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# The effects of vaccines in patients with sickle cell disease: a systematic review protocol

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## ABSTRACT

### Introduction

Sickle cell disease (SCD) is an inherited haematological disorder caused by a single point mutation (Glub6Val) that promotes polymerization of haemoglobin (Hb) S and sickling of erythrocytes. Inflammation, haemolysis, microvascular obstruction, and organ damage characterize the highly variable clinical expression of SCD. People with sickle cell disease are at increased risk of severe infections hence the need for vaccination against common disease causing organisms in this population. We aim to assess the efficacy and safety of vaccines in people with SCD.

### Methods and Analysis

The present systematic review will examine the current data as indexed in PubMed, CENTRAL, EMBASE, EBSCOHost, conference abstracts, reference lists of relevant articles, and WHO ICTRP trial registry. Two authors will independently screen search outputs, select studies, extract data, and assess risk of bias; resolving discrepancies by discussion and consensus between the two authors or arbitration by a third author when necessary. We will perform a meta-analyses for clinically homogenous studies. Should studies be clinically diverse, we will do a narrative synthesis of the findings. In either case, we will use GRADE to assess the strength of the available evidence.

**Ethics and dissemination**: The study draws on data that are readily available in the public domain, hence no formal ethical review and approval is required. The findings of this review will be disseminated through conference presentations and a publication in a peer-reviewed journal.

**Registration details**: This systematic review is under registration with the International Prospective Register of Systematic Reviews (PROSPERO), ID 84051.



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## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review of randomised controlled trials will provide the best level of evidence to inform policy on vaccination in sickle cell disease.
- It will provide a summary of all existing reviews addressing the effects of vaccines in people living with sickle cell disease.
- It will review the evidence on areas where no systematic review currently exists.
- We will assess the quality of the evidence found using GRADE.

## INTRODUCTION

Sickle cell disease (SCD) is a group of inheritable blood disorders that is caused by the substitution of valine for glutamic acid at the sixth position of the β-globin subunit of the haemoglobin molecule. This genetic mutation which is inherited as an autosomal recessive trait, promotes polymerization of hemoglobin (Hb) S and sickling of erythrocytes. Inflammation, hemolysis, microvascular obstruction, and organ damage characterize the highly variable clinical expression of SCD resulting in structural variations of the normal adult haemoglobin (Hb) A.[1] SCD presents in several forms with the most prevalent and severe form being the homozygous form (Hb SS), which results from the inheritance of the βs mutation from both parents. Other forms commonly seen include the Hb SC and Hb S/β-thalassaemia.[2]

SCD was initially identified in malaria endemic zones but now has a wide distribution globally as a result of migration.[3] It is estimated that 305,800 babies are born each year with SCD worldwide with nearly 75% of the births occurring in sub-Saharan Africa (SSA).[4] As a result of migration and improved quality of care, its global burden has increased.[5] Despite this high incidence, there is currently no effective public health programs in any SSA country focused on SCD.[5–8] As a consequence, up to 90% of infants with SCD in SSA are believed to die needlessly by five years, mostly as a result of infections.[9,1011,12]

People living with sickle cell are at increased risk of infection. They present with an enlarged spleen during the first decade of life, which progressively atrophies due to repeated vaso-occlusion and infarction, resulting in "auto-splenectomy". [13] "Auto-splenectomy" often occurs around 5 years of age and causes a loss of splenic function, making SCD patients



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particularly susceptible to encapsulated organisms which are often responsible for invasive infections. [14,15] A defect in compliment activation, impaired opsonisation,[16] decreased immune responses, [17] and genetic variations among patients with sickle cell disease further increase their susceptibility to infections. Genetic polymorphism of the human leukocyte antigen system and the haplotype of the β-globin gene cluster modulates the intrinsic susceptibility to bacteraemia in patients living with SCD. While some alleles such as the HLA class II DRB1*15 have been shown to be protective, others like the HLA class II DQB1*03 occur significantly more in patients with major infections, supporting an increase susceptibility of the latter to infections. [18,19]

The pathogens commonly associated with severe bacteraemia in sickle cell patients include *Streptococcus pneumoniae*, nontyphi *Salmonella species* and *Haemophilus influenzae* type b. Children with SCD experience more complications of influenza, with hospitalisation rates for influenza being 56 times higher than in children without SCD.[20,21] There is growing evidence that other pathogens such as *Staphylococcus sp, Salmonella typhimurium*, *Klebsiella pneumoniae*, *Escherichia coli, Acinetobacter* sp, *Enterobacter sp, parvovirus,* Hepatitis C virus (HCV) and Hepatitis B virus (HBV) cause severe morbidity and mortality. [22–30]

**Description of the intervention**

Immunizations with conjugate vaccines against *S. pneumoniae* and *Haemophilus influenza* type b have significantly reduced bacteraemia in sickle cell disease. [31–33] The introduction of pneumococcal conjugate vaccines resulted in a significant reduction of the incidence of invasive pneumococcal disease by 90.8% in children <2 years and 93.4% in children <5 years living with SCD. [34]

Two reviews aimed at assessing the efficacy, immunogenicity and safety of Conjugate *Haemophilus influenzae* type b vaccines and vaccines for preventing severe salmonella infections each highlight the absence of randomized controlled trials addressing this topic.[35,36]

**Why it is important to do this review**

Evidence from the West indicates that the institution of interventions such as newborn screening and penicillin prophylaxis can reduce this horrendous disease burden in SSA.[37] Such programs are credited with the ~70% reduction in mortality rate among children with SCD. [38,39] However, the death rate in adult SCD patients has not improved in the last thirty



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years, due to additional debilitating cardiovascular complications. [40–43] Hence disease prevention by vaccination is encouraged in this group of patients.

