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Streptococcus pneumoniae, serotypes and penicillin resistance in children with sickle cell disease in sub-Saharan Africa: a critical narrative review of the available data

Streptococcus pneumoniae, serótipos e resistência à penicilina em crianças com drepanocitose na África subsariana: revisão narrativa crítica dos dados disponíveis

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Abstract

Background: Children with sickle cell disease (SCD) in sub-Saharan Africa are at increased risk of invasive *Streptococcus pneumoniae* infection owing to early functional asplenia. Penicillin prophylaxis and pneumococcal vaccination assume that circulating strains remain susceptible and covered by available vaccines, yet African data to test this assumption are scarce.

Objective: To provide a structured, critical narrative synthesis of data on carriage, invasive disease, penicillin susceptibility and serotypes in children with SCD in sub-Saharan Africa, drawing on general paediatric African data where SCD-specific data are lacking.

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Methods: Structured narrative review (SANRA-guided) based on searches from October 2025 to September 2026 of PubMed/MEDLINE, Scopus, Web of Science, Embase and Google Scholar. Single-reader selection and extraction; no formal risk-of-bias assessment.

Results: Six African studies focusing on children with SCD and one Nigerian genomic study including an SCD subgroup (n = 37) were retained. Reported nasopharyngeal carriage ranged from 10% to 39%. Penicillin non-susceptibility ranged from 0% (Ghana, 2006-2007) to 100% (Uganda), with 30% in Gabon and 37.4% in Accra (almost entirely intermediate-level). No study reported serotype-specific resistance in children with SCD; serotype data were scarce (PCV13 coverage 32.4% among Accra children with SCD). Four main limitations hamper comparability: few studies, methodological heterogeneity, no harmonised definition of resistance, and scarce molecular data.

Conclusion: Available data do not allow identification of resistant serotypes in these children and do not, as they stand, justify questioning penicillin prophylaxis. Standardised prospective multicentre studies combining serotyping, MIC determination and molecular characterisation are needed, particularly in Central Africa.

Keywords: *Streptococcus pneumoniae*; penicillin resistance; serotypes; sickle cell anemia; child; sub-Saharan Africa; narrative review.

Resumo

Contexto: As crianças com drepanocitose da África subsariana estão expostas a um risco acrescido de infeções invasivas por *Streptococcus pneumoniae*, devido a uma asplenia funcional precoce. A profilaxia com penicilina e a vacinação antipneumocócica pressupõem que as estirpes em circulação permanecem sensíveis e cobertas pelas vacinas disponíveis; os dados africanos que permitem verificá-lo são, porém, escassos.

Objetivo: Sintetizar, de forma narrativa e crítica, os dados sobre a colonização nasofaríngea, a doença invasiva, a sensibilidade à penicilina e os serótipos na criança com drepanocitose da África subsariana, recorrendo a dados pediátricos gerais quando faltam dados específicos.

Métodos: Revisão narrativa estruturada (orientação SANRA) baseada numa pesquisa realizada de outubro de 2025 a setembro de 2026 no PubMed/MEDLINE, Scopus, Web of Science, Embase e Google Scholar. Seleção e extração por um único leitor, sem avaliação formal do risco de viés.

Resultados: Foram retidos seis estudos africanos centrados na criança com drepanocitose e um estudo genómico nigeriano com um subgrupo drepanocítico (n = 37). A colonização nasofaríngea referida varia entre 10 % e 39 %. A não sensibilidade à penicilina varia entre 0 % (Gana, 2006-2007) e 100 % (Uganda), com 30 % no Gabão e 37,4 % em Acra (quase exclusivamente de nível intermédio). Nenhum estudo refere resistência por serótipo na criança com drepanocitose; os dados serotípicos são raros (cobertura da PCV13 de 32,4 % nas crianças com drepanocitose de Acra). Quatro limitações principais restringem a comparabilidade: o reduzido número de estudos, a heterogeneidade metodológica, a ausência de uma definição harmonizada de resistência e a escassez de dados moleculares.

Conclusão: Os dados não permitem identificar os serótipos resistentes nestas crianças e não justificam, no estado atual, pôr em causa a profilaxia com penicilina. São necessários estudos prospetivos multicêntricos padronizados, associando serotipagem, CMI e caracterização molecular, em particular na África Central.

