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Pneumococcal pneumonia and carriage in Africa before and after introduction of pneumococcal conjugate vaccines, 2000-2019: protocol for systematic review.

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Manuscripts

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3 1 **Pneumococcal pneumonia and carriage in Africa before and after introduction**
4 **of pneumococcal conjugate vaccines, 2000-2019: protocol for systematic**
5 **review.**
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3 29 **Abstract**

4 30 **Introduction:** Africa harbours a high burden of pneumococcal disease, with
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6
7 31 associated high mortality rates. Despite 34 countries introducing the pneumococcal
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9 32 conjugate vaccine, which reduces the risk of pneumococcal carriage (a prerequisite
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11 33 for disease) of some of the most pathogenic pneumococcal serotypes, it remains
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13 34 uncertain whether they will achieve the sustained direct or indirect protection
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15 35 necessary to reduce pneumococcal carriage to levels sufficient to interrupt
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17 36 transmission and disease. We will therefore summarise the available data on the
18
19 37 impact of the pneumococcal conjugate vaccine in reducing vaccine serotype carriage
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21 38 and pneumococcal pneumonia in Africa between 2000-2019.

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23 39 **Methods and analysis:** Using a pre-determined search strategy, we will conduct a
24
25 40 comprehensive search of PubMed, MEDLINE database, the Excerpta Medica
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27 41 Database (EMBASE), the ISI Web of Science (Science Citation Index), Scopus and
28
29 42 the African Index Medicus to identify published studies reporting the prevalence of
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31 43 *Streptococcus pneumoniae* carriage (vaccine type and non-vaccine type), incidence
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33 44 rates of pneumococcal pneumonia and mortality among children, adults and HIV-
34
35 45 infected (all-ages) pre- and post-PCV introduction (published between 1st January
36
37 46 2000 and 31st December 2019) in African countries that have introduced
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39 47 pneumococcal conjugate vaccines (PCV7/10/13) in their routine national
40
41 48 immunisation programs. The studies retained and data extracted will be assessed for
42
43 49 bias using pre-validated tools and checklists. Heterogeneity across studies will be
44
45 50 assessed using the χ^2 test on Cochran Q statistic. A random effect meta-analysis
46
47 51 will be used to estimate the overall prevalence of pneumococcal carriage and
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49 52 incidence of pneumococcal pneumonia across studies with similar characteristics.
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51 53 Results will be reported in compliance with the Meta-Analysis Of Observational
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3 54 Studies in Epidemiology (MOOSE) guidelines. The protocol has been prepared in
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5 55 accordance to the 2015 guidelines on Preferred Reporting Items for Systematic
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8 56 Reviews and Meta-Analyses.

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10 57 **Ethics and dissemination:** This systematic review will not require ethical approval
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12 58 as we will be using already published data. The final manuscript will be submitted for
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14
15 59 publication in a peer-reviewed journal and presented at conferences.

16
17 60 **PROSPERO registration number:** CRD42019130976

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19 61
20 62 **Keywords:** *Streptococcus pneumoniae*, Carriage, Pneumococcal conjugate vaccine,
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23 63 Pneumococcal pneumonia, mortality, Africa

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Strengths and limitations

- To the best of our knowledge, this study will be the first systematic review that will comprehensively compare and explore the impact of PCV on carriage, pneumococcal pneumonia (invasive and non-invasive) and mortality associated with the disease pre-and post-vaccine introduction in adults and other at risk groups living in Africa.
- Small number of studies eligible across regions could impact the quality of our estimates.
- Presence of high heterogeneity across studies, particularly in countries where PCV7, PCV10 or PCV13 were in use around the same time and were serotyping was only done for vaccine-type pneumococcal strains.

79

80 Introduction

81 *Streptococcus pneumoniae* (“the pneumococcus”) is a common coloniser of the
82 nasopharynx and a major cause of morbidity and mortality among children under the
83 age of 5 years worldwide.^{1,2} High rates of pneumococcal disease are found in Africa
84 and other low- and middle-income countries (LMICs), which harbour an
85 accumulation of factors conducive for high and persistent pneumococcal carriage
86 and transmission including, high-density living conditions, poverty and high HIV
87 seroprevalence.^{3–5} In 2015, pneumococcal pneumonia accounted for 55.4% (95%
88 Uncertainty Interval (UI): 31.5–79.1) of lower respiratory deaths in all ages.¹
89 Implementation of treatment strategies, which focus on early detection and
90 antimicrobial therapy of suspected pneumonia cases, has been difficult in Africa.⁶
91 Therefore, introduction of an effective vaccine against pneumococcal carriage for
92 children is crucial in this region as carriage is a prerequisite for disease.

