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Review Article

Sickle Cell Disease and Infections in High- and Low-Income Countries

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Abstract. Infections, especially pneumococcal septicemia, meningitis, and *Salmonella* osteomyelitis, are a major cause of morbidity and mortality in patients with sickle cell disease (SCD). SCD increased susceptibility to infection, while infection leads to SCD-specific pathophysiological changes. The risk of infectious complications is highest in children with a palpable spleen before six months of age. Functional splenectomy, the results of repeated splenic infarctions, appears to be a severe host-defense defect. Infection is the leading cause of death, particularly in less developed countries. Defective host-defense mechanisms enhance the risk of pneumococcal complications. Susceptibility to *Salmonella* infections can be explained at least in part by a similar mechanism. In high-income countries, the efficacy of the pneumococcal vaccine has been demonstrated in this disease. A decreased in infection incidence has been noted in SCD patients treated prophylactically with daily oral penicillin. Studies in low-income countries suggest the involvement of a different spectrum of etiological agents.

Keywords: Sickle cell disease; Infections; Prognosis; Prophylaxis; Socio-economics.

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Introduction. Sickle cell disease (SCD) represents an increasing global health problem. It corresponds to an autosomal recessive disorder in which structurally abnormal hemoglobin (HbS) leads to chronic hemolytic anemia and a variety of severe clinical manifestations. This disorder is caused by a point mutation. A single DNA base change leads to substitution of valine for glutamic acid at the 6th position on beta globin chain. SCD is one of the most common monogenic disorder.[1] SCD is mainly widespread throughout most of the African continent, the Middle East and India, and in localized areas in Mediterranean countries because of a selective advantage conferred by this disorder in protecting against *Plasmodium falciparum* malaria infection in heterozygotes.[2]

Because population movements, the distribution of SCD has spread far beyond non-endemic regions with an increase in the prevalence and genetic heterogeneity of hemoglobinopathies across the world.[3] The increase of inherited hemoglobin disorders will represent a severe global health burden for the future, both in high-income and lower-income countries.[4] In high-income countries, this increase is in part related to significant gains in life expectancy with a significant decrease in childhood mortality because of better newborn screening, antibiotic prophylaxis, and hydroxyurea therapy. Clinical outcomes have gradually improved over the years, mostly as a result of developments in supportive care and treatment with hydroxyurea, for

many years the sole approved pharmacologic therapy for SCD.[5] Hydroxyurea has multiple beneficial effects for patients with SCD. Hydroxyurea causes an increase in HbF, which interferes with the polymerization of HbS and reduces the frequency and severity of the painful crisis.[6] Hydroxyurea also lowers the leukocyte and platelets counts and improves blood rheology. Vaso-occlusion typically causes acute complications, including ischemic damage of tissues. With growing evidence of the safety and efficacy of hydroxyurea, its use has increased in high- and lower-income countries, but it continues to be underused.[7] Alongside hydroxyurea, novel therapeutic agents inducing HbF are currently under investigations.[8] The survival of children with SCD approaches that of unaffected children.[9] However, this does not always apply to patients in lower-income countries because disease management remains costly, with full access to care only for the most privileged.[10] Life expectancy among African people with SCD is probably less than 20 years.[11] Although over the last decade childhood mortality has been reduced, mortality among children younger than five years remains as high as 90%.[12] Increased early mortality in Africa among children with SCD is primarily due to increased risk of infection.[13] The lack of basic health care infrastructures often limits in most of these countries the development of management and prevention of the disease. Furthermore, a much more severe course of the disease is usually observed in patients living in low-income countries compared to genetically similar patients living in the northern hemisphere because of environmental factors.[14]

This short review summarizes published data regarding infections in SCD, including interactions with environmental factors, and their specificities according to patients living in high- or low-income countries in order to improve patients' care and to guide future areas for research.

