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# Bacteremia among Febrile Children with Sickle Cell Disease and Antibiotic Susceptibility Patterns in Mwanza City, Northwestern Tanzania

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**Abstract**

***Background***

Children with Sickle Cell Disease (SCD) are prone to bacterial infections due to compromised immunity resulting in significant morbidity and mortality. Routine use of oral penicillin prophylaxis in patients with SCD and pneumococcal conjugate vaccine over the past three decades has led to a drastic decline in morbidity and mortality. However, there are reports of increasing antibiotic resistance globally, including penicillin. This study determined the proportion of bacteremia, antibiotic susceptibility patterns, and associated factors among febrile children with SCD.

***Method***

This was a hospital-based cross-sectional study conducted in Northwestern Tanzania between January and June 2021. A convenient sampling technique was used to select the study participants. The socio-demographic and clinical characteristics of the study participants were collected using a structured questionnaire upon obtaining consent from the parents/guardians. Blood samples for culture were collected aseptically before antibiotics use. Univariate and multivariable logistic regression analysis determined factors independently associated with bacteremia using odds ratios, 95% confidence intervals, and a p-value cut-off of < 0.05.

***Results***

The proportion of febrile children with bacteremia was 8.7% (28/321), predominately caused by *S. aureus* (64.3%) and *K. pneumoniae* (17.9%). The gram-positive isolates were more resistant to penicillin, erythromycin, and co-trimoxazole, with resistance rates ranging from 56 - 78%. Gram-negative bacteria showed a high resistance rate (60-100 %) to ceftriaxone, amoxicillin-clavulanic acid, and cefepime. Children aged 0-5 years had twice the odds of having bacteremia (AOR=2.1, 95% CI=1.2-6.9) compared to children above five years, p =0.04. Furthermore, the odds of having bacteremia among males were 1.5 times (AOR=1.5, 95% CI=1.1-3.9) compared to females, p =0.03.

***Conclusion***

Our findings show that many children with SCD still acquire bacterial infection with *S. aureus*, constituting most bacteremic episodes. Additionally, we observed high resistance rates toward penicillin and other commonly used antibiotics. The high resistance rates call for introducing the routine culture and AST at health facilities that lack the services.

***Keywords****: Bacteremia, Sickle cell disease, Antibiotic susceptibility pattern.*

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**Introduction**

Around 300,000 infants are born annually with sickle cell disease (SCD) globally; sub-Saharan Africa (SSA) accounts for 75% of the burden (1). As a result of compromised immune function, patients with SCD are prone to invasive bacterial infections, particularly *Streptococcus pneumoniae* and *Haemophilus influenzae* (2). Bacteremia remains the leading cause of morbidity and mortality in SCD patients in low and middle-income countries (3). In SSA, where access to healthcare is limited, the probability of early death among children born with SCD ranges between 50-90% (4). The mortality due to infections among patients with SCD is as high as 38% in the United States (5).

SCD is still an under-recognized global health problem in SSA that contributes substantially to mortality in children younger than five years of age (6). Several interventions have been widely deployed over the past three decades to reduce the burden related to SCD. These interventions include screening newborns for SCD, routine use of penicillin prophylaxis for under-five, and conjugate pneumococcal vaccine against invasive *S. pneumoniae* and *H. influenzae* type b. The inventions have resulted in a drastic decline in mortality due to sepsis (7). For example, studies indicate that before prophylactic oral penicillin, the case fatality rate was as high as 35%, with *S. pneumoniae* infections causing death in less than 24 hours from onset (8). With the improved access to healthcare services in developed nations, children with SCD now have a better chance of surviving to adulthood (9). Nonetheless, infections remain the major cause of morbidity and mortality in low- and middle-income countries due to increased co-morbidities such as malnutrition, lower levels of vaccination, and reduced access to care (10). Studies in SSA reported a prevalence of bacteremia ranging between 14-32%, with a spectrum of organisms differing from one place to another (11, 12).

