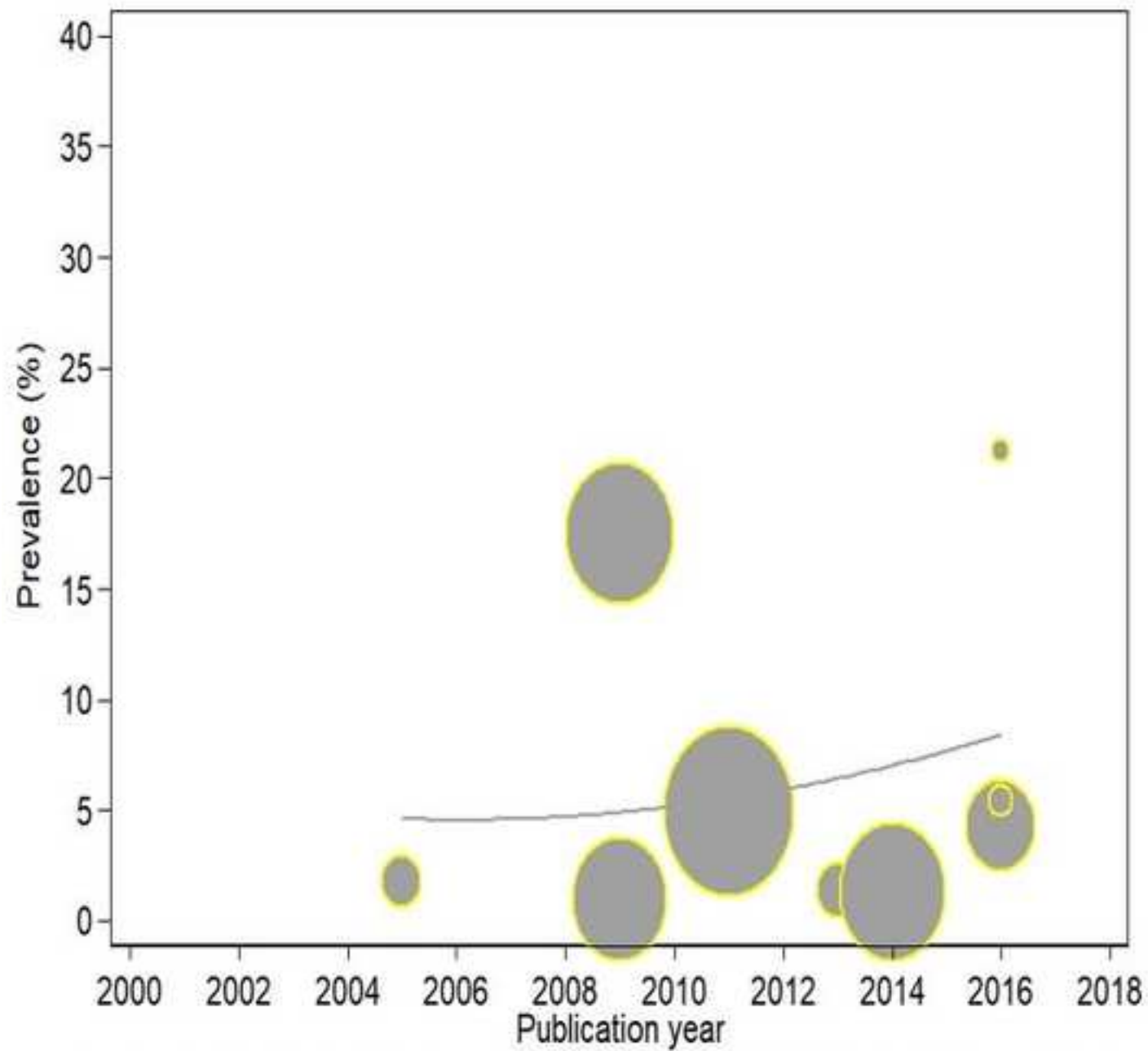
