Increased risk of invasive bacterial infections in African people with sickle-cell disease: a systematic review and meta-analysis

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Children with sickle-cell disease are at great risk of serious infections and early mortality. Our Review investigates the association between sickle-cell disease and invasive bacterial disease among populations in Africa. We systematically searched published work extracted data on pneumonia, meningitis, and bacteraemia by sickle-cell disease status. Most studies identified lacked a control group and did not use best laboratory methods for culturing fastidious bacteria. Only seven case-control or case-cohort studies provided data on the association between invasive bacterial disease and sickle-cell disease status. For all-cause laboratory-confirmed invasive bacterial disease, the pooled odds of sickle-cell disease was 19-times greater among cases than controls. For disease caused by *Streptococcus pneumoniae*, the pooled odds of sickle-cell disease was 36-times greater; and for *Haemophilus influenzae* type b disease it was 13-times greater.

Lancet Infect Dis 2010; 10: 329–37

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Introduction

Sickle-cell disease encompasses various combinations of abnormal haemoglobin genes that include at least one copy of the gene for haemoglobin S paired with another structural β-chain haemoglobin variant or β-thalassaemia gene. People living in Africa have the highest burden of sickle-cell disease, predominantly due to four types of abnormal haemoglobin combinations: haemoglobin SS (sickle-cell anaemia), haemoglobin SC, haemoglobin Sβ+ thalassaemia, and haemoglobin Sβ0 thalassaemia.[1] Every year 230 000 infants with sickle-cell anaemia are born in Africa, representing 60% of all births worldwide associated with severe haemoglobin disorders.[2] The prevalence of haemoglobin S varies by country and is highest in equatorial Africa where *Plasmodium falciparum* malaria is endemic. People that are heterozygotes or carriers of the haemoglobin S trait are protected against serious complications of malaria in early childhood.[3,4] This relative advantage among people that are heterozygotic for the sickle-cell gene maintains the presence of the gene in populations living in malarial areas despite the survival disadvantage of inheriting the homozygous state of sickle-cell anaemia, illustrating the concept of a balanced polymorphism.[3] Up to 25% of adults in some countries such as Nigeria, Gabon, and the Democratic Republic of the Congo are heterozygous for haemoglobin S,[5–7] and greater than 1% of infants are born with sickle-cell anaemia (figure 1).[9]

Children with sickle-cell anaemia have an increased risk of mortality that peaks between the ages of 6 months and 3 years in both low-income and high-income settings.[2,10–14] In Africa, an estimated 6·4% of deaths in children younger than 5 years are attributable to sickle-cell anaemia; in west Africa the population-attributable risk might be as high as 9%.[1,15]

Increased early mortality among children with sickle-cell disease is primarily due to increased risk of infection. Immune function is compromised in sickle-cell disease because of deficiency in serum opsonin activity, abnormal neutrophil kinetics, and repeated sickling in the spleen that leads to loss of splenic function.[11,16] These immunological deficiencies render children with sickle-cell disease particularly vulnerable to malaria and infections from encapsulated bacteria such as *Streptococcus pneumoniae* (the pneumococcus). The greater risk of early invasive pneumococcal disease has been well documented: in the USA, before the introduction of pneumococcal conjugate vaccine, children with sickle-cell disease younger than 3 years had a 53-times greater risk of invasive pneumococcal disease compared with the general population.[17] Comprehensive care with parental education, penicillin prophylaxis, pneumococcal vaccination, and aggressive treatment with intravenous antibiotics for febrile episodes has increased the life expectancy of people with sickle-cell disease in developed countries and the Caribbean to 45–55 years.[12,18]

Life expectancy among African people with sickle-cell disease is probably less than 20 years.[19] Some studies have questioned the relative importance of the pneumococcus as a cause of bacterial infection in African people with sickle-cell disease and, therefore, the applicability of antipneumococcal strategies used in developed countries and the Caribbean to African settings.[20,21] The objective of this Review is to summarise the data from Africa on the association between sickle-cell disease and invasive bacterial disease, with a focus on the pneumococcus. The implications of these findings for the care of patients with sickle-cell disease in Africa and the introduction of pneumococcal conjugate vaccine are discussed.

Methods

Search strategy and selection criteria

We systematically searched published work to identify articles investigating populations from continental Africa and containing information on sickle-cell disease and invasive bacterial disease. We focused on pneumonia, meningitis, and bacteraemia, the most common invasive pneumococcal syndromes.[22,23] Professional librarians,

