Vaccines for preventing invasive salmonella infections in people with sickle cell disease (Review)

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[Intervention Review]

Vaccines for preventing invasive salmonella infections in people with sickle cell disease

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ABSTRACT

Background

Salmonella infections are a common bacterial cause of invasive disease in people with sickle cell disease especially children, and are associated with high morbidity and mortality rates. Although available in some centres, people with sickle cell anaemia are not routinely immunized with salmonella vaccines. This is an update of a previously published Cochrane Review.

Objectives

To determine whether routine administration of salmonella vaccines to people with sickle cell disease reduces the morbidity and mortality associated with infection.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register which comprises of references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.

We also conducted a search of the LILACS database.

Date of most recent searches: 05 May 2015.

Selection criteria

We planned to select all randomized controlled trials that compared the use of either the inactivated vaccine or an oral attenuated vaccine with a placebo among people with sickle cell disease. Equally, studies that compared the efficacy of one vaccine type over another were to be selected for the review.

Data collection and analysis

No trials of salmonella vaccines in people with sickle cell disease were found.

Main results

There is an absence of randomized controlled trial evidence relating to the scope of this review.

Authors' conclusions

It is expected that salmonella vaccines may be useful in people with sickle cell disease, especially in resource-poor settings where the majority of those who suffer from the condition are found. Unfortunately, there are no randomized controlled trials on the efficacy and safety of the different types of salmonella vaccines in people with sickle cell disease. We conclude that there is a need for a well-designed, adequately-powered, randomized controlled trial to assess the benefits and risks of the different types of salmonella vaccines as a means of improving survival and decreasing mortality from salmonella infections in people with sickle cell disease.

PLAIN LANGUAGE SUMMARY

Vaccines for preventing severe salmonella infections in people with sickle cell disease

Salmonella organisms are probably second only to pneumococcus among bacterial causes of infection in people with sickle cell disease. Infection with these bacteria can lead to complications and reduce the quality of life of people with the disease and sometimes result in death. Immunization with salmonella vaccines is one of the interventions available to reduce infection by these bacteria. There are different types of vaccines available: the inactivated vaccines and the oral vaccines. We did not find any randomized controlled trials assessing these vaccines in people with sickle cell diseases. We therefore conclude that there is a need for a randomized controlled trial to assess the benefits and risks of the different types of vaccines to evaluate the potential for improving survival and decreasing mortality from salmonella infections in people with sickle cell disease.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) refers to a group of inherited conditions where there is abnormal haemoglobin (Hb) production. This includes the homozygous HbSS (inheritance of HbS from each parent), and heterozygous states such as HbSC (inheritance of HbS from one parent and HbC from another). Sickle cell trait occurs when there is inheritance of a normal Hb from one parent and a sickle cell Hb from another. Sickle cell disease is widely believed to have originated from the malarial regions of the world where the trait has been sustained due to the conferred advantage against malaria infection (Aidoo 2002). Thus regions with indigenous prevalence of the condition include Africa, South Asia, and the Mediterranean. Migration has extended the geographical distribution of SCD to the wider African Diaspora and now the disease is found all over the world (Davies 1997). The gene is widely distributed with trait prevalence ranging from 1% to 40% of the different populations at risk and the highest frequencies occurring in Africa (Davies 1997). Among people with SCD, mortality is highest in the first five years of life between 2% and 30% (Overturf 1977; Vichinsky 1988; Serjeant 1994).

Infections account for a substantial percentage of the high mortality. Bacteria that commonly cause severe infections are the encapsulated organisms (Adeyokunnu 1980; Bennet 1990; Wright 1997; Elbashier 2003). The most common bacteria that cause invasive infections in SCD are pneumococcus species followed by salmonella species (Magnus 1999; Wierenga 2001). Salmonella septicaemia has been described as an overlooked complication of SCD (Wright 1997). Other bacteria that have been implicated as aetiologic agents in invasive infections in SCD are *Haemophilus influenzae type b*, *Escherichia coli* and *Klebsiella spp* (Magnus 1999; Wierenga 2001). Salmonella invasive disease occurs more frequently in children with SCD than in adults with the same condition. It is a common cause of septicaemia in people with SCD (Wright 1997; Elbashier 2003).