Palavras-chave: *Streptococcus pneumoniae*; resistência à penicilina; serótipos; anemia falciforme (drepanocitose); criança; África subsariana; revisão narrativa.

1. Introduction

1.1 Background and state of knowledge

Sickle cell disease is the most common inherited haemoglobinopathy worldwide, and sub-Saharan Africa accounts for the majority of affected births each year. Early splenic infarction and impaired opsonisation, complement activity and phagocytosis expose children to invasive infections by encapsulated bacteria, foremost among them *S. pneumoniae* [1,2]. In Africa, a meta-analysis estimated the odds ratio of invasive pneumococcal disease in people with sickle cell disease compared with controls at 36 [3], and the Kilifi study (Kenya) reported an adjusted odds ratio of 26.3 for bacteraemia in children with sickle cell disease [4]. In a North American randomised trial, prophylactic oral penicillin reduced invasive pneumococcal infections by 84% in children under three years of age [5]; together with conjugate and polysaccharide vaccination, it lies at the heart of international recommendations [6].

The bacterial spectrum in African children with sickle cell disease is, however, not uniform. In Kilifi, *S. pneumoniae* is the leading cause of bacteraemia (41% of isolates) [4], whereas in

Uganda *Staphylococcus aureus* predominated in a hospital series [7], and in Cameroon Enterobacteriaceae and *Salmonella* largely predominate in a series of 96 hospitalised children [8]. This heterogeneity justifies documenting the characteristics of the pneumococci involved at local level.

Pneumococcal resistance to penicillin results mainly from alterations of the penicillin-binding proteins (PBPs) encoded by the *pbp1a*, *pbp2b* and *pbp2x* genes, often as mosaic genes arising from recombination with commensal streptococci, without β-lactamase production [9,10]. Other resistance determinants (macrolides, tetracyclines) are carried by mobile genetic elements of the Tn*916* type [11]. The spread of resistant clones, documented by the PMEN network, and their evolution under antibiotic and vaccine pressure are well described [12,13]. Conjugate vaccination reduces the circulation of serotypes carrying resistance but may be accompanied by replacement with non-vaccine serotypes [14,15]. In children with sickle cell disease, North American studies have reported more frequent penicillin resistance before the introduction of PCV7 [16]; the specific role of prophylaxis in selecting less susceptible strains remains debated.

In Central Africa, data are scarce: there is one carriage study in Gabon [17], one hospital series in Cameroon [8] and one series in the Democratic Republic of the Congo [18]. Surveillance there is insufficient. Circulating serotypes are poorly identified. Local resistance profiles, notably to prophylactic penicillin, are poorly characterised. Vaccination and treatment policies are therefore difficult to adapt [19]. In Angola, a carriage study conducted in Luanda and Saurimo among 940 children aged 4 to 12 years, four years after the introduction of PCV13, reported 35% carriage, 41% of serotypes covered by PCV13 and 40% penicillin non-susceptibility [19]. However, it does not concern children with sickle cell disease. Yet knowledge of the serotypes and the susceptibility profile of the strains determines both the expected effectiveness of prophylaxis and the coverage offered by available vaccines (PCV10, PCV13) or poorly accessible ones (PPSV23).

1.2 Research question

What is known, in children with sickle cell disease in sub-Saharan Africa, about (i) carriage and invasive disease due to *S. pneumoniae*, (ii) the penicillin susceptibility of the strains, and (iii) the circulating serotypes and their vaccine coverage; and do these data make it possible to identify resistant serotypes?

1.3 Objectives

This structured, critical narrative review aims to:

- synthesise data on the epidemiology of pneumococcal carriage and invasive disease in African children with sickle cell disease and on the penicillin susceptibility of the strains;
- analyse the distribution of circulating serotypes and its vaccine implications;
- critically assess the methodological limitations of the literature in order to guide research priorities.

2. Review methodology

2.1 Type of review and rationale

This is a structured, critical narrative review, conducted according to the items of the SANRA guide [20]. Given the expected heterogeneity of populations, locations, methods of identification, serotyping and susceptibility determination, and study periods, the results are synthesised narratively and organised by theme, with a critical reading of the strengths and weaknesses of each source.