Environmental Determinants SCD and Infections. Non-genetic factors have been shown to influence the outcome of SCD. Potential relevant environmental factors include the climate and air quality, housing and socio-economic status, physical activities, each of which being able to impact on SCD outcome. However, study results are confusing and sometimes conflicting because of the complex relationships between environmental factors and potential infections. The rate of HbS polymerization is dependent on hypoxia, pH, temperature, and patient's hydration, which could be altered by environmental factors.[15] However, inconsistencies among studies, especially according to high- or lower-income countries, may reflect differences in housing and social factors. Cold weather can cause increased infections and peripheral vasoconstriction leading to higher deoxygenation.[15] Increased blood viscosity and cold diuresis could participate in increased sickle pain in cold winter months.[16] However, if studies conducted in both high-income countries and lower-income countries reported a relationship between cold weather and acute pain,[17-19] this was not confirmed by others.[20,21] Conversely, fresh accommodation may be important in tropical countries by protecting patients from the effects of extreme heat.[15] Similarly, higher wind speeds have been associated with increased hospital admissions for pain.[22,23] Both high and low humidity have also been associated with increased hospital admissions for pain.[22] Increased episodes of pain were reported during the rainy season under tropical climates,[17] but not in Western countries with rainy climates.[22] Air pollution has also been reported as a leading cause of illness in SCD. There is also evidence of a relationship between tobacco smoke and SCD through infections, inflammation, oxidative stress and endothelial dysfunction.[24,25] Socio-economic factors influence the course of SCD. Increased poverty is associated with a worth outcome in which infections may play significant part.[26] Deficiencies in micronutrients could affect immune function and contribute to susceptibility to infection. Suppressed cell-mediated immunity with zinc deficiency and decreased nucleoside phosphorylase activity has been described in SCD.[27] Giving supplementation has been shown to increase levels of IL-2, a cytokine needed for expansion and maintenance of T cells, and reduce the incidence of bacterial infections.[28]

Impaired Splenic Function in SCD and Infections. The spleen performs several essential host defense functions and plays a key role in the increased susceptibility to certain bacterial infections in SCD. As a phagocytic filter, it can nonspecifically survey and present intravascular antigen to T and B cells that reside in or transit through this lymphoid organ. The spleen is also an important site of IgM production and memory B-cell differentiation during primary humoral responses. It is responsible for generating antibody responses to polysaccharide antigens. Increased susceptibility to infections is observed in individuals undergoing splenectomy and in those with nonfunctioning spleens. In these situations, slow flow is created, enabling splenic macrophages to remove defective red blood cells and bacteria and to present antigen to lymphocytes.[29] A deficient opsonization due to a defect in the alternative pathway of complement has been demonstrated.[30] Impaired antibody formation may be the central factor responsible for the observed serum opsonizing defects. While macrophages directly recognize opsonized bacteria, poorly opsonized bacteria are only cleared effectively by the spleen. Such pathogens include encapsulated bacteria. The hyposplenic state observed in individuals with SCD is

initially reversible, then with repeated episodes of sickling and ischemic damage spleen shrinks to a small remnant and the individual is rendered asplenic.

Interactions Between SCD and Infections. SCD increased susceptibility to infection, while infection leads to SCD-specific pathophysiological changes (**Figure 1**). SCD can create an environment supporting infections. The vast majority of SCD patients live in low-income countries with high prevalence and transmission rates of infections. The potential mechanisms leading red cell sickling and vaso-occlusive crisis in SCD patients with infections have been recently reviewed focusing on the challenging issue of infectious diseases given the background immunodeficiency associated with SCD and the high prevalence of infections in underdeveloped countries.[31] Areas of necrotic bone act as foci for infection. Salmonella is the most common agent of cases of acute osteomyelitis in SCD (42% to 57%),[32,33] followed by *Staphylococcus aureus*, and then Gram-negative enteric bacteria.[34] Most of Salmonella infections were *Salmonella typhimurium*.[35] Infarctions of bowel secondary to microvascular occlusion favor gut bacteria to enter the bloodstream. *Edwardsiella tarda* is an enterobacterium that has been reported with increased incidence in SCD.[36] SCD also carries an increased risk of severe respiratory infections involving particularly Mycoplasma and Chlamydia.[37] Reversely, infection is one of the most common factors susceptible to induce crisis in SCD. Infection can lead to a range of complications in SCD. During infections, changes occurring at a cellular level predispose to crises. Circulating leukocytes and the levels of inflammatory cytokines increase. Adhesion molecule expressions increase on both the vascular endothelium and leukocytes. Leukocyte adhesion may be the initiating event in vaso-occlusive episodes, as microvascular occlusion occurs in post-capillary venules.[38] Cytotoxic proteins are produced and generate reactive O_2 radicals leading to oxidative damage. The sickling process is initially reversible when HbS is re-oxygenated, but dehydration increases HbS concentration leading to extensive polymerization and irreversible membrane damage. In addition, infections increase the risk of sickling by non-specific effects through fever, anorexia, nausea, vomiting, and diarrhea, which all contribute to dehydration.