The routine immunization schedule of most countries is not sufficient for patients with SCD as they are more prone to infections.[12,25] People with sickle cell disease remain under-protected despite being vaccinated, as they do not maintain sufficient immunological responses to vaccines over time.[35,36] Furthermore, there is growing evidence that there are other pathogens such as *Salmonella typhimurium*, responsible for invasive disease in patients with sickle cell disease, especially in Africa. This implies that SCD patients require a vaccination schedule that is optimized and unique. This equally raises concerns as to the immune response generated by this population to other routine vaccines.

Studies performed to determine the safety, immunogenicity and effectiveness of vaccines prior to licensure often exclude immune compromised people such as sickle cell patients. Post licensure studies do include this group of patients, but often in small numbers, making the generalizability of their findings difficult. [44] Given that people with sickle cell disease particularly need these vaccines due to their defective immune system, it is important to determine the efficacy, safety, immunogenicity and effectiveness of routine vaccines amongst this population.

The review by Davies et al. provides evidence from randomized controlled trials on the immunogenicity of Pneumococcal vaccines in healthy people. However, the recommendation on the use of conjugate pneumococcal vaccines in people with sickle cell is based on evidence from observational studies.[45] Two systematic reviews have evaluated the efficacy and safety of the Conjugate *Haemophilus influenzae* type b vaccines, and vaccines for preventing invasive salmonella infections in SCD and found no randomized controlled trials addressing the subject. [36,35]

The authors of this review aim to determine the efficacy and safety of vaccines in reducing morbidity and mortality amongst children and adults with sickle cell disease. We will summarise all existing reviews addressing the effects of vaccines in people living with sickle cell, in addition to reviewing the evidence on areas where no systematic review currently exists.



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## METHODS AND ANALYSIS

### Types of studies:

We will summarize all other existing systematic reviews examining the efficacy and safety of vaccines in people with SCD.

For vaccines whose efficacy and safety have not been assessed by a systematic review, we plan to perform a systematic review that will include both cohort studies and interventional studies (randomized trials, quasi randomized trials and non-randomised trials)

### Types of participants

People with all forms of SCD (SS, SC, SD, Sß0, Sß+), irrespective of age, race, gender, or setting. The diagnosis of SCD must be confirmed by high performance liquid chromatography, Haemoglobin electrophoresis and sickle solubility test with family studies or DNA tests as appropriate.

### Types of interventions

Eligible interventions include any vaccine, compared to placebo, no vaccination, or a different vaccine

### Types of outcome measures

### Primary outcome

Mortality from vaccine preventable diseases after vaccination in children and adults living with SCD.

### Secondary outcomes

1. Vaccine immunogenicity as measured by antibody levels and serum opsonic activity
2. Acute morbidity (e.g. Incidence of infection, frequency of vaso-occlusive crises, acute chest syndrome)
3. Incidence and frequency of adverse events related to the vaccines



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### Search methods for identification of studies

The review authors will search for relevant studies in PubMed, CENTRAL, EMBASE, and EBCOHost from inception to the date the search strategy will be run. The terms sickle cell AND vaccines will be used to develop a comprehensive strategy. Eligible studies will be included irrespective of their language of publication or publication status.

We will review the advisory committee on immunization practices statements, conference abstracts, and the reference lists of retrieved included trials, and (systematic) reviews. We will also search Clinical trials.gov, and the WHO International Clinical Trials Registry for ongoing trials. Experts in the field of immunization and sickle cell disease will be contacted in order to access unpublished literature.

### Data collection and analysis

#### Selection of studies

Two authors [Alison Wiyeh (AW) and Leila Abdullahi (LA)] will independently examine the titles and abstracts of search outputs from the different sources of data for potentially eligible studies. Their results will be compared and disagreements resolved by discussion and consensus. A third Author (Charles Wiysonge CW) will arbitrate in situations where the two authors fail to reach consensus after discussions.

The full texts of the remaining potentially eligible studies will then be independently assessed to determine whether the studies meet the inclusion criteria. Discrepancies in the list of eligible studies between the two authors will be resolved through discussion and consensus and CW will be invited to resolve discrepancies when discussions fail. Excluded studies will be reported alongside their reason for exclusion.

#### Data extraction and management

Data will be extracted from eligible studies independently by two authors using a pre-structured and tested data collection form. The form will collect information on the study design, methods, participants, intervention details, outcomes and risk of bias. The information from the data extraction forms will then be entered into RevMan 5.1 (RevMan 2011) by one author and double checked by a second author for accuracy. Missing data considered to be important to this review will be obtained by contacting the authors of the studies involved.



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**Assessment of risk of bias in included studies**

The risk of bias of included studies will be independently assessed by two authors. The risk of bias in randomized studies will be assessed using the Cochrane risk of bias tool. [46] This tool evaluates methodological details relating to sequence generation, allocation concealment, blinding (participants, personnel and outcome assessment), incomplete outcome data and selective outcome reporting. Non randomized studies will be assessed for risk of bias using the ROBINS-I tool.[47]

**Measurement of treatment effects**

The vaccines will be grouped into two categories: Inactivated vaccines and live attenuated vaccines. For each vaccine all studies that meet the eligibility criteria will be included. Vaccine efficacy defined as the ability of the vaccine to reduce the number of cases of illness will be measured by calculating the relative risk reduction for each disease following vaccination alongside the 95% confidence intervals (95% CI). Immunogenicity will be determined by measuring the antibody levels and opsonic activity. The safety of vaccines will be measured by the proportion of patients with severe adverse advents (as defined by the included studies) and the proportion of patients who died following vaccine administration.

Risk ratios (RR), and the 95% confidence intervals will be calculated for dichotomous outcome data such as mortality, incidence of adverse events related to the vaccines. For continuous outcome data such as antibody levels, serum opsonic activity and frequency of vaso-occlusive crises, we will calculate the mean difference (MD) or standardised mean difference (SMD) as indicated, with their corresponding 95% CI.