2.2 Literature search strategy

The search was conducted in PubMed/MEDLINE, Web of Science and Google Scholar; the date of the last search was 30 September 2026; the languages retained were French, English and Portuguese; and reference lists were searched manually. The following terms and their English equivalents were combined: "*Streptococcus pneumoniae*", "penicillin resistance / non-susceptibility", "serotype", "sickle cell disease / sickle cell anaemia / HbSS", "child / paediatrics", "sub-Saharan Africa" and country names. The full search equation is given in the appendix. No time window was imposed a priori, so as to include historical studies [4,7] as well as recent genomic studies [21,22].

2.3 Eligibility criteria

Inclusion criteria. Studies concerning, wholly or in part, children with sickle cell disease in sub-Saharan Africa and reporting data on carriage or invasive disease due to *S. pneumoniae*, with information on penicillin susceptibility and/or serotyping; studies in the general African paediatric population, systematic reviews and regional syntheses, retained as background (Table 1, part B); and studies from outside Africa, retained separately for international

comparison. Studies in mixed populations (children and adults) were included when the paediatric data were identifiable or when the bias was made explicit.

Exclusion criteria. Studies not concerning a paediatric or mixed population; isolated case reports; conference abstracts without sufficient extractable data, except where they were the only source on a specific question (the case of Carsillo et al. [23], flagged as such).

2.4 Selection, extraction and limitations of the approach

Selection and extraction were carried out by a single reader, without independent double reading or formal risk-of-bias assessment. This limitation, inherent in the narrative format, means the results must be read as a reasoned qualitative synthesis and not as a pooled estimate of the prevalence of resistance or of the serotype distribution.

The diagram below represents the conceptual flow of selection and interpretation of the data used.

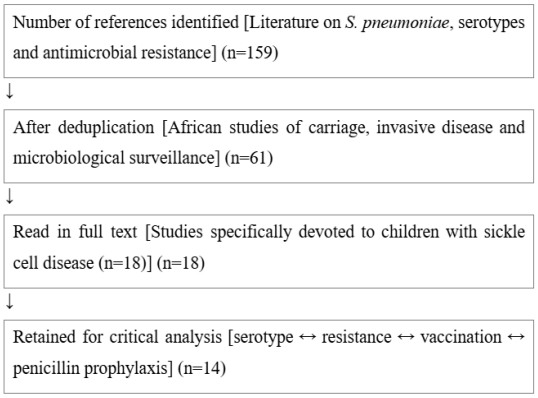


Figure 1. Conceptual flow of the critical narrative synthesis

3. Results and thematic synthesis

3.1 Pneumococcal vulnerability and bacterial spectrum in children with sickle cell disease

The Kilifi study identified 108 HbSS children among 1,749 genotyped bacteraemic children; *S. pneumoniae* accounted for 41% (44/108) of isolates, ahead of non-typhoidal *Salmonella* (18%) and *Haemophilus influenzae* type b (12%) [4]. Conversely, a Ugandan series reported a predominance of *S. aureus* [7], and in Cameroon only two isolates of *S. pneumoniae* (two cases of meningitis) were found among 99 positive samples from 96 hospitalised children with sickle cell disease, the stated coverage by the 23-valent vaccine being only 18.8% in children over 24 months of age [8]. In the Democratic Republic of the Congo, the

pneumococcus is described as one of the main isolates in bacteraemic children with sickle cell disease [18].

The work of Kateete et al. reveals a paradox: nasopharyngeal carriage of 33% in Ugandan children with sickle cell disease, whereas pneumococcal bacteraemia is reported there as uncommon [24]. This dissociation remains poorly explained; among the hypotheses, antibiotic exposure (65% of the children had recently received an antimicrobial), under-detection of bacteraemia (blood-culture sensitivity, death before hospital admission) and competition from other pathogens cannot be distinguished with the available data.

3.2 Nasopharyngeal carriage

Reported carriage ranges from 10% among 92 HbSS children examined in Accra in 2006-2007, before the introduction of PCV [25], to 33% (27/81) in Kampala [24] and 39.1% (79/202) among children with sickle cell disease in Accra in 2016-2017, four times the carriage in adults with sickle cell disease (10.0%, 20/200) [26]. In Gabon, a matched study (73 children with sickle cell disease, 143 controls) concluded that carriage and resistance levels were comparable to those of controls, despite a much higher exposure to penicillin (70.1 versus 0.1 days per year) [17]. These rates are not directly comparable: sampling sites, ages, periods relative to vaccination and culture methods differ.