Although children with SCD receive oral penicillin prophylaxis and pneumococcal conjugate vaccines to reduce related morbidity and mortality, there are increasing reports on penicillin and other antibiotic resistance (13). In addition, the extended-spectrum beta-lactamases (ESBL) producing bacteria have also been reported among the SCD population (14). Nevertheless, treatment of the most common bacterial infections in SCD among institutions is based on consensus guidelines, clinical experience, or adapting treatment applied to other diseases. Variations in treatment among institutions may give room for the emergence of antibiotic resistance (9). Therefore, we conducted a study to determine the proportion of bacteremia, antibiotic susceptibility pattern, and associated factors among febrile pediatrics with SCD.

## Materials and Methods

### Study design, setting, and population

This was a hospital-based cross-sectional study conducted in Mwanza, Northwestern zone of Tanzania, between January and June 2021. The study included three hospitals: Bugando Medical Centre (BMC), Sekou-Toure Regional Referral Hospital, and Nyamagana District Hospital. The three serve around 50 to 60 per day, operating twice a week. The study involved all febrile children patients with SCD aged six months to 12 years with a history of fever at the time of presentation to the healthcare facility. Children on antibiotic medication at the time of enrolment were excluded from the study.

### Sample size, Sampling, and data collection

The sample size of 321 was estimated using the Kish Leslie formula based on the prevalence of 4.8% by Makani et al. for bacteremia among SCD patients in Tanzania in 2015 (15). The number of participants enrolled from each facility was calculated based on probability proportional to size sampling. A convenient sampling technique was used to select the study participants. Upon obtaining assent from the children or consent from the parent/guardians at the study sites, children meeting enrollment criteria were recruited. The socio-demographic and clinical characteristics of the study participants were collected using a structured questionnaire. Body temperature was measured and recorded. Any patient with readings above 37.5$^{o}$C was considered febrile and was selected for blood sample collection. Samples were collected from the patients and taken to BMC laboratory for processing and analysis. The BMC laboratory is accredited by the Kenya Accreditation Service (KENAS).

### Laboratory procedure

### Blood collection and Bacterial isolation

Blood samples for culture were collected aseptically by trained laboratory personnel before antibiotics use. About 5 ml of venous blood was collected, 2-3 mls dispensed into blood culture broth for blood culture, and the remaining 2 ml into the Ethylene Diamine Tetra acetic Acid (EDTA) tube for malaria and HIV testing using the national testing algorithms.

Following the manufacturer's instructions, we performed blood culture using the BACTEC system (Becton Dickinson BACTEC FX Blood Culture System, USA) at Bugando Medical Centre laboratory. Aerobic blood culture bottles were incubated at 37°C with agitation overnight. Upon alerts of a positive sample by the BACTEC within five days, the samples were

sub-cultured on blood agar and MacConkey agar plates and incubated aerobically under 5% $CO_2$ conditions at 37°C for 24 hours.

**Bacteria identification**

Bacteria isolates were identified based on colonial appearance, Gram stain reaction, biochemical tests, and serological methods. The biochemical tests for gram-positive cocci included catalase and Staphylase. The biochemical tests for Gram-negative bacilli included oxidase, Kliger's Iron Agar, citrate utilization, urease, and Sulphur Indole Motility. In addition, we used API20E (Bio-Merieux, France) to identify other members of *Enterobacteriaceae* that conventional biochemical tests failed.

**Antimicrobial Susceptibility Testing**

The Antimicrobial Susceptibility Testing (AST) was done using Kirby–Bauer disk diffusion method on Mueller Hinton Agar (Oxoid, Hampshire, United Kingdom) according to the Clinical and Laboratory Standards Institute guidelines (16). In addition, the following antibiotics were tested: ciprofloxacin (30 µg), gentamicin (10µg), ampicillin (10 µg), amoxicillin-clavulanic acid (20/10 µg), ceftriaxone (30 µg), meropenem (10 µg), cefotaxime (30 µg), cefepime (30 µg) and ceftazidime (30 µg) (Bioanalyse, Turkey) for gram-negative organisms, and erythromycin (15 µg), penicillin G (10 µg), ciprofloxacin (30 µg), clindamycin (2 µg), gentamicin (10µg) and trimethoprim-sulfamethoxazole (1.25/23.75 µg) (Bioanalyse, Turkey) for gram-positive organisms.