**Data Synthesis**

The findings of this study will be presented in several tables. For each vaccine, there will be a table of included studies, detailing the setting, type of participants, vaccine, comparator, site of vaccine administration and outcomes. The risk of bias in included studies will be assessed and presented in a table.

Data from studies that are sufficiently similar will be combined using a meta-analysis with random effects model. Heterogeneity across studies will be determined using $I^2$ values. An $I^2$ value greater than 50% will be considered to imply substantial statistical heterogeneity. We will examine for statistical heterogeneity between study results using the $\chi 2$ test of



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homogeneity (with a significance α-level of 0.1). Heterogeneity will be explored using subgroup analysis and sensitivity analysis.

Data from studies that are not similar enough to be combined using a meta-analysis will be combined using narrative syntheses. We will assess publication bias using a funnel plot if more than 10 studies are available for each type of vaccine examined by this review. Finally, we will assess the strength of the evidence found using the GRADE approach.

**Ethics and dissemination**

This systematic review is under registration with the International Prospective Register of Systematic Reviews (PROSPERO), ID 84051. It will be drawn on data that is readily available on the public domain; hence does not require formal ethical review and approval. We plan to disseminate the findings of this systematic review through peer-reviewed journal publications and conference presentations.

**Author's contributions:** The study was conceived by MK, CW and AW. The study protocol was drafted by ABW and LA, reviewed and amended by all authors.

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**Competing interests statement:** The authors declare no conflicts of interest

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**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | Information reported |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | Yes |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | NA |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | Yes |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | Yes |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | Yes |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | Yes |
| Support: | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | Yes |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | Yes |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | Yes |
| **INTRODUCTION** | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | Yes |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | Yes |
| **METHODS** | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | Yes |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | Yes |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | Yes |

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| | | | |
|---|---|---|---|
| Study records: | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | Yes |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | Yes |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | Yes |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | Yes |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | Yes |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | Yes |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | Yes |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | Yes |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | Yes |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | Yes |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | Yes |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | Yes |

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# The effects of vaccines in patients with sickle cell disease: a systematic review protocol

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# The effects of vaccines in patients with sickle cell disease: a systematic review protocol

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## ABSTRACT

### Introduction

Sickle cell disease (SCD) is an inherited haematological disorder caused by a single point mutation (Glub6Val) that promotes polymerization of haemoglobin (Hb) S and sickling of erythrocytes. Inflammation, haemolysis, microvascular obstruction, and organ damage characterize the highly variable clinical expression of SCD. People with sickle cell disease are at increased risk of severe infections hence the need for vaccination against common disease causing organisms in this population. We aim to review the evidence on the efficacy and safety of vaccines in people with SCD.

### Methods and Analysis

The present systematic review will examine the current data as indexed in PubMed, CENTRAL, EMBASE, EBSCOHost. We will consult SAGE practice statements, conference abstracts, reference lists of relevant articles, WHO ICTRP trial registry and experts in the field. Two authors will independently screen search outputs, select studies, extract data, and assess risk of bias; resolving discrepancies by discussion and consensus between the two authors or arbitration by a third author when necessary. We will perform a meta-analyses for clinically homogenous studies. Evidence from clinically diverse studies will be aggregated using narrative synthesis of the findings. In either case, we will use GRADE to assess the strength of the available evidence.

**Ethics and dissemination**: The study draws on data that are readily available in the public domain, hence no formal ethical review and approval is required. The findings of this review will be disseminated through conference presentations and a publication in a peer-reviewed journal.

**PROSPERO registration number:** CRD42018084051.



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## STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This systematic review will provide a summary of all existing evidence addressing the effects of vaccines in people living with sickle cell disease and highlight gaps in the evidence for further research.
2. We will assess the certainty of the evidence found using the GRADE approach.
3. This review will include non-randomised studies which tend to over-estimate the efficacy of an intervention and are prone to selection bias.

## INTRODUCTION

Sickle cell disease (SCD) is a group of inheritable blood disorders that is caused by the substitution of valine for glutamic acid at the sixth position of the β-globin subunit of the haemoglobin molecule. This genetic mutation which is inherited as an autosomal recessive trait, promotes polymerization of haemoglobin (Hb) S and sickling of erythrocytes. Inflammation, hemolysis, microvascular obstruction, and organ damage characterize the highly variable clinical expression of SCD resulting in structural variations of the normal adult haemoglobin (Hb) A.[1] SCD presents in several forms with the most prevalent and severe form being the homozygous form haemoglobin SS, which results from the inheritance of the $\beta^S$ mutation from both parents. Other forms commonly seen include the haemoglobin C (HbC), haemoglobin C with haemoglobin S (HbSC), Haemoglobin S with β-thalassaemia (Hb S/β-thalassaemia) and haemoglobin S with other beta-globin variants such as haemoglobin D and O (HbSD and HbSO). People who inherit one $\beta^S$ mutation and one normal β gene carry the sickle cell trait which despite being associated with adverse health outcomes, is not considered a form of sickle cell disease.[2]

SCD was initially identified in malaria endemic zones but now has a wide distribution globally as a result of migration.[3] It is estimated that 305,800 babies are born each year with SCD worldwide with nearly 75% of the births occurring in sub-Saharan Africa (SSA).[4] As a result of migration and improved quality of care, its global burden has increased.[5] Despite this high incidence, there is currently no effective public health programs in any SSA country focused on SCD.[5–8] As a consequence, up to 90% of infants with SCD in SSA are believed to die needlessly by five years, mostly as a result of infections.[9–12]



