Journal of Infection 90 (2025) 106441

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Infectious Disease Practice

Risk of invasive meningococcal disease in people with sickle cell disease: A systematic review

Catherine Isitt [a,c], Helen Campbell [b], Catherine A. Cosgrove [a,d], Mary E. Ramsay [b], Paul T. Heath [a], Ray Borrow [e], Shamez N. Ladhani [a,b,*]

[a] Centre for Neonatal and Paediatric Infections (CNPI), City St George's University of London, London, UK
[b] Immunisation Department, UK Health Security Agency (UKHSA), London, UK
[c] Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden
[d] Department of Infectious Disease, St George's University Hospital NHS Foundation Trust, London, UK
[e] Vaccine Evaluation Unit, UK Health Security Agency (UKHSA), Manchester, UK

ARTICLE INFO

Article history:
Accepted 7 February 2025
Available online 12 February 2025

Keywords:
Sickle cell anaemia
Invasive meningococcal disease
Meningococcal vaccines

SUMMARY

Background: Asplenia and splenic dysfunction is associated with an increased risk of severe and fatal infections, especially due to encapsulated bacteria including *Streptococcus pneumoniae*, *Haemophilus influenzae* serotype b (Hib) and *Neisseria meningitidis*. People with sickle cell disease (SCD) develop recurrent splenic infarcts rendering them functionally asplenic. Consequently, additional vaccination against these three pathogens is recommended. There is robust evidence of an increased risk for invasive pneumococcal (IPD) and Hib disease, in people with SCD, but for not invasive meningococcal disease (IMD).

Methods: We conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) recommendations. Studies published in any language before June 2024 and including people with SCD of all ages and from all geographical locations were included. Studies were included if they documented bacterial culture and/or PCR in patients with SCD with suspected infection. The primary outcome was to estimate IMD risk in people with SCD. Secondary outcomes included estimating the risk of IMD and Hib disease in people with SCD.

Findings: We identified 3804 publications and included 86 in the final analyses. Among 74 cohort studies published during 1971–2023, there were three IMD cases among 26,404 persons with SCD compared with 570 IPD and 113 Hib cases. Eight case-control studies published during 1983–2022 reported one IMD case among 932 people with SCD (0.1%) compared to 118 IMD cases among 7143 people without SCD (1.65%). In contrast, there were 126 IPD cases (126/932, 13.5%) in people with SCD compared to 588 (588/7143, 8.2%) in those without SCD. For Hib, the rates were 32/932 (3.4%) and 316/7143 (4.4%), respectively. After including all published studies, we identified five IMD cases in people with SCD across studies published worldwide during 1965–1995 and all five survived their infection.

Interpretation: We found no evidence of any increased risk of IMD in people with SCD. This has important implications for policymakers in countries and organisations that currently recommend meningococcal vaccination for people with SCD.

* Correspondence to: Immunisation Department, UK Health Security Agency (UKHSA), 62 Colindale Avenue, London NW9 5EQ, UK.
E-mail address: shamez.ladhani@ukhsa.gov.uk (S.N. Ladhani).

https://doi.org/10.1016/j.jinf.2025.106441

Research in Context

Evidence before the study

We searched PubMED, MEDLINE, EMBASE and Web of Science using the following search terms: Mening* AND sickle, Mening* AND haemoglobinopathy, Sickle AND bacteraemia, Sickle AND infection. We identified 3804 publications and included 86 in the final analyses, including 74 cohort studies published during 1971–2023, eight case-control studies published during 1983–2022, two case series and one case report on invasive meningococcal disease (IMD) in people with SCD and a systematic review and meta-analysis. Most studies pre-dated meningococcal vaccination and daily antibiotic prophylactic recommendations for people with SCD. After assessing all published studies, we found an ongoing increased risk of invasive pneumococcal disease and invasive *Haemophilus influenzae* type b (Hib) disease in people with SCD, but no evidence of any increased risk of IMD. Across all studies published worldwide during 1965–1995, we identified only five IMD cases in people with SCD and all five survived their infection. We also searched the literature for guidelines, policies and recommendations for additional vaccination of people with SCD. We found that most guidelines include SCD as part of the asplenia and splenic dysfunction risk group and recommend additional vaccination against pneumococcal, Hib and meningococcal disease. In contrast, Nigeria, which lies within the African meningitis belt, an area known for seasonal IMD epidemics, does not recommend meningococcal vaccination for people with SCD.

Added value of the study

This is the first study to question the dogma of increased risk of IMD in people with SCD. Our thorough and extensive systematic review of the literature with no limitations did not find any evidence of an increased IMD risk in people with SCD. Recommendations for additional vaccination of people with SCD are usually incorporated into guidelines for people with asplenia and splenic dysfunction, which currently recommend vaccination against IMD in addition to pneumococcal and Hib vaccination.

Implications of all the available evidence

Unlike asplenia and splenic dysfunction, there is no evidence of any increased risk of IMD in people with SCD. Policymakers need to consider whether people with SCD require additional vaccination against IMD, especially given that people with SCD are already recommended daily antibiotic prophylaxis during early childhood, when this risk of IMD is highest.

Introduction

Sickle cell disease (SCD) refers to a group of inherited disorders of haemoglobin synthesis, composed mainly of sickle cell anaemia due to the homozygous haemoglobin (Hb) S state (HbSS), as well as compound heterozygous states for HbS and other hemoglobinopathies, such as HbC (HbSC) and beta-thalassemia ($HbS\beta^{thal}$).[1,2] The gene for HbS occurs most commonly in persons of African ancestry and, therefore, the greatest burden of SCD occurs disproportionately in sub-Saharan Africa.[3]

The association between sickle cell disease (SCD) and increased susceptibility to serious infections is well-described.[1,4–6] People with SCD are more likely to develop severe, recurrent and fulminant sepsis, particularly with encapsulated bacteria, with the highest risk in the first five years of life.[1] Encapsulated bacteria that typically cause invasive bacterial infections such as meningitis and septicaemia in young children include *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis*.[7] This increased risk is attributed to the development of functional asplenia resulting from repeated sickling episodes in the spleen, leading to splenic infarction and atrophy, usually in early childhood.[8] The spleen has a key role in opsonisation of encapsulated bacteria which allows phagocytosis by macrophages. Opsonisation can occur via antibody coating, which occurs in the spleen, or via the complement cascade whereby the bacteria are coated with complement factor C3b. The spleen also generates tuftsin[1] (a tetrapeptide located in the Fc-domain of the heavy chain of immunoglobulin G which is released by enzymatic cleavage by an endocarboxypeptidase in the spleen), which stimulates phagocytosis by macrophages.[9]

Prior to the licensure of effective vaccines and recommendations for daily antibiotic prophylaxis, children with SCD were 600 times more likely to develop pneumococcal meningitis[4] and 116 times more likely to develop Hib meningitis than children without SCD from the same community.[10] In a longitudinal follow-up study of 422 patients with SCD in the United States, 10% developed one or more serious bacterial infections during the first five years of life, with half the infection-related deaths occurring in this age group.[11]

Preventive strategies have, therefore, focussed on long-term antibiotic prophylaxis and vaccination against the main pathogens responsible for serious infections in patients with SCD.[12] The implementation of the Hib conjugate vaccine into national childhood immunisation programmes since the early 1990s led to large and sustained declines in the incidence of invasive Hib disease in all populations, including in persons with SCD.[13,14] Similarly, pneumococcal conjugate vaccines (PCVs) have significantly reduced the risk of invasive pneumococcal disease due to the respective vaccine serotypes.[15] There are, however, at least 100 different pneumococcal serotypes and, since PCVs only protect against some pneumococcal serotypes, patients with SCD are recommended daily antibiotic prophylaxis at least in the first five years of life, which has significantly reduced their risk of pneumococcal disease and infection-related mortality.[16,17]

Although *N. meningitidis* is also an encapsulated bacterium, unlike Hib and *S. pneumoniae*, there are very limited data published on the risk of invasive meningococcal disease (IMD) in people with SCD, despite multiple national and international guidelines recommending immunisation against IMD for persons with SCD, often with relatively expensive vaccines[12,18] (Table 1). This is particularly notable given that there are no published studies reporting any increased risk of IMD in persons with SCD in the sub-Saharan African meningitis belt, which has the highest population of persons with SCD and regularly experience large IMD epidemics. In the UK, too, enhanced national surveillance of IMD, which has been in place for more than three decades, did not identify SCD as a risk factor among patients with confirmed IMD.[19]

We, therefore, conducted a systematic review of the literature to identify studies reporting the incidence and risk of meningococcal disease in people with SCD globally.

Methods

This systematic review was conducting according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) recommendations using a Population, Intervention, Comparison, Outcome (PICO) methodology [24] (Fig. 1).

Eligibility criteria

Participants

Participants with any type of Sickle Cell Disease were included (HbSS, HbSC, HbSD, $HbSO_{ARAB}$, HbS/β^0-thalassaemia, HbS/β^+-thalassaemia etc.). Patients of all ages, from all geographical locations and sexes, were included. Studies including only Sickle Cell Trait were not included.

Table 1
Recommendations for the use of meningococcal vaccines in people with Sickle Cell Disease.