Infections with Specific Pathogens in SCD.
Bacteria. Local infections can become systemic. High fever is a medical emergency in patients with SCD

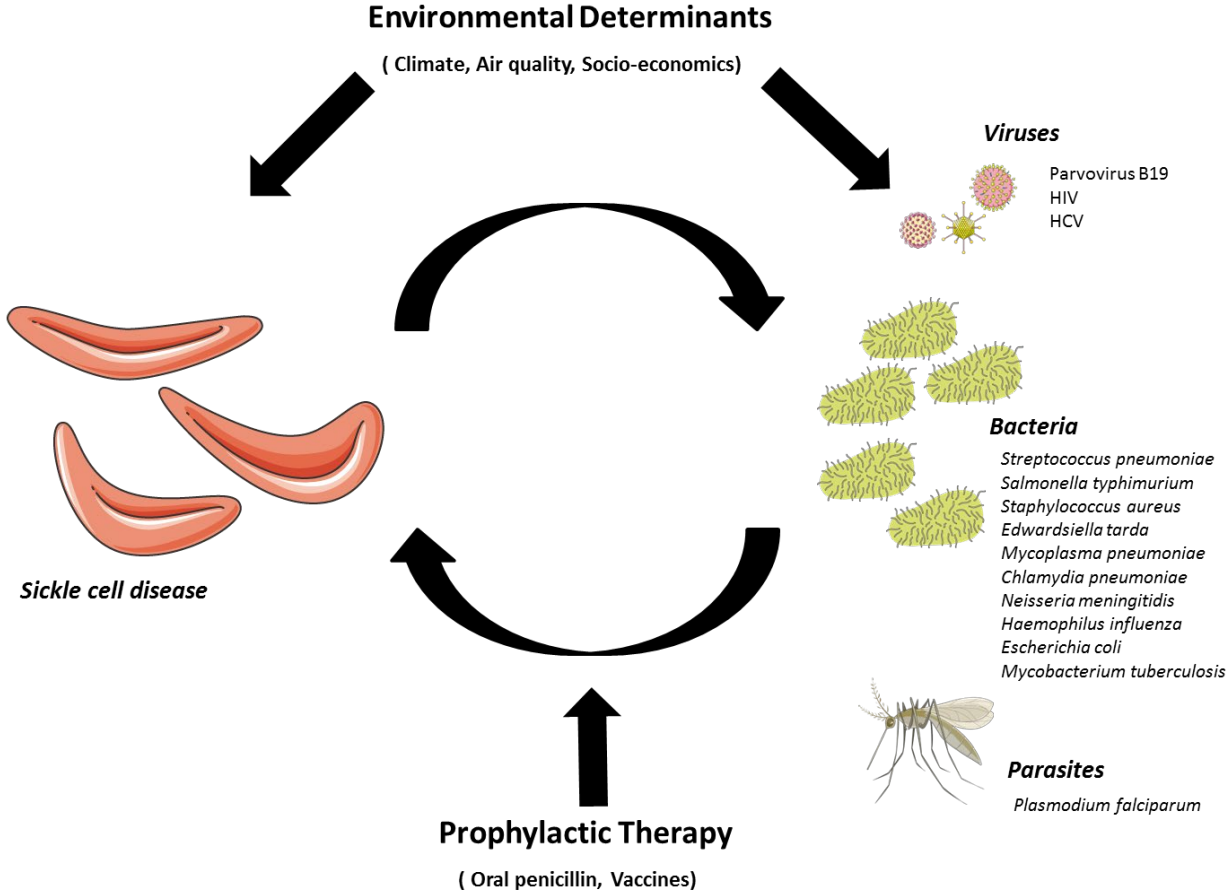

Figure 1. Relationship between SCD and infections under the potential influence of environmental determinants: SCD increases susceptibility to infections, while infections lead to SCD-specific pathophysiological changes. Prophylactic therapy could lead to substantial improvement in both low- and high-income countries.

since it can be the first sign of bacteremia, and a broad-spectrum parenteral antibiotic should be given without delay after obtaining samples for blood cultures. A wide variety of organisms have been reported to cause overwhelming sepsis, but the pneumococcus accounts for 50-70% of such infections, with the bulk of the remainder being accounted for *Neisseria meningitidis*, *Haemophilus influenza*, and to a lesser extent *Escherichia coli*. The typical presentation is that of septic shock, disseminated intravascular coagulopathy, and respiratory distress syndrome occurring in the absence of a primary site of infection.[39] Mortality can reach 35% to 50% from septicemia, and 10% in meningitis with a risk confined almost exclusively to young children. Additional immune deficits, including complement system deficit and reduced leukocyte function, are present and also predispose to bacterial infections.[40-42] These infections include *Escherichia coli* urinary tract infections, *Mycoplasma pneumonia* respiratory infections, dental infections, and cholecystitis caused by anaerobes. Polymorphisms of genes involved in the immune response also contribute to increased susceptibility to infection in SCD. Particular HLA II subtypes, polyphormisms of the FcR receptor, mannose-binding lectin, insulin-like growth factor 1 receptor, genes from the TGFβ/ bone morphogenetic protein pathway have been involved in an increased risk of bacteremia.[43]