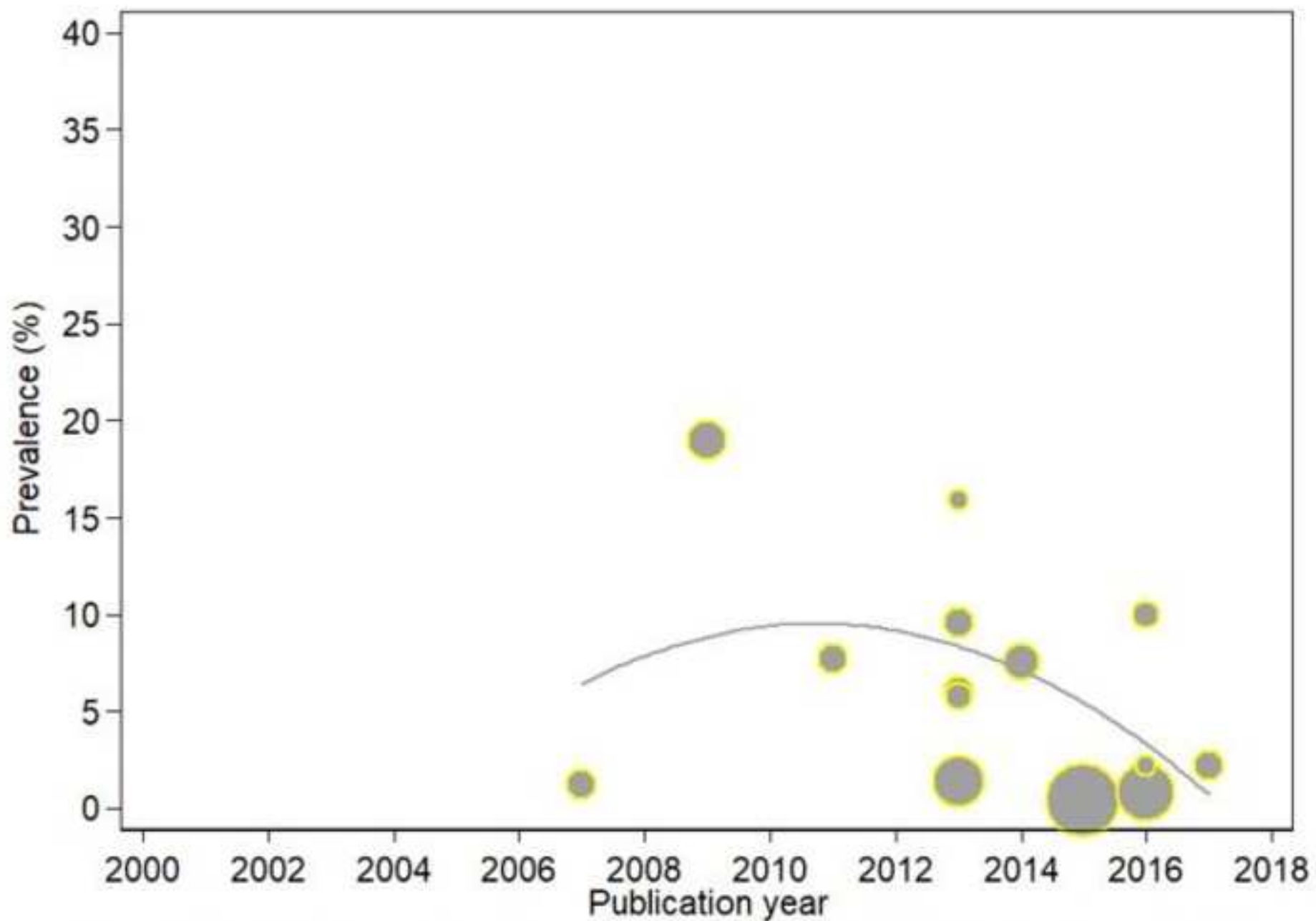