Organisation	Source	Country	Year	Recommendation	Notes
Centers for Disease Control[18]	Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020	USA	2020	MenACWY vaccination recommended from 2 months of age, MenB vaccination recommended from 10 years of age	MenB vaccines first licensed in USA 2015, MenACWY vaccine first licensed 2005
Australian Government Department of Health and Aged Care[20]	Australian Immunisation Handbook	Australia	2022	MenB and MenACWY vaccination recommended to all over 2 months of age	MenB can be given from 6 weeks
UK Health Security Agency[21]	The Green book of immunisation: chapter 7 – Immunisation of Individuals with underlying medical conditions	UK	2020	MenB and MenACWY vaccination recommended to all over 2 months of age	Age-dependent schedules
Sickle Cell Society[12]	Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK	UK	2018	Men B and MenACWY vaccination recommended to all adults	
Federal Ministry of Health[22]	National Guideline for the Control and Management of Sickle Cell Disease	Nigeria	2014	No national meningococcal vaccine recommendations	PCV13 and PPSV23 recommended
WHO	Vaccine Schedule for Jamaica	Jamaica		No meningococcal vaccine recommendations	PCV13 recommended at 6, 10 and 14 weeks of age plus booster at 15 months. PPSV23 recommended at 4 years.
The United Republic of Tanzania National Audit Office[23]	Performance audit report on the management of immunization and Vaccination Project activities	Tanzania	2020	No meningococcal vaccine recommendations	No specific recommendations for SCD

Fig. 1. PICO diagram.

Interventions

Studies were included if they documented bacterial culture and/or bacterial PCR results for patients with SCD presenting with undifferentiated fever and/or symptoms/signs of infection. Studies that specifically only reported non-Neisserial infections, such as pneumococcal disease only, and studies focussing on non-invasive infections, such as bacterial colonisation only, were excluded.

Comparisons

Studies that included a control group of patients without SCD were included in the primary analysis and also formed part of a separate analysis.

Outcome measures

The primary outcome measure was to estimate the risk of IMD in people with SCD who presented with undifferentiated fever and/or symptoms/signs of infection. Secondary outcome measures were to estimate the risk of invasive pneumococcal disease (IPD) and invasive Hib disease in people with SCD who presented with undifferentiated fever and/or symptoms/signs of infection.

Search strategy

The databases PubMED, MEDLINE, EMBASE and Web of Science were searched on (31/05/2024) using the following search terms: Mening* AND sickle, Mening* AND haemoglobinopathy, Sickle AND bacteraemia, Sickle AND infection. No limitation was placed on year of publication or language. Articles of any age which met criteria for inclusion were considered. Snowball searching was performed by reviewing the reference lists of included papers for additional relevant publications.

Study design

Randomised controlled trials, surveillance studies, observational studies including case-series, case-reports, cohort studies, case-

control studies, retrospective studies and cross-sectional studies were included. Non-human studies, in vitro studies, opinion pieces and conference proceedings were excluded. Review articles were searched for relevant original study references.

Data collection and analysis

Titles and abstracts were reviewed by two reviewers (Catherine Isitt and Shamez Ladhani). The full texts of any publication that appeared to meet the criteria for inclusion were obtained and reviewed before a decision on inclusion was reached. Data were extracted from each included study using a structured data extraction form. Extracted data included study details (year of study, geographical location, place of publication), intervention details (patient age, criteria for inclusion in the study, type of microbiological sampling), comparison details (use of a control group or not) and outcome details (identification of IMD cases, identification of IPD or Hib cases).

Assessment of risk of bias

All publications that reported patients with SCD and microbiological diagnostics were included in order to fulfil the main objective of the study, which was to find IMD cases in people with SCD. Care was taken not to include studies that reported the same data as had already been reported in another included study. One study was excluded on this basis.

Data management

Results from the literature searches were imported into EndNote software and de-duplicated. Titles and abstracts were screened for potentially eligible studies and then full texts of the publications were obtained. Excel was used for recording information from included studies using a standardised form.

Results

The search identified 3804 records, of which 1756 were duplicates. Therefore, 2048 unique titles were put forward for screening, of which 1708 were excluded after title screening because they did not meet the inclusion criteria, while 191 were excluded after the full abstract was reviewed. Thus, 144 titles were identified for full text review. Of these, five publications were unavailable for full text review, a further 58 were excluded after full text review and 86 were identified for inclusion (Fig. 2).

Cohort studies

There were 74 cohort studies published during 1971–2023 that included patients with SCD who were either investigated for or who had confirmed infections (Table 4). Of these, 30 were from the USA, 14 from the African continent and 8 from the Middle East (most from Saudi Arabia) (Fig. 3). Most studies were either prospective or retrospective studies that included patients with SCD who presented to healthcare with fever or acute illness over a set time-period. Infectious aetiologies were then identified by reviewing microbiological

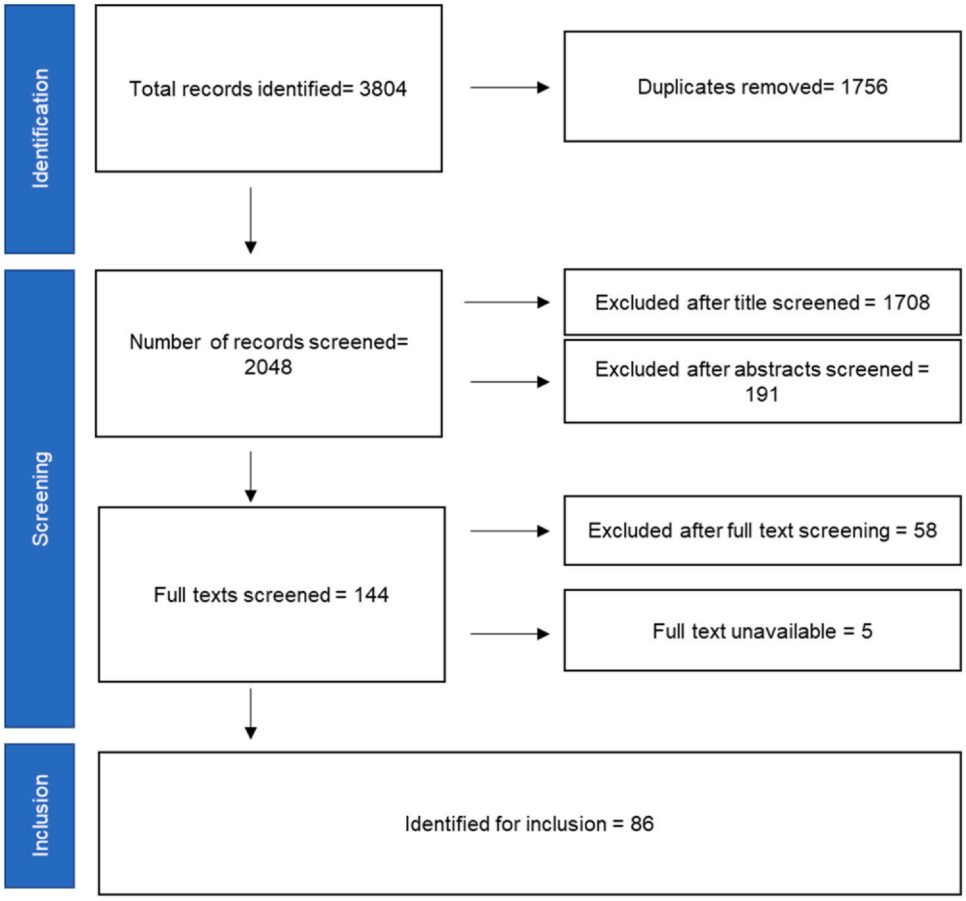

Fig. 2. PRISMA diagram of systematic review study inclusion.

Table 2
Case reports included.

Study	Year of publication	Study period	Country	Description of study	N. meningitidis identified?
Al Ansari et al.[40]	2007	2007	Bahrain	Case report, patient with SCD presenting with Sepsis	No, Staph aureus causative agent
Angelini et al.[41]	1997	1989–1995	France	Case series of pneumonia caused by Neisseria meningitidis, one case in a patient with SCD	Yes, in one patient with SCD
Chenou et al.[42]	2020	1999–2011	Brazil	Case series, reports of cases of bacterial meningitis in 10 patients with SCD	No, 5 cases *Streptococcus pneumoniae* identified and one case with Hib

culture/PCR results. Ten studies followed-up a pre-defined cohort of

Case reports

Table 3
Description of the five cases of IMD identified in the included studies.

Study	Study period	Description of patient
Angelini et al.[41]	1989–1995	Isolated in pulmonary tract excretions and blood from a patient with clinical diagnosis of pneumonia. 23-year-old Male, meningococcal serogroup C. Patient described as having heterozygotic Sickle Cell Anaemia, unclear if this means HbSC or Sickle cell trait. Patient recovered.
Abu-Srair et al.[43]	1989	One case of meningococcal meningitis in a child < 18 years. Patient recovered.
Akuse et al.[44]	1987	Neisseria meningitidis isolated from CSF from a child. Patient recovered. Discussion states that meningococcal vaccination common in the study area.
Barrett-Connor et al.[10]	1958–1968	One case of meningococcal meningitis in 3-year-old girl, *N. meningitidis* isolated from CSF and blood. The child had previously had both episodes with pneumococcal pneumonia and pneumococcal meningitis. Patient recovered.
Overturf et al.[45]	1965–1975	One case of meningococcal meningitis in a child aged between 5–9 years, unclear whether isolated from blood or CSF or both. Patient recovered.

patients with SCD over a specified time-period and then identified episodes of infection in the cohort.[25–34] Five studies analysed the causes of death in a cohort of patients with SCD, including death from infectious aetiologies.[35–39] Across all 74 cohort studies, there were only three cases of IMD identified among 26,404 included persons with SCD. This compared with 570 cases of IPD and 113 cases of Hib (Table 4).