*S. aureus* isolates were screened for Methicillin-Resistance by the use of cefoxitin disc (30 µg), and strains showing a zone of inhibition of ≤ 21 mm were considered as Methicillin-resistant *Staphylococcus aureus* (MRSA) (16). Screening for phenotypic ESBL producing *Enterobacteriaceae* was done using a cut-off zone of inhibition of ≤ 25 mm for ceftriaxone and ≤ 22 mm for ceftazidime (16). We confirmed ESBL production *Enterobacteriaceae* by the double-disc synergy method. Disks of ceftazidime (30 µg), cefotaxime (30 µg), and amoxicillin-clavulanic acid (20/10 µg) were placed 20 mm apart on the Mueller Hinton agar plate in a straight line, with amoxicillin-clavulanic acid in the middle. Any increase in the inhibition zone towards the amoxicillin-clavulanic acid disk was a positive result for ESBL enzyme production. *E. coli* ATCC 25922, *Klebsiella pneumonia* ATCC 700603, and *S. aureus* ATCC 25923 were used as reference strains.

### Data analysis

Data analysis was done using STATA version 15.0 software (College Station, Texas, USA). Proportions of children with culture-confirmed bacteremia, bacterial species, and resistance to various antimicrobial agents were determined. Univariate logistic regression analysis was done on all variables, and those with a *p-value* cut-off of ≤ 0.2 were subjected to multivariate logistic regression analysis. In addition, independently associated factors for bacteremia among febrile children with SCD were determined by univariate and multivariate logistic regression analysis using odds ratios, 95% confidence intervals, and a p-value cut-off < 0.05.

### Ethics approval

The ethical approval was obtained from the Institutional Review Board of the Muhimbili University of Health and Allied Sciences (Ref. No DA 282/298/01.C/). The permission to conduct this study was obtained from the hospital management of Bugando Medical Centre, Sekou-Toure Regional Referral Hospital, and Nyamagana District Hospital. Each participant/guardian provided written informed consent/assent before enrollment. The laboratory results were communicated through the nurse counselor and the attending clinician for patient management. All information and issues relating to patients in the study were treated confidentially.

## Results

### Socio-demographic and clinical characteristics

Three hundred twenty-one febrile children with SCD were included in the study. Females accounted for more than half, 175/321 (54.5%) of the study participants. The study participants' median age (IQR) was 5 (3-8) years. The majority of participants, 241/321 (75.1%), had received pneumococcal conjugate vaccination (PCV). About a quarter of the participants, 80/321 (24.9%), had a history of antibiotic use in the past three weeks before blood culture, of which 33/80 (41.3%) had used penicillin V Potassium (Table 1).

### Proportion of bacteremia

Twenty-eight (8.7%) out of 321patients had bacteria pathogens isolated in the blood culture. The gram-positive bacteria constituted 18/28 (64.3%), all being *S. aureus*. Conversely, *K. pneumoniae* 5/28(17.9%) was the predominant gram-negative bacteria isolated (Figure 1).

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**Table 1: Socio-demographic and clinical characteristics of the febrile children with SCD**

| Characteristic | Number (%) |
|---|---|
| **Sex** | |
| Males | 146(45.5) |
| Females | 175(54.5) |
| **Age group** | |
| ≤ 5 | 187(58.3) |
| > 5 | 134(41.7) |
| **PCV vaccination status** | |
| Yes | 241 (75.1) |
| No | 80 (24.9) |
| **Prophylactic antibiotic use** | |
| Yes | 66 (33.7) |
| No | 130 (66.3) |
| **Antibiotic use in the past three weeks** | |
| Yes | 80 (24.9) |
| No | 241 (75.1) |
| **Co-infection** | |
| Malaria | 33 (10.3) |
| HIV | 8 (2.5) |