Pneumococcal infections in patients with splenectomy follow a rapidly fatal clinical course. Disseminated intravascular coagulopathy may occur in these patients, and organisms can be demonstrated in peripheral blood smears. The first presentation of the disease may be sudden death due to overwhelming sepsis. The pneumococcus is the most common cause of bacteremia and meningitis in children with SCD. The incidence of invasive pneumococcal disease is 300-500 times higher in SCD than in the general population because of the loss of splenic filter function due to infarction. Prophylactic oral penicillin reduced the risk of invasive pneumococcal disease by 84% in children aged less than three years.[44] Fatal pneumococcal sepsis is now therefore rare in children with SCD in developed countries.[45] However, vigilance is still required because of the recent emergence of non-vaccine serotypes of *Streptococcus pneumonia*.[46]

Acute chest syndrome is the second most common cause of hospital admission in SCD and is responsible for 25% of deaths, particularly in early childhood.[47] Infection is one of the triggers of acute chest syndrome. Evidence of infection was found in one-third of cases, with a demonstration of isolated pathogens or sometimes found in combination.[38] Acute chest syndrome is common in young children in whom it is associated with viral respiratory infections. Acute chest syndrome could involve *Chlamydia pneumoniae* (14%), *Mycoplasma pneumoniae* (9%), and viruses in all patients with SCD regardless of age.