Case-control studies

Eight case-control studies published during 1983–2022 were identified for inclusion (Table 5). These were predominantly studies conducted in Africa (three from Nigeria, one from Angola and one from Kenya) with two other studies from the USA and one from Saudi Arabia. A total of 932 people with SCD were included and compared to 7143 people without SCD. Across the eight studies, there was one IMD case identified among 932 people with SCD (0.1%) compared to 118 IMD cases among 7143 people without SCD (1.65%) in the control group. This case was identified in Saudi Arabia in a study published in 1989 in a child < 18 years of age[43] (Table 3). In contrast, there were 126 IPD cases (126/932, 13.5%) identified in people with SCD compared to 588 (588/7143, 8.2%) in those without SCD. For Hib, the numbers were 32/932 (3.4%) and 316/7143 (4.4%), respectively. One of the largest case-control studies included all children aged < 14 years admitted from a defined area of Kenya to a single hospital over a 10-year period.[101] Those with significant positive blood cultures were defined as cases in their study. A control group of children from the same geographic area who did not have an infection was included. All cases and controls were retrospectively tested for SCD. Of those with positive blood cultures (the cases), 108/1749 tested had a diagnosis of SCD. For the purposes of this systematic review, we compared the pathogens identified in those with positive cultures in children with and without SCD (Table 5). In the largest case-control study conducted in 1989 by Abu-Srair and colleagues [43] in Saudi Arabia, 450 patients with SCD admitted to a paediatric ward were compared with 3700 patients without SCD admitted to the same ward during the same time period. The incidence of serious infection was higher in the SCD group (8.6%) compared to the group without SCD (1%). In this study, one case each of meningococcal meningitis was identified in the SCD group and in the control group.

Two case series and one case report considered the diagnosis of IMD in people with SCD (Table 2). A case series by Angelini et al.[41] included fifteen patients with meningococcal pneumonia in France between 1989–1995. One case in this series was a 23 year-old man with SCD who presented with symptoms and signs of pneumonia, and *N. meningitidis* serogroup C was subsequently isolated in blood and bronchial fluid cultures. Classic symptoms of meningococcal septicaemia were not described.

In another case series of bacterial meningitis diagnosed between 1999–2011 in 10 patients with SCD in Brazil, none were due to *N. meningitidis.* Five were due to *S. pneumoniae* and one due to Hib.[42] Finally, a single case report from Bahrain, published in 2007, describes a patient with SCD presenting with signs and symptoms of meningococcal septicaemia but blood cultures identified *Staphylococcus aureus* as the causative agent.

Systematic reviews and meta-analysis

One systematic review and meta-analysis was identified.[2] The systematic review was conducted in 2010 and aimed to estimate the risk of pneumococcal infections, bacteraemia or meningitis in children with SCD in Africa. Seven studies were included in the final analysis and the authors estimated a 35-fold increased risk of IPD and a 13-fold increased risk of Hib compared to children without SCD. No cases of IMD were reported in this analysis.

IMD in people with SCD

In total, after assessment of all published studies so far, we identified only five IMD cases in people with SCD in studies published worldwide (Table 3). The reported IMD cases spanned across 1965–1995, with no IMD case reported in a person with SCD since 1995. The ages of the patients ranged from 3–23 years and all five survived their infection.

Discussion

We undertook a comprehensive and systematic review of the literature to identify all published data across all continents, time-periods and languages to assess whether people with SCD had an increased risk of meningococcal disease. We assessed 2048 potential

Table 4
Cohort studies included.

Study	Year of publication	Study period	Geographic location	Inclusion criteria	Patients with SCD included (N)	Confirmed *N. meningitidis*	Confirmed Streptococcus pneumoniae	Confirmed HiB
Akuse et al.[44]	1996	1987	Nigeria	Child with SCD 3m–15 years, acutely unwell	304	1	6	1
Al Saif et al.[46]	2021	2005–2015	Saudi Arabia	Child < 14 years with SCD presenting with fever	320	0	0	0
Al Salman et al.[47]	2014	2012	Bahrain	Admitted patients with SCD who also had fever	59	0	0	0
Al Tawfiq et al.[48]	2021	2000–2017	Saudia Arabia	All ages, people with SCD presenting to ED with fever and who had blood cultures taken	124	0	5	0
Alima Yanda et al.[49]	2017	2012–2015	Cameroon	Children < 15 years hospitalised due to suspected invasive infection	987	0	2	0
Almahmoud et al.[50]	2023	2017–2019	Saudi Arabia	Child with SCD < 14 years, acutely unwell	212	0	0	0
Alzomor et al.[51]	2022	2014–2019	Saudi Arabia	Children < 12 years with SCD presenting with fever	833	0	5	0
Bansil et al.[52]	2013	2000–2009	USA	Children < 18 with SCD presenting to ED with fever	188	0	0	0
Barrett Connor et al.[10]	1971	1958–1968	USA	Children and adults with SCD presenting acutely unwell	166	1	21	4
Baskin et al.[53]	2013	1993–2010	USA	Children and young people < 21 years with SCD presenting to ED with fever and who had blood cultures taken	627	0	2	0
Brown et al.[54]	2017	2013–2014	Nigeria	Children < 17 years with SCD presenting with fever and who had blood cultures taken	116	0	1	0
Brozovic et al.[55]	1987	1985–86	UK	All ages, acute admissions of people with SCD	63	0	0	1
Buchanan et al.[25]	1983		USA	Episodes of severe infection in a cohort of 51 patients with Sickle Cell Disease	51	0	5	2
Chang et al.[56]	2013	1993–2009	USA	Children and young people ages < 21 years with SCD presenting with fever	466	0	8	0
Chulamokha et al.[57]	2006	1999–2003	USA	Adults > 18 years with SCD presenting with fever	193	0	1	0
Elenga et al.[58]	2018		French Guyana	Children aged 4–8 years with SCD and fever	46	0	0	2
Ellison et al.[26]	2013	2000–2010	USA	All patients < 22years at a single centre. All medical records reviewed to identify cases of blood stream infection.	815	0	12	0
Esimai et al.[59]	1995	1994	Nigeria	Unwell child with anaemia. SCD tested for.	46	0	4	0
Gaschignard et al.[60]	2023	2014–2019	Western Europe	Children aged 1 month–18 years with SCD and documented invasive bacterial infection	169	0	31	6
Gbadoe et al.[61]	2023	2014–2019	Togo	Children < 15 years with SCD hospitalised with a confirmed bacterial infection	265	0	4	0
Gill et al.[28]	1995	1978–1988	USA	Children < 10 years from a cohort with SCD presenting with an acute event	694	0	74	14
Gomez-Chiari et al.[29]	2003	1985–2001	Spain	Children aged 8m–13 years. Cohort of 22 people newly diagnosed with SCD, presenting complaints recorded.	22	0	0	0
Halwani[62]	2023	2015–2018	Saudi Arabia	Children < 14 years with SCD presenting to ED with documented fever	304	0	0	0
Ibrahim et al.[63]	2021	2015–2017	Nigeria	Children aged 6 months to 15 years with SCD presenting with signs and symptoms of infection	242	0	0	0
Khalife et al.[64]	2021	2002–2015	Lebanon	All ages, people with SCD presenting to ED with fever	158	0	0	0
Kizito et al.[65]	2007	2001–2002	Uganda	Children < 15 years with SCD presenting with fever	155	0	3	9
Koko et al.[35]	1998	1990–1992	Gabon	Children < 18 years with SCD who died, investigation of causes of death	23	0	1	1
Koko et al.[66]	1999	1994–1995	Gabon	Children < 16 years with SCD presenting with fever	32	0	2	1
Kondani et al.[67]	2014	2009–2011	Democratic Republic of Congo	Children < 5 years with SCD, hospitalised with severe infection	19	0	0	1
Kravis et al.[68]	1982	1979–1980	USA	Children aged 3 months–19 years with SCD presenting to ED 153	153	0	4	0
Lalhmunsangi et al.[69]	2022	2013–2015	India	Children < 12 with SCD, admitted to paediatric wards with fever	412	0	3	0
Leikin et al.[39]	1989	1979–1988	USA	Children and adolescents < 20 years, causes of death from a cohort of patients with SCD	2824	0	24	3

(*continued on next page*)

Table 4 (*continued*)