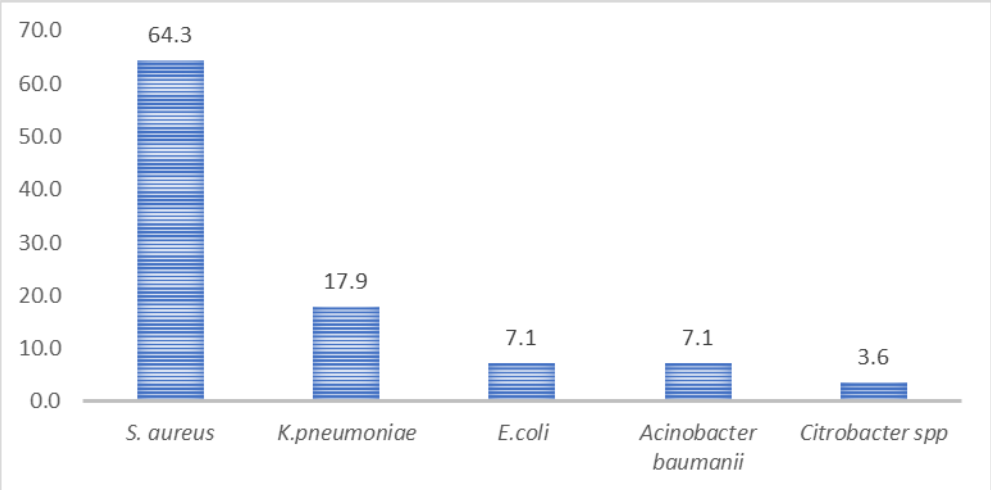


**Figure 1. Proportion of bacteria isolates among febrile children with SCD**

**Antimicrobial resistance pattern**

*S. aureus* strains showed high resistance rates from 56 to 78% to erythromycin, penicillin, and co-trimoxazole. Gram-negative bacteria displayed high resistance rates to ceftriaxone, amoxicillin-clavulanic, and cefepime, ranging from 60 to 80%. All the Gram-negative isolates

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showed no resistance to meropenem. All the *K. pneumoniae* and *E. coli* strains isolated had resistance rates to third-generation cephalosporin with an overall resistance rate of 80% while *Citrobacter* spp had no resistance to a third-generation cephalosporin (Table 2). About 15 out of 28 (53.6%) isolates had multidrug-resistant (MDR) with a predominance of gram-negative bacteria 8/15(53.3%). On the other hand, the ESBL producing bacteria was observed in 3/10 (30%) of all the gram-negative bacteria. Additionally, MRSA was observed in 4/18 (22.2%) of the *S. aureus* isolates.

**Table 2: AMR patterns of bacteria causing bacteremia among the febrile pediatric patients with SCD**

| Isolates | | Proportion of antimicrobial resistance n (%) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bacteria species | N | SXT | GN | AMC | CIP | AMP | CRO | CAZ | CPM | MEM | FOX | P | DA | E |
| *K. pneumoniae* | 5 | 2(40) | 1(20) | 2 (40) | 5(100) | 1 (20) | 4 (80) | 4(80) | 4(80) | 0 | - | - | - | - |
| *E. coli* | 2 | 2(100) | 2(100) | 2(100) | 2(100) | 2(100) | 2(100) | 2(100) | 2(100) | 0 | - | - | - | - |
| *Acinetobacter* spp | 2 | 2(100) | 2(100) | 2(100) | 2(100) | 2(100) | 2(100) | 2(100) | 2(100) | 0 | - | - | - | - |
| *Citrobacter* spp | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | - | - | - | - |
| *S. aureus* | 18 | 14(78) | 6 (33) | - | 4 (22) | - | - | - | - | - | 4(22) | 14(78) | 4(22) | 10(56) |
| Overall | 28 | 20(71) | 11(39) | 6(60)* | 13(46) | 5 (50)* | 8 (80)* | 8(80)* | 8(80)* | | 4(22)# | 14(78)# | 4(22)# | 10(56)# |

N - Number of isolates, SXT - Trimethoprim-sulfamethoxazole, GN - Gentamycin, AMC - Amoxycillin-clavulanate, CIP - Ciprofloxacin, AMP - Ampicillin, CRO - Ceftriaxone, CAZ - Ceftazidime, CPM - Cefepime, MEM - Meropenem, FOX - Cefoxitin, P - Penicillin, DA - Clindamycin, E - Erythromycin, * Total isolates tested is 10; # Total isolates tested is 18.