SCD predisposes to osteomyelitis, which results from secondary infection of the ischemic or avascular bone. It is often challenging to differentiate thrombotic marrow crisis from osteomyelitis in patients with SCD because they produce similar findings on radiographs, scans, and magnetic resonance imaging. Clinical features are mainly a single focus of pain, fever, and bacteremia.[48] However, children with SCD may have multiple sites of bone infection simultaneously. Early cultures of blood and stool offer the only clue to the correct diagnosis. There is no standardized approach to antibiotic therapy, and treatment is likely to vary from country to country.[49] Presumptive antibiotic therapy should include agents effective against *Salmonella.*[50] Indeed, the infecting organisms were mainly gram-negative rods. *Salmonella* species accounted for approximately 80%. Other microorganisms included *Staphylococcus aureus* and *Mycobacterium tuberculosis*. Empiric therapy should be directed against *Salmonella* and *Staphylococcus* until an organism is identified.

Studies on the etiological agents responsible for bacteremia in patients with SCD in African low-income countries are few. They, however, reveal a different spectrum of organisms than that observed in other parts of the world. In Africa, bacteremia was found in 14% to 32% in children with SCD. [51-54] This was much higher than the incidence observed in high-income countries.[55,56] Reversely, to what is observed in Western countries, pneumococcal infection in Africa does not contribute significantly to the morbidity and mortality of children with SCD because of the involvement of other infections, rending preventive measures inappropriate.[57] Gram-negative bacteremia constitute more than 60% of all isolates, while the predominant isolates were *Klebsiella pneumonia* (25%), *Staphylococcus aureus* (25%), and *Salmonella* species.[51,52,54,58-62] One given explanation for these discrepancies in terms of patterns of bacterial isolates was the unregulated use of antibiotics (mainly penicillins or penicillin derivatives) before hospital admission in some African countries, which could affect the results of bacterial cultures.[51,63] Increased resistance to commonly used antibiotics has been reported, but treatment with ciprofloxacin and some third-generation cephalosporin is still active.[61,64] Because infections by these agents are not vaccine-preventable, it has been suggested that disparity in terms of vaccinations among low-income and high-income countries may not account for the higher incidence of bacteremia in Africa, but could be explained by differences in terms of patient's immunity and environment.[51,65] In Africa, patients with SCD were shown to be at increased risk of contracting tuberculosis. They were shown to have significantly lower hematocrit and a higher level of circulating

sickle cells those patients without tuberculosis.[66]

Viruses. In SCD, Parvovirus B19 commonly causes a transient aplastic crisis which occurs in 65% to 80% of infections. It specifically infects erythroid progenitor cells resulting in a temporary cessation of erythropoiesis leading to severe anemia.[67] Although most children recover within two weeks, most of them require a blood transfusion. The aplastic crisis is uncommon after 15 years old.[68] Parvovirus aplastic crisis does not recur due to long-lasting humoral immunity. However, infections are observed among other household members in about 50% of cases because of the highly contagious features of the virus.[69]

HIV prevalence in SCD patients varies between 0% and 11.5% in published studies.[70] Few data are available regarding the impact of coexistent HIV infection and SCD. However, this represents a challenge, particularly in Africa, where both conditions are highest, and resources are low. Both diseases have a common risk for stroke, splenic dysfunction, avascular necrosis, and pulmonary arterial hypertension. HIV infection increases the risk of sepsis and bacterial infection, mainly of pneumococcal infection.[71] However, both diseases seem to interact closely. HIV infection tends to decrease the risk of vaso-occlusive crisis while SCD seems to improve the frequency of HIV long-term non-progressors.[72] Interactions of antiretroviral therapy with SCD have been demonstrated. A better understanding of the interactions between these diseases would lead to better treatment approaches, especially in regions of co-prevalence.

At least 10% of adult sickle cell patients are hepatitis C-virus (HCV) positive and often have liver dysfunction.[73] Although the incidence of transfusion-acquired infection has decreased; the risk is still present. The HCV antibody positivity is directly related to the number of transfusions given.[74] Iron overload following blood transfusions is additive to the liver damage caused by HCV infection. The standard of care for patients with chronic HCV infection combines interferon and ribavirin. Ribavirin (a guanosine nucleoside analog used to treat HCV) can also increase hemolysis in patients with SCD. In order to decrease the severity of ribavirin-related hemolysis, it has been suggested to pre-treat HCV patients with hydroxyurea to increase HbF.[75] Transfusions may not be the primary route of HCV transmission in lower-income countries.[76] Practices, such as circumcision and medicinal and other scarifications, may be additional risk factors.