This population also has a high susceptibility to salmonella osteomyelitis (Adeyokunnu 1980; Ebong 1986; Bennet 1990). Salmonella organisms (especially the non-typhoidal serotypes *Salmonella typhimurium, Salmonella enteritidis, Salmonella choleraesuis,* and *Salmonella paratyphi B*) are the commonest cause of osteomyelitis in this group of people. Salmonella organisms are reported to be two to five times more common among people with SCD than *Staphyloccocal aureus* (Adeyokunnu 1980; Burnett 1998), which is the commonest cause of osteomyelitis among non-SCD patients. People with SCD suffer much from bone infection caused by salmonella species because their white blood cells lack the component that usually enables them to destroy the bacteria (Constantopoulos 1973).

There are two main options to the management of SCD: preventive and supportive. Preventive measures include administra-

tion of regular prophylactic penicillin, immunization (against both pneumococcus and haemophilus) and education and support for parents caring for these children. A Cochrane Systematic Review has shown immunization with conjugate pneumococcal vaccines against pneumococcus infection to be useful in people with SCD (Davies 2004). Immunization against invasive salmonella disease, though available, is not given routinely to people with SCD.

Description of the intervention

Three types of salmonella vaccines are available today: the whole cell vaccine and the two newer Ty21a and Vi vaccines. The whole cell vaccine, consisting of relatively crude preparations of *Salmonella typhi* (*S. typhi*) administered parenterally, have been found to be effective, but have a high incidence of side effects (Yug Ty Comm 1964; Ashcroft 1967). Two vaccines developed more recently, Ty21a (an attenuated strain of *S. typhi* administered orally) and Vi (the purified bacterial capsule, given parenterally), have appeared less toxic than the older whole cell vaccines and are thought to be equally effective (Bennish 1995). Both vaccines have been licensed for use in the USA and several other countries. All the vaccines currently available for salmonella disease are specific for *S. typhi*, as vaccines for non-typhoidal salmonella are not yet licensed for use in humans.

Why it is important to do this review

There is one systematic review on salmonella vaccines in the general population (Engels 1998). However, the review did not assess the usefulness of salmonella vaccines among people with SCD, a group that appears to be in a position to benefit from routine use of salmonella vaccines. Whether any of the available vaccines would be useful in preventing invasive salmonella disease in people with SCD is uncertain. A clearer understanding of typhoid vaccine efficacy and toxicity among these individuals will be useful especially for physicians in developing nations. We therefore aim to conduct a systematic review of available evidence to evaluate the usefulness or otherwise of salmonella vaccines in people with SCD.
This is an update of previously published versions of this review (Odey 2009).

OBJECTIVES

To determine whether routine administration of salmonella vaccines to people with SCD reduces the morbidity and mortality associated with infection.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

People with SCD including SS, SC, SD, Sß0, Sß+ (confirmed by Hb electrophoresis and sickle solubility test, with family studies or DNA tests as appropriate) of all ages and both sexes, in any setting.

Types of interventions

We had planned to review all studies that compared the use of either the inactivated vaccine or an oral attenuated vaccine with a placebo. Studies that also compare the efficacy of one vaccine type over another were to be examined as follows:

1. inactivated vaccine versus placebo;
2. oral attenuated vaccine versus placebo;
3. inactivated vaccine versus oral attenuated vaccine.

Types of outcome measures

Primary outcomes

1. Acute morbidity from salmonella infection (e.g. vaso-occlusive, hyperhaemolytic, sequestration and aplastic crises; septicaemia; pneumonia; meningitis;osteomyelitis; acute chest syndrome)
2. Mortality from salmonella infection

Secondary outcomes

1. Chronic complications from salmonella infection (e.g. osteoarthrosis; septic arthritis; stroke; cerebral thrombosis; renal papillary nephrosis; nephrotic syndrome; chronic leg ulcer; priapism)
2. Immunogenicity of vaccines (antibody levels, serum opsonic activity)
3. Quality of life measures
   i) limitation of physical activity
   ii) limitation in role activity
   iii) frequency of bodily pains
   iv) perception of general health
   v) absence from school
   vi) lost time at work
   vii) frequency of hospitalization

Adverse effects

We also planned to note any reported unacceptable adverse events associated with the use of these vaccines.

Search methods for identification of studies

There was no language restriction on included studies and we arranged to translate and report on any relevant non-English papers.