**Factors associated with bacteremia**

Only sex and age were associated with bacteremia in univariate logistic regression analysis. Even after adjusting with other factors, febrile SCD patients aged 0-5 years had twice the odds of having bacteremia (AOR=2.1, 95% CI=1.2-6.9) compared to those aged above five years, p =0.04. Furthermore, the odds of having bacteremia among males were 1.5 times compared to females (AOR=1.5, 95% CI=1.1-3.9, p =0.03) (Table 3).

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**Table 3: Associated factors for bacteremia among febrile pediatric patients with SCD**

| Description | BSIs (n, %) | Univariate | | Multivariable | |
|---|---|---|---|---|---|
| | | COR (95%CI) | p-value | AOR (95%CI) | p-value |
| **Sex** | | | | | |
| Males (146) | 19(13.0) | 2.5 (1.2-5.3) | 0.015 | 1.5 (1.1-3.9) | 0.03 |
| Females (175) | 9(5.1) | 1 | | | |
| **Age** | | | | | |
| ≤ 5 years (196) | 24(12.2) | 3.0 (1.1-7.6) | 0.013 | 2.1 (1.2-6.9) | 0.04 |
| > 5 years (125) | 4(3.2) | 1 | | | |
| **PCV vaccination history** | | | | | |
| Yes (241) | 20 (8.3) | 0.9 (0.4-2.0) | 0.742 | | |
| No (80) | 8(10.0) | 1 | | | |
| **Prophylactic antibiotic use** | | | | | |
| Yes (66) | 3(4.5) | 0.8 (0.3-2.1) | 0.688 | | |
| No (121) | 25(17.7) | 1 | | | |
| **Antibiotic use in the past three weeks** | | | | | |
| Yes (80) | 5(6.3) | 1.0 (0.4-2.2) | 0.924 | | |
| No (241) | 23(9.5) | 1 | | | |
| **Co-infection** | | | | | |
| Malaria (33) | 1(3.0) | 0.3 (0.7-2.1) | 0.255 | | |
| HIV (8) | 0(0.0) | 1 | | | |

## Discussion

Our study suggests that a large proportion of children with SCD still acquire bacterial infections, with *S. aureus* being the leading aetiological agent. Consequently, there are high levels of penicillin resistance, the antibiotic used for prophylaxis. Furthermore, our findings showed that male children with SCD and those aged five years or below are more prone to bacterial infection. Also, the proportion of bacteremia observed in the current study is relatively higher than previous studies done in Kenya in 2009 and Tanzania in 2015 (15, 17) but slightly lower than a study in Cameroon and Nigeria in 2017 (11, 18). The variation in the proportion of bacteremia among children with SCD observed in these studies could be due to differences in sample size and variation in immunization coverage.

Our finding on the proportion of bacteremia in SCD is lower than findings from a systematic review conducted in 2020 which found that bacteremia in the African region ranges from 14 - 32% (11, 12). The consumption of antibiotics before presenting to a healthcare facility may account for the slightly lower proportion of bacteremia. At least a quarter of SCD patients had used penicillin or amoxicillin in the past three weeks before attending a healthcare facility. The

antibiotics might have inhibited the growth of some bacteria, including *S. pneumoniae,* and consequently lowered isolation rates. In addition, a high rate of PCV vaccination may have contributed to reducing the frequency of hospital attendances and/or admissions (19).

The current study found *S. aureus*, a gram-positive bacteria, the predominant cause of bacteremia in SCD. A similar study conducted in Dar es Salaam, Tanzania, in 2015 reported the same *S. aureus* as the leading cause of bacteremia among children with SCD (15). On the contrary, a study in Nigeria (20) and Kenya (17) revealed gram-negative bacteria and *S. pneumoniae,* respectively, the most cause of bacteremia episodes in SCD. Likewise, the spectrum of bacteria strains obtained in this study is almost the same as that observed in a study conducted in Uganda which found *K. pneumoniae, S. aureus,* and *Salmonella* spp the most prevalent strains (21). On the other hand, our findings are different from another similar study conducted in Kenya which reported *S. pneumoniae*, *non-Typhi Salmonella,* and *H. influenza type b,* the leading causes of bacteremia (17).