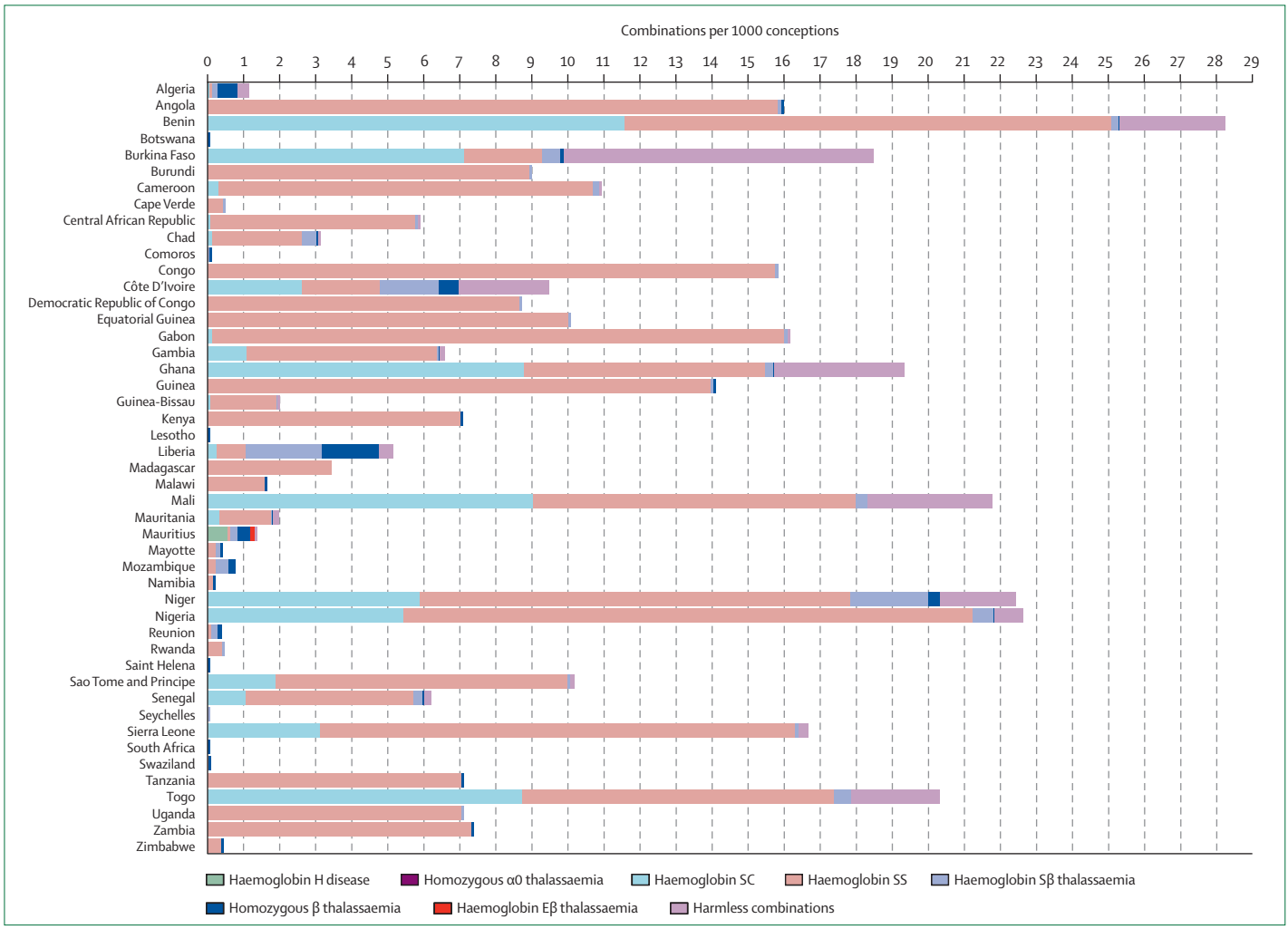

Figure 1: **Combinations of significant haemoglobin variants per 1000 conceptions in the WHO African Region by country**
Reproduced with permission from Modell B, Darlison M.[1,8]

Claire Twose and Donna Hesson (Johns Hopkins University), searched eight databases using keywords relating to sickle-cell disease, *Streptococcus pneumoniae*, bacteraemia, sepsis, febrile illness, pneumonia, and penicillin prophylaxis. Eight databases were searched from their start year (shown in parentheses) up to Dec 11, 2009: PubMed/Medline (1950), Global Health Database (1973), Embase (1974), Biological Abstracts (1985), Pascal Biomed (1987), Web of Science (1900), the Cochrane Library (1898–1996 depending on section), and African Index Medicus (1964). We screened the reference lists of two global reviews[24,25] and all citations found through a concurrent review of published work of bacterial meningitis in African countries for any data on patients with sickle-cell disease.[26] Additionally, we contacted seven clinical researchers in Cameroon, Nigeria, and Ghana for relevant unpublished data. Citations were uploaded into an EndNote XI library where duplications were removed.

