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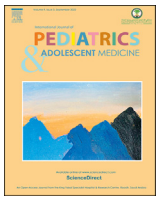

Original article

Frequency of serious bacterial infection among febrile sickle cell disease children in the era of the conjugate vaccine: A retrospective study

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ABSTRACT

Background: Sickle cell disease (SCD) is a wide prevalence disease worldwide. It has a spectrum of clinical manifestations. However, SCD patients are more susceptible to have a serious bacterial infection (SBI) as compared to other individuals.
Objective: The main objective of this study was to investigate the prevalence rate of serious bacterial infection (SBI) in febrile children with sickle cell disease (SCD), whose vaccinations are up to date and are on regular penicillin prophylaxis, presented to the emergency department (ED) to assist in the management approach of such patients.
Methods: A retrospective study included febrile SCD children under 12 years of age between 2014 and 2019 at King Saud Medical City (KSMC) in Riyadh, Saudi Arabia. Patients were stratified according to the true culture result of each febrile event. Descriptive statistics were used to report data from the patient's medical records.
Results: From 833 febrile events, 40 events were assessed for eligibility with positive culture results. Of these, 10 were excluded due to contamination. The rest, 30 children with confirmed SBI (3.6%, 30/833) (95% CI = 2.4%–5.1%) were recruited. The highest prevalence rate of SBI was for urinary tract infection (UTI) (2.2%, 19/833) (95% CI = 1.4%–3.5%), followed by bacteremia (1.3%, 11/833) (95% CI = 0.7–2.4), osteomyelitis (0.24%, 2/833) (95% CI = 0.03–0.86) and meningitis (0.12%, 1/833) (95% CI = 0.00–0.67). Pneumococcal was the most common isolate among children with bacteremia (46%, 5/11) followed by *Salmonella* species (36%, 4/11). All the children fully recovered.
Conclusion: As the prevalence of SBI, particularly bacteremia, continues to decline with a favorable outcome in our population, ambulatory management practices for well-presented febrile SCD children should be encouraged, for there are no further reasons for admission and the patient can return soon to their hospital if his condition worsens or there is growth in the blood culture. Further effort is needed to determine whether blood culture and empiric antibiotics are necessary for each febrile event in the probable highly active vaccination era.

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1. Introduction

Hemoglobin is a tetramer composed of two pairs of globin chains. Abnormalities of these proteins are referred to as hemoglobinopathies. Sickle cell disease (SCD) is one of the hemoglobinopathy disorders that have arisen in the Saudi population. Lehmann et al. [1] recognized the first sickle cell gene in the Eastern Province of Saudi Arabia in 1963. The prevalence rate of SCD in

Abbreviations: CI, confidence interval; ED, emergency department; KSMC, king Saud Medical City; PCV, pneumococcal conjugate vaccine; SBI, serious bacterial infection; SCD, sickle cell disease.

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Saudi Arabia (4.50%) is high compared to nearby Middle East countries [2].

Many factors may lead to an increased risk of infections among children with SCD. Splenic dysfunction, defect in opsonization, and disturbed antibody response are considered a major contributor to several infectious organisms, in particular invasive pneumococcal diseases [3–6].

Bacteremia, meningitis, urinary tract infection, osteomyelitis, septic arthritis, and pneumonia are commonly associated with SCD infections [3,6,7]. Infection may lead to exacerbation of numerous health crises, including but not limited to aplastic, hemolytic, and vaso-occlusive episodes [8].

However, the bacteremia incidence rate reported is continuously decreasing. Previous studies in 2009 showed a 6% increased risk of bacteremia in children with SCD in sub-Saharan Africa [9], while <1% risk of bacteremia was reported in 2013 in febrile children and adolescents <21 years with SCD, who presented to Boston children's hospital [10]. The annual incidence of *Streptococcus pneumoniae* in children with SCD was approximately 5% before the administration of penicillin prophylaxis, and the addition of protein-conjugated pneumococcal vaccine (PCV) series in early childhood decreased the risk of sepsis to as low as 0.8% [11]. Not many reports on the prevalence of serious bacterial infections among SCD children at the regional level were encountered. However, a recent study from the Eastern Province of Saudi Arabia reported that the incidence rate for serious bacterial infection is 8% [12].