3.3 Penicillin susceptibility

The reported rates range from 0% to 100%: 0% for penicillin in HbSS children in Accra in 2006-2007 (disc diffusion, NCCLS standard) [25]; 30% non-susceptibility in Gabon, whether oral breakpoints or parenteral meningitis breakpoints are applied [17]; 37.4% (37/99) in Accra in 2016-2017, of which 36 isolates were of intermediate level and one was resistant (MIC = 2 μg/mL), according to CLSI oral breakpoints after oxacillin screening [26]; and 100% (27/27) of isolates in Kampala [24]. This last figure calls for cautious reading: in the same study, the 38 isolates from non-sickle-cell controls were all classified as "intermediate" and those from children with sickle cell disease all as "resistant", which suggests a methodological or classification artefact rather than a biological difference. In a Nigerian series of children with invasive disease, 52% (99/192) of isolates were resistant to penicillin, with no significant difference between children with and without sickle cell disease or sickle cell trait [22].

International data point in the same direction of dependence on vaccination context: in 25 years of surveillance in Georgia (USA), penicillin resistance was more frequent in children

with sickle cell disease before the introduction of PCV7 [16]. This observation is more plausibly explained by the pre-vaccination circulation of vaccine serotypes carrying resistance than by antibiotic pressure alone; it has not been documented prospectively in sub-Saharan Africa.

3.4 Serotype distribution and vaccine implications

In African children with sickle cell disease, serotype data are scarce. In Kilifi, about three quarters of the pneumococcal isolates from bacteraemia were of serotypes included in PCV10 (a figure taken from a secondary summary of the study [4]). In Accra, non-vaccine serotypes predominated in children with sickle cell disease and PCV13 coverage reached only 32.4% [26]. In the Nigerian series, the distribution of serotypes did not differ significantly between children with and without sickle cell disease or trait [22]. To our knowledge, no study reports penicillin resistance by serotype in children with sickle cell disease; the Accra study collected both serotypes and MICs [26].

In the general population, the synthesis by Carsillo et al., presented as a conference abstract and based on the West African literature from 1990 to 2017, attributes about 80% of invasive disease to serotypes 1, 5, 6A, 12F, 14 and 23F; serotypes 2 and 12F were covered only by PPSV23 among the vaccines available at the time [23]. It should be noted that PCV20 includes serotype 12F (but not 2), which qualifies the argument in favour of PPSV23 alone. In Ghanaian children under six years of age, serotypes 19F, 6B, 23F and 6A predominated, mostly covered by PCV13 [27]. In Ethiopia, five to six years after the introduction of PCV10, serotype 19A (not included in PCV10, included in PCV13) was dominant, illustrating possible serotype replacement [21]. The review by Fletcher et al. stresses the persistent scarcity of post-PCV serotype data in many African countries [28]. None of these studies specifically concerns children with sickle cell disease, which limits transposition. In the United States, after 2010, none of the serotypes responsible for invasive disease in children with sickle cell disease was included in PCV13 [16].

3.5 Available molecular data

Negash et al. sequenced 103 paediatric isolates from Addis Ababa (86 from carriage, 4 from blood, 13 from otorrhoea): penicillin resistance (MIC > 0.06 µg/mL, the CLSI meningitis breakpoint) was predicted for 57% of isolates, with 27 *pbp1a*/*pbp2b*/*pbp2x* allelic combinations; 31.1% of isolates were multidrug-resistant, of which 46.8% belonged to the GPSC1 lineage (serotype 19A, CC320) [21]. The Nigerian study by Lo et al., conducted by

whole-genome sequencing of 192 invasive isolates from Kano and Abuja (2014-2018), is to our knowledge the only African genomic study including an SCD subgroup (37 children with sickle cell disease or trait); it reports 52% penicillin resistance, 44% (85/192) multidrug resistance and 2% erythromycin resistance, with no difference by sickle cell status [22]. This subgroup is, however, small and combines sickle cell disease with trait. South African work on resistant clones [29,30] provides a historical framework for comparison.