To be included in this study, articles needed to have original data on at least one of the invasive syndromes of interest—bacteraemia, meningitis, or pneumonia—in 20 or more people screened for sickle-cell disease from continental Africa. For the purposes of this Review, sickle-cell disease was defined as haemoglobin SS, haemoglobin SC, haemoglobin Sβ+ thalassaemia, or haemoglobin Sβ0 thalassaemia genotypes, and people without sickle-cell disease included those with haemoglobin AA, haemoglobin AC, or haemoglobin AS (sickle-cell trait) genotypes. Because our primary focus was to estimate risk pertaining to pneumococcal disease, articles were excluded if they enrolled patients with sickle-cell disease with infectious disease caused by only one type of bacterial pathogen that was not the pneumococcus: for example, if the article only enrolled patients with *Salmonella* spp bacteraemia. Articles in all languages were considered.

Data extraction

All articles were reviewed by two trained data abstractors (two of MR, JCM, MM-E, Joachim Chijide, and Lola Dosunmu) who systematically extracted information on the incidence, prevalence, and mortality due to pneumonia, meningitis, and bacteraemia in people with and without sickle-cell disease and entered it into an electronic database. Pneumonia was defined as a lung infection with a suspected, presumed, or confirmed bacterial cause. Meningitis was defined as an infection of the meninges with a suspected, presumed, or confirmed bacterial cause. Bacteraemia was defined as a systemic bacterial infection with bacteria isolated by blood culture and no diagnosis of meningitis or pneumonia—eg, non-pneumonia non-meningitis disease with a positive blood culture that might or might not have another focus of infection (such as osteomyelitis).

The database also included information on study design and methods. Studies that identified patients with suspected bacterial illness and ascertained sickle-cell disease exposure among them were categorised as case-series if they had no control group, case-control studies if they recruited people without infection as controls, and case-cohort studies if they used the general population as a comparison group. Studies that identified patients with sickle-cell disease and ascertained the presence of bacterial illness—with or without a non-sickle-cell-disease control group—were categorised as cohort studies if they followed up a group of patients with sickle-cell disease over time and cross-sectional studies if they identified patients with sickle-cell disease on admission to hospital.

Quality scoring

The articles found through our search of published work were heterogeneous in study design and methods. We therefore developed a standardised scoring form to evaluate study quality. Quality scoring was on the basis of six criteria: relevance of the article's study questions to the objective of this Review; rigorous and clearly described methods for selecting participants; use of a standard approach for ascertainment of sickle-cell disease and bacterial infection among participants; inclusion of a control group (people without bacterial infection or sickle-cell disease); exploration of the statistical significance of study results, if appropriate; and overall impression of the study quality. Points were assigned to each quality question for a total of ten possible points per article. Two reviewers (two of MR, JCM, and MM-E) scored each article considered for inclusion in the study and a final score was obtained by consensus. Articles scoring more than seven points were categorised as A quality, those scoring five to seven points were designated as B quality, and those scoring less than five points as C quality.

Data analysis

We calculated the odds ratios (ORs) and 95% CIs for sickle-cell disease among patients with invasive bacterial disease compared with controls without invasive bacterial disease (in case-control studies) or to the general population (in case-cohort studies). We obtained pooled ORs and 95% CIs by syndrome and by pathogen, using fixed-effects models for outcomes without interstudy heterogeneity and random-effects models for outcomes with significant heterogeneity. All analyses were done in Stata 10.0.

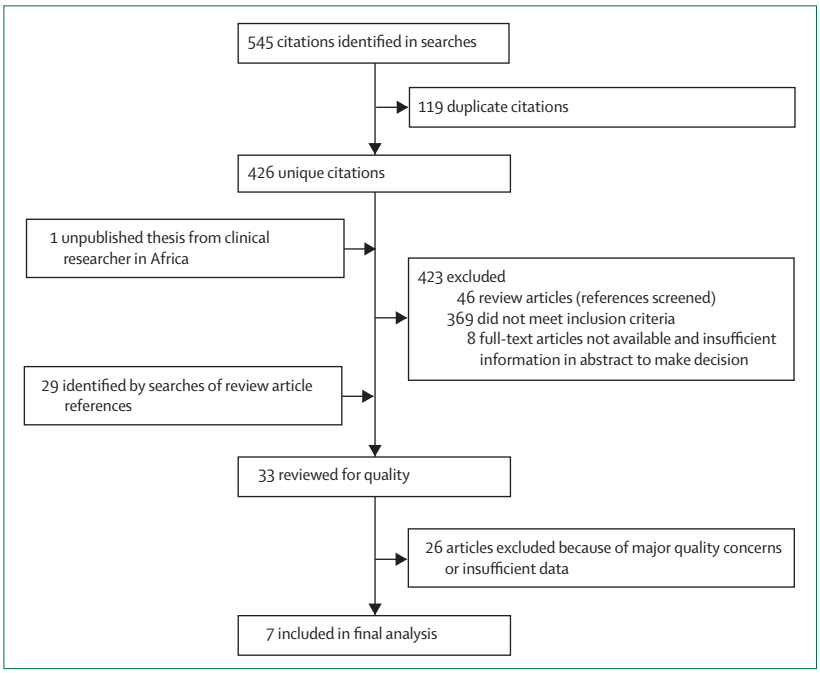

Figure 2: **Flow diagram of search of published work**

Results

Figure 2 presents the number and final designation of citations found through the search of published work. A total of 545 citations were initially identified, and 426 citations remained after removal of duplicates. One unpublished thesis was obtained from direct inquiries to clinical researchers.[27] 33 potentially relevant articles moved forward to the quality review and data extraction phase.