Figure 5: Trends in the incidence of tuberculosis in HIV-infected and exposed children with respect to publication years

Figure 6



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

Figure 7

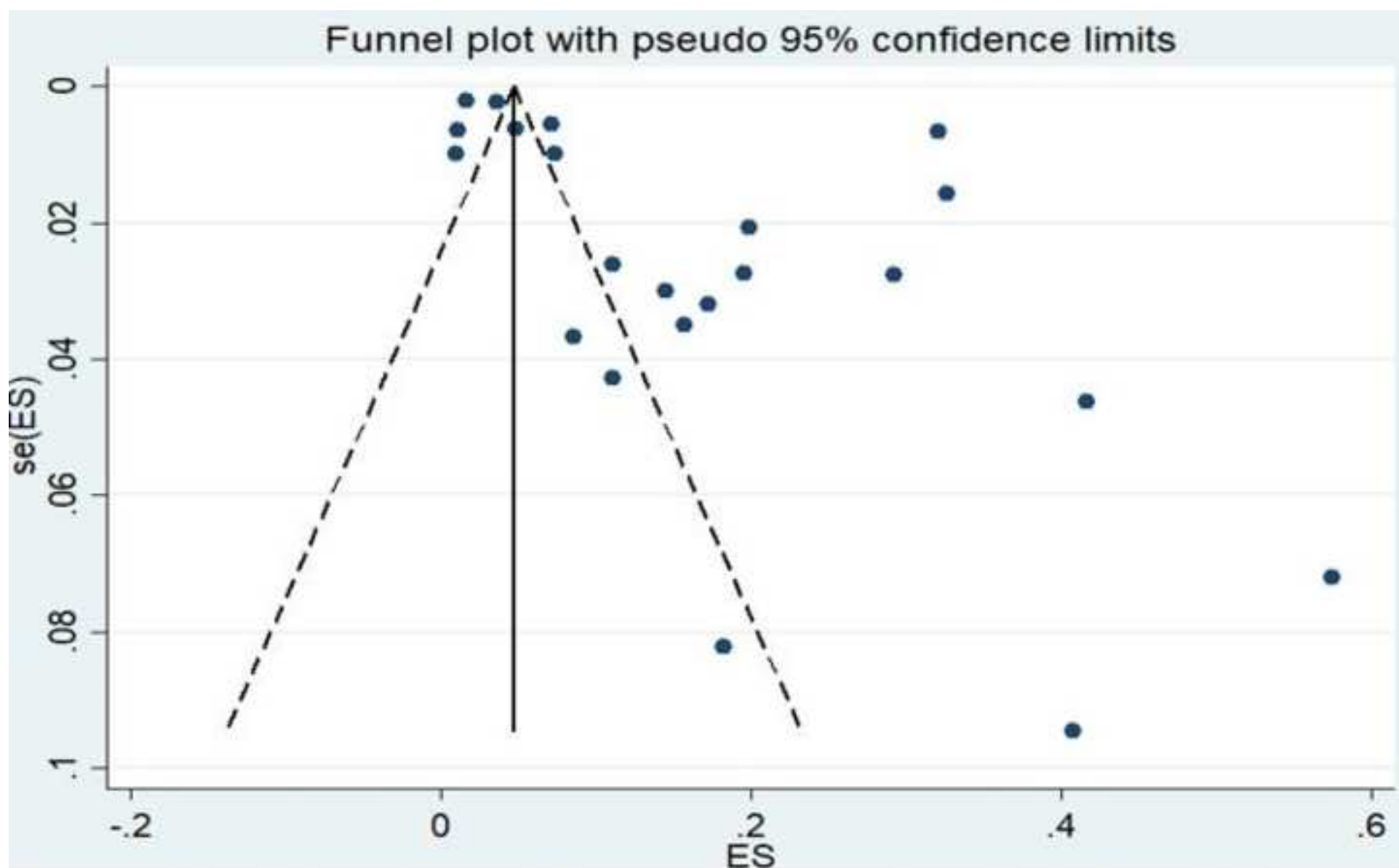


Figure 7: Funnel plot of studies reporting on the prevalence of tuberculosis in HIV-infected children