The Saudi National Immunization Program included the PCV13, haemophilus influenzae type b (Hib), and quadrivalent meningococcal vaccine (MCV4) in basic vaccines, which began in early infancy. Children with SCD would also obtain a 23-valent pneumococcal polysaccharide (PPSV23) vaccine from 2 years of age. Incidence of invasive pneumococcal infection was observed to decrease, but a precise reported rate about such cases is unclear. In Kuwait and Saudi Arabia, PCVs have resulted in a decline in the incidence of certain vaccine serotypes and the emergence of certain non-PCV13 serotypes [13].

The main objective of this study was to establish the prevalence rate of serious bacterial infections in febrile children with sickle cell disease presented to the pediatric emergency department (ED) of King Saud Medical City (KSMC) in Riyadh, Saudi Arabia, correlated to their vaccination status and regular penicillin prophylaxis. Once we prove that the risk in this group of patients is minimal, a deferential management approach could be suggested.

2. Materials and methods

We conducted a retrospective study at the KSMC. This is a 1300-bed tertiary medical facility of the Ministry of Health that began to provide healthcare services to people in Riyadh in 1956. The children's hospital has a 241 active bed capacity and 19 beds for day medical care, ED, and intensive care unit. The hospital also has all the necessary subspecialties required for any pediatric hospital.

The study subjects consisted of 833 febrile events in SCD children below 12 years of age who came into the ED. Each febrile event was considered an individual case. The sample size included all patients who fitted in the inclusion criteria in the period between February 2014 and February 2019. For any patient involved in the data collection, a telephone contact and a photocopy of the vaccination card were required to provide evidence that all recommended vaccinations had been received (including PCV13, MCV4, and Hib). Patients' status for regular penicillin prophylaxis was also verified. The fever should be documented in ED. However, patients who came to our inpatient unit after being admitted to a local ED in other healthcare centers or discharged from our hospital within 2 weeks were excluded from the study. Other excluded subjects were patients showing subjective fever and temperature less than 38 °C, patients admitted for different sickle cell conditions but showed fever as they were admitted and patients who received antibiotics other than the baseline prophylaxis prior to ED.

The febrile illness was defined as temperature ≥38 °C measured (oral or axillary) and documented in the ED. SBI was defined as bacteremia, meningitis, pneumonia, urinary tract infection, pleuritis, pericarditis, peritonitis, arthritis, and osteomyelitis based on positive culture results from blood, urine, cerebrospinal fluid (CSF), synovial fluid, pleural fluid, pericardial fluid, peritoneal fluid, and surgical tissue culture. Urine cultures were considered for UTI when urine cultures in the symptomatic patient grew more than 50,000 colony-forming units per milliliter (CFUs/ml) of a single organism from a catheterized urine specimen or more than 100,000 CFU/ml midstream or clean catch urine. Growth of ≥10,000 CFU/mL of a single uropathogen from a urinary sample collected by either catheter or clean voided method should be considered sufficient for UTI diagnosis in symptomatic patients with fever and pyuria. Blood cultures were considered significant for bacteremia if a true pathogen was recovered, and contamination results were excluded.

The following bacteria were defined as contaminants unless they were clearly documented as pathogens and were fully treated: *Coagulase negative staphylococci*, *Streptococcus constellatus*, *Bacillus* species, *Corynebacterium* species, *Micrococcus* species, and non-Meningitidis *Neisseria* species. Other body fluid cultures were considered positive if a true pathogen was recovered from the sterile body fluid. Pneumonia cases were considered only if blood or respiratory sample culture results were positive to avoid overlapping with the acute chest syndrome. Osteoarticular infection was considered only if confirmed blood, synovial fluid, or bone tissue positive culture correlated clinically and radiologically to avoid overlapping with vaso-occlusive crisis.

We screened medical records and their details on the digital platform for 833 febrile events. The data were analyzed using SPSS 24 for the following characteristics: age, gender, immunization status, previous hemoglobin electrophoresis results, penicillin prophylaxis, ER temperature, white blood cell (WBC) count, hemoglobin level, platelet count, relevant culture results, and the patient outcome. Descriptive statistics were used to report data from the patients' medical records. Discrete data are expressed as frequency and percentages. Continuous data is expressed as mean ± SDs. A value of CI > 95% was considered statistically significant. The confidentiality of the patients is maintained according to the national bioethics' rules and regulations.

3. Results

A total of 833 febrile events were screened (Fig. 1). The outcomes involved 40 subjects with positive bacterial culture results from different body fluids. However, 10 results from the collected data were excluded due to contamination culture results based on case definition criteria; therefore, 30 febrile events for 30 children were assessed and it was concluded that hospitalization was justified.