Study	Year of publication	Study period	Geographic location	Inclusion criteria	Patients with SCD included (N)	Confirmed *N. meningitidis*	Confirmed Streptococcus pneumoniae	Confirmed HiB
Lobel et al.[30]	1982	1972–1980	USA	Children and adolescents < 21 years, medical notes review of a cohort of patients over 9 years to identify cases of septicaemia and bacterial meningitis	210	0	16	2
Macharia et al.[70]	2018	2000–2004	Kenya	Children aged < 13 years with SCD, acute admission to hospital	576	0	19	7
Makani et al.[71]	2015	2006–2008	Tanzania	All ages, people with SCD admitted acutely to hospital	648	0	3	0
Mallouh et al.[72]	1985	1977–1985	Saudi Arabia	Children and adolescents < 20 years, review of all SCD patients with discharge diagnosis of meningitis, septicaemia or osteomyelitis	40	0	3	0
McIntosh et al.[73]	1980	1972–1978	USA	Children < 5 years with SCD presenting with fever	22	0	4	2
Morrissey et al.[74]	2015	2010	UK	Children < 16 years with SCD, hospitalised with suspected BSI	59	0	1	0
Murtaza et al.[75]	1981	1960–1979	UK	Children aged 1 month −17 years with SCD attending hospital with a complication	171	0	8	2
Narang et al.[76]	2012	1997–2006	USA	Children < 18 years with SCD presenting with fever	120	0	2	0
Neonato et al.[77]	2000	1987–1997	France	All ages, cohort of 299 people with SCD, review of acute events including infections	299	0	9	0
Norris et al.[78]	2003	1993–2001	USA	Children and adolescents < 21 years with SCD who had positive blood cultures	105	0	23	1
Overturf et al.[45]	1977	1965–1975	USA	All ages, cohort of 422 people with SCD all episodes of septicaemia or bacterial meningitis recorded	422	1	32	5
Ozgonenel et al.[79]	2014	2010	USA	Children < 18 years presenting with fever with blood cultures taken	242	0	1	0
Patel et al.[80]	2013	2006–2012	USA	Children < 18 years with SCD hospitalised with fever	133	0	2	0
Pegelow et al.[81]	1989	1984–1987	USA	Children < 5 years in a cohort with SCD with bacteraemia	117	0	10	6
Rahimy et al.[82]	1999	1995–1996	Benin	Children < 18 years with SCD presenting to clinic with fever, seriously ill children excluded	61	0	0	0
Rao et al.[83]	1987	1980–1985	USA	Adults with SCD admitted to hospital with infection	283	0	0	0
Rincon-Lopez et al.[84]	2019	2004–2015	Spain	Children < 18 years with SCD with fever	77	0	0	0
Rogers et al.[85]	1995	1978–1994	USA	Children and adolescents < 21 years in a cohort with SCD with positive blood or CSF culture	242	0	11	2
Rogovik et al.[86]	2010	2005–2006	Canada	Children < 18 years with SCD who attended ED	180	0	0	0
Saqqaf et al.[87]	2023	2019–2021	India	Children < 18 years with SCD presenting with fever	70	0	1	0
Savlov et al.[88]	2014	1990–2007	Canada	Children < 18 years with SCD presenting with fever	160	0	17	2
Serjeant et al.[38]	2018	1973–2016	Jamaica	All ages, cohort of 311 patients with SCD, examination of causes of death including deaths from infections	311	0	7	3
Shihabuddin et al.[89]	2014	2001–2011	USA	Children and adolescents < 20 years with SCD hospitalised with suspected blood stream infection	307	0	1	0
Sirigaddi et al.[90]	2018	1999–2016	USA	Children < 18 years with SCD presenting with fever	155	0	6	0
Sokol et al.[91]	2016	2011–2013	USA	Children < 18 years with SCD who presented to ED with fever who were managed as outpatients	154	0	1	0
Soothill et al.[14]	2016	2010–2015	Gambia	Children < 15 years with SCD hospitalised with fever	126	0	1	0
Tarer et al.[31]	2006	1980–1999	Guadeloupe	Children and adolescents < 19 years in a cohort of children with SCD attending ED with complication	153	0	2	0
Telfer et al.[92]	2007	1983–2005	UK	Cohort of children identified by new-born screening and followed until aged 24 years	252	0	5	0
Teoh et al.[93]	2013	1999–2009	Australia	Children < 18 years with SCD requiring hospitalisation	37	0	0	0
Thomas et al.[37]	1996	1985–1992	France	Children < 19 years, review of causes of death of children with SCD	26	0	8	2
Thomas et al.[36]	1982	1952–1982	Jamaica	All ages, review of causes of death in patients with SCD	276	0	19	2
Thornburg et al.[32]	2011	2003–2009	USA	Children aged 9–42 months enrolled in an RCT of hydroxyurea treatment presenting with fever during study follow-up	193	0	3	0

(*continued on next page*)

Table 4 (*continued*)

Study	Year of publication	Study period	Geographic location	Inclusion criteria	Patients with SCD included (N)	Confirmed *N. meningitidis*	Confirmed Streptococcus pneumoniae	Confirmed HiB
Vichinsky et al.[94]	2000	1993–1997	USA	All ages, people with SCD admitted with suspected chest syndrome, blood cultures taken	538	0	11	5
Wall et al.[95]	2018	2015–2017	UK	Children < 18 years with SCD, review of episodes of severe sepsis in a cohort of 388	388	0	3	0
West et al.[96]	1994	1990–1992	USA	Children < 18 years with SCD presenting with fever	199	0	3	0
West et al.[97]	2002	1989–1999	USA	Children < 18 years with SCD, cohort of 128 patients reviewed for fever episodes	128	0	3	1
Wieranga et al.[98]	2001	1993–1996	Jamaica	Children < 17 years with SCD presenting with fever	144	0	3	2
Williams et al.[99]	1996	1992–1993	USA	Children 6 months–14 years with SCD presenting with fever without signs of severe sepsis requiring admission	80	0	1	0
Workman et al.[33]	1994	1976–1991	UK	All ages, cohort of patients with SCD, review of all blood cultures taken in cohort	620	0	3	1
Yee et al.[100]	2022	2010–2019	USA	Children < 18 years, review of all blood cultures taken from children with SCD	2641	0	25	11
Zarkowsky et al.[27]	1986	1979-	USA	All ages, people with SCD presenting with fever from a cohort of 3451 people with SCD	3451	0	79	12
Zarrouk et al.[34]	2006	1997–2002	France	Adults aged > 18 years in a cohort of 900 people with SCD, all cases of bacteraemia identified and reviewed	900	0	6	0
Totals					26404	3	570	113

studies and finally included 86 studies in the analysis, including 74 cohort studies, 8 case-control studies, 2 case series, 1 case report and a systematic review and meta-analysis. Overall, we assessed the risk of IMD in 26,404 people with SCD in cohort studies and 932 people with SCD in case-control studies, with some studies allowing for comparison of IMD risk in people without SCD in the same geographical regions and over the same time-period. Despite an extensive review of the literature, we only identified five IMD cases in people with SCD in the global literature. In contrast, we identified multiple reports of IPD and Hib disease in people with SCD along with studies demonstrating a significantly higher risk of these two infections in people with SCD compared to those without SCD.

Our findings indicate that people with SCD do not have an increased risk of IMD, however do appear to have an increased risk of both pneumococcal and Hib disease, this is especially true for young children. This increased risk has been attributed to loss of splenic function that develops as a result of splenic infarction - this has been considered the basis for increased risk for serious infections caused by encapsulated bacteria,[1] of which Hib, *S. pneumoniae* and *N. meningitidis* are the major but not exclusive pathogens.[21] People with asplenia also have an increased risk of infection with some Gram-negative organisms such as non-typhoidal *Salmonella*, which is also encapsulated, and *Capnocytophagia* spp.[108,109]

Multiple epidemiological studies have reported an increased risk of IPD of up to 600-fold in people with SCD compared to people without SCD[4] as well as in increased risk of Hib disease with reported incidence ranging from 5.4–12.4/1000 person-years[5,28] in the absence of vaccination and antibiotic prophylaxis.[4] In contrast, we did not identify any study reporting an increased risk of IMD in people with SCD. Indeed, the data to support an increased risk of IMD in people with SCD appears to have been extrapolated from studies of post-splenectomy patients, where there does appear to be an increased risk of IMD, with 2.3% of post-splenectomy infections caused by *N. meningitidis* in one study,[108] and associated with high case-fatality rates of up to 58.8%.[110] The highest risk for infection post-splenectomy appears to be in the first 5 years.[108,110]

Consequently, guidelines for the prevention of serious bacterial infections in people with asplenia or splenic dysfunction specifically target strategies for protection against these three main encapsulated bacteria. These strategies primarily include vaccination and, since the current vaccines do not protect against all strains, daily antibiotic prophylaxis at least until the age of 5 years.[111]

The development and licensure of Hib and pneumococcal polysaccharide vaccines in the 1980s was a major step toward preventing serious infections in those at highest risk, including people with SCD. These polysaccharide vaccines, which were soon found to be ineffective in infants and young children whose immune systems recognise bacterial polysaccharide poorly, were soon replaced by highly effective conjugate vaccines which not only protected vaccinated children against invasive disease but, by preventing carriage acquisition, also reduced onward transmission to other, unvaccinated children and adults. Consequently, Hib disease is now rare in most countries with an established national childhood immunisation programme, including in people with SCD.[111] While asplenia guidelines in many countries continue to recommend additional Hib conjugate vaccination for people with asplenia or splenic dysfunction including SCD, the UK no longer recommends additional Hib vaccination because the risk is very low and there are no monovalent Hib conjugate vaccines available in the UK.[112]Of note, however, a number of European countries with established Hib conjugate vaccine programmes have recently reported an increase in invasive Hib disease cases recently – this will require close monitoring in the coming years.[113]

Unlike Hib, the prevention of IPD has been more challenging. The licensure and implementation of PCVs against the main pneumococcal serotypes responsible for IPD has resulted in large and