This current study found no *S. pneumoniae* strains from the blood culture of SCD patients similar to the study in the same region two years ago among children below five years (22). The similarity of findings in the two studies could have resulted from PCV vaccination. A study conducted in Kenya found that PCV vaccination was beneficial in preventing the acquisition of invasive bacteria, including pneumococcal strains among children with SCD (17). In addition, a study in Moshi, Tanzania, two years ago, reported the reduction of PCV13 serotypes colonization from 56% in 2013 to 23% in 2015 (23). It is thus tempting to assume that not being able to isolate any *S. pneumoniae* could be linked to exposure to PCV vaccination which may have reduced hospital attendance. The majority of the isolates were resistant to penicillin, co-trimoxazole, ceftriaxone, amoxicillin-clavulanic acid, and cefepime, with resistance rates ranging from 60 to 80%. However, all the gram-negative isolates were susceptible to meropenem. A study in Nigeria in 2018 also found increased resistance to ceftriaxone, co-trimoxazole, and ampicillin ranging from 56% to 78% (20). On the other hand, the current study found that majority of the gram-positive isolates had less resistance to gentamicin, clindamycin, and ciprofloxacin, with resistance patterns ranging from 22% to 46%. These findings are congruent with similar studies that found treatment with ciprofloxacin was still promising (20, 24).

The widely recommended penicillin prophylactic antibiotic showed a high resistance rate, highlighting the need to select a prophylactic antibiotic based on the current antibiogram pattern. The observed resistance to penicillin could be related to sub-optimal adherence to

prophylaxis. We found that more than a third of children with SCD on penicillin prophylaxis had non-optimal compliance. Another study in Kenya reported slightly higher compliance on penicillin prophylaxis (25). Additionally, this study found that the majority of the gram-negative isolates were more resistant to gentamicin than gram-positive isolates. A similar study conducted in Nigeria found a slightly lower resistance to gentamicin among the gram-negative bacteria (20). A somewhat higher proportion of gram-negative MDR strains isolated in this study may account for the difference in the resistance rates. Furthermore, the proportion of ESBL pathogens and MRSA recovered in this study was lower than reported findings on children below five years in the same region (22).

We assessed the association of children's characteristics with bacteremia: age and sex were directly associated with bacteremia. Children five years and below had twice the odds of acquiring bacteremia than children above five years of age. These findings agree with a study conducted in Nigeria three years ago which also found a higher proportion of bacteremia in children with SCD aged 1-2 years (20). Developing immunity as the child grows can explain the higher chances of bacteremia in children under five years. We also observed that males had more odds of having bacteremia than females. One study suggests that female children mount more robust humoral and cellular responses than their male counterparts (26), which could be beneficial in protecting and clearing a proportion of pathogens.

**Conclusion and recommendations**

Our study findings show that a large proportion of children with SCD still acquire bacterial infection with *S. aureus,* constituting most of the bacteremic episodes. Also, a high rate of resistance was observed towards penicillin and other commonly used antibiotics. We recommend continuing with routine culture and AST in order to guide the patient's management. Consequently, studies involving a large sample size should be conducted in order to provide sufficient data on AST pattern which will be useful even at the health facilities that lack culture services.

**Availability of data and materials**

The datasets used in this study are available and can be obtained from the corresponding author when requested.

**Conflict of interest**

The authors declare that there is no conflict of interest regarding the publication of this paper.

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The Tanzania Field Epidemiology and Laboratory Training (TFELTP) provided financial support for data collection but did not have any role in designing the study, data collection, analysis, and interpretation of data or writing the manuscript.

**Author Contribution**

SY, LU, RS, EM, DS, and AJ contributed to the study's design, analysis, and interpretation of data. SY, RS, DS, and EM collected the data. SY drafted the manuscript while LU, DK, MM, AJ, critically reviewed the manuscript. All authors read and approved the manuscript.

**Abbreviations**

| | |
|---|---|
| AMR | Antimicrobial Resistance |
| AST | Antimicrobial Susceptibility |
| ESBL | Extended Spectrum Beta-Lactamases |
| MDR | Multidrug Resistance |
| MRSA | Methicillin-resistant *Staphylococcus aureus* |
| SCD | Sickle Cell Disease |
| BMC | Bugando Medical Centre |
| PCV | Pneumococcal Conjugate Vaccination |

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