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People living with sickle cell are at increased risk of infection. They present with an enlarged spleen during the first decade of life, which progressively atrophies due to repeated vaso-occlusion and infarction, resulting in "auto-splenectomy".[13] "Auto-splenectomy" often occurs around 5 years of age and causes a loss of splenic function, making SCD patients particularly susceptible to encapsulated organisms which are often responsible for invasive infections.[14,15] A defect in compliment activation, impaired opsonisation,[16] decreased immune responses,[17] and genetic variations among patients with sickle cell disease further increase their susceptibility to infections. Genetic polymorphism of the human leukocyte antigen system and the haplotype of the β-globin gene cluster modulates the intrinsic susceptibility to bacteraemia in patients living with SCD. While some alleles such as the HLA class II DRB1*15 have been shown to be protective, others like the HLA class II DQB1*03 occur significantly more in patients with major infections, supporting an increase susceptibility of the latter to infections.[18,19]

Despite initially controversy regarding the role of some pathogens such as *Streptococcus pneumoniae*,[20] there is now evidence suggesting that globally, *Streptococcus pneumonia*, nontyphi *Salmonella species* and *Haemophilus influenzae* type b are commonly associated with severe bacteraemia in sickle cell patients. Children with SCD experience more complications of influenza, with hospitalisation rates for influenza being 56 times higher than in children without SCD.[21–26] Also, pathogens such as *Staphylococcus sp, Salmonella typhimurium*, *Klebsiella pneumoniae*, *Escherichia coli, Acinetobacter* sp, *Enterobacter sp, parvovirus,* Hepatitis C virus (HCV) and Hepatitis B virus (HBV) cause severe morbidity and mortality in this population.[27–35]

**Description of the intervention**

Immunizations with conjugate vaccines against *S. pneumoniae* and *Haemophilus influenza* type b have significantly reduced bacteraemia in sickle cell disease.[36–38] The introduction of pneumococcal conjugate vaccines resulted in a significant reduction of the incidence of invasive pneumococcal disease by 90.8% in children <2 years and 93.4% in children <5 years living with SCD.[39]

**Why it is important to do this review**

There is evidence that the institution of interventions such as newborn screening and penicillin prophylaxis can reduce this horrendous disease burden.[22,40] Such programs are



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credited with the ~70% reduction in mortality rate among children with SCD.[41,42] As a result of the role vaccination plays in the prevention of diseases, it is recommended in this group of patients.[43] Considering the fact that SCD is becoming a globalized disease, with patients worldwide suffering from invasive diseases due to similar organisms, it is imperative to synthesis the global evidence regarding the effects of vaccines in this population.

The routine immunization schedule of most countries is not sufficient for patients with SCD as they are more prone to infections.[12,30] People with sickle cell disease remain under-protected despite being vaccinated, as they do not maintain sufficient immunological responses to vaccines over time.[44,45] Furthermore, there is growing evidence that there are other pathogens such as *Salmonella typhimurium*, responsible for invasive disease in patients with sickle cell disease, especially in Africa. This implies that SCD patients require a vaccination schedule that is optimized and unique. This equally raises concerns as to the immune response generated by this population to other routine vaccines.

Studies performed to determine the safety, immunogenicity and effectiveness of vaccines prior to licensure often exclude immune compromised people such as sickle cell patients. Post licensure studies do include this group of patients, but often in small numbers, making the generalizability of their findings difficult.[46] Given that people with sickle cell disease particularly need these vaccines due to their defective immune system, it is important to determine the efficacy, safety, immunogenicity and effectiveness of routine vaccines amongst this population.

The review by Davies et al. provides evidence from randomized controlled trials on the immunogenicity of Pneumococcal vaccines in healthy people. However, the recommendation on the use of conjugate pneumococcal vaccines in people with sickle cell is based on evidence from observational studies.[47] Two systematic reviews have evaluated the efficacy and safety of the Conjugate *Haemophilus influenzae* type b vaccines, and vaccines for preventing invasive salmonella infections in SCD and found no randomized controlled trials addressing the subject.[44,45] The objective of this study is to provide an up to date review of the evidence on the efficacy and safety of vaccines in reducing morbidity and mortality amongst people with sickle cell disease.



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## METHODS AND ANALYSIS

### Types of studies:

Randomised trials, non-randomised trials, and cohort studies are eligible for inclusion in this review.

### Types of participants

People with all forms of SCD (HbC, HbSC, HbS/$\beta^0$-thalassaemia, HbS/$\beta^+$-thalassaemia, HbSD or $HbSO_{Arab}$), irrespective of age, race, gender, or setting. The diagnosis of SCD must be confirmed by high performance liquid chromatography, Haemoglobin electrophoresis and sickle solubility test with family studies or DNA tests as appropriate. We will exclude studies in people with the sickle cell trait.[22]

### Types of interventions

Eligible interventions include any vaccine, compared to placebo, no vaccination, or a different vaccine

### Types of outcome measures

### Primary outcome

Mortality from vaccine preventable diseases after vaccination in children and adults living with SCD.

### Secondary outcomes

1. Vaccine immunogenicity as measured by antibody levels and serum opsonic activity
2. Acute morbidity (e.g. Incidence of infection, vaso-occlusive crises, acute chest syndrome)
3. Incidence of adverse events related to the vaccines

### Search methods for identification of studies

We will search for relevant studies in PubMed, CENTRAL, EMBASE, and EBSCOHost from inception to the date of the search. The terms sickle cell and vaccines will be used to develop a comprehensive search strategy (Supplementary material, Appendix 1).[45] Eligible studies will be included irrespective of their language of publication or publication status.



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We will also review reference lists of relevant reviews and included studies, meeting reports of the Strategic Advisory Group of Experts on Immunisation (SAGE), WHO vaccine position papers, abstracts of vaccine conferences held in the last five years, and the WHO International Clinical Trials Registry. In addition, we will provide the references of included studies to corresponding authors of included studies and ask them if they know of potentially eligible studies that we may have missed.