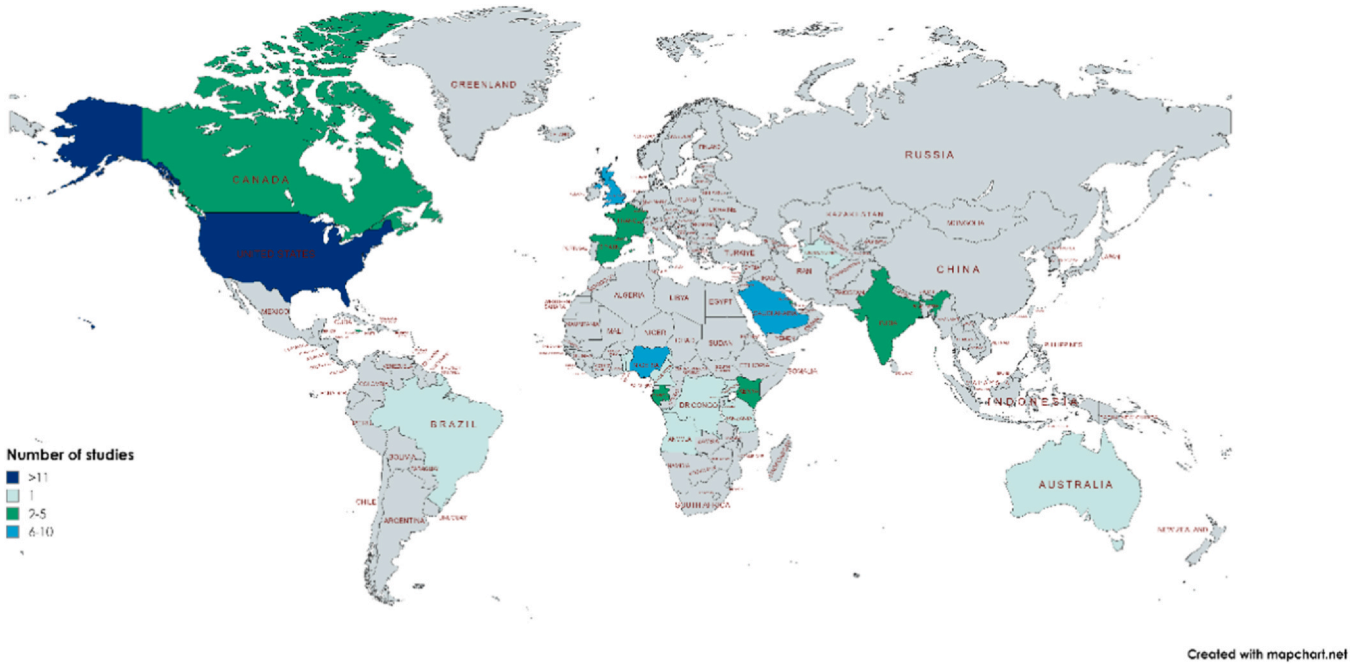

Fig. 3. Map of countries that studies were included from. Created with mapchart.net.

sustained decline in IPD caused by the vaccine serotypes but given that there are at least 100 different serotypes identified so far, the current licensed pneumococcal vaccines aim to protect against only 23 of the serotypes and do not offer any protection against the remaining serotypes that can cause invasive disease. Consequently, daily antibiotic prophylaxis is recommended for additional protection, at least until the age of five years. Antibiotic prophylaxis would also help protect against IMD because, until recently, there were no vaccines against serogroup B (MenB) IMD, which is responsible for the majority of IMD cases in Europe and some other parts of the world. There are currently 12 distinct meningococcal serogroups identified through their unique capsular polysaccharide, of which six (A, B, C, W, X, Y) are responsible for the majority of IMD worldwide.[114] Highly effective conjugate vaccines are available against serogroups A, C, W and Y, and a newly licensed meningococcal pentavalent conjugate also includes protection against serogroup X in addition to A, C, W and Y for use in the African Meningitis Belt.[115]

Conjugate vaccines against MenB have been challenging to develop because the structure of the MenB capsular polysaccharide is similar to human nerve cells, making it poorly immunogenic and raising concerns about potential development of autoantibodies.[116] In the past decade, however, two recombinant protein-based MenB vaccines have been licensed in 2013 and 2017,[117] respectively. The first vaccine, 4CMenB (Bexsero®, GSK Biologicals) has been implemented in several national immunisation programmes and has been shown to be highly effective in preventing most but not all MenB cases in vaccinated individuals. In the UK for example, MenB cases declined by 75% in vaccine-eligible children during the first 3 years of the infant immunisation programme which began in 2015.[118] Breakthrough MenB cases can, however, occur in vaccinated individuals because not all MenB strains possess and/or express the surface protein antigens including in 4CMenB.[119] This is important for at-risk persons, including those with asplenia or splenic dysfunction, because it highlights the important of daily antibiotic prophylaxis for protection in addition to vaccination.

Table 1 summarises national guidelines that recommend meningococcal vaccination for high-risk individuals, including people with asplenia and more specifically with SCD. We noted that most of the studies used to develop the recommendations pre-dated the widespread use of meningococcal vaccination, both for people with SCD and the in general population. Interestingly, whilst the UK, USA and Australia recommend meningococcal vaccination for people with SCD, Nigeria for example, which lies within the African meningitis belt, an area known for seasonal IMD epidemics, does not recommend meningococcal vaccines for people with SCD (Table 1).

Whilst it is always difficult to confirm a negative association, our extensive literature review covered all continents and all time periods, including historical studies before meningococcal vaccines were licensed and before routine use of daily antibiotic prophylaxis. In addition, we identified multiple case-control studies across different geographies and time-periods that continue to report an increased risk of IPD and Hib, but not IMD in people with SCD compared to those without SCD. This is an important observation because it demonstrates that the methodology of the published studies was sufficiently robust to identify the increased IPD risk but did not find increased risk for IMD.

Of the published studies, the Kenyan case-control study provided the most robust findings.[101] The study included all children presenting to the hospital with a positive blood culture between 1998–2008 in rural Kenya and, for each case, recruited a matched control without infection from the same area as the case. The strength of this study lies in the retrospective testing of the children for SCD. By reanalysing the published data, we found no IMD cases in children with SCD compared to 10 cases in the control group without SCD. Importantly, an excess of IPD and Hib were found in the children with SCD compared to the control group.

The observed discrepancy in IPD and Hib compared to IMD cannot be explained by, for example, use of daily antibiotic prophylaxis in people with SCD. Another explanation for the discrepancy may be that people with SCD were protected against IMD through vaccination. This, too, is unlikely because most of the case-control studies took place before meningococcal vaccines were licensed, especially in African countries where meningococcal vaccines were not used until the introduction of a conjugate MenA vaccine (MenAfriVac) in 2010.[120] In high-income countries such as the UK, too, the uptake of additional vaccines by people with SCD is also known to be low[121] and, in one study performed at our own hospital in London, < 1% adults with SCD had received two doses of

Table 5
Case-Control studies included.

Study	Year of publication	Study period	Country	People with SCD included (n)	Confirmed meningococcal infection SCD	Confirmed pneumococcal infection SCD	Confirmed Hib infection SCD	Number of controls	Confirmed meningococcal infection controls	Confirmed pneumococcal infection controls	Confirmed HiB infection controls
Abu-Srair et al.[43]	1991	1989	Saudi Arabia	450	1	9	2	3700	1	4	7
Bello[102]	2018	-	Nigeria	68	0	10	2	73	0	1	2
Fraser[103]	1973	1961–1971	USA	10	0	5	2	250	61	54	104
Obaro[104]	2011	2008–2009	Nigeria	59	0	3	0	910	0	5	2
Okuonghae[105]	1992	1987	Nigeria	162	0	1	0	150	2	2	2
Pelkonen[106]	2022	2005–2008 and 2012 to 2017	Angola	57	0	34	12	395	43	94	80
Rao[107]	1983	1976–1978	USA	18	0	20	1	24	1	3	19
Williams[101]	2009	1998–2008	Kenya	108	0	44	13	1641	10	425	100
Totals				932	1	126	32	7143	118	588	316

4CMenB which is the recommended according to national guidelines (unpublished data).

Taken together, our findings indicate that IMD is very rare in people with SCD. This finding is likely to be genuine as the results were consistent across different types of studies in different parts of the world and during different time periods. Furthermore, given the high prevalence of both SCD and IMD in the same regions the African Meningitis Belt, the lack of association between SCD and IMD raises the question as to whether SCD might in fact be protective against IMD. Why people with asplenia but not those with SCD have an increased risk of IMD is unclear, especially given that both groups have an increased risk of IPD and Hib disease. This needs further investigation.

Our findings have important immunisation policy implications. The lack of an increased IMD risk in people with SCD would indicate that they do not require additional meningococcal vaccination compared to the rest of the population. In countries such as the UK, where an established adolescent MenACWY conjugate vaccine programmes continues to provide excellent direct and indirect protection against serogroups A, C, W and Y such that IMD due to these serogroups are extremely rare across all age groups and risk groups. Additionally, many countries now also include MenB vaccination in their national childhood immunisation programmes which will also include children with SCD. Whilst Hib disease remains rare in most countries with established national Hib immunisation programmes, including the UK, the risk of IPD remains very high. Consequently, people with SCD should continue to receive additional pneumococcal vaccination as recommended for people with asplenia.[21] Given that IPD in countries with established PCV programmes is now mostly due to non-vaccine pneumococcal serotypes, daily antibiotic prophylaxis would also be recommended. Antibiotic prophylaxis would also provide additional protection against IMD due to all meningococcal serogroups in people with SCD.

The strengths of our study are that we used all published data with very few limitations in terms of geography, date of publication or language. We also included studies from the early published literature, which were less likely to be affected by more recent recommendations of antibiotic prophylaxis and vaccinations against the main pathogens responsible for serious infections in SCD. Limitations include the lack of randomised controlled trials and the small number of published studies in this field, many of them from LMIC settings with limited access to healthcare, vaccinations and diagnostics. Most studies also had limited data on pre-hospital care and, therefore, their findings would be influenced by antibiotic use prior to hospital or clinic attendance, which would result in negative bacterial cultures.

Conclusions

We found no evidence of any increased risk of IMD in people with SCD, despite an extensive review of the global literature, however similarly to asplenia and splenic dysfunction, we found that people with SCD had an increased risk of IPD and Hib disease. This has important implications for policymakers in countries and organisations that currently recommend meningococcal vaccination for people with SCD.