Parasites. The tropical environment within which most of the SCD patients live has a very high prevalence of parasitic diseases. Malaria is a significant pathogen in SCD. It contributes to excess mortality among patients with SCD in Africa.[77,78] Immunological deficiencies due to SCD render children with SCD particularly vulnerable to malaria. Although homozygous SCD is known to confer higher resistance to malaria, the co-existence of SCD and malaria is associated with increased morbidity and mortality. Malaria is the most common cause of crisis via a massive release of inflammatory cytokines. The parasite is both erythrocytotropic and erythrocytopathic. Infected red cells sickle as a result of metabolic changes induced by the replicating parasites with cells becoming extremely adherent to the vascular endothelium promoting stasis and vaso-occlusive crisis.[79] In Africa, the tropical rainy season has been shown to be associated with increased frequency of vaso-occlusive crisis in relationship with increased stagnant surface waters ideal for reproduction and survival of mosquito vectors for the malaria parasites.[79] Splenectomized individuals with *Plasmodium falciparum* have reduced clearance of parasitized red blood cells and can cause dyserythropoiesis and chronic hemolysis leading to folate-deficiency anemia.[80] Long-term prophylaxis has been shown to lower the incidence of crisis and to reduce mortality.[81]

A higher prevalence of protozoan and helminthic intestinal parasites in SCD patients has been reported as a result of their weak immune response to infection.[82] A study from Nigeria showed that anemia in SCD patients might be exacerbated by intestinal parasites, and suggested that these patients should have regular stool examinations.[83] Infections were predominantly due to soil-transmitted helminths and protozoans, strongly associated with poverty and poor hygiene. In addition, intestinal parasites may cause iron deficiency, which could favor cell aggregation.

Pneumonitis-induced hypoxia and increased eosinophil counts due to tropical parasitic diseases may increase cell adhesion to vascular endothelium predisposing to red cell sickling and vaso-occlusive crisis.[79] This condition includes Loffler's syndrome in ascariasis and ancylostomiasis, schistosomiasis, filariasis, and larva migrans in toxocariasis.

Urinary schistosomiasis is a major cause of chronic illness endemic in Africa in both rural and urban communities with significant socioeconomic and public health burden. A Nigerian study showed that urinary schistosomiasis adversely affected the severity and prognosis of SCD.[84] SCD patients with schistosomiasis had lower hematocrit and higher reticulocyte count due to hematuria. Higher reticulocyte, leucocyte, and thrombocyte counts increase viscosity and accounts for the higher frequency of vaso-occlusive crisis. Schistosomiasis was also associated with a higher prevalence of secondary urinary tract infections including *Salmonella* species, *Escherichia coli*, *Klebsiella* and *Staphylococcus* species.

Prophylactic Therapy. Screening programs have been established in high-income countries, and begin to be developed in lower-income countries with a very high prevalence of SCD. However, even if diagnostic tests can be quickly introduced in these lower-income countries, preventive interventions not always follow, 85 including penicillin prophylaxis in children[44] and pneumococcal vaccine.[86] Such interventions, currently used in high-income countries, could save millions of lives if implemented in lower-income countries.

Since the end of the 80s, prophylactic oral penicillin V has been shown to reduce the risk of invasive pneumococcal disease by 84% in children aged less than three years, with minimal adverse reactions.[44,87] This simple intervention was rapidly recommended with a beginning of administration at 3 months in children with homozygous state for βS (HbSS) and variants sickle-β0-thalassemia ($HbS\beta^0$) and doses of 62.5 mg twice daily until one year, 125 mg twice daily between one and 5 years, and 250 mg twice daily after 5 years old.[88,89] Erythromycin is a suitable alternative in case of penicillin allergy. For children with heterozygous state sickle-hemoglobin C disease (HbSC) and variants sickle-β+-thalassemia ($HbS\beta^+$), hyposplenism occurring later, practice varies among centers. However, penicillin prophylaxis is usually considered starting at age 4-5 years or for a history of pneumococcal sepsis or surgical splenectomy.[90] The duration of penicillin prophylaxis remains controversial. The absence of significant benefit has been suggested to stop prophylaxis after five years,[89] long-term administration being a potential source of resistance development.[91] However, guidelines for asplenic patients recommend that penicillin prophylaxis be continued lifelong.[92]