We found substantial variations in study methods and quality among these 33 articles. Most studies included paediatric patients but the age groups studied varied widely; three studies enrolled only children older than 11 years and adults. 22 studies used a cohort or cross-sectional design to investigate the bacterial cause of invasive infection in patients with sickle-cell disease, but none of these studies had appropriate control groups and thus could not be used to calculate relative risk of infection in patients with sickle-cell disease. Most studies relied on passive hospital surveillance and collected data retrospectively from existing records.

26 articles (79%) did not mention laboratory methods used to culture and identify bacteria from clinical specimens. Of the seven articles that reported their laboratory procedures, only one specified the type of

	Country	Median study year	Age range of patients (mean age)	Number of patients	Study design	Diagnosis of sickle-cell disease	Diagnosis of invasive bacterial disease	Controls
Omanga et al[32]	Democratic Republic of the Congo	1975	5–156 months (53)	275	Case cohort	Probably haemoglobin electrophoresis, but not explicitly stated	Positive blood culture; clinical syndromes of pleuropneumonia, meningitis, etc; not expressly defined	Referenced earlier study done in 1969 involving 1000 newborns in Kinshasa (local population); found prevalence of sickle-cell disease of 20 (2·0%) in 1000
Omanga[7]	Democratic Republic of the Congo	Not stated	3–156 months (27)	568	Case cohort	Haemoglobin electrophoresis	Positive blood culture, CSF culture, or both; clinical bacterial syndromes not expressly defined	Referenced earlier study done in 1969 involving 1000 newborns in Kinshasa (local population); found prevalence of sickle-cell disease of 20 (2·0%) in 1000
Eeckels et al[34]	Democratic Republic of the Congo	1963	Not stated (26)	196	Case cohort	Haemoglobin electrophoresis of 196 of 265 potential cases; reason for not testing for sickle-cell disease was that patients either too young or died too quickly	Positive blood culture, CSF culture, or both	Referenced earlier study done in 1969 involving 1000 newborns in Kinshasa (local population); found prevalence of sickle-cell disease of 20 (2·0%) in 1000
Chiron et al[33]	Senegal	1978	Not stated (not stated)	302	Case control	Haemoglobin electrophoresis, precipitation of haemoglobin S, Emmel's test, sickling test	Positive CSF culture	Two of 1383 people used as controls had sickle-cell anaemia; no information provided on controls; no age ranges given
Nottidge[35]	Nigeria	1975	7–60 months (not stated)	71	Case cohort	Haemoglobin electrophoresis in 71 of 261 children with pneumococcal meningitis	Positive CSF culture for *Streptococcus pneumoniae*	Local population of Ibadan, Nigeria: 3000 people of unknown age tested and 76 (2·5%) of 3000 diagnosed with sickle-cell disease
Lontie et al[31]	Democratic Republic of the Congo	1965	0–143 months (not stated)	172	Case cohort	Probably haemoglobin electrophoresis but not explicitly stated; 172 of 360 children were typed for sickle-cell disease	Positive CSF culture	Referenced earlier study done in 1969 involving 1000 newborns in Kinshasa (local population); found prevalence of sickle-cell disease of 20 (2·0%) in 1000
Williams et al[36]	Kenya	2003	0–168 months (not stated)	1749	Case control	Haemoglobin electrophoresis, high performance liquid chromatography, confirmation by PCR for haemoglobin S	Postive blood culture, lumbar puncture done when CSF white-blood-cell count raised or CSF:plasma glucose ratio decreased	Children recruited by random sampling from the local district into other studies, representative with respect to age when compared with cases: 13 (0·3%) of 4741 had sickle-cell anaemia; another control group of children born consecutively in district was more representative of geographical location, their haemoglobin SS prevalence was 76 (0·9%) of 8751

Table 1: **Articles included in final analysis**

blood agar plates used—expired human blood.[28] MacConkey agar plates were used in addition to blood agar plates in two studies,[29,30] and chocolate agar plates were used in three studies.[28,29,31]

Of the 33 pertinent articles identified, only seven met most quality criteria and included a control group, enabling us to explore the association between sickle-cell disease and invasive bacterial disease. Six of these articles received an A quality score, and one received a B score.[32] These seven articles were published between 1967 and 2009 and include five case-cohort studies and two case-control studies representing a total of 3333 patients with invasive bacterial disease and data on sickle-cell disease status. All articles come from countries with a high prevalence of sickle-cell disease: four studies are from the Democratic Republic of the Congo (formerly Zaire), and one each from Nigeria, Kenya, and Senegal. Three articles had data on patients with pneumonia, all seven had data on patients with meningitis, and four had data on non-pneumonia non-meningitis cases. Six articles included only paediatric patients younger than 14 years, and one study[33] did not specify the age range of its patients. Table 1 presents more details on the seven included studies and their methods of diagnosing sickle-cell disease and invasive bacterial disease and selecting a control group. In only one study[36] was the control group representative of the age distribution among patients. Four studies[7,31,32,34] referenced the same historical control group from the same local region. In three studies,[31,34,35] testing for sickle-cell disease was done on only a subset of the eligible patients with invasive bacterial disease.