Table 1 summarises the characteristics and results of the studies retained.

Table 1. Comparative summary of the studies retained

Study	Country / design	Population (sample size)	Methods	Key results	Main limitations
Schaumburg et al., 2013 [17]	Gabon; matched cross-sectional	73 children with sickle cell disease; 143 matched controls	Culture; susceptibility testing; capsular typing	Penicillin non-susceptibility 30% (oral and meningitis breakpoints); carriage and resistance comparable to controls; penicillin: 70.1 vs 0.1 days/year	Detailed serotype data still to be extracted; single-centre
Dayie et al., 2018 [26]	Ghana (Accra); cross-sectional, 2016-2017 (post-PCV13)	202 children and 200 adults with HbSS; 99 isolates (79 children, 20 adults)	Oxacillin then MIC (E-test), CLSI oral breakpoints; serotyping	Carriage 39.1% (children) vs 10.0% (adults); non-susceptibility 37.4% (37/99), 36 intermediate and 1 resistant; PCV13 coverage in children 32.4%; non-vaccine serotypes predominant	Resistance calculated on children and adults combined; no molecular confirmation; single-centre
Cameroonian study, 2017 [8]	Cameroon; hospital-based descriptive	96 hospitalised children with sickle cell disease (99 samples)	Cultures	Septicaemia 65.6%; *S. pneumoniae*: 2 isolates (meningitis); PPSV23 coverage 18.8% (13/69 children ≥ 24 months)	No serotyping or pneumococcal susceptibility; few isolates

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Cameroonian study, 2017 [8]	Cameroon; hospital-based descriptive	96 hospitalised children with sickle cell disease (99 samples)	Cultures	Septicaemia 65.6%; *S. pneumoniae*: 2 isolates (meningitis); PPSV23 coverage 18.8% (13/69 children ≥ 24 months)	No serotyping or pneumococcal susceptibility; few isolates

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Lo et al., 2023 [22]	Nigeria (Kano, Abuja); genomic, 2014-2018	192 invasive isolates; 37 children with sickle cell disease or trait	Whole-genome sequencing	Penicillin 52% (99/192); multidrug resistance 44% (85/192); erythromycin 2%; no difference by sickle cell status	Small SCD subgroup (trait included); MIC breakpoint to be specified
B. Background studies (general population, syntheses, outside Africa)					
Dayie et al., 2013 [27]	Ghana; general population	Children < 6 years (233)	Serotyping; susceptibility testing	Serotypes 19F, 6B, 23F, 6A (mostly PCV13)	Not specific to sickle cell disease
Uddén et al., 2020 [19]	Angola (Luanda, Saurimo); cross-sectional, 2017 (4 years after PCV13)	940 children aged 4 to 12 years, general population	Culture; serotyping; susceptibility (EUCAST)	Carriage 35% (332/940); 41% PCV13 serotypes; penicillin non-susceptibility 40%, more frequent among PCV13 serotypes	Not specific to sickle cell disease; carriage only
Negash et al., 2025 [21]	Ethiopia (Addis Ababa); 5-6 years after PCV10	103 isolates (86 carriage, 4 blood, 13 otorrhoea); children < 15 years	Whole-genome sequencing; *in silico* prediction	Predicted resistance 57% (MIC > 0.06); multidrug resistance 31.1%; GPSC1 = 46.8% of multidrug-resistant isolates; 19A dominant; 27 *pbp* combinations	Not specific to sickle cell disease; mostly carriage

Study	Country / design	Population (sample size)	Methods	Key results	Main limitations
Carsillo et al., 2018 [23]	West Africa; retrospective analysis 1990-2017	Invasive disease, all ages	Compilation of published serotyping	Serotypes 1, 5, 6A, 12F, 14, 23F ≈ 80%; 2 and 12F exclusive to PPSV23: 8.1%	Conference abstract; mostly pre-vaccine data
Fletcher et al., 2024 [28]	WHO regions including Africa; systematic review 2010-2021	Invasive disease	Compiled serotypes	Scarcity of post-PCV serotype data in Africa	Not specific to sickle cell disease
Adamkiewicz et al., 2023 [16]	United States (Georgia); 25-year surveillance	3,707 HbSS/HbSC children < 10 years; 104 invasive episodes	Active surveillance; serotyping; MIC	Resistance more frequent before PCV7; after 2010, no PCV13 serotype	Outside Africa; comparison only

Note: the data in the table were cross-checked against the available abstracts or texts of the source studies; items marked are to be confirmed in the full texts. HbSS: homozygous sickle cell disease; PCV: pneumococcal conjugate vaccine; PPSV23: 23-valent pneumococcal polysaccharide vaccine; MIC: minimum inhibitory concentration.