**Data collection and analysis**

**Selection of studies**

Two authors [Alison B. Wiyeh (ABW) and Leila Abdullahi (LA)] will independently examine the titles and abstracts of search outputs from the different sources of data for potentially eligible studies. Their results will be compared and disagreements resolved by discussion and consensus. A third Author (Charles Wiysonge CW) will arbitrate in situations where the two authors fail to reach consensus after discussions.

The full texts of the remaining potentially eligible studies will then be independently assessed to determine whether the studies meet the inclusion criteria. Discrepancies in the list of eligible studies between the two authors will be resolved through discussion and consensus and CW will be invited to resolve discrepancies when discussions fail. Excluded studies will be reported alongside their reason for exclusion.

**Data extraction and management**

Data will be extracted from eligible studies independently by two authors using a pre-structured and tested data collection form. The form will collect information on the study design, methods, participants, intervention details, outcomes, source of funding and risk of bias. The information from the data extraction forms will then be entered into RevMan 5.1 by one author and double checked by a second author for accuracy.[48] Missing data considered to be important to this review will be obtained by contacting the authors of the studies involved.

**Assessment of risk of bias in included studies**

The risk of bias of included studies will be independently assessed by two authors. The risk of bias in randomized studies will be assessed using the Cochrane risk of bias tool. This tool evaluates methodological details relating to sequence generation, allocation concealment,



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blinding (participants, personnel and outcome assessment), incomplete outcome data and selective outcome reporting. The risk of bias for each domain, will be classified as 'low', 'unclear' or 'high', depending on how adequately the criterion was addressed.[49] Non randomized studies will be assessed for risk of bias using the ROBINS-I tool.[50]

**Measurement of treatment effects**

The vaccines will be grouped into two categories: Inactivated vaccines and live attenuated vaccines. For each vaccine, all studies that meet the eligibility criteria will be included. Vaccine efficacy defined as the ability of the vaccine to reduce the number of cases of illness will be measured by calculating the relative risk reduction for each disease following vaccination alongside the 95% confidence intervals (95% CI). Immunogenicity will be determined by measuring the antibody levels and opsonic activity. The safety of vaccines will be measured by the proportion of patients with severe adverse advents (as defined by the included studies) and the proportion of patients who died following vaccine administration.

Risk ratios (RR), and the 95% confidence intervals will be calculated for dichotomous outcome data such as mortality, incidence of adverse events related to the vaccines. For continuous outcome data such as antibody levels, serum opsonic activity and frequency of vaso-occlusive crises, we will calculate the mean difference (MD) or standardised mean difference (SMD) as indicated, with their corresponding 95% CI.

**Data Synthesis**

The findings of this study will be presented in several tables. For each vaccine, there will be a table of included studies, detailing the country, type of participants, vaccine, comparator, site of vaccine administration, source of funding and outcomes. The risk of bias in included studies will be assessed and presented in a table.

We will aggregate the findings of included studies based on the vaccine type and the study population (children versus adults). Data from studies that are sufficiently similar will be combined using a meta-analysis with random effects model. Heterogeneity across studies will be determined using $I^2$ values. An $I^2$ value greater than 50% will be considered to imply substantial statistical heterogeneity. We will examine for statistical heterogeneity between study results using the $\chi 2$ test of homogeneity (with a significance $\alpha$-level of 0.1). Heterogeneity will be explored using subgroup analysis and sensitivity analysis.



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Subgroup analysis will be conducted for mortality from vaccine preventable diseases after vaccination and vaccine immunogenicity and incidence of acute morbidity. Subgroups will be defined by study design (RCTs vs non-RCTs) and the age of participant (children versus adults).

Data from studies that are not similar enough to be combined using a meta-analysis will be combined using narrative syntheses. We will assess publication bias using a funnel plot if more than 10 studies are available for each type of vaccine examined by this review. Finally, we will assess the strength of the evidence found using the GRADE approach which rates the quality of evidence for each outcome by taking into consideration the methodological quality, directness of evidence, heterogeneity, precision and risk of publication bias.[51,52]

**Ethics and dissemination**

This systematic review is registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42018084051. The review will draw on data which is readily available on the public domain; hence does not require formal ethical review and approval. This protocol was written following the PRISMA-P guidelines,[53] and the findings of this review and any amendments will be reported according to the PRISMA statement.[54] We plan to disseminate the findings of this systematic review through peer-reviewed journal publications and conference presentations.

**Authors' contributions:** ABW is the guarantor for this review. The study was conceived by MK, CW and AW. AW provided expertise on sickle cell disease, MK provided expertise on immunology and CW provided expertise on the systematic review methodology. The study protocol was drafted by ABW and LA, reviewed, amended and approved by all authors.

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**Competing interest declaration:** The authors declare no conflicts of interest.