Figure 8

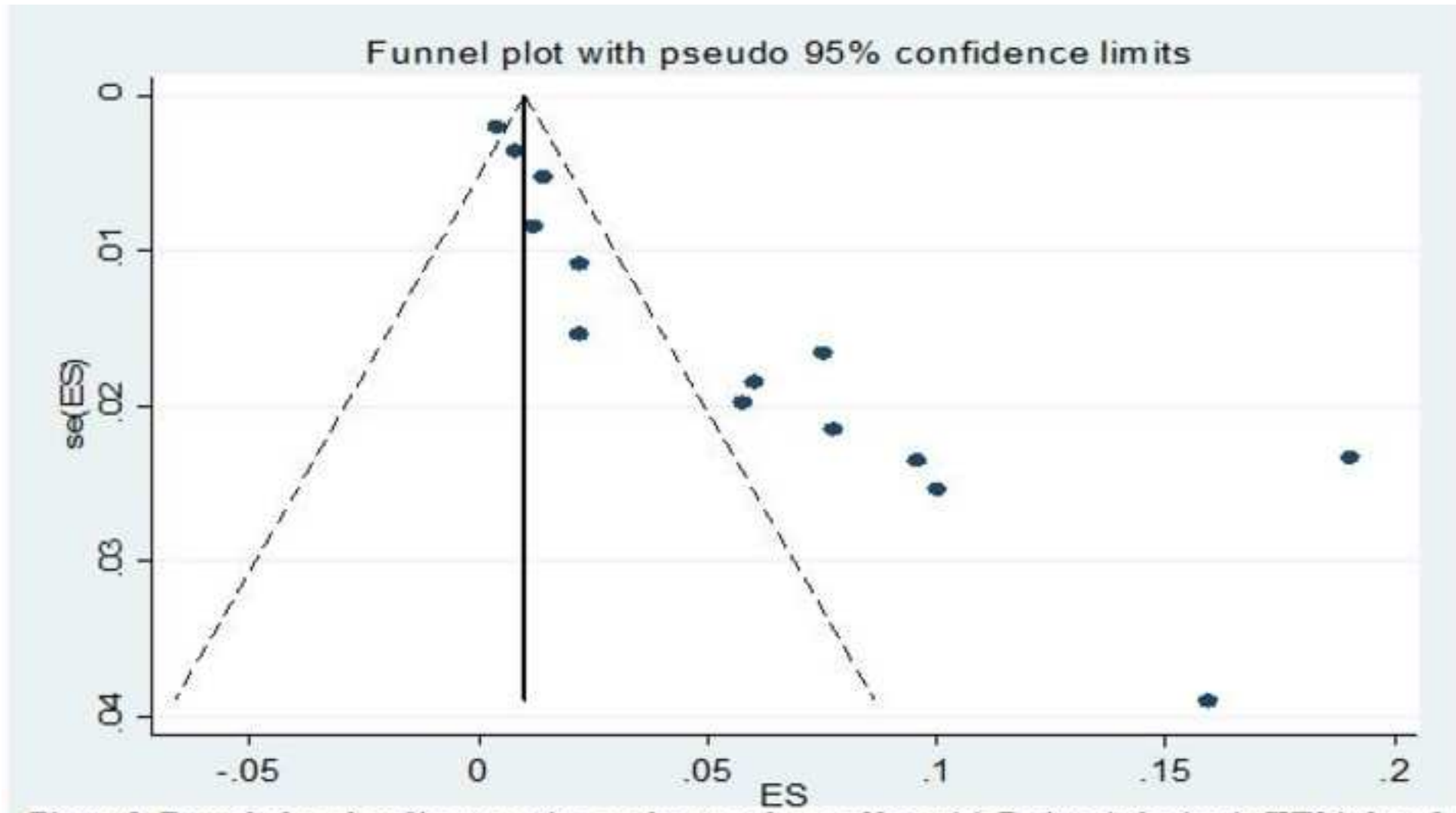