Funding

None.

Declaration of Competing Interest

CI has previously received an educational grant from Pfizer. RB performs contract research on behalf of UKHSA for GlaxoSmithKline

(GSK), Pfizer and Sanofi. PTH and CAC coordinate vaccinology research on behalf of St George's University of London, which is funded by vaccine manufacturers (Pfizer, Novavax, Moderna, Valneva, Janssen). PTH is a member of the UK Joint Committee on Vaccination and Immunization. SNL performs contract research on behalf of St George's University of London and the UKHSA for pharmaceutical companies but receives no personal remuneration.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2025.106441.

References

1. Booth C, Inusa B, Obaro SK. *Infection in sickle cell disease: a review. Int J Infect Dis* 2010;**14**(1):2–12.
2. Ramakrishnan M, Moïsi JC, Klugman KP, Iglesias JM, Grant LR, Mpoudi-Etame M, et al. *Increased risk of invasive bacterial infections in African people with sickle-cell disease: a systematic review and meta-analysis. Lancet Infect Dis* 2010;**10**(5):329–37.
3. Hickman M, Modell B, Greengross P, Chapman C, Layton M, Falconer S, et al. *Mapping the prevalence of sickle cell and beta thalassaemia in England: estimating and validating ethnic-specific rates. Br J Haematol* 1999;**104**(4):860–7.
4. Oligbu G, Collins S, Sheppard C, Fry N, Dick M, Streetly A, et al. *Risk of invasive pneumococcal disease in children with sickle cell disease in England: a National Observational Cohort Study, 2010-2015. Arch Dis Child* 2018;**103**(7):643–7.
5. Powars D, Overturf G, Turner E. *Is there an increased risk of Haemophilus influenzae septicemia in children with sickle cell anemia? Pediatrics* 1983;**71**(6):927–31.
6. Wong WY, Overturf GD, Powars DR. *Infection caused by Streptococcus pneumoniae in children with sickle cell disease: epidemiology, immunologic mechanisms, prophylaxis, and vaccination. Clin Infect Dis* 1992;**14**(5):1124–36.
7. Sadarangani M. *Protection against invasive infections in children caused by encapsulated bacteria. Front Immunol* 2018;**9**:2674.
8. Pearson HA, Spencer RP, Cornelius EA. *Functional asplenia in sickle-cell anemia. N Engl J Med* 1969;**281**(17):923–6.
9. Najjar VA. *Tuftsin, a natural activator of phagocyte cells: an overview. Ann N Y Acad Sci* 1983;**419**(1):1–11.
10. Barrett-Connor E. *Bacterial infection and sickle cell anemia. An analysis of 250 infections in 166 patients and a review of the literature. Medicine (Baltimore)* 1971;**50**(2):97–112.
11. Powars DR. *Natural history of sickle cell disease—the first ten years. Semin Hematol* 1975;**12**(3):267–85.
12. Society SC. Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK, 2nd Edition; 2018. ⟨https://www.sicklecellsociety.org/wp-content/uploads/2018/05/Standards-for-the-Clinical-Care-of-Adults-with-Sickle-Cell-in-the-UK-2018.pdf⟩ (accessed 20/11/2022).
13. Allali S, Chalumeau M, Launay O, Ballas SK, de Montalembert M. *Conjugate Haemophilus influenzae type b vaccines for sickle cell disease. Cochrane Database Syst Rev* 2018;**8**(8):CD011199.
14. Soothill G, Darboe S, Bah G, Bolarinde L, Cunnington A, Anderson ST. *Invasive bacterial infections in Gambians with sickle cell anemia in an era of widespread pneumococcal and hemophilus influenzae type b vaccination. Medicine (Baltimore)* 2016;**95**(49):e5512.
15. Martin OO, Moquist KL, Hennessy JM, Nelson SC. *Invasive pneumococcal disease in children with sickle cell disease in the pneumococcal conjugate vaccine era. Pediatr Blood Cancer* 2018;**65**(1):1–3.
16. Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G, et al. *Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. N Engl J Med* 1986;**314**:1593–9.
17. Quinn CT, Rogers ZR, Buchanan GR. *Survival of children with sickle cell disease. Blood* 2004;**103**(11):4023–7.
18. Mbaeyi SA, Bozio CH, Duffy J, Rubin LG, Hariri S, Stephens DS, et al. *Meningococcal vaccination: recommendations of the Advisory Committee on Immunization Practices, United States, 2020. MMWR Recomm Rep* 2020;**69**(9):1–41.
19. Parikh SR, Campbell H, Gray SJ, Beebeejaun K, Ribeiro S, Borrow R, et al. *Epidemiology, clinical presentation, risk factors, intensive care admission and outcomes of invasive meningococcal disease in England, 2010–2015. Vaccine* 2018;**36**(26):3876–81.
20. (ATAGI) ATAGoI. Australian Immunisation Handbook. In: Care AGDoHaA, editor. Canberra; 2022. https://immunisationhandbook.health.gov.au/. (accessed 02/10/2024).
21. UKHSA. The Green book of immunisation – chapter 7 – Immunisation of individuals with underlying medical conditions; 2020. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/857279/Greenbook_chapter_7_Immunsing_immunosupressed.pdf. (accessed 19/01/2023).
22. Health NFMo. National Guideline for the Control and Management of Sickle Cell Disease. In: Health FMo, editor.; 2014. https://scsn.com.ng/wp-content/uploads/2014/11/National-Guideline-for-the-Control-and-Management-of-Sickle-Cell-Disease.pdf. (accessed 02/10/2024).
23. Mainland MoHCDGEaCT. Immunization and Vaccine Development Programme 2016; 2020. https://www.nao.go.tz/uploads/MANAGEMENT_OF_IMMUNIZATION_AND_VACCINATION_PROJECT_ACTIVITIES.pdf. (accessed 02/10/2024).
24. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ* 2021;**372**:n71.
25. Buchanan GR, Smith SJ, Holtkamp CA, Fuseler JP. *Bacterial infection and splenic reticuloendothelial function in children with hemoglobin SC disease. Pediatrics* 1983;**72**(1):93–8.
26. Ellison AM, Ota KV, McGowan KL, Smith-Whitley K. *Epidemiology of bloodstream infections in children with sickle cell disease. Pediatr Infect Dis J* 2013;**32**(5):560–3.
27. Zarkowsky HS, Gallagher D, Gill FM, Wang WC, Falletta JM, Lande WM, et al. *Bacteremia in sickle hemoglobinopathies. J Pediatr* 1986;**109**(4):579–85.
28. Gill FM, Sleeper LA, Weiner SJ, Brown AK, Bellevue R, Grover R, et al. *Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative study of sickle cell disease. Blood* 1995;**86**(2):776–83.
29. Gomez-Chiari M, Tusell Puigbert J, Ortega Aramburu J. *[Sickle cell anemia: experience in a center]. An Pediatr (Barc)* 2003;**58**(2):95–9.
30. Lobel JS, Bove KE. *Clinicopathologic characteristics of septicemia in sickle cell disease. Am J Dis Child* 1982;**136**(6):543–7.
31. Tarer V, Etienne-Julan M, Diara JP, Belloy MS, Mukizi-Mukaza M, Elion J, et al. *Sickle cell anemia in Guadeloupean children: pattern and prevalence of acute clinical events. Eur J Haematol* 2006;**76**(3):193–9.
32. Thornburg C, Luo Z, Kalpatthi R, et al. *Febrile episodes and infections in young children with sickle cell anemia (SCA): results from the BABY HUG trial. Pediatr Blood Cancer* 2011;**56**(6):946.
33. Workman MR, Philpotthoward JN, Casewell MW, Bellingham AJ. *Salmonella bacteremia in sickle-cell disease at Kings College Hospital – 1976-1991. J Hosp Infect* 1994;**27**(3):195–9.
34. Zarrouk V, Habibi A, Zahar JR, Roudot-Thoraval F, Bachir D, Brun-Buisson C, et al. *Bloodstream infection in adults with sickle cell disease: association with venous catheters, Staphylococcus aureus, and bone-joint infections. Medicine (Baltimore)* 2006;**85**(1):43–8.
35. Koko J, Dufillot D, M'Ba-Meyo J, Gahouma D, Kani F. *[Mortality of children with sickle cell disease in a pediatric department in Central Africa]. Arch Pediatr* 1998;**5**(9):965–9.
36. Thomas AN, Pattison C, Serjeant GR. *Causes of death in sickle-cell disease in Jamaica. Br Med J (Clin Res Ed)* 1982;**285**(6342):633–5.
37. Thomas C, Lemerle S, Bernaudin F, Feingold J, Guillou-Bataille M, Reinert P. *[Sickle cell anemia: study of the pediatric mortality in Ile de France from 1985 to 1992]. Arch Pediatr* 1996;**3**(5):445–51.
38. Serjeant GR, Chin N, Asnani MR, Serjeant BE, Mason KP, Hambleton IR, et al. *Causes of death and early life determinants of survival in homozygous sickle cell disease: the Jamaican cohort study from birth. PLoS One* 2018;**13**(3):e0192710.
39. Leikin SL, Gallagher D, Kinney TR, Sloane D, Klug P, Rida W. *Mortality in children and adolescents with sickle cell disease. Cooperative Study of Sickle Cell Disease. Pediatrics* 1989;**84**(3):500–8.
40. Al-Ansari MA. *A patient with sickle cell disease with septic shock, purpura, and cold extremities. Chest* 2007;**131**(5):1608–11.
41. Angelini S, Guibourdenche M, Vergez P, Riou JY. *Neisseria meningitidis: fifteen cases of bronchopulmonary infections associated with septicaemia. Pathol Biol (Paris)* 1997;**45**(4):274–80.
42. Chenou F, Azevedo J, Leal HF, Goncalves MDS, Reis JN. *Bacterial meningitis in patients with sickle cell anemia in Salvador, Bahia, Brazil: a report on ten cases. Hematol Transfus Cell Ther* 2020;**42**(2):139–44.
43. Abu-Srair HA, El-Bashier AM, Al-Dabous IS, Al-Khater M. *Incidence of major infection in sickle cell pediatric patients at Qatif Central Hospital. Ann Saudi Med* 1991;**11**(3):267–70.
44. Akuse RM. *Variation in the pattern of bacterial infection in patients with sickle cell disease requiring admission. J Trop Pediatr* 1996;**42**(6):318–23.
45. Overturf GD, Powars D, Baraff LJ. *Bacterial meningitis and septicemia in sickle cell disease. Am J Dis Child* 1977;**131**(7):784–7.
46. Alsaif MA, Abdulbaqi M, Al Noaim K, Aghbari M, Alabdulqader M, Robinson JL. *Prevalence of serious bacterial infections in children with sickle cell disease at King Abdulaziz Hospital, Al Ahsa. Mediterr J Hematol Infect Dis* 2021;**13**:2021002.
47. Al Salman J, Al Agha RA, Al Taitoon S, Al Arrayed A. *Fever in sickle cell disease patients in the Kingdom of Bahrain. J Infect Public Health* 2014;**7**(4):333–8.
48. Al-Tawfiq JA, Rabaan AA, AlEdreesi MH. *Frequency of bacteremia in patients with sickle cell disease: a longitudinal study. Ann Hematol* 2021;**100**(6):1411–6.
49. Alima Yanda AN, Nansseu JR, Mbassi Awa HD, Tatah SA, Seungue J, Eposse C, et al. *Burden and spectrum of bacterial infections among sickle cell disease children living in Cameroon. BMC Infect Dis* 2017;**17**(1):211.
50. Almahmoud T, Alnashwan T, Al Kuhaimi L, Essa MF, Al Balawi N, Jamaan KA, et al. *Management of fever and acute painful crises in children with sickle cell disease in emergency departments: a tertiary hospital experience. Front Pediatr* 2023;**11**:1195040.
51. Alzomor O, Aljobair F, Al Kasim F, Azmet F, Alorini S, Alshihayb Y, et al. *Frequency of serious bacterial infection among febrile sickle cell disease children in the era of the conjugate vaccine: a retrospective study. Int J Pediatr Adolesc Med* 2022;**9**(3):165–70.
52. Bansil NH, Kim TY, Tieu L, Barcega B. *Incidence of serious bacterial infections in febrile children with sickle cell disease. Clin Pediatr (Phila)* 2013;**52**(7):661–6.
53. Baskin MN, Goh XL, Heeney MM, Harper MB. *Bacteremia risk and outpatient management of febrile patients with sickle cell disease. Pediatrics* 2013;**131**(6):1035–41.