**Patient consent**: Not applicable



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# Supplementary Material

## Appendix 1

## Search strategy for PubMed

| Search | Query | Items found |
|---|---|---|
| #35 | Search **#33 AND #34** | 326 |
| #34 | Search **Vaccine OR Vaccines** | 296558 |
| #33 | Search **"Anemias, Sickle Cell" OR "Sickle Cell Anemias" OR "Hemoglobin S Disease" OR "Disease, Hemoglobin S" OR "Hemoglobin S Diseases" OR "Sickle Cell Anemia" OR "Sickle Cell Disorders" OR "Cell Disorder, Sickle" OR "Cell Disorders, Sickle" OR "Sickle Cell Disorder" OR "Sickling Disorder Due to Hemoglobin S" OR "HbS Disease" OR "Sickle Cell Disease" OR "Cell Disease, Sickle" OR "Cell Diseases, Sickle" OR "Sickle Cell Disease"** | 24896 |

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**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | Information reported | Page number |
|---|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | | |
| Title: | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | Yes | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | NA | |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | Yes | 2 |
| Authors: | | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | Yes | 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | Yes | 9 and 1 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | Yes | 9 |
| Support: | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | Yes | 9 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | Yes | 9 |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | Yes | 9 |
| **INTRODUCTION** | | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | Yes | 5 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | Yes | 5 |
| **METHODS** | | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | Yes | 6 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | Yes | 6-7 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that | Yes | Appendix 1, |

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| | | | | |
|---|---|---|---|---|
| | | it could be repeated | | supplementary material |
| Study records: | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | Yes | 7 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | Yes | 7 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | Yes | 7 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | Yes | 7 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | Yes | 6 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | Yes | 7 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | Yes | 8 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | Yes | 8-9 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | Yes | 9 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | Yes | 9 |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | Yes | 9 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | Yes | 9 |

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BMJ Open

# The effects of vaccines in patients with sickle cell disease: a systematic review protocol

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| Primary Subject Heading: | Haematology (incl blood transfusion) |
| Secondary Subject Heading: | Public health, Immunology (including allergy) |
| Keywords: | sickle cell disease, Vaccines, Immunization |
| | |

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# The effects of vaccines in patients with sickle cell disease: a systematic review protocol

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## ABSTRACT

### Introduction

Sickle cell disease (SCD) is an inherited haematological disorder caused by a single point mutation (Glub6Val) that promotes polymerization of haemoglobin (Hb) S and sickling of erythrocytes. Inflammation, haemolysis, microvascular obstruction, and organ damage characterize the highly variable clinical expression of SCD. People with sickle cell disease are at increased risk of severe infections hence the need for vaccination against common disease causing organisms in this population. We aim to review the evidence on the efficacy and safety of vaccines in people with SCD.

### Methods and Analysis

The present systematic review will examine the current data as indexed in PubMed, CENTRAL, EMBASE, EBSCOHost. We will consult SAGE practice statements, conference abstracts, reference lists of relevant articles, WHO ICTRP trial registry and experts in the field. Two authors will independently screen search outputs, select studies, extract data, and assess risk of bias; resolving discrepancies by discussion and consensus between the two authors or arbitration by a third author when necessary. We will perform a meta-analyses for clinically homogenous studies. Evidence from clinically diverse studies will be aggregated using narrative synthesis of the findings. In either case, we will use GRADE to assess the strength of the available evidence.

**Ethics and dissemination**: The study draws on data that are readily available in the public domain, hence no formal ethical review and approval is required. The findings of this review will be disseminated through conference presentations and a publication in a peer-reviewed journal.

**PROSPERO registration number:** CRD42018084051.



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## STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This systematic review will include both published and unpublished literature, hence reducing the risk of publication bias.
2. Duplicate and independent screening and data extraction will minimize the risk of error when identifying eligible studies and extracting relevant data.
3. This review will include non-randomised studies which tend to over-estimate the efficacy of an intervention and are prone to selection bias.

## INTRODUCTION

Sickle cell disease (SCD) is a group of inheritable blood disorders that is caused by the substitution of valine for glutamic acid at the sixth position of the β-globin subunit of the haemoglobin molecule. This genetic mutation which is inherited as an autosomal recessive trait, promotes polymerization of haemoglobin (Hb) S and sickling of erythrocytes. Inflammation, hemolysis, microvascular obstruction, and organ damage characterize the highly variable clinical expression of SCD resulting in structural variations of the normal adult haemoglobin (Hb) A.[1] SCD presents in several forms with the most prevalent and severe form being the homozygous form haemoglobin SS, which results from the inheritance of the $\beta^S$ mutation from both parents. Other forms commonly seen include the haemoglobin C (HbC), haemoglobin C with haemoglobin S (HbSC), Haemoglobin S with β-thalassaemia (Hb S/β-thalassaemia) and haemoglobin S with other beta-globin variants such as haemoglobin D and O (HbSD and HbSO). People who inherit one $\beta^S$ mutation and one normal β gene carry the sickle cell trait which despite being associated with adverse health outcomes, is not considered a form of sickle cell disease.[2]

SCD was initially identified in malaria endemic zones but now has a wide distribution globally as a result of migration.[3] It is estimated that 305,800 babies are born each year with SCD worldwide with nearly 75% of the births occurring in sub-Saharan Africa (SSA).[4] As a result of migration and improved quality of care, its global burden has increased.[5] Despite this high incidence, there is currently no effective public health programs in any SSA country focused on SCD.[5–8] As a consequence, up to 90% of infants with SCD in SSA are believed to die needlessly by five years, mostly as a result of infections.[9–12]



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People living with sickle cell are at increased risk of infection. They present with an enlarged spleen during the first decade of life, which progressively atrophies due to repeated vaso-occlusion and infarction, resulting in "auto-splenectomy".[13] "Auto-splenectomy" often occurs around 5 years of age and causes a loss of splenic function, making SCD patients particularly susceptible to encapsulated organisms which are often responsible for invasive infections.[14,15] A defect in compliment activation, impaired opsonisation,[16] decreased immune responses,[17] and genetic variations among patients with sickle cell disease further increase their susceptibility to infections. Genetic polymorphism of the human leukocyte antigen system and the haplotype of the β-globin gene cluster modulates the intrinsic susceptibility to bacteraemia in patients living with SCD. While some alleles such as the HLA class II DRB1*15 have been shown to be protective, others like the HLA class II DQB1*03 occur significantly more in patients with major infections, supporting an increase susceptibility of the latter to infections.[18,19]