4. Critical appraisal of the available studies

The cross-cutting reading reveals four interdependent methodological limitations.

4.1 A small number of African studies dedicated to this population

The body of work addressing both paediatric sickle cell disease and pneumococcal susceptibility or serotyping is limited: 81 children in Kampala [24], 92 in Accra in 2006-2007 [25], 73 in Gabon [17] and 202 children (99 isolates, children and adults combined) in Accra in 2016-2017 [26]. These sample sizes are insufficient for a fine-grained analysis of serotype distribution, and the samples are not independent of the vaccination periods. Only the Accra study combines carriage, serotypes and MICs, but it is single-centre and has not been replicated. This scarcity is consistent with the geographical concentration of carriage data in sub-Saharan Africa noted by Usuf et al. [31] and with the absence, in many countries, of sickle cell registries linked to microbiological surveillance.

4.2 Marked methodological heterogeneity

The studies differ in the nature of the isolates (carriage or invasive disease), in serotyping techniques (latex, Quellung, *in silico* prediction), and above all in the period of collection relative to the introduction of PCVs: 2006-2007 for the Accra study without PCV [25],

2016-2017 for the one carried out after the introduction of PCV13 [26], which precludes direct comparison of their results; serotype 19A noted after PCV10 in Ethiopia is an illustration [21]. The designs are heterogeneous: single-centre cross-sectional studies (Ghana, Uganda, Gabon), a retrospective cohort without susceptibility data (Kenya), and a regional synthesis in abstract form (Carsillo). Finally, the North American cohorts from Georgia/Atlanta [16,32] come from the same catchment and do not constitute two independent sources. Any direct quantitative aggregation is therefore hazardous.

4.3 No consensus on the definition of penicillin resistance

Comparison of rates is weakened by divergent methods and breakpoints: oxacillin disc screening, MIC by strip, NCCLS/CLSI/EUCAST standards, oral, non-meningitis parenteral or meningitis breakpoints. Since the 2008 CLSI revision, the same isolate can be classified as susceptible, intermediate or resistant depending on the route of administration and the site of infection [33]. For oral prophylaxis, the relevant breakpoints are those for oral penicillin, which is not always specified. Negash et al. use the meningitis breakpoint (MIC > 0.06 µg/mL), markedly stricter than the non-meningitis breakpoints [21]. The figure of 100% reported in Kampala, obtained by disc diffusion with unspecified breakpoints and with discordant classification between children with sickle cell disease and controls [24], illustrates this fragility. The lack of harmonisation between CLSI and EUCAST and the variable grouping of the "intermediate" and "resistant" categories add artificial heterogeneity. The clinical significance of intermediate-level resistance for oral prophylaxis remains poorly documented.

4.4 Insufficient molecular data

Almost all studies centred on African children with sickle cell disease rely on phenotypic methods. Sequencing of *pbp* genes or whole genomes has been used only by Negash et al. (general paediatric population) [21] and Lo et al. (SCD subgroup of 37 children) [22]. This gap prevents identification of the spread, in these children, of the resistant clones described in southern Africa [29,30] or of the GPSC1 lineage observed in Ethiopia, and prevents anticipation of post-vaccine serotype replacement. Logistical and financial constraints largely explain this reliance on phenotypic methods.

5. Discussion

5.1 Main findings

The central finding is a paradox: the pneumococcal vulnerability of African children with sickle cell disease is well established [3,4], but the profile of the strains that threaten them is very poorly characterised. The available studies report serotype and susceptibility separately; none makes it possible to answer the initial question on resistant serotypes. The other lessons are: a bacterial spectrum that varies by region (pneumococcus predominant in Kilifi, other pathogens in Uganda and Cameroon); carriage of 10% to 39% whose link with invasive disease remains uncertain; and penicillin non-susceptibility rates (0% to 100%) that are difficult to interpret. The only study combining explicit MICs and CLSI oral breakpoints reports 37.4% non-susceptibility, almost entirely intermediate [26].