All seven studies found an increased prevalence of sickle-cell disease in people with invasive bacterial disease compared with those without invasive bacterial disease. Table 2 presents the number of patients with invasive bacterial disease studied and the proportion of cases and controls with sickle-cell disease, enabling us to calculate the ORs for sickle-cell disease among cases compared with controls. Six studies reported ORs ranging from 9·27 to 23·94 for all-cause, laboratory-confirmed invasive bacterial disease with a pooled OR of

	Overall quality Score	Laboratory-confirmed diagnoses	Pathogen	Total number of patients	Proportion of patients with sickle-cell disease	OR* (95% CI)
Omanga et al[32]	B	Non-pneumonia non-meningitis bacteraemia, meningitis, and pneumonia	All bacteria	275	25%	16·4 (9·8–27·6)
		Reference group†			2%	NA
Omanga[7]	A	Non-pneumonia non-meningitis bacteraemia, meningitis, and pneumonia	All bacteria	568	27%	18·1 (11·2–29·2)
		Non-pneumonia non-meningitis bacteraemia, meningitis, and pneumonia	*Streptococcus pneumoniae*	104	49%	47·2 (26·2–84·8)
		Non-pneumonia non-meningitis bacteraemia, meningitis, and pneumonia	*Haemophilus influenzae* type b	92	15%	8·8 (4·3–18·1)
		Reference group†			2%	NA
Eeckels et al[34]	A	Non-pneumonia non-meningitis bacteraemia and meningitis	All bacteria	196	23%	14·6 (8·4–25·4)
		Non-pneumonia non-meningitis bacteraemia and meningitis	*S pneumoniae*	45	51%	51·2 (24·6–106·6)
		Non-pneumonia non-meningitis bacteraemia and meningitis	*H influenzae* type b	25	12%	6·7 (1·9–24·2)
		Reference group†			2%	NA
Chiron et al[33]	A	Meningitis	All bacteria	302	1%	9·3 (1·7–50·8)
		Meningitis	*S pneumoniae*	121	2%	11·6 (1·6–83·1)
		Meningitis	*H influenzae* type b	135	1%	10·4 (1·5–74·3)
		Controls‡		1383	0%	NA
Nottidge[35]	A	Meningitis	*S pneumoniae*	71	25%	13·2 (7·4–23·7)
		Reference group§		3000	3%	NA
Lontie et al[31]	A	Meningitis	All bacteria	172	31%	22·4 (13·0–38·8)
		Meningitis	*S pneumoniae*	61	61%	75·5 (38·3–148·8)
		Meningitis	*H influenzae* type b	58	16%	9·0 (3·9–20·8)
		Reference group†			2%	NA
Williams et al[36]	A	Non-pneumonia non-meningitis bacteraemia, meningitis, and pneumonia	All bacteria	1749	6%	23·9¶ (13·4–42·7)
		Non-pneumonia non-meningitis bacteraemia, meningitis, and pneumonia	*S pneumoniae*	469	9%	37·7 (20·1–70·5)
		Non-pneumonia non-meningitis bacteraemia, meningitis, and pneumonia	*H influenzae* type b	113	12%	47·3 (21·4–104·6)
		Reference group		4741	0·3%	NA

Any sickle-cell disease includes SS genotype and, when available, SC genotype. *Odds of sickle-cell disease in cases divided by odds of sickle-cell disease in control group or in reference population, not adjusted for age. †Controls from the reference population of Kinshasa, Democratic Republic of the Congo. ‡Controls from a group of non-invasive bacterial disease patients enrolled in the study. §Controls from a reference population of Ibadan, Nigeria. ¶The crude odds ratios reported here do not correspond to those reported in the published study because the study adjusted for age.

Table 2: **Distribution and odds of bacterial disease by haemoglobin status**

18·72 (95% CI 14·69–23·85) on the basis of a fixed-effects model (test for heterogeneity p>0·05; figure 3). For invasive pneumococcal disease six studies found ORs ranging between 11·61 and 75·54, with a pooled OR of 35·65 (20·00–63·56) on the basis of a random-effects model (test for heterogeneity p<0·01, I^2=74%; figure 3). Five studies reporting on *Haemophilus influenzae* type b invasive disease found ORs ranging from 6·68 to 47·28, with a pooled OR of 12·79 (5·63–29·06) on the basis of a random-effects model (test for heterogeneity p<0·01, I^2=70%; figure 3).