Despite initially controversy regarding the role of some pathogens such as *Streptococcus pneumoniae*,[20] there is now evidence suggesting that globally, *Streptococcus pneumonia*, nontyphi *Salmonella species* and *Haemophilus influenzae* type b are commonly associated with severe bacteraemia in sickle cell patients.[12,21–26] Children with SCD have more hospitalisations,[23,27] and complications from influenza than children without SCD.[28] Also, pathogens such as *Staphylococcus sp, Salmonella typhimurium*, *Klebsiella pneumoniae*, *Escherichia coli, Acinetobacter* sp, *Enterobacter sp, parvovirus,* Hepatitis C virus (HCV) and Hepatitis B virus (HBV) cause severe morbidity and mortality in this population.[29–37]

Immunizations with conjugate vaccines against *S. pneumoniae* and *Haemophilus influenza* type b have significantly reduced bacteraemia in sickle cell disease.[38–40] The introduction of pneumococcal conjugate vaccines resulted in a significant reduction of the incidence of invasive pneumococcal disease by 90.8% in children <2 years and 93.4% in children <5 years living with SCD.[41]

**Why it is important to do this review?**

There is evidence that the institution of interventions such as newborn screening and penicillin prophylaxis can reduce this horrendous disease burden.[22,42] Such programs are credited with the ~70% reduction in mortality rate among children with SCD.[43,44] As a result of the role vaccination plays in the prevention of diseases, it is recommended in this group of patients.[45] Considering the fact that SCD is becoming a globalized disease, with



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patients worldwide suffering from invasive diseases due to similar organisms, it is imperative to synthesis the global evidence regarding the effects of vaccines in this population.

The routine immunization schedule of most countries is not sufficient for patients with SCD as they are more prone to infections.[12,32] People with sickle cell disease remain under-protected despite being vaccinated, as they do not maintain sufficient immunological responses to vaccines over time.[46,47] Furthermore, there is growing evidence that there are other pathogens such as *Salmonella typhimurium*, responsible for invasive disease in patients with sickle cell disease, especially in Africa. This implies that SCD patients require a vaccination schedule that is optimized and unique. This equally raises concerns as to the immune response generated by this population to other routine vaccines.

Studies performed to determine the safety, immunogenicity and effectiveness of vaccines prior to licensure often exclude immune compromised people such as sickle cell patients. Post licensure studies do include this group of patients, but often in small numbers, making the generalizability of their findings difficult.[48] Given that people with sickle cell disease particularly need these vaccines due to their defective immune system, it is important to determine the efficacy, safety, immunogenicity and effectiveness of routine vaccines amongst this population.

The review by Davies et al. provides evidence from randomized controlled trials on the immunogenicity of Pneumococcal vaccines in healthy people. However, the recommendation on the use of conjugate pneumococcal vaccines in people with sickle cell is based on evidence from observational studies.[49] Two systematic reviews have evaluated the efficacy and safety of the Conjugate *Haemophilus influenzae* type b vaccines, and vaccines for preventing invasive salmonella infections in SCD and found no randomized controlled trials addressing the subject.[46,47] The objective of this study is to provide an up to date review of the evidence on the efficacy and safety of vaccines in reducing morbidity and mortality amongst people with sickle cell disease.



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## METHODS AND ANALYSIS

### Types of studies:

Randomised trials, non-randomised trials, and cohort studies are eligible for inclusion in this review.

### Types of participants

People with all forms of SCD (HbC, HbSC, HbS/$\beta^0$-thalassaemia, HbS/$\beta^+$-thalassaemia, HbSD or $HbSO_{Arab}$), irrespective of age, race, gender, or setting. The diagnosis of SCD must be confirmed by high performance liquid chromatography, Haemoglobin electrophoresis and sickle solubility test with family studies or DNA tests as appropriate. We will exclude studies in people with the sickle cell trait.[22]

### Types of interventions

Eligible interventions include any vaccine, compared to placebo, no vaccination, or a different vaccine

### Types of outcome measures

### Primary outcome

Mortality from vaccine preventable diseases after vaccination in children and adults living with SCD.

### Secondary outcomes

1. Vaccine immunogenicity as measured by antibody levels and serum opsonic activity
2. Acute morbidity (e.g. Incidence of infection, vaso-occlusive crises, acute chest syndrome)
3. Incidence of adverse events related to the vaccines

### Search methods for identification of studies

We will search for relevant studies in PubMed, CENTRAL, EMBASE, and EBSCOHost from inception to the date of the search. The terms sickle cell and vaccines will be used to develop a comprehensive search strategy (Supplementary material, Appendix 1).[47] Eligible studies will be included irrespective of their language of publication or publication status.



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We will also review reference lists of relevant reviews and included studies, meeting reports of the Strategic Advisory Group of Experts on Immunisation (SAGE), WHO vaccine position papers, abstracts of vaccine conferences held in the last five years, and the WHO International Clinical Trials Registry. In addition, we will provide the references of included studies to corresponding authors of included studies and ask them if they know of potentially eligible studies that we may have missed.

**Data collection and analysis**

**Selection of studies**

Two authors [Alison B. Wiyeh (ABW) and Leila Abdullahi (LA)] will independently examine the titles and abstracts of search outputs from the different sources of data for potentially eligible studies. Their results will be compared and disagreements resolved by discussion and consensus. A third Author (Charles Wiysonge CW) will arbitrate in situations where the two authors fail to reach consensus after discussions.

The full texts of the remaining potentially eligible studies will then be independently assessed to determine whether the studies meet the inclusion criteria. Discrepancies in the list of eligible studies between the two authors will be resolved through discussion and consensus and CW will be invited to resolve discrepancies when discussions fail. Excluded studies will be reported alongside their reason for exclusion.