Of the patients with the true positive culture in the study, the majority were male children (57%, 17/30) (Table 1). Hemoglobin electrophoresis was high (50%, 15/30) for homozygous sickle cell anemia (HbSS) followed by sickle-β^o-thalassemia ($HbSB^0$) (27%, 8/30) and sickle-$\beta\pm$thalassemia ($HbSB^+$) (23%, 7/30). For immunization status (93%, 28/30), it was possible to provide documentation that all vaccines including PCV13, MCV4, and Hib had been given; of the two (7%, 2/30) remaining patients, one could not be reached since they had left the country and the other had been vaccinated at

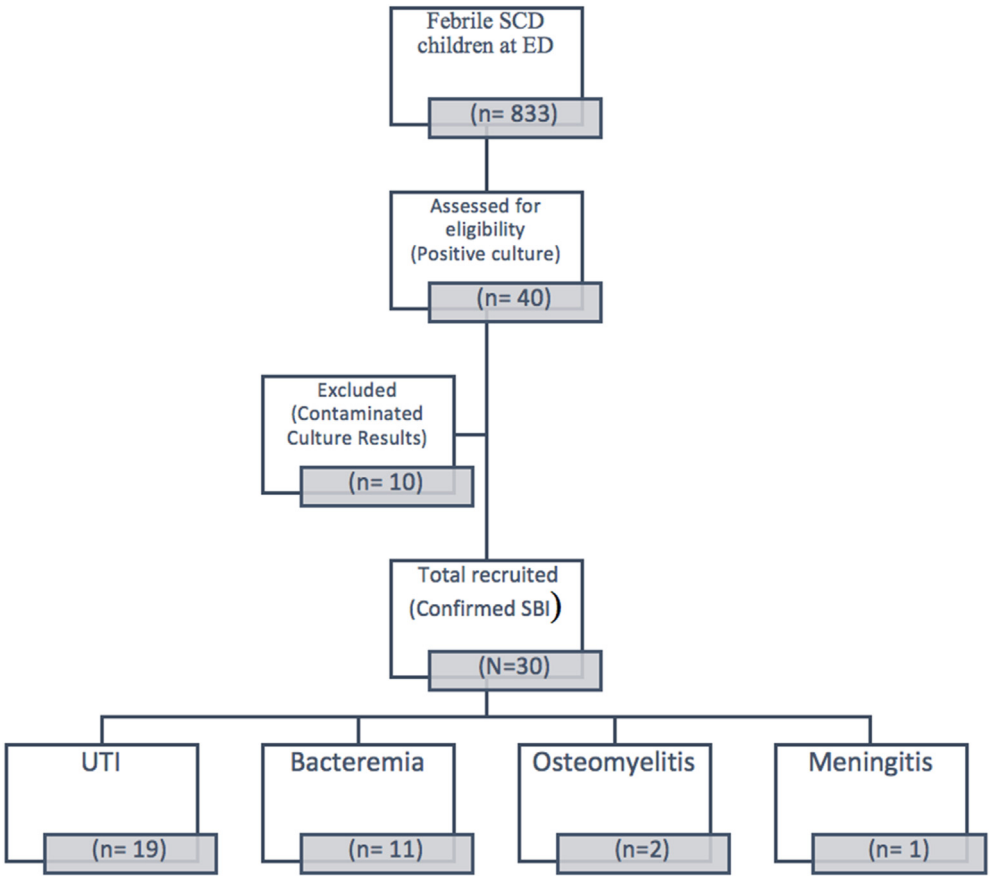

Fig. 1. Patient screening and enrolment.
Abbreviation: ED: Emergency department; SBI: Serious bacterial infection; UTI: Urinary tract infection.

Table 1
Baseline clinical and laboratory characteristics of confirmed SBI cases ($n = 30$) in 833 febrile events in children with SCD at enrolment, KSMC (Saudi Arabia), 2014–2019.