Three studies separately assessed the outcome of bacterial meningitis (figure 4). Two studies reported on all-cause, laboratory-confirmed bacterial meningitis with ORs of 9·27 and 22·42, with a fixed-effects pooled OR of 20·46 (95% CI 12·15–34·44, test for heterogeneity p>0·05). Three studies found ORs of 11·61, 13·23, and 75·54 for pneumococcal meningitis with a random-effects pooled value of 24·95 (6·18–100·67, test for heterogeneity p<0·01, I^2=87%). For *H influenzae* type b meningitis, individual ORs were 9·00 and 10·38 with a fixed-effects pooled value of 9·22 (4·27–19·92, test for heterogeneity p>0·05).

Discussion

In our Review, we identified 33 studies from Africa with data on sickle-cell disease and bacterial disease including pneumococcal disease, of which seven were included in the final analysis. These seven studies from Nigeria, Senegal, Kenya, and the Democratic Republic of the Congo consistently showed a significant association between sickle-cell disease and the risk of invasive bacterial disease. Patients with any invasive bacterial disease syndrome had 19-times greater odds of having sickle-cell disease than controls, whereas those with invasive pneumococcal disease had 36-times higher odds, and those with invasive *H influenzae* type b disease had 13-times higher odds. Similarly strong associations were obtained for all-cause, pneumococcal and *H influenzae* type b meningitis. Although the pooled ORs were highest for pneumococcal syndromes, there was significant heterogeneity in the study-specific ORs for both pneumococcus and *H influenzae* type b. Due to the interstudy variability and wide CIs associated with the pooled ORs, we did not calculate the population-attributable risk of invasive bacterial disease due to sickle-cell disease. Nevertheless, our findings clearly show that African children with sickle-

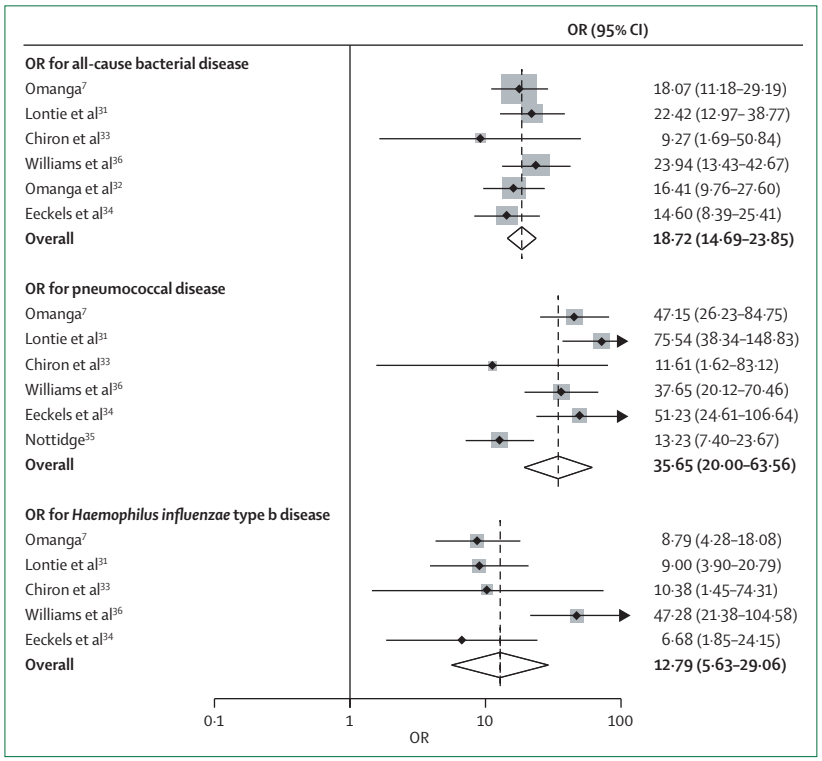

Figure 3: **Study-specific and pooled ORs for laboratory-confirmed invasive bacterial disease**
Weights for pneumococcal and *Haemophilus influenzae* type b disease are from random-effects analysis.