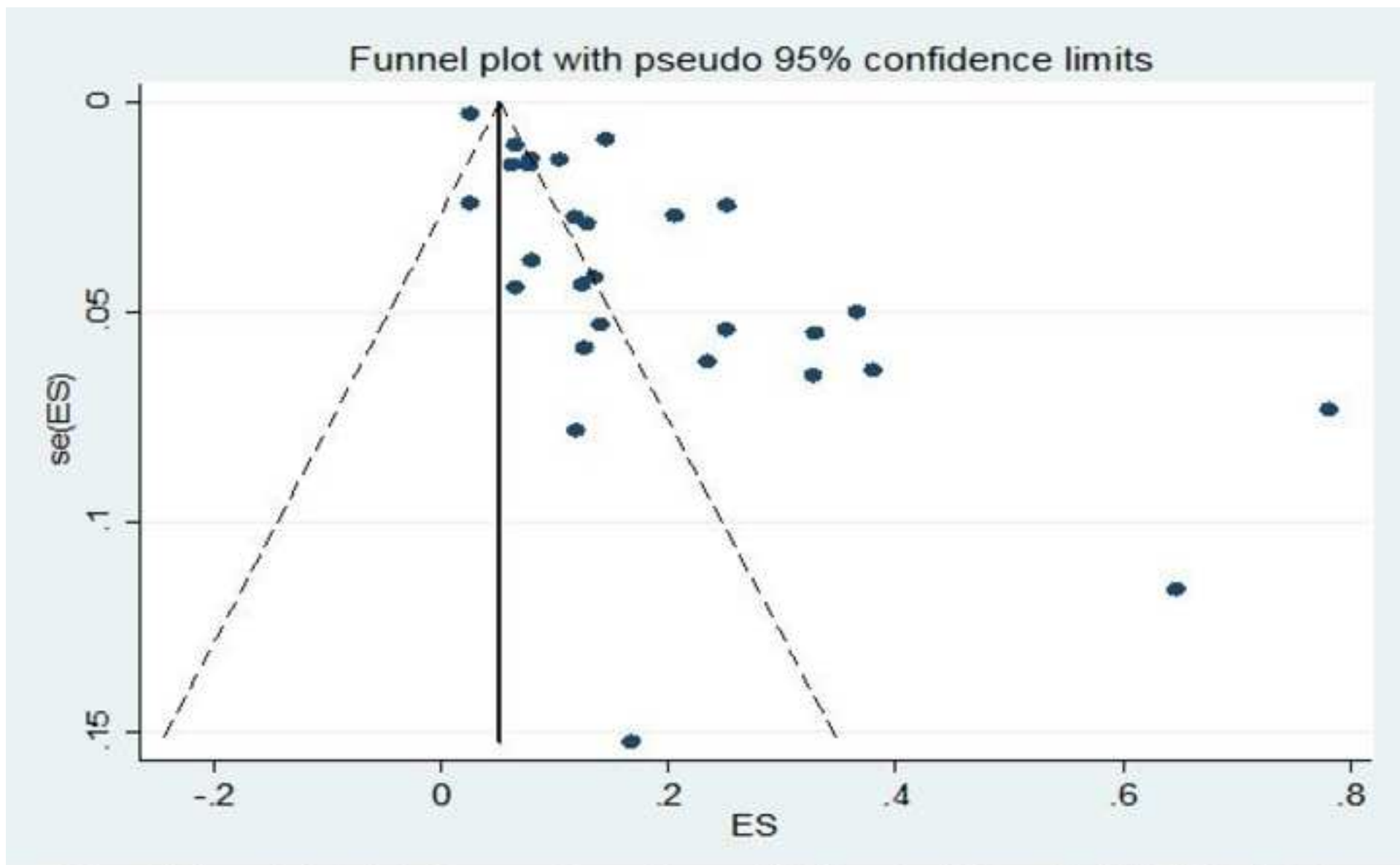