Another major key in the prevention of infection is vaccination. Early studies with vaccination against pneumococcal bacteria suggested a 50% reduction of invasive pneumococcal disease.[93] The current vaccines should protect against 75% of infections, with another 14% prevented via cross-protection. For all forms of SCD, the standard vaccine series of childhood should be considered, including the 13-valent pneumococcal conjugate vaccine. The 23-valent pneumococcal polysaccharide vaccine should also be given at two years (and 5-yearly after that) at least two months after the 13-valent vaccine. Other vaccines are lifesaving in children with SCD. The 4-valent meningococcal conjugate vaccine should be given at two years with re-immunization considered at 5-year intervals. Annual influenza immunization should be offered (**Table 1**).[89] It is expected that Salmonella vaccines may be useful in people with SCD, especially in resource-poor settings.[94] In addition, meningitidis A and C vaccination and malaria prophylaxis should be recommended for travel to endemic areas.

Table 1. Immunization recommendations for all forms of SCD.

Vaccine	Age
Diphteria/tetanus/pertussis/Haemophilus influenza/polio 13-valent pneumococcal vaccine	2 months
Diphteria/tetanus/pertussis/Haemophilus influenza/polio Meningitis C	3 months
Diphteria/tetanus/pertussis/Haemophilus influenza/polio Meningitis C 13-valent pneumococcal vaccine	4 months
Hepatitis B Haemophilus influenza Meningitis C	12 months
Hepatitis B 13-valent pneumococcal vaccine Measles/mumps/rubella	13 months
Hepatitis B	18 months
23-valent pneumococcal vaccine	2 years
23-valent pneumococcal vaccine	7 years
23-valent pneumococcal vaccine	12 years
23-valent pneumococcal vaccine	17 years
Influenza	Annually from 6 months

Conclusions. Infection is a major determinant of the outcome in patients with SCD. It represents the primary cause of premature deaths among children with SCD in Africa. A substantial proportion of invasive pneumococcal and *Haemophilus influenza* type B disease could be attributable to SCD.[13] The burden of SCD in Africa warrants a strong emphasis on infection prevention, as recently stated by the World Health Organization, which pointed to "the urgent need to develop models of care appropriate to the management of SCD in sub-Saharan Afric".[95] While encapsulated bacterial agents are recognized as the most important microbes associated with severe illness, there is evidence that SCD increases the risk for several

other infections that warrant additional preventive measures. In this setting, better identification of risk factors could have, through the development of appropriate public health policies, an immediate impact in preventing complications in these patient populations. Simple measures such as better hygiene with hand-washing, avoidance of food contamination, nutritional supplementation can reduce infection risk.[96] Although in a lesser extent, infections in high-income countries can also contribute to morbidity and mortality among patients with SCD, especially in children. However, with current multidisciplinary care, almost all children with SCD in developed countries now survive to adulthood. The burden of mortality has now shifted to adults. Early identification of infections and their prompt treatment can avoid severe complications. However, treatment of the most common bacterial infections in SCD is not based on the results of randomized controlled trials but based on consensus guidelines, clinical experience or adapting treatment applied on other diseases, leading to wide variations in treatment among institutions.[97] Primary interventions, including penicillin prophylaxis and vaccinations, have led to substantial improvement in higher-income countries.[98] Recent studies showed a different problematic in non-developed countries with a different spectrum of organisms involved in severe infections, and highlighted the rarity of Streptococcus pneumonia, adding to the debate regarding the need for pneumococcal vaccines in this setting.[51]

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