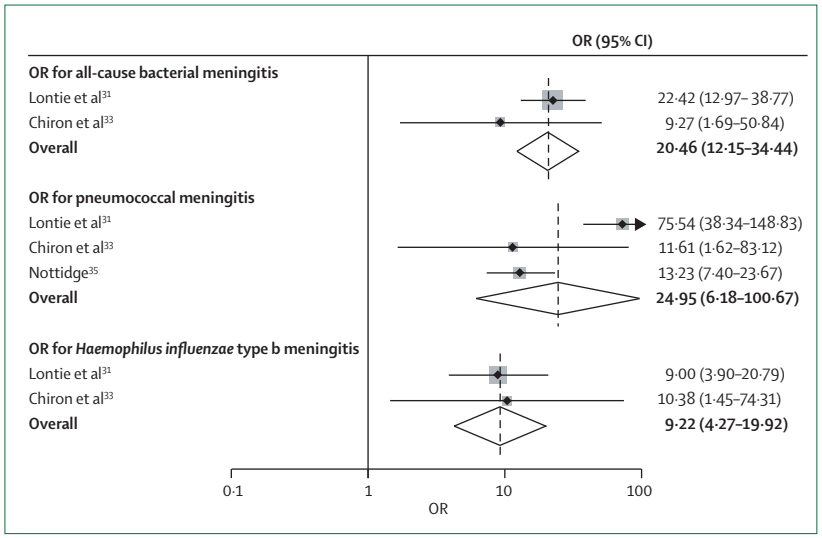

Figure 4: **Study-specific and pooled ORs for laboratory-confirmed bacterial meningitis**
Weight for pneumococcal meningitis is from random-effects analysis.

cell disease are at increased risk of bacterial illness compared with their peers without sickle-cell disease, with the pneumococcus being of particular concern. Our findings also suggest children with sickle-cell disease should be targeted by disease prevention programmes.

Most of the studies identified had major limitations in their methods. 26 articles were excluded from the final analysis because they lacked appropriate control groups without sickle-cell disease or invasive bacterial disease, which precluded calculation of a measure of the association between sickle-cell disease and invasive bacterial disease. Additionally, the few laboratory details provided suggest that many studies used suboptimum procedures for isolating the pneumococcus: sheep-blood agar, the preferred culture media for pneumococcus, was not mentioned in any of the studies. Furthermore, many articles lacked information on the use of antibiotics before collection of specimens: one article reported a prevalence of antibiotic use before admission of 15%,[27] another of 25%,[20] and a third of 48%.[28] Prior antibiotic use is an important obstacle to isolating bacteria from normally sterile specimens and should be accounted for when interpreting culture results.

Several potential biases might limit the validity of our findings and contribute to the heterogeneity of results with respect to pneumococcal and *H influenzae* type b disease. Six studies analysed in our Review were done at teaching hospitals in urban centres, and one study was done in a rural setting.[36] Patients included in these studies likely have better access to medical care than the general population. Furthermore, children with a known diagnosis of sickle-cell disease might have been more likely to seek care at a teaching hospital quickly after the onset of illness than those without sickle-cell disease, which would lead us to overestimate the prevalence of sickle-cell disease among cases of invasive bacterial disease and therefore the OR for sickle-cell disease in cases versus controls. People enrolled in these studies also differ insofar as they survived long enough to reach the hospital and be diagnosed. The patients that are most sick are most likely to die quickly and thus not be included in the studies. The prevalence of sickle-cell disease in the group of most ill patients might be greater, and so this selection bias would tend to underestimate the odds of sickle-cell disease among cases of invasive bacterial disease studied. Additionally, only one of the seven studies included in the final analysis was done prospectively. Three of the six retrospective studies mentioned that some children with invasive bacterial disease did not have haemoglobin typing done. One retrospective study did include haemoglobin typing on all specimens from children with invasive bacterial disease if they could access them.[36] In two of the retrospective studies, however, the investigators did not clearly state the reasons for incomplete haemoglobin testing. Haemoglobin testing might have been done only in patients with a prior clinical suspicion of sickle-cell disease, which would lead to an overestimation of the strength of the association between sickle-cell disease and invasive bacterial disease. Finally, controls had a similar age distribution to cases in only one study.[36] The other studies used the neonatal prevalence of sickle-cell disease for comparison: the high early mortality rate among children with sickle-cell disease likely results in

this choice of control group underestimating the strength of association between the risk of sickle-cell disease and invasive bacterial disease in childhood. Overall, the different selection and ascertainment biases might influence the OR in different directions. However, if these biases were eliminated we believe the consistent strong associations between sickle-cell disease and invasive bacterial disease would remain.

Africa bears the greatest burden of sickle-cell disease worldwide, yet routine access to specialised sickle-cell disease services is beyond the reach of most African children. Clinical services for people living with sickle-cell disease are limited to teaching hospitals in major urban centres, whereas neonatal screening, rural services, health information, and national policies for haemoglobin disorders are lacking in most countries.[8] Numerous articles refer to patients with sickle-cell disease having poor access to formal health care: many of the children with sickle-cell disease are taken to traditional healers and die early in life before diagnosis of sickle-cell disease, generally outside of a hospital setting.[3,37,38] Few children with sickle-cell disease are on routine antibiotic prophylaxis or receive any immunisations beyond those recommended by national immunisation schedules. The small number and heterogeneous quality of studies on sickle-cell disease and bacterial infections corroborates the relative lack of attention and resources focused on sickle-cell disease in Africa and is particularly striking in view of the public health importance of this disease. Furthermore, poor quality studies continue to call into question the importance of pneumococcal disease as a pathogen of particular risk in children with sickle-cell disease. Even among the seven articles included in our Review, the ability to widely apply the results are limited by the fact that four studies took place in the same hospital, used the same control group for comparison, and might have some overlap of patients included in the studies. Better-designed, prospective epidemiological studies that further characterise the burden of invasive disease in children with sickle-cell disease are warranted, particularly as baseline studies to help monitor the effect of newly introduced vaccines in this vulnerable population. These studies, however, should not delay ministries of health from formulating national policies to systematically improve sickle-cell disease preventive and clinical services, as sufficient evidence shows that people with sickle-cell disease experience a disproportionately high risk of early mortality and morbidity due to invasive bacterial disease as they did in developed countries before the use of comprehensive care strategies.