Figure 8: Funnel plot of studies reporting on the prevalence of hepatitis B virus infection in HIV-infected children

Figure 9



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



**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 <sup>15</sup>	2009 - 2010	Cohort	Kenya	689	Tuberculosis	C, I, P	HI	7
Adams 2014 <sup>16</sup>	2006 - 2012	Cross-sectional	Tanzania	1193	Tuberculosis	C, P	HI	4
Alemu 2016 <sup>17</sup>	2009 - 2014	Cohort	Ethiopia	645	Tuberculosis	I	HI	6
Anigilaje 2016 <sup>18</sup>	2010 - 2013	Cohort	Nigeria	368	Tuberculosis	P	HI	8
Auld 2014 <sup>19</sup>	2004 - 2008	Cohort	Cote d' Ivoire	2110	Tuberculosis	I, P	HI	8
Bakeera 2011 <sup>20</sup>	2003 - 2006	Cohort	Uganda	1806	Tuberculosis	I, C	HI	8
Bonnet 2018 <sup>21</sup>	2012 - 2014	Cohort	Uganda	113	Tuberculosis	C	HI	7
Braitstein 2009 <sup>22</sup>	2001 - 2007	Cohort	Kenya	6,535	Tuberculosis	I, P	HI	8
Buck 2013 <sup>23</sup>	2010	Cohort	Malawi	4874	Tuberculosis	C, P	HI	8
Carlucci 2017 <sup>24</sup>	2012 - 2014	Cohort	Multiple	386	Tuberculosis	C	HI	8
Cavanaugh 2012 <sup>25</sup>	2006 - 2007	Cross-sectional	Kenya	323	Tuberculosis	C	HI	6
Chaya 2016 <sup>26</sup>	2006 - 2011	Cross-sectional	South Africa	47	Tuberculosis	I	HI	6
Cruc 2015 <sup>27</sup>	NR	Cohort	Botswana	100	Tuberculosis	P	HI	6
Dangor 2013 <sup>28</sup>	2005 - 2009	Time-series analysis	South Africa	1985	Tuberculosis	I	HI	7
De Maayar 2011 <sup>29</sup>	NR	Cross-sectional	South Africa	58	Tuberculosis	P	HI	7
Ebonyi 2016 <sup>30</sup>	2005 - 2013	Cohort	Nigeria	260	Tuberculosis	C	HI	8
Ebonyi 2016b <sup>31</sup>	2005-2012	Cohort	Nigeria	876	Tuberculosis	P	HI	8
Elenga 2005 <sup>32</sup>	2000-2003	Cohort	Cote d' Ivoire	282	Tuberculosis	I	HI	8
Ferrand 2010 <sup>33</sup>	2007-2008	Cross-sectional	Zimbabwe	139	Tuberculosis	P	HI	7
Hall 2017 <sup>34</sup>	2005-2008	Cohort	South Africa	224	Tuberculosis	C	HI	8
Hesseling 2009a <sup>35</sup>	2004-2006	Cross-sectional	South Africa	3321	Tuberculosis	C	HI	6
Hesseling 2005 <sup>36</sup>	1992-2000	Cohort	South Africa	93	Tuberculosis	C	HI	8
Hesseling 2006 <sup>37</sup>	2002-2005	Cohort	South Africa	108	Tuberculosis	C, P	HI	7
Hesseling 2009b <sup>38</sup>	2004-2006	Cross-sectional	South Africa	3321	Tuberculosis	I, P	HI	7
Hicks 2014 <sup>39</sup>	2009-2010	Cohort	South Africa	64	Tuberculosis	C	HI	6
Jeena 2000 <sup>40</sup>	1995-1998	Cross-sectional	South Africa	27	Tuberculosis	P	HI	5
Kasambira 2011 <sup>41</sup>	2006-2009	Cross-sectional	South Africa	270	Tuberculosis	P	HI	6
Madhi 2000b <sup>42</sup>	1996-1997	Cross-sectional	South Africa	67	Tuberculosis	C	HI	5
Meyers 2000 <sup>43</sup>	1996	Cross-sectional	South Africa	144	Tuberculosis	P	HI	5