93

94 With support from Gavi (the Vaccine Alliance), 34 African countries introduced the
95 pneumococcal conjugate vaccines (PCV7/10/13) into their extended immunisation
96 programmes between 2009 and 2015^{7,8} in line with WHO recommendations.⁹ These
97 vaccines have been shown to be highly effective in reducing both incidence of
98 pneumococcal disease and prevalence of carriage by some of the most pathogenic
99 of the 97 known pneumococcal serotypes.¹⁰ Furthermore, the vaccine indirectly
100 protects the PCV-unvaccinated population against pneumococcal carriage and
101 disease by reducing pneumococcal transmission from PCV-vaccinated children who
102 are at greater risk of carriage and, therefore, sources of transmission.^{2,11–13}

103 However, PCV’s indirect protection on other high-risk populations (including HIV-
104 infected individuals) remains to be seen in Africa.^{11,14} Studies conducted in Africa

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3 105 have demonstrated high nasopharyngeal (NP) carriage of pneumococcus among the
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5 106 HIV-infected adults on antiretroviral therapy (ART), with estimated point prevalence
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7 107 ranging between 40-80%.^{12,15} Therefore, it remains uncertain whether the
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9 108 introduction of PCV in Africa will achieve the sustained direct or indirect protection
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11 109 necessary to reduce pneumococcal carriage to levels sufficient to interrupt
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13 110 transmission and disease.¹⁶
14
15 111 Systematic reviews that have been done so far on the impact of PCV in Africa have
16
17 112 focused on carriage and clinical pneumonia endpoints in children.^{17,18} None have
18
19 113 summarised these data in the adult or important at-risk populations like HIV-infected
20
21 114 individuals. We therefore plan to synthesise the available published data and update
22
23 115 the evidence on the impact of the PCV vaccine introduction on pneumococcal
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25 116 carriage (VT and NVT), pneumococcal pneumonia and associated mortality in Africa
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27 117 between 2000–2019.
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4 121 **Objectives**

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7 122 **General objectives**

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9 123 1. To summarise available data on the impact of the pneumococcal conjugate
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11 124 vaccine on the prevalence of pneumococcal carriage (VT and NVT) and its impact
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13 125 on pneumococcal pneumonia and associated mortality in Africa between 2000–
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16 126 2019.

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18 127 **Specific objectives**

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20 128 Using data published between 2000 and 2019, this review will assess the impact of
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23 129 PCV by:

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25 130
26 131 1. Comparing the trend in pneumococcal carriage prevalence in Africa before and
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28 132 after PCV introduction.
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30 133 2. Comparing the trends in the incidence and/ prevalence of pneumococcal
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32 134 pneumonia (invasive and non-invasive) in Africa before and after PCV
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34 135 introduction.
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37 136 3. Estimating the mortality associated with pneumococcal pneumonia in Africa.
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4 140 **Methods**

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7 141 ***Information sources, search strategy and study identification***

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9 142 We will conduct a comprehensive literature search in PubMed, MEDLINE database,
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11 143 the Excerpta Medica Database (EMBASE), the ISI Web of Science (Science Citation
12
13 144 Index), Scopus and the African Index Medicus to identify all studies published
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15 145 between 1st January 2000 to 31st December 2019, meeting our inclusion and
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17 146 exclusion criteria using the literature search strategy outlined in **table 1**. Using a
18
19 147 structured screening guide, we will screen the reference lists for eligible articles and
20
21 148 relevant reviews as well as conference abstracts to identify additional sources of
22
23 149 information. Search results will be compiled and managed using the EndNote X9
24
25 150 citation software.
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32 152 ***Eligibility criteria of relevant studies***

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34 153 ***Inclusion criteria***

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36 154 **Population:** Children (1-15 years), adults (15-64 years) the elderly (>65yrs), and
37
38 155 HIV-infected individuals (all ages) residing in African countries.

39
40 156 **Intervention:** Pneumococcal conjugate vaccines (PCV 7, 10, and 13) introduction
41
42 157 into the country's routine infant immunisation programmes.

43
44 158 **Comparators:** 10-year period (2000-2010) before PCV introduction versus 10 year-
45
46 159 period (2011-2019) after PCV introduction.

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48 160 **Outcomes:** Percentage difference in the pooled point prevalence of pneumococcal
49
50 161 carriage post when compared to pre PCV introduction; adjusted prevalence ratios in
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52 162 the pooled prevalence of pneumococcal pneumonia between post and pre PCV
53
54 163 introduction; and adjusted mortality rate ratios for post and pre PCV introduction.
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3 165 **Type of studies:** We will include randomised control trials (RCTs), non-randomised
4
5 166 trials and observational studies reporting prevalence of pneumococcal carriage
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7 167 and/or incidence rates for disease and/or deaths and were published between 1st
8
9 168 January 2000 and 31st December 2019 without language restriction.