Characteristic	Value ($n = 30$)
Mean age at enrollment, months (mean ± SD)	3.66 years (±2.74)
Gender *n* (%)	
Male	17 (57)
Female	13 (43)
Hemoglobin phenotype n (%)	
HbSS	15 (50)
$HbSb^0$	8 (27)
$HbSb^+$	7 (23)
Immunization status *n* (%)	
Confirmed	28 (93.33)
Not confirmed	2 (6.6)
Penicillin prophylaxis *n* (%)	
Yes	30 (100)
No	0 (0.00)
Temperature *n* (%)	
≥38 °C	30 (100)
<38 °C	0 (0.00)
White blood cells *n* (%)	
Normal (4–12*10^9/L)	5 (16)
Leukocytosis (>12*10^9/L)	25 (68)
Leukopenia (<4*10^9/L)	0 (0.00)

Abbreviations: SBI, serious bacterial infection; SCD, sickle cell disease; KSMC, King Saud Medical City; SD, standard deviation; HbSS, homozygous HbS disease; HbSb0, sickle-β0-thalassemia; HbSb+, sickle−β ± thalassemia.

birth. All children had daily penicillin prophylaxis (100%, 30/30). Leukocytosis was associated with the majority (68%, 25/30) of patients and no one had leukopenia (0.0%, 0/30). The age was analyzed to find the median year, where 3.66 years (±2.74) resulted as the median for all febrile events from the sample range of 5 months–144 months.

In all, 30 of the 833 patients were determined to have an SBI, revealing a total prevalence rate of 3.6% (30/833, 95% CI = 2.4%–5.1%) (Table 1). Urinary tract infection was found in 19 patients, revealing the highest prevalence rate of 2.2% (19/833, 95% CI = 1.4%–3.5%). Blood cultures were obtained in all patients seen in the emergency departments as SCD with fever, and 11 positive blood cultures were identified revealing a prevalence rate of 1.3% (11/833, 95% CI = 0.7%–2.4%) for bacteremia. Osteomyelitis was confirmed with a positive blood culture of two patients with a prevalence rate of 0.24% (2/833, 95% CI = 0.03%–0.86%). One case of SBI was diagnosed with meningitis, revealing the lowest prevalence rate of 0.12% (1/833, 95% CI = 0.00%–0.67%). No patient was diagnosed with pericarditis, pleuritis, peritonitis, bone tissue, or synovial fluid culture-positive osteoarticular infection.

Among the patients with confirmed UTI ($n = 19$), the most frequently isolated uropathogen was *Escherichia coli* (*E. coli*; 42%, 8/19), followed by *Enterococcus* species (32%, 6/19) and *Klebsiella pneumoniae* (*K. pneumoniae*; 11%, 2/19). Overall, 32% (6/19) uropathogens were extended-spectrum beta-lactamases (ESBLs). Another isolate was Salmonella group C, *Pseudomonas aeruginosa* and *Pantoea agglomerans* (5%, 1/19) for each (Table 3) (see Table 4).

Pneumococcal bacteremia was reported in five febrile cases, representing a prevalence rate of 0.6% (5/833) of all febrile events and 46% (5/11) of patients with bacteremia (Table 2). All five patients were immunized on regular basis with daily penicillin prophylaxis. Four of them had been treated with ceftriaxone and had

Table 2
Prevalence rate of confirmed SBI cases (30) in (833) febrile events in children with SCD.

Febrile event outcome	Value ($n = 833$); n (%)	Prevalence % (95% CI)
Overall SBI	30	3.6 (2.4–5.1)
UTI	19	2.2 (1.4–3.5)
Bacteremia	11	1.3 (0.7–2.4)
Osteomyelitis	2	0.24 (0.03–0.86)
Meningitis	1	0.12 (0.00–0.67)

Abbreviations: SBI, serious bacterial infection; SCD, sickle cell disease; CI, confidence interval; UTI, urinary tract infection.

Table 3
The percentage rates for each isolated uropathogen of confirmed UTI cases ($n = 19$).

Uropathogen	Value ($n = 19$); n (%)
E. coli	
ESBLs	5 (26.3)
Non-ESBLs	3 (15.7)
Total	8 (42.1)
Enterococcus	6 (31.5)
K. pneumoniae	
ESBLs	1 (5.26)
Non-ESBLs	1 (5.26)
Total	2 (10.52)
Salmonella	1 (5.26)
P. aeruginosa	1 (5.26)
Pantoea agglomerans	1 (5.26)

Abbreviations: SBI, serious bacterial infection; SCD, sickle cell disease; CI, confidence interval; UTI, urinary tract infection; E. Coli, *Escherichia coli*; ESBLs, extended spectrum beta-lactamases; K. Pneumoniae, *Klebsiella pneumoniae*; P. Aeruginosa, *Pseudomonas aeruginosa*.

been discharged to their home in good health. One patient was treated with clindamycin due to ceftriaxone allergy for a total duration of 10 days and initially showed a good response. But he was readmitted four days after discharge with fever and headache and found to have pneumococcal meningitis that had been successfully treated with vancomycin. *Salmonella* was reported in four patients (0.48%, 4/833) of all febrile events representing 36% (4/11) of the bacteremic patients, and two of these patients developed a complication diagnosis of osteomyelitis verified by clinical and radiological correlation and underwent adequate therapy with a satisfactory outcome. The culture results of the other two patients with bacteremia revealed *Klebsiella pneumonia* and *Pantoea agglomerans* with the same prevalence rate of 0.12% (1/833), representing 9% (1/11) of all cases with bacteremia (Table 2).