Mwangwa 2017 <sup>44</sup>	2012-2013	Cohort	Multiple	17	Tuberculosis	C	HI	7
Obiagwu 2013 <sup>45</sup>	2010	Cross-sectional	Nigeria	22	Tuberculosis, Measles	P	HI	6
Okechukwu 2011 <sup>46</sup>	2007-2008	Cross-sectional	Nigeria	210	Tuberculosis	C, P	HI	6
Osman 2017 <sup>47</sup>	2005-2012	Cohort	South Africa	3143	Tuberculosis	C	HI	6
Padayatchi 2006 <sup>48</sup>	1993-2002	Cross-sectional	South Africa	6	Tuberculosis	C	HI	5
Palme 2002 <sup>49</sup>	1995-1997	Cohort	Ethiopia	58	Tuberculosis	C	HI	6
Patel 2013 <sup>50</sup>	2007-2009	Cohort	Congo DRC	31	Tuberculosis	C	HI	7
Robinson 2007 <sup>51</sup>	1999-2001	Case-control	South Africa	47	Tuberculosis	P	HI	6
Rose 2012 <sup>52</sup>	2008-2010	Cohort	Tanzania	54	Tuberculosis	P	HI	6
Schaaf 2007 <sup>53</sup>	2003-2005	Cross-sectional	South Africa	133	Tuberculosis	C	HI	5
Soeters 2005 <sup>54</sup>	2000-2001	Cross-sectional	South Africa	43	Tuberculosis	C	HI	4
Walters 2014 <sup>55</sup>	2003-2010	Cohort	South Africa	494	Tuberculosis	C	HI	6
Walters 2008 <sup>56</sup>	2003-2005	Cross-sectional	South Africa	137	Tuberculosis	C	HI	6
Westerlund 2014 <sup>57</sup>	2003-2008	Cohort	Ethiopia	138	Tuberculosis	P	HI	7
Wiseman 2011 <sup>58</sup>	2004-2006	Cross-sectional	South Africa	52	Tuberculosis	C	HI	5
Yotebieng 2010 <sup>59</sup>	2004-2008	Cohort	South Africa	573	Tuberculosis	C	HI	6
Kouakoussui 2004 <sup>60</sup>	2003	Cohort	Cote d'Ivoire	270	Tuberculosis	I	HI	7
Abera 2014 <sup>61</sup>	2014	Cross-sectional	Ethiopia	253	HBV infection	P	HI	6
Ashir 2009 <sup>62</sup>	2007	Case-control	Nigeria	284	HBV infection	P	HI	5
Beghin 2017 <sup>63</sup>	2014	Cross-sectional	South Africa	183	HBV infection	P	HI	6
Chotun 2015 <sup>64</sup>	2011 - 2012	Cross-sectional	South Africa	1000	HBV infection	P	HE	6
Uleanya 2016 <sup>65</sup>	NR	Cross-sectional	Nigeria	140	HBV infection	P	HI	4
Dziuban 2013 <sup>66</sup>	2009 - 2011	Cross-sectional	Swaziland	500	HBV infection	P	HI	3
Ikpeme 2013 <sup>67</sup>	2010-2011	Cross-sectional	Nigeria	166	HBV infection	P	HI	4
Jooste 2016 <sup>68</sup>	2015-2016	Cohort	South Africa	625	HBV infection	P	HI	7
Muro 2013 <sup>69</sup>	2006-2008	Cross-sectional	Tanzania	157	HBV infection	P	HI	5
Mutwa 2013 <sup>70</sup>	2010	Cohort	Rwanda	88	HBV infection	P	HI	7
Nwolisa 2013 <sup>71</sup>	2010	Cross-sectional	Nigeria	139	HBV infection	P	HI	4
Sadoh 2011 <sup>72</sup>	NR	Cross-sectional	Nigeria	155	HBV infection	P	HI	5
Telatela 2007 <sup>73</sup>	2006	Cross-sectional	Tanzania	167	HBV infection	P	HI	4
Varo 2016 <sup>74</sup>	2008-2010	Cross-sectional	Malawi	91	HBV infection	P	HI	3
Moss 2002 <sup>75</sup>	1998-2000	Cross-sectional	Zambia	93	Measles	P	HI	6