54. Brown B, Dada-Adegbola H, Trippe C, Olopade O. *Prevalence and etiology of bacteremia in febrile children with sickle cell disease at a Nigeria Tertiary Hospital. Mediterr J Hematol Infect Dis* 2017;**9**(1):e2017039.
55. Brozovic M, Davies SC, Brownell AI. *Acute admissions of patients with sickle cell disease who live in Britain. Br Med J (Clin Res Ed)* 1987;**294**(6581):1206–8.
56. Chang TP, Kriengsoontorkij W, Chan LS, Wang VJ. *Predictors for bacteremia in febrile sickle cell disease children in the post-7-valent pneumococcal conjugate vaccine era. J Pediatr Hematol Oncol* 2013;**35**(5):377–82.
57. Chulamokha L, Scholand SJ, Riggio JM, Ballas SK, Horn D, DeSimone JA. *Bloodstream infections in hospitalized adults with sickle cell disease: a retrospective analysis. Am J Hematol* 2006;**81**(10):723–8.
58. Elenga N, Placide L, Cuadro-Alvarez E, Long L, Njuieyon F, Martin E, et al. *Does procalcitonin predict bacterial infection in febrile children with sickle cell disease? Indian J Pediatr* 2019;**86**(1):95–6.
59. Esimai VC, Aladekomo TA, Oseni SB, Adeoba EA, Ariyibi SS. *Incidence of bacteraemia among children with severe anaemia in Wesley Guild Hospital, Ilesa, Nigeria. J Trop Pediatr* 1995;**41**(1):50–1.
60. Gaschignard J, Koehl B, Rees DC, Rincón-López E, Vanderfaeillie A, Pascault A, et al. *Invasive bacterial infections in children with sickle cell disease: 2014-2019. Pediatrics* 2023;**152**(4):1–9.
61. Gbadoé AD, Guédénon KM, N'Zonou M, Adamou M, Akolly D, Guédéhoussou T, et al. *Severe acute bacterial infections in children with sickle cell disease in Togo. J Pediatr Hematol Oncol* 2023;**45**(7):404–8.
62. Halwani MA. *Causes and recommendations for fever in sickle cell pediatric patients in the emergency department: a single-center study. Cureus* 2023;**15**(9):e44959.
63. Ibrahim HA, Yakubu YM, Farouk AG, Ambe P, Gadzama GB. *Profile of bacterial pathogens causing infections in children with sickle cell anaemia in Maiduguri. Niger Postgrad Med J* 2021;**28**(3):218–24.
64. Khalife S, Hanna-Wakim R, Ahmad R, Haidar R, Makhoul PG, Khoury N, et al. *Emergence of gram-negative organisms as the cause of infections in patients with sickle cell disease. Pediatr Blood Cancer* 2021;**68**(1):e28784.
65. Kizito ME, Mworozi E, Ndugwa C, Serjeant GR. *Bacteraemia in homozygous sickle cell disease in Africa: is pneumococcal prophylaxis justified? Arch Dis Child* 2007;**92**(1):21–3.
66. Koko J, Kani F, Reymond-Yeni A, Onewin-Andjanga G, Moussavou A, Gahouma D. *[Bacterial infections in children with sickle cell disease in Libreville]. Arch Pediatr* 1999;**6**(10):1131–2.
67. Kondani DA, Gini-Ehungu JL, Bodi JM, Ekulu PM, Kunuanunua TS, Aloni MN. *Prevalence of sickle cell disease in a pediatric population suffering from severe infections: a Congolese experience. Hemoglobin* 2014;**38**(4):225–9.
68. Kravis E, Fleisher G, Ludwig S. *Fever in children with sickle cell hemoglobinopathies. Am J Dis Child* 1982;**136**(12):1075–8.
69. Lalhmunsangi J, Bhise SM, Katkar V, Surpam R, Roy S. *Pattern of bacterial infections among children with sickle cell disease in a tertiary care hospital of Nagpur, Maharashtra, India. J Clin Diagn Res* 2022;**16**(8):DC64–9.
70. Macharia AW, Mochamah G, Uyoga S, Ndila CM, Nyutu G, Makale J, et al. *The clinical epidemiology of sickle cell anemia In Africa. Am J Hematol* 2018;**93**(3):363–70.
71. Makani J, Mgaya J, Balandya E, Msami K, Soka D, Cox SE, et al. *Bacteraemia in sickle cell anaemia is associated with low haemoglobin: a report of 890 admissions to a tertiary hospital in Tanzania. Br J Haematol* 2015;**171**(2):273–6.
72. Mallouh AA, Salamah MM. *Pattern of bacterial infections in homozygous sickle cell disease. A report from Saudi Arabia. Am J Dis Child* 1985;**139**(8):820–2.
73. McIntosh S, Rooks Y, Ritchey AK, Pearson HA. *Fever in young children with sickle cell disease. J Pediatr* 1980;**96**(2):199–204.
74. Morrissey BJ, Bycroft TP, Almossawi O, Wilkey OB, Daniels JG. *Incidence and predictors of bacterial infection in febrile children with sickle cell disease. Hemoglobin* 2015;**39**(5):316–9.
75. Murtaza LN, Stroud CE, Davis LR, Cooper DJ. *Admissions to hospital of children with sickle-cell anaemia: a study in south London. Br Med J (Clin Res Ed)* 1981;**282**(6269):1048–51.
76. Narang S, Fernandez ID, Chin N, Lerner N, Weinberg GA. *Bacteremia in children with sickle hemoglobinopathies. J Pediatr Hematol Oncol* 2012;**34**(1):13–6.
77. Neonato MG, Guilloud-Bataille M, Beauvais P, Bégué P, Belloy M, Benkerrou M, et al. *Acute clinical events in 299 homozygous sickle cell patients living in France. French Study Group on Sickle Cell Disease. Eur J Haematol* 2000;**65**(3):155–64.
78. Norris CF, Smith-Whitley K, McGowan KL. *Positive blood cultures in sickle cell disease: time to positivity and clinical outcome. J Pediatr Hematol Oncol* 2003;**25**(5):390–5.
79. Ozgonenel B, Mushrif SK, McGrath E, Roy S, Sarnaik S. *Bacteremia in febrile children with sickle cell disease. J Pediatr Hematol Oncol* 2014;**36**(1):83.
80. Patel A, Zuzo A, Imran H, Siddiqui AH. *Prevalence of pneumococcal bacteremia in children with sickle cell disease. Pediatr Hematol Oncol* 2013;**30**(5):432–6.
81. Pegelow CH. *Increased incidence of bacteremia in Haitian children with sickle cell anemia. South Med J* 1989;**82**(7):833–6. 40.
82. Rahimy MC, Gangbo A, Ahouignan G, Anagonou S, Boco V, Alihonou E. *Outpatient management of fever in children with sickle cell disease (SCD) in an African setting. Am J Hematol* 1999;**62**(1):1–6.
83. Rao KR, Patel AR, Sonnenberg M. *Five years' experience of bacteraemia in sickle-cell anaemia. J Infect* 1987;**14**(3):225–8.
84. Rincón-López EM, Navarro Gómez ML, Hernández-Sampelayo Matos T, Saavedra-Lozano J, Aguilar de la Red Y, Hernández Rupérez B, et al. *Low-risk factors for severe bacterial infection and acute chest syndrome in children with sickle cell disease. Pediatr Blood Cancer* 2019;**66**(6):27667.
85. Rogers ZR, Buchanan GR. *Bacteremia in children with sickle hemoglobin C disease and sickle beta(+)-thalassemia: is prophylactic penicillin necessary? J Pediatr* 1995;**127**(3):348–54.
86. Rogovik AL, Friedman JN, Persaud J, Goldman RD. *Bacterial blood cultures in children with sickle cell disease. Am J Emerg Med* 2010;**28**(4):511–4.
87. Saqqaf SA, Gomase SV, Borkar R, Taksande A, Rao R, Yedve S. *Frequency and patterns of bacteraemia in children with sickle cell disease: a prospective cohort study. J Clin Diagn Res* 2023;**17**(9):SC10–4.
88. Savlov D, Beck CE, DeGroot J, Odame I, Friedman JN. *Predictors of bacteremia among children with sickle cell disease presenting with fever. J Pediatr Hematol Oncol* 2014;**36**(5):384–8.