**Data extraction and management**

Data will be extracted from eligible studies independently by two authors using a pre-structured and tested data collection form. The form will collect information on the study design, methods, participants, intervention details, outcomes, source of funding and risk of bias. The information from the data extraction forms will then be entered into RevMan 5.1 by one author and double checked by a second author for accuracy.[50] Missing data considered to be important to this review will be obtained by contacting the authors of the studies involved.

**Assessment of risk of bias in included studies**

The risk of bias of included studies will be independently assessed by two authors. The risk of bias in randomized studies will be assessed using the Cochrane risk of bias tool. This tool evaluates methodological details relating to sequence generation, allocation concealment,



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blinding (participants, personnel and outcome assessment), incomplete outcome data and selective outcome reporting. The risk of bias for each domain, will be classified as 'low', 'unclear' or 'high', depending on how adequately the criterion was addressed.[51] Non randomized studies will be assessed for risk of bias using the ROBINS-I tool.[52]

**Measurement of treatment effects**

The vaccines will be grouped into two categories: Inactivated vaccines and live attenuated vaccines. For each vaccine, all studies that meet the eligibility criteria will be included. Vaccine efficacy defined as the ability of the vaccine to reduce the number of cases of illness will be measured by calculating the relative risk reduction for each disease following vaccination alongside the 95% confidence intervals (95% CI). Immunogenicity will be determined by measuring the antibody levels and opsonic activity. The safety of vaccines will be measured by the proportion of patients with severe adverse advents (as defined by the included studies) and the proportion of patients who died following vaccine administration.

Risk ratios (RR), and the 95% confidence intervals will be calculated for dichotomous outcome data such as mortality, incidence of adverse events related to the vaccines. For continuous outcome data such as antibody levels, serum opsonic activity and frequency of vaso-occlusive crises, we will calculate the mean difference (MD) or standardised mean difference (SMD) as indicated, with their corresponding 95% CI.

**Data Synthesis**

The findings of this study will be presented in several tables. For each vaccine, there will be a table of included studies, detailing the country, type of participants, vaccine, comparator, site of vaccine administration, source of funding and outcomes. The risk of bias in included studies will be assessed and presented in a table.

We will aggregate the findings of included studies based on the vaccine type and the study population (children versus adults). Data from studies that are sufficiently similar will be combined using a meta-analysis with random effects model. Heterogeneity across studies will be determined using $I^2$ values. An $I^2$ value greater than 50% will be considered to imply substantial statistical heterogeneity. We will examine for statistical heterogeneity between study results using the $\chi 2$ test of homogeneity (with a significance $\alpha$-level of 0.1). Heterogeneity will be explored using subgroup analysis and sensitivity analysis.



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Subgroup analysis will be conducted for mortality from vaccine preventable diseases after vaccination and vaccine immunogenicity and incidence of acute morbidity. Subgroups will be defined by study design (RCTs vs non-RCTs) and the age of participant (children versus adults).

Data from studies that are not similar enough to be combined using a meta-analysis will be combined using narrative syntheses. We will assess publication bias using a funnel plot if more than 10 studies are available for each type of vaccine examined by this review. Finally, we will assess the strength of the evidence found using the GRADE approach which rates the quality of evidence for each outcome by taking into consideration the methodological quality, directness of evidence, heterogeneity, precision and risk of publication bias.[53,54]

**Ethics and dissemination**

This systematic review is registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42018084051. The review will draw on data which is readily available on the public domain; hence does not require formal ethical review and approval. This protocol was written following the PRISMA-P guidelines,[55] and the findings of this review and any amendments will be reported according to the PRISMA statement.[56] We plan to disseminate the findings of this systematic review through peer-reviewed journal publications and conference presentations.

**Authors' contributions:** ABW is the guarantor for this review. The study was conceived by MK, CW and AW. AW provided expertise on sickle cell disease, MK provided expertise on immunology and CW provided expertise on the systematic review methodology. The study protocol was drafted by ABW and LA, reviewed, amended and approved by all authors.

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**Competing interest declaration:** The authors declare no conflicts of interest.

**Patient consent**: Not applicable



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## Search strategy for PubMed

| Search | Query | Items found |
|---|---|---|
| #35 | Search **#33 AND #34** | 326 |
| #34 | Search **Vaccine OR Vaccines** | 296558 |
| #33 | Search **"Anemias, Sickle Cell" OR "Sickle Cell Anemias" OR "Hemoglobin S Disease" OR "Disease, Hemoglobin S" OR "Hemoglobin S Diseases" OR "Sickle Cell Anemia" OR "Sickle Cell Disorders" OR "Cell Disorder, Sickle" OR "Cell Disorders, Sickle" OR "Sickle Cell Disorder" OR "Sickling Disorder Due to Hemoglobin S" OR "HbS Disease" OR "Sickle Cell Disease" OR "Cell Disease, Sickle" OR "Cell Diseases, Sickle" OR "Sickle Cell Disease"** | 24896 |

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**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | Information reported | Page number |
|---|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | | |
| Title: | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | Yes | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | NA | |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | Yes | 2 |
| Authors: | | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | Yes | 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | Yes | 9 and 1 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | Yes | 9 |
| Support: | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | Yes | 9 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | Yes | 9 |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | Yes | 9 |
| **INTRODUCTION** | | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | Yes | 4 and 5 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | Yes | 5 |
| **METHODS** | | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | Yes | 6 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | Yes | 6-7 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that | Yes | Appendix 1 |

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| | | | | |
|---|---|---|---|---|
| | | it could be repeated | | supplementary material |
| Study records: | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | Yes | 7 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | Yes | 7 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | Yes | 7 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | Yes | 7 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | Yes | 6 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | Yes | 7 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | Yes | 8 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | Yes | 8-9 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | Yes | 9 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | Yes | 9 |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | Yes | 9 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | Yes | 9 |

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