Wirth 2015 <sup>76</sup>	2009-2010	Case-control	Botswana	189	Measles	C	HI	5
du Plessis 2018 <sup>14</sup>	2013 - 2015	Cross-sectional	South Africa	300	Pertussis	P	HI	6
Gill 2016 <sup>77</sup>	2015	Cohort	Zambia	347	Pertussis	I	HI	7
Soofie 2016 <sup>78</sup>	2015	Cross-sectional	South Africa	599	Pertussis	C, I, P	HE	5
Johnson 2000 <sup>79</sup>	1996-1997	Cross-sectional	South Africa	31	Rotavirus gastroenteritis	P	HI	6
Moyo 2014 <sup>80</sup>	2010-2011	Case-control	Tanzania	26	Rotavirus gastroenteritis	P	HI	5
Asbjörnsdóttir 2013 <sup>81</sup>	1999-2002	Cohort	Kenya	388	Pneumococcal infection	C,I	HI	6
Nathoo 1996 <sup>82</sup>	1993-1994	Cohort	Zimbabwe	168	Pneumococcal infection	P	HI	7
Zar 2001 <sup>83</sup>	1998	Cross-sectional	South Africa	151	Pneumococcal infection	P	HI	6
Jones 1998 <sup>84</sup>	1996	Cross-sectional	South Africa	25	Pneumococcal infection	C	HI	5
Roca 2010 <sup>85</sup>	2004-2006	Cross-sectional	Mozambique	54	Pneumococcal infection	C	HI	6
Cohen 2016 <sup>86</sup>	2009 - 2013	Cross-sectional	South Africa	211	Pneumococcal infection	I	HEU,HI	4
Nunes 2011 <sup>87</sup>	2003-2008	Cross-sectional	South Africa	938	Pneumococcal infection	I	HI	6
von Mollendorf 2017a <sup>88</sup>	2009–2013	Cross-sectional	South Africa	495	Pneumococcal infection	C, I	HI	5
von Gottberg 2013 <sup>89</sup>	2003-2008	Cross-sectional	South Africa	1749	Pneumococcal infection	I	HI	5
Nyasulu 2011 <sup>90</sup>	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.

## Appendix

### Search strategy - PubMed

Search	Add to builder	Query	Items found
<a href="#"><u>#6</u></a>	<a href="#"><u>Add</u></a>	Search (((#1) AND #2) AND #3) AND #4) AND #5 Sort by: Best Match	<a href="#"><u>1364</u></a>
<a href="#"><u>#4</u></a>	<a href="#"><u>Add</u></a>	Search (newborn* OR bab* OR infan* OR child* OR adolescen* OR teen*) Sort by: Best Match	<a href="#"><u>3843580</u></a>
<a href="#"><u>#2</u></a>	<a href="#"><u>Add</u></a>	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	<a href="#"><u>707401</u></a>
<a href="#"><u>#5</u></a>	<a href="#"><u>Add</u></a>	Search (incidence OR prevalence OR mortality) Sort by: Best Match	<a href="#"><u>3171459</u></a>
<a href="#"><u>#3</u></a>	<a href="#"><u>Add</u></a>	Search ("HIV infected" OR "HIV exposed" OR "HIV-infected" OR "HIV-exposed" OR "HIV positive" OR "HIV exposed uninfected") Sort by: Best Match	<a href="#"><u>74539</u></a>
<a href="#"><u>#1</u></a>	<a href="#"><u>Add</u></a>	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	<a href="#"><u>558013</u></a>