In 2006, the World Health Assembly stated that there is an "urgent need to develop models of care appropriate to the management of [sickle cell] disease in sub-Saharan Africa" because there is a widening "gap in terms of quality of life between patients in developed countries and those in developing countries".[15] The burden of sickle-cell disease in Africa warrants a strong emphasis on prevention of bacterial disease, especially because of the pneumococcus.

Parental education, antibiotic prophylaxis, haemoglobin screening, and access to conjugate vaccines are key components of an integrated preventive approach to reduce the risk of serious infections in African children with sickle-cell disease. Parental education can be effective in addressing the traditional cultural attitudes prevalent in the population that might stigmatise sickle-cell disease and delay the seeking of care.[19] Antibiotic prophylaxis is complicated by compliance issues and might contribute to selective pressure for resistant bacteria. Country-wide haemoglobin screening would be expensive and logistically challenging. So far, newborn screening has only been done in four African cities and on a demonstration basis.[19] Extending such screening services to rural areas would need dedicated and coordinated resources. Screening of newborns has the advantage of increasing public awareness about the effect of sickle-cell disease and identifying newborns who could benefit from community-based services such as antimalarial strategies, parental education, and vaccination.

Routine immunisation against *H influenzae* type b and pneumococcus has the greatest potential to affect the mortality and morbidity among children with sickle-cell disease. In countries where greater than 1% of all births are affected by sickle-cell disease, a substantial proportion of invasive pneumococcal and *H influenzae* type b disease could be attributable to sickle-cell disease. In the absence of early diagnosis of sickle-cell disease, routine, country-wide immunisation against *H influenzae* type b and pneumococcus is the best strategy to improve the quality of life for all African children, particularly those with sickle-cell disease. *H influenzae* type b conjugate vaccine is already in use in most African countries. Pneumococcal conjugate vaccine (PCV) is safe and immunogenic in infants and children with sickle-cell disease.[39–43] In the USA, invasive pneumococcal infections have decreased by 68% among children with sickle-cell disease younger than 10 years and by over 90% in those younger than 5 years since the introduction of seven-valent PCV in 2000.[44,45] In Africa, the proportion of paediatric pneumococcal disease due to seven-valent PCV serotypes is lower (62%) than in the USA and Europe, where vaccine serotypes represent more than 80% of disease before the introduction of vaccine.[46,47] However, because of the higher baseline incidence of invasive pneumococcal disease in low-income countries, the potential effect of PCV on absolute cases and deaths due to serious pneumococcal infection is greater in Africa than in high-income settings.[48,49] Moreover, ten-valent and 13-valent PCVs are becoming available and will offer broader serotype coverage for African children. With the support of the GAVI Alliance, routine use of PCV is now economically feasible and should be a public health priority in countries aiming to reduce morbidity and mortality among children with sickle-cell disease.

Search strategy and selection criteria

These are described in detail in the Methods section.

On March 23, 2010, it was announced that GlaxoSmithKline and Pfizer had made long-term commitments to supply new vaccines against pneumococcal disease.[50]

Contributors

MR coordinated the project, abstracted data, helped complete the data analysis and drafted the written report. JM abstracted data, oversaw the data analysis and completed the portion in Stata, and edited the written report. KK and JF gave technical input at key points throughout the process and edited the written report. LG designed the data abstraction method. MM abstracted data, helped complete the data analysis, and designed the quality review method. OL gave key input and feedback throughout the process.

Conflicts of Interest

KK has received research funding and consulted for Wyeth and GlaxoSmithKline. All other authors declare that they have no conflicts of interest.

Acknowledgments

Funding support for our Review was made available from the GAVI Alliance and the Sabin Vaccine Institute. We would like to thank Claire Twose and Donna Hesson, librarians at Johns Hopkins, for their help in the searching of published work, finding articles, and providing input at many points throughout the process. We would also like to thank our data extractors Joachim Chijide and Lola Dosunmu. Thanks also to Hope Johnson for providing the databases of published work of the Global Disease Burden and Global Serotypes projects, to Maria Deloria Knoll and Aaron Ulland for their constructive feedback on the paper, and to Olufemi Akinyanju for sharing his expertise and publications. Our Review would not have been possible without the logistical support of Michelle Moncrieffe-Foreman at PneumoADIP and Ana Carvalho and Ciro de Quadros at the Sabin Vaccine Institute.

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