4. Discussion

We observed that the overall prevalence rate of SBI is 3.6% in our sample of febrile children with SCD and it was within the lower range of recorded rates relative to the general pediatric population of 3 %–14% [14,15]. Some variables (leukocytosis 68%, HbSS 50%) were reported to be frequently associated with our SBI cases. A similar finding has been reported in previous studies for leukocytosis [11].

The prevalence rate of bacteremia is 1.3%. Previous studies have shown the bacteremia rate at 1.9% of 1853 febrile patients (age ≤21 years) in a systematic analysis of 10 studies [16]. This result of lower prevalence of bacteremia could be attributed to the routine penicillin prophylaxis and conjugated pneumococcal vaccination, which was verified for those cases [9]. However, the five pneumococcal isolates in our study are most likely of a different serotype not covered by the conjugate pneumococcal vaccine, and although they were all susceptible to penicillin, poor adherence to penicillin prophylaxis may have played a role in infection. Contrary to expectations, this research did not find a substantial difference in the rates between pneumococcal and salmonella bacteremia, both of which were close to each other (0.6%, 0.48%). Many studies have shown that most encapsulated organism prevalence rates have declined, while *Salmonella* has become the most common isolate [17]. Perhaps, it is time to suggest vaccination against *Salmonella* with observed virulent infection in these children, which may otherwise end up with an unfavorable result, such as osteomyelitis, as it happened in two of our cases. This is also in accordance with our earlier observations, which showed that multiple sites of infection and delay in response for management led to a high virulence of Salmonella in SCD patients [18].

Although UTI were the most common SBI in our study, their prevalence rate was lower of 2.5% compared to the Patel et al. study of African American children in 2020, with a reported prevalence rate of 4.1% [19]. Their study population group, type of sickle cell disease, and age might have contributed to the reported difference in the rate of UTI. We found that 32% of uropathogens were producers of extended spectrum beta-lactamases (ESBLs), which were observed to have increased recently among SCD children and the general population compared to that reported by Mava et al. in Nigerian children [20,21].

Previous studies have reported that people with SCA are more than 300 times likely to develop bacterial meningitis than the general public [22]. A systematic review undertaken in 2019 to evaluate the serotype distribution, clinical presentation, and outcomes of invasive pneumococcal disease in children with SCD in PCV programs revealed that bacterial meningitis in children with SCD was the third incidence of clinical presentation preceded by septicemia and lower respiratory tract infections [23]. However, this does not appear to be the case in our study since we encountered a very low rate of meningitis with only one patient suffering from pneumococcal meningitis. This patient was treated for 10 days with clindamycin due to ceftriaxone allergy and initially showed a good response. But 4 days after discharge, he showed another headache-related fever where the CSF culture grew pneumococcal isolate. The patient was treated with vancomycin with a good outcome. We did not quantify this case as an individual occurrence,

Table 4
Percentage rates for each isolated pathogen of confirmed bacteremia cases.

Blood culture	Value ($n = 11$); n (%)	Outcome
Pneumococcus	5 (45.4)	One case developed meningitis (treated successfully) All other cases treated successfully with no morbidity
Salmonella	4 (36.4)	Two cases developed osteomyelitis (treated successfully) All other cases treated successfully with no morbidity
K. pneumoniae	1 (9.1)	Treated successfully with no morbidity
Pantoea agglomerans	1 (9.1)	Treated successfully with no morbidity
Total	11 (100)	All Fully recovered

Abbreviations: SBI, serious bacterial infection; SCD, sickle cell disease; K. Pneumoniae, *Klebsiella pneumoniae*.

and we believed that it was within the spectrum of the same initial illness due to the inferiority of clindamycin, as it is only a bacteriostatic for bloodstream infection, has poor blood brain–barrier penetration, and is not prescribed as a drug of choice. The child received the conjugated pneumococcal vaccine, and the serotype of this *S. pneumoniae* is not possible to treat within the spectrum of the PCV13 vaccine. This inconsistency in meningitis rate in this systematic review may be due to genetic differences and then there were multiple studies involved in Godwin Oligbu et al. [23] systematic review in comparison to our single tertiary center study.

