

BMJ Open 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 (Glu6Val) that promotes polymerisation of haemoglobin S and sickling of erythrocytes. Inflammation, haemolysis, microvascular obstruction and organ damage characterise the highly variable clinical expression of SCD. People with SCD 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 and EBSCOHost. We will consult Strategic Advisory Group of Experts 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-analysis for clinically homogenous studies. Evidence from clinically diverse studies will be aggregated using narrative synthesis of the findings. In either case, we will use the GRADE approach 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.

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 (Hb) molecule. This genetic mutation, which is inherited as an autosomal recessive trait, promotes polymerisation of Hb S and sickling of erythrocytes. Inflammation, haemolysis, microvascular obstruction and organ damage characterise the highly variable clinical expression of SCD

Strengths and limitations of this study

- This systematic review will include both published and unpublished literature, hence reducing the risk of publication bias.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

resulting in structural variations of the normal adult 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 β^S mutation from both parents. Other forms commonly seen include the Hb C (HbC), Hb C with Hb S (HbSC), Hb S with β -thalassaemia (Hb S/ β -thalassaemia) and Hb S with other β -globin variants such as Hb D and O (HbSD and HbSO). People who inherit one β^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 SCD.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 programme in any SSA country focused on SCD.³⁻⁸ As a consequence, up to 90% of infants with SCD in SSA are believed to die needlessly by 5 years, mostly as a result of infections.⁹⁻¹²

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 patients with SCD particularly susceptible to encapsulated organisms which are often responsible for invasive infections.^{14 15} A defect in complement activation, impaired opsonisation,¹⁶ decreased immune responses¹⁷ and genetic variations among patients with SCD further increase their susceptibility to infections. Genetic polymorphism of the human leucocyte antigen (HLA) 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 increased 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, *S. pneumoniae*, non-typhi *Salmonella* sp 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 and hepatitis B virus cause severe morbidity and mortality in this population.^{20 29–36}

Immunisations with conjugate vaccines against *S. pneumoniae* and *H. influenzae* type b have significantly reduced bacteraemia in SCD.^{37–39} 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.⁴⁰

Why is it 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 41} Such programmes are credited with the ~70% reduction in mortality rate among children with SCD.^{42 43} As a result of the role vaccination plays in the prevention of diseases, it is recommended in this group of patients.⁴⁴ Considering the fact that SCD is becoming a globalised disease, with patients worldwide suffering from invasive diseases due to similar organisms, it is imperative to synthesise the global evidence regarding the effects of vaccines in this population.

The routine immunisation schedule of most countries is not sufficient for patients with SCD as they are more prone to infections.^{12 31} People with SCD remain under-protected despite being vaccinated, as they do not maintain sufficient immunological responses to vaccines over time.^{45 46} Furthermore, there is growing evidence that there are other pathogens such as *S. typhimurium*,

responsible for invasive disease in patients with SCD, especially in Africa. This implies that patients with SCD require a vaccination schedule that is optimised 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. Postlicensure studies do include this group of patients, but often in small numbers, making the generalisability of their findings difficult.⁴⁷ Given that people with SCD particularly need these vaccines due to their defective immune system, it is important to determine the efficacy, safety, immunogenicity and effectiveness of routine vaccines among this population.

The review by Davies *et al*⁴⁸ provides evidence from randomised controlled trials (RCT) 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. Two systematic reviews have evaluated the efficacy and safety of the conjugate *H. influenzae* type b vaccines, and vaccines for preventing invasive salmonella infections in SCD and found no RCTs addressing the subject.^{45 46} 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 among people with SCD.

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/ β^0 -thalassaemia, HbS/ β^+ -thalassaemia, HbSD or HbSO_{Arab}), irrespective of age, race, gender or setting. The diagnosis of SCD must be confirmed by high-performance liquid chromatography, Hb 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 with 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 (eg, 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 (online supplementary appendix 1).⁴⁶ Eligible studies will be included irrespective of their language of publication or publication status.

We will also review the reference lists of relevant reviews and included studies, meeting reports of the Strategic Advisory Group of Experts on immunisation, WHO vaccine position papers, abstracts of vaccine conferences held in the last 5 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 (ABW and LHA) 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 (CSW) 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 CSW 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 prestructured 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 V.5.1 by one author and double-checked by a second author for accuracy.⁴⁹ 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 randomised studies will be assessed using the Cochrane risk of bias tool. This tool evaluates methodological details relating to sequence generation, allocation concealment, 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.⁵⁰ Non-randomised studies will be assessed for risk of bias using the Risk Of Bias in Non-randomized Studies - of Interventions (ROBINS-I tool).⁵¹

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% CIs. 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 events (as defined by the included studies) and the proportion of patients who died following vaccine administration.

Risk ratios and the 95% CIs 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 or standardised mean difference 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 vs 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 χ^2 test of homogeneity (with a significance α level of 0.1). Heterogeneity will be explored using subgroup analysis and sensitivity analysis.

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 vs 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.^{52 53}

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 are readily available on the public domain; hence does not require formal ethical review and approval. This protocol was written following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines,⁵⁴ and the findings of this review and any amendments will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.⁵⁵ We plan to disseminate the findings of this systematic review through peer-reviewed journal publications and conference presentations.

Contributors ABW is the guarantor for this review. The study was conceived by MK, CSW and AW. AW provided expertise on sickle cell disease, MK provided expertise on immunology, and CSW provided expertise on the systematic review methodology. The study protocol was drafted by ABW and LHA, and reviewed, amended and approved by all authors.

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Disclaimer The sponsors played no role in the design of the protocol, writing of the report and in the decision to submit the protocol for publication.

Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

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