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12 169 **Serotyping methods:** For pneumococcal carriage, identification and serotyping of
13
14 170 *S. pneumoniae* must be from a pernasal swab using culture (as per WHO guidelines
15
16 171 ¹⁹, polymerase chain reaction (Lyt-A gene amplification), microarray or based on
17
18 172 whole genome sequencing (WGS).

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21 173 **Pneumococcal pneumonia:** For a pneumococcal pneumonia diagnosis among
22
23 174 adults, a minimum of either (i) symptoms consistent with an acute chest infection (at
24
25 175 least cough or dyspnoea) or (ii) new infiltrates on radiograph and (iii) pneumococcal
26
27 176 antigen detection in either blood, urine or pleural fluid. For children (1-15 years), the
28
29 177 case definition is the criteria for adults plus symptoms of fast breathing, chest-
30
31 178 indrawing and nasal flaring. These definitions have been adopted in order to
32
33 179 increase the specificity of identifying pneumococcal pneumonia but are limited in
34
35 180 their sensitivity.

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38 181
39 182 *Study exclusion criteria*

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43 183 1. Any study reporting impact data of vaccines within 12-months of PCV
44
45 184 introduction into routine extended programme of immunisation and data reported
46
47 185 in such a way that impact cannot be defined without data from within 12 months
48
49 186 of PCV introduction.
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52 187 2. Studies with small sample size (less than 50 participants), letters, commentaries,
53
54 188 narratives and editorials, will be excluded as they are likely to have biased
55
56 189 estimates, and this could affect our estimates.
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3 190 3. Studies that did not distinguish between pre- and post-PCV introduction periods
4
5 191 in the data presented.
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9 193 **Data extraction**

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11 194 Three independent reviewers (NLK, TKN and TDS) will assess the articles for
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13 195 inclusion based on a pre-determined inclusion and exclusion criteria. Those included
14
15 196 after initial screening will be further evaluated for methodological quality and
16
17 197 presence of bias. Refer to section *Appraisal of quality of reporting and the risk of*
18
19 198 *bias for methods* below for further details. Discordance will be resolved by discussion
20
21 199 between reviewers to reach consensus or by a fourth member of the team (KJ). All
22
23 200 articles retrieved will be stored and managed using Endnote X9 throughout the
24
25 201 review process. A standardised data extraction form designed specifically for each
26
27 202 outcome of interest, will be used to collect information on the following parameters:
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- 30
31 203 1. Study identification: name of first author, year of publication, year of participant
32
33 204 inclusion, country, type of publication, language of publication.
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35 205 2. Study characteristics: study design (e.g. cross-sectional, cohort, case control,
36
37 206 clinical trial), setting (hospital, outpatient, population, institution (e.g. school or
38
39 207 care facility), urban/rural), period of surveillance/recruitment, sample size, age
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41 208 (mean or median; range), proportion of HIV-infected participants and method of
42
43 209 confirmation (if any), proportion on ART (if any), proportion PCV-vaccinated (if
44
45 210 any), proportion with natural pneumococcal carriage (VT, NVT, total), diagnostic
46
47 211 method for pneumococcal carriage detection and serotyping (culture, PCR, DNA
48
49 212 microarray, WGS), diagnostic criteria for pneumococcal pneumonia, duration of
50
51 213 follow up for cohort studies, mortality rates.
52
53 214 3. Epidemiological estimates of pneumococcal carriage: prevalence of VT and NVT
54
55 215 carriage
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3 216 4. Epidemiological estimates for pneumococcal pneumonia: prevalence and/or
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5 217 incidence of pneumococcal pneumonia and/or mortality in all subpopulations,
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7 218 where reported (infants below age of 1 year, children 1-4 years, children 5-15
8
9 219 years and adults (16+ years), the elderly and HIV infected. When estimates are
10
11 220 not available or cannot be computed, the corresponding authors will be
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13 221 contacted to request for any missing information of these estimates.
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18 223 ***Appraisal of quality of reporting and the risk of bias***

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20 224 We will assess the quality of reporting of the studies using either the Strengthening
21
22 225 the Reporting of Observation studies in Epidemiology (STROBE) or the Consolidated
23
24 226 Standard of Reporting Trials (CONSORT) checklist depending on the nature of the
25
26 227 study (observational study or clinical trial).²⁰⁻²²