Central Africa remains the poor relation in this literature: one carriage study in Gabon [17], one Cameroonian hospital series [8], one Congolese series [18], and no serotyping or genomic data dedicated to children with sickle cell disease. In Angola, only one carriage study in the general paediatric population was identified [19]; data dedicated to children with sickle cell disease would be an original contribution.

On the vaccine side, the low PCV13 coverage in children with sickle cell disease in Accra [26] and the persistence, in the United States, of infections by non-PCV13 serotypes in these children [16] argue for vaccines with broader coverage. PPSV23 remains poorly accessible in sub-Saharan Africa [23]; PCV20 covers serotype 12F but not 2. Recent syntheses on the relationship between serotypes and resistance [34], antimicrobial resistance in sickle cell disease [35], the impact of PCV10/13 on resistant pneumococci [15], post-PCV serotype distribution [36] and the pneumococcal profile in Ghana [37] provide a complementary framework.

5.2 Cautious clinical implications

These data do not justify abandoning penicillin prophylaxis: the resistance reported is heterogeneous, derives mainly from carriage studies, is often of intermediate level and is measured by non-comparable methods, whereas the benefit of prophylaxis has been demonstrated by a randomised trial [5]. In the Atlanta cohort, deaths from recent pneumococcal bacteraemia occur in children who had stopped penicillin [32]. Practical priorities concern access to and adherence with prophylaxis, vaccine coverage (low in

Cameroon for PPSV23 [8]), urgent management of fever, and local surveillance. These findings do not constitute clinical recommendations and call for prospective data, as stressed by Obaro and Iroh Tam [38].

5.3 Strengths and limitations of this review

The strengths are the explicitly critical angle, the distinction between studies centred on sickle cell disease and background studies, and the highlighting of inconsistencies in the classification of resistance. The limitations are selection by a single reader, the absence of formal risk-of-bias assessment, the risk of publication bias, the use of a conference abstract for part of the serotype data [23], and the impossibility of quantitatively aggregating heterogeneous studies.

6. Practical implications and research perspectives

- Set up prospective multicentre studies dedicated to African children with sickle cell disease, combining nasopharyngeal carriage with surveillance of invasive episodes, with sample sizes sufficient for robust serotype analysis and including countries of Central Africa.
- Harmonise the definition of resistance (CLSI or EUCAST, explicit breakpoints, oral / parenteral / meningitis specified, categories reported separately) in order to allow meta-analyses.
- Systematically cross-tabulate serotype, MIC and vaccination and prophylaxis status for each isolate, which would make it possible to answer the question of resistant serotypes.
- Develop access to whole-genome sequencing or targeted typing of *pbp* genes, including through regional partnerships (for example with the Global Pneumococcal Sequencing project).
- Evaluate, in children with sickle cell disease, the impact of the PCVs introduced or being updated (PCV13, PCV15, PCV20) on serotype distribution and resistance, and reassess the place of PPSV23 in light of the complementary coverage it provides.

7. Conclusion

This review confirms that children with sickle cell disease in sub-Saharan Africa remain at high risk of invasive pneumococcal disease, in a context where penicillin susceptibility and

circulating serotypes are insufficiently characterised and where no data cross-tabulate serotype and resistance. The small number of dedicated studies, the methodological heterogeneity, the divergence in definitions of resistance and the scarcity of molecular data limit the scope of current data. Filling these gaps is a prerequisite for optimising antibiotic prophylaxis and vaccination policies for this population, particularly in Central Africa.

Declarations

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Conflict of interest

There was no conflict of interest in this study; all the authors were genuinely active in the production of this article.

Author contributions

KKD and BKJP supervised the study and gave final approval of the version to be submitted for publication. **SK** conceived the project and the data collection, analysed and interpreted the results and wrote the first version of the manuscript. **CJF and SK** contributed to the development of the protocol and took part in the discussion. All authors read and approved the final version of the manuscript.

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