89. Shihabuddin BS, Scarfi CA. *Fever in children with sickle cell disease: are all fevers equal? J Emerg Med* 2014;**47**(4):395–400.
90. Sirigaddi K, Aban I, Jantz A, Pernell BM, Hilliard LM, Bhatia S, et al. *Outcomes of febrile events in pediatric patients with sickle cell anemia. Pediatr Blood Cancer* 2018;**65**(11):e27379.
91. Sokol E, Obringer E, Palama B, Hageman J, Peddinti R. *Outpatient management of febrile children with sickle cell disease. Clin Pediatr* 2016;**55**(3):268–71.
92. Telfer P, Coen P, Chakravorty S, Wilkey O, Evans J, Newell H, et al. *Clinical outcomes in children with sickle cell disease living in England: a neonatal cohort in East London. Haematologica* 2007;**92**(7):905–12.
93. Teoh Y, Greenway A, Savoia H, Monagle P, Roy J, Barnes C. *Hospitalisations for sickle-cell disease in an Australian paediatric population. J Paediatr Child Health* 2013;**49**(1):68–71.
94. Vichinsky EP, Neumayr LD, Earles AN, Williams R, Lennette ET, Dean D, et al. *Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study. N Engl J Med* 2000;**342**(25):1855–65.
95. Wall E, Brent J, Velangi M. *Severe sepsis among paediatric patients with sickle cell disease: a regional case series. Arch Dis Child* 2018;**103**(Supplement 1):A147–1.
96. West TB, West DW, Ohene-Frempong K. *The presentation, frequency, and outcome of bacteremia among children with sickle cell disease and fever. Pediatr Emerg Care* 1994;**10**(3):141–3.
97. West DC, Andrada E, Azari R, Rangaswami AA, Kuppermann N. *Predictors of bacteremia in febrile children with sickle cell disease. J Pedia Hematol Oncol* 2002;**24**(4):279–83.
98. Wierenga KJ, Hambleton IR, Wilson RM, Alexander H, Serjeant BE, Serjeant GR. *Significance of fever in Jamaican patients with homozygous sickle cell disease. Arch Dis Child* 2001;**84**(2):156–9.
99. Williams LL, Wilimas JA, Harris SC, Day SW, Dancy RM, Wang WC. *Outpatient therapy with ceftriaxone and oral cefixime for selected febrile children with sickle cell disease. J Pediatr Hematol Oncol* 1996;**18**(3):257–61.
100. Yee ME, Lai KW, Bakshi N, Grossman JK, Jaggi P, Mallis A, et al. *Bloodstream infections in children with sickle cell disease: 2010-2019. Pediatrics* 2022;**149**(1):1–10.
101. Williams TN, Uyoga S, Macharia A, Ndila C, McAuley CF, Opi DH, et al. *Bacteraemia in Kenyan children with sickle-cell anaemia: a retrospective cohort and case-control study. Lancet* 2009;**374**(9698):1364–70.
102. Bello N, Kudu ATD, Adetokun AB, Taura DW, Jobbi YD, Umar M, et al. *Characterization and antimicrobial susceptibility profile of bacteraemia causing pathogens isolated from febrile children with and without sickle cell disease in Kano, Nigeria. Mediterr J Hematol Infect Dis* 2018;**10**(1):e2018016.
103. Fraser DW, Darby CP, Koehler RE, Jacobs CF, Feldman RA. *Risk factors in bacterial meningitis: Charleston County, South Carolina. J Infect Dis* 1973;**127**(3):271–7.
104. Obaro S, Lawson L, Essen U, Ibrahim K, Brooks K, Otuneye A, et al. *Community acquired bacteremia in young children from central Nigeria—a pilot study. BMC Infect Dis* 2011;**11**:137.
105. Okuonghae HO, Nwankwo MU, Offor E. *Malarial parasitaemia in febrile children with sickle cell anaemia. J Trop Pediatr* 1992;**38**(2):83–5.
106. Pelkonen T, Roine I, Bernardino L, Jahnukainen K, Peltola H. *Bacterial meningitis in children with sickle cell disease in Angola. Pediatr Infect Dis J* 2022;**41**(8):e335–8.
107. Rao SP, Schmalzer E, Kaufman M, Brown AK. *Meningitis in patients with sickle-cell-anemia – normocellular CSF at initial diagnosis. Am J Pediatr Hematol Oncol* 1983;**5**(1):101–3.
108. Holdsworth RJ, Irving AD, Cuschieri A. *Postsplenectomy sepsis and its mortality rate: actual versus perceived risks. Br J Surg* 1991;**78**(9):1031–8.
109. Wen SC, Best E, Nourse C. *Non-typhoidal Salmonella infections in children: review of literature and recommendations for management. J Paediatr Child Health* 2017;**53**(10):936–41.
110. Bisharat N, Omari H, Lavi I, Raz R. *Risk of infection and death among post-splenectomy patients. J Infect* 2001;**43**(3):182–6.
111. Yee ME, Bakshi N, Graciaa SH, Lane PA, Jerris RC, Wang YF, et al. *Incidence of invasive Haemophilus influenzae infections in children with sickle cell disease. Pediatr Blood Cancer* 2019;**66**(6):27642.
112. UKHSA. Complete Routine Immunisation Schedule from 1 September 2023; 2023. ⟨https://www.gov.uk/government/publications/the-complete-routine-immunisation-schedule/the-complete-routine-immunisation-schedule-from-february-2022#complete-routine-immunisation-schedule-from-1-september-2023⟩ (accessed 02/10/2024).
113. ECDC. *Haemophilus influenzae* disease; Annual epidemiological report for 2022, 2024. ⟨https://www.ecdc.europa.eu/sites/default/files/documents/Haemophilus%20influenzae_AER_2022_Report-final.pdf⟩ (accessed 02/10/2024).
114. Borrow R, Findlow J. *The important lessons lurking in the history of meningococcal epidemiology. Expert Rev Vaccines* 2024;**23**(1):445–62.
115. WHO. Meeting of the Strategic Advisory Group of Experts on Immunization, September 2023: Conclusions and recommendations. 2023. p. 599–620. https://www.who.int/publications/i/item/WER-9847-599-620. (accessed 02/10/2024).
116. Holst J, Oster P, Arnold R, Tatley MV, Næss LM, Aaberge IS, et al. *Vaccines against meningococcal serogroup B disease containing outer membrane vesicles (OMV): lessons from past programs and implications for the future. Hum Vaccin Immunother* 2013;**9**(6):1241–53.

117. Isitt C, Cosgrove CA, Ramsay ME, Ladhani SN. *Success of 4CMenB in preventing meningococcal disease: evidence from real-world experience. Arch Dis Child* 2020;**105**(8):784–90.
118. Ladhani SN, Andrews N, Parikh SR, Campbell H, White J, Edelstein M, et al. *Vaccination of infants with Meningococcal Group B vaccine (4CMenB) in England. N Engl J Med* 2020;**382**(4):309–17.
119. Mensah AA, Campbell H, Clark SA, Ribeiro S, Lucidarme J, Bai X, et al. *Outcomes of meningococcal serogroup B disease in children after implementation of routine infant 4CMenB vaccination in England: an active, prospective, national surveillance study. Lancet Child Adolesc Health* 2023;**7**:190–8.
120. Borrow R, Alarcón P, Carlos J, Caugant DA, Christensen H, Debbag R, et al. *The Global Meningococcal Initiative: global epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection. Expert Rev Vaccines* 2017;**16**(4):313–28.
121. Gorham MW, Smith CR, Smith SK, Wong L, Kreze O. *Vaccinations in sickle cell disease: an audit of vaccination uptake in sickle cell patients attending Newham University Hospital. Vaccine* 2015;**33**(38):5005–11.