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29 228 We will use the 10-item risk of bias tool for prevalence studies developed by Hoy et
30
31 229 al²³ to assess the risk of bias for all the studies included using the full text
32
33 230 publications. Bias risk scores will be presented in a table and inter-rater agreement
34
35 231 will be assessed using a weighted Cohen's kappa statistic.²⁴⁻²⁵
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41 233 ***Data analyses and reporting***

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43 234 We will use the metaprop command provided within the STATA software v15 to
44
45 235 analyse the data.²⁶ Heterogeneity of studies with similar study characteristics will be
46
47 236 evaluated by the χ^2 test on Cochrane's Q statistic²⁷ and quantified using I^2 values
48
49 237 assuming that I^2 of 25%, 50% and 75% represent low, medium and high
50
51 238 heterogeneity respectively.²⁸ Study specific estimates will be pooled through a
52
53 239 random effect meta-analysis to obtain an overall summary estimate of the
54
55 240 prevalence of *S. pneumoniae* carriage, incidence of pneumococcal pneumonia and
56
57 241 mortality after stabilizing the variance of individual studies using the Free man-Tukey
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3 242 double arcsine transformation.²⁹ For impact of PCV on carriage, the percentage
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5 243 change in point prevalence will be calculated to compare pooled prevalence
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7 244 estimates in the before and after PCV introduction periods. Mortality rate ratios will
8
9 245 be calculated to compare pooled mortality rates for the periods before and after PCV
10
11 246 introduction. Meta-analysis results will be presented on a forest plot. Visual analysis
12
13 247 of funnel plot and Egger's test will be done to detect small study effect.^{30,31} All tests
14
15 248 will be two-sided and statistical significance will be defined as $p < 0.05$. In case of
16
17 249 marked heterogeneity, a descriptive analysis will be done instead of a meta-analysis.
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19 250
20 251 We will report our results according to the Meta-Analysis Of Observational Studies in
21
22 252 Epidemiology (MOOSE) guidelines.³² The process with which studies were selected
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24 253 will be summarised using a flow diagram. Reasons for study exclusion will be
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26 254 described and quantitative data will be presented in summary tables and graphs (for
27
28 255 trends) where appropriate.
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34 256 35 257 ***Ethics and dissemination***

36
37 258 This systematic review will not require ethical approval as we will be using already
38
39 259 published data. The findings will be summarised in a manuscript and submitted in
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41 260 peer-reviewed journals and presented at relevant conferences.
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45 261 46 262 ***Patient and public involvement***

47
48 263 This systematic review will use published scientific data and will not involve patients
49
50 264 or members of the public.
51

52 265
53 266 **Contributions:** NLK, TKN, KCJ and TDS conceived the study and drafted the
54
55 267 manuscript. The manuscript was revised by DE, SBG, NF, RSH and KCJ. All authors
56
57 268 approved the final version of the manuscript. TKN is the guarantor of the manuscript.
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8

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12 274
13 275 **Conflict of interests:** No competing interests were reported by authors.
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For peer review only

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Table 1 Search strategy	
Search	Search terms and combinations
1	("Pneumococc*" OR "Strep* pneumo" OR "S. pneumo*" OR "Streptococc*")
2	("Pneumococcal vaccines" OR "streptococcal vaccines" OR "Pneumococcal conjugate vaccine")
3	((("Africa" OR "Africa*" OR "Algeria" OR "Angola" OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cape Verde" OR "Cameroon" OR "Central African Republic" OR "Chad" OR "Comoros" OR "Democratic Republic of Congo" OR "Congo" OR "Ivory Coast" OR "Djibouti" OR "Egypt" OR "Equatorial Guinea" OR "Eritrea" OR "Ethiopia" OR "Gabon" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Kenya" OR "Lesotho" OR "Liberia" OR "Libya" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Morocco" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Rwanda" OR "Sao Tome and Principe" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" OR "Swaziland" OR "Tanzania" OR "Togo" OR "Tunisia" OR "Uganda" OR "Zambia" OR "Zimbabwe") NOT ("pig*" OR "Papua"))
4	("carriage" OR "Carriage" OR "coloniz*" OR "Coloniz*" OR "colonis*" OR "Colonis*" OR "acquisition" OR "acquir*" OR "carrier state" OR "Carrier state")
5	("Pneumococc* pneumonia" OR "Community acquired pneumonia" OR "Non-invasive pneumonia" OR "Invasive pneumococc* pneumonia" OR "CAP" OR "IPD")
6	("mortality rate" OR "case fatality" OR "death rate")
7	Carriage: #1 AND #2 AND #3 AND #4
8	Pneumococcal pneumonia and associated mortality: #1 AND #2 AND #3 AND (#5 AND/OR #6)
9	Filters: Publication date from 2000/01/01 to 2019/06/30; Humans

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be	16

repeated			
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9-10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10-11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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