Despite previously receiving PCV13, *S. pneumoniae* may still be considered to be one of the primary pathogens in SCD children. Children with SCD may be more vulnerable to *S. pneumoniae* serotypes not protected by (PCV) [23,24]. A case series by McCavit et al. [25] found that children with SCD caused by non-vaccine serotypes had an increased number of invasive pneumococcal diseases, including bacteremia and septic arthritis.

To avoid the risk of morbidity and mortality from bacteremia, febrile children with SCD have been historically hospitalized for intravenous antibiotics [26]. The result of a low incidence of bacteremia in SCD patients, however, has decreased the rate of hospitalization. Effective alternative treatment of SCD patients with fever is the latest practice of outpatient empiric antibiotics in children not suspected of bacteremia [4,27]. Since our research has found a lower prevalence of SBI in SCD children, the practice of outpatient management of empiric antibiotics should continue. We observed that the majority of the blood culture of the febrile children with SCD showed no growth. Sirigaddi et al. reported that the time to positive blood culture was in rare cases >48 h and most of the culture showed no growth [28]. This observation may support the hypothesis that not every febrile child with SCD needs blood culture as a baseline workup.

Our study, however, had many limitations. Most notably, this was a retrospective analysis, patients could have failed to scan their medical records or miscoded them. Since our purpose was to assess patients only presenting to the ED, we did not consider children presenting to specialty clinics or outside emergency areas. Again, we did not include reported cases of pneumonia and osteoarticular infections until a confirmed culture was isolated to prevent a common clinical problem in the distinction of acute chest syndrome and vaso-occlusive crises, which would also be difficult to judge retrospectively. Thus, the true occurrence of SBI may have been under-evaluated in febrile children with SCD. It was not possible to assess the serotype of the isolated organism; therefore, it remains unknown whether the standard vaccine failed to prevent targeted serotypes in some vaccinated children. Our information was limited to a single tertiary care center. This may restrict the ability to generalize our results to a broader SCD pediatric population.

There is no doubt that the findings of this study will be subjected to much review, but there are some immediate reliable conclusions for the low prevalence rate of serious bacterial infection among children with febrile sickle cell disease. However, further research work is required to establish the validity of the risk factors for a serious bacterial infection that is required to be considered in such patients.

5. Conclusions

The high risk of morbidity and mortality in febrile pediatric patients with SCD is always a concern. Risks originate from SBI due to bacteremia with encapsulated organisms, in particular *S. pneumoniae*. Developed vaccines and policies such as penicillin prophylaxis have been put in place to reduce infection and death in such patients. Our study showed that bacteremia occurs less frequently in vaccinated children, but its occurrence is serious and could end up with complications if not treated early and effectively. As the prevalence of SBI continues to decline, the practice of ambulatory management of empirical antibiotics in such patients should be encouraged. However, further evidence-based studies are needed to determine whether blood culture and empiric antibiotics are needed for every febrile event in vaccinated children with sickle cell disease.

Ethical Statement

Hereby, I Omar Alzomor consciously assure that for the manuscript Frequency of serious bacterial infection among febrile sickle cell disease children in the era of the conjugate vaccine: a retrospective study. The following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.
7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

The violation of the Ethical Statement rules may result in severe consequences.

I agree with the above statements and declare that this submission follows the policies of Solid State Ionics as outlined in the Guide for Authors and in the Ethical Statement.

Ethical consideration

Approval for our study was obtained from the Research Innovation Center at King Saud Medical City (Ref. #: H1RI-14-May19-02).

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Author statement

Omar Alzomor: Conceptualization, Formal analysis, Project administration, Supervision, Writing - original draft, Writing - review and editing.

Fahad Aljobair: Writing - review and editing.

Fawaz Al Kasim: Writing - review and editing.

Fauzia Azmet: Data curation, Methodology, Supervision, Writing - review and editing.

Sultan Alorini: Data curation, Formal analysis, Investigation, Methodology, Writing - original draft.

Yazeed Alshihayb": Data curation, Formal analysis, Investigation, Methodology, Writing - original draft.

Yazeed Bahamdan: Data curation, Formal analysis, Investigation, Methodology, Writing - original draft.

Declaration of competing interest

This manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose.

Visual abstract

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpam.2022.05.002.

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