Electronic searches

We searched for relevant randomized controlled trials from the Group's Haemoglobinopathies Trials Register using the terms: sickle cell AND immunization AND vaccine AND salmonella.
The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), and weekly searches of MEDLINE. Unpublished work was identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology Conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Health Research Council Meetings; and the National Sickle Cell Disease Program Annual Meeting.
For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group.
Date of the most recent search of the Groups Haemoglobinopathies Trials Register: 05 May 2015.
In addition to the above search, we conducted a further subject-specific electronic search of LILACS on the 26 June 2014 for all publication years. Please refer to the appendices section for further details (Appendix 1).

Searching other resources

We examined the reference lists of any potential clinical trials and the review authors' personal databases of trial reports in an attempt to identify any additional studies or those not identified in the searches. We also attempted to contact investigators of included studies by either conventional or electronic mail to ask for details of additional published and unpublished trials.

Data collection and analysis

We did not apply the process described below, as we were not able to identify any trials eligible for inclusion in this review. However, we will apply the methods outlined below should we identify any eligible trials for inclusion in this systematic review in the future.

Selection of studies

Two authors Friday Odey (FO) and Uduak Okomo (UO) will independently assess the abstracts of studies resulting from the searches. We will obtain full copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision. We will also assess the full text papers independently and resolve any disagreement on the eligibility of included studies through discussion and consensus. Any discrepancies occurring in the trial selection will be resolved by the third author (AO). After assessment, we will eliminate from further review any remaining studies that do not match the inclusion criteria and note the reasons for their exclusion in the Characteristics of excluded studies table.

Data extraction and management

Two authors (FO and AO) will independently extract the data. One authors (FO) will enter the data into the Review Manager software (RevMan 2014), while the second author (AO) will confirm that any data entered are accurate. The authors will seek advice from the Cochrane Cystic Fibrosis and Genetic Diseases Group with regards to data synthesis when necessary.
We will collect outcome data using a pre-determined form designed for this purpose. Extracted data will be entered into Review Manager (RevMan 2014). Friday Odey (FO) will hold the master copy. We aim to resolve any disagreements regarding data entry through discussion between the authors. If necessary, we will seek advice from the editor. We will record the following information.

1. Study methods
   i) method of allocation
   ii) masking of participants and outcomes
   iii) exclusion of participants after randomization and proportion of losses at follow-up
2. Participants
   i) country of origin
   ii) number of participants
   iii) age
   iv) sex
   v) inclusion and exclusion criteria
3. Intervention
   i) type of the vaccine
   ii) dose
   iii) route of administration
   iv) duration and length of time in follow-up
4. Control
   i) control or placebo
5. Outcomes
   i) primary and secondary outcomes listed in 'Types of outcome measures'. We will use dichotomous and continuous variables in analysing data. We will use this information to help assess heterogeneity and the external validity of the trials.

Assessment of risk of bias in included studies

In order to assess the risk of bias, two authors (FO and UO) will assess the selected studies independently and assess every study reporting a randomized clinical trial according to the system described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will compare the assessments and discuss and resolve any inconsistencies in the interpretation of inclusion criteria and their significance to the selected studies. We will assess the risk of bias as follows.

1. Randomization

These will be assessed as either 'low risk', 'unclear risk', or 'high risk' of bias. Those assessed as 'low risk' will include, for example, methods such as: computer-generated or table of random numbers, drawing of lots, coin-toss, shuffling cards or throw of a dice. We will assess as 'unclear risk', studies stated as being randomised, but where no description of the methods used to allocate participants to treatment group was given. We will judge as 'high risk' methods of randomisation such as use of case record number, date of birth, or alternate numbers.

2. Concealment of allocation

We will assess this as 'low risk', 'unclear risk', or 'high risk' of bias. Those assessed as 'low risk' will include use of a central independent randomisation unit or sequentially numbered sealed opaque envelopes. We will assess as 'unclear risk' if the method used to conceal the allocation was either not described, or not described in sufficient detail to enable a judgement to be made. We will make the judgment of 'high risk' if there was an open allocation sequence and the participants and study investigators could potentially foresee the upcoming assignment.

3. Blinding of outcomes assessment

We will assess blinding using the following criteria (detection and performance bias):
a. blinding of participants;
b. blinding of caregiver;
c. blinding of outcome assessment.
We will assess this as 'low risk', 'unclear risk', or 'high risk' of bias. Those assessed as 'low risk' will include no blinding (where a judgement is made that the outcome and outcome assessment are not likely to be influenced by lack of blinding) and blinding of participants and key trial personnel ensured, and unlikely that blinding could have been broken. We will assess as 'unclear risk' where there was insufficient information to permit judgement of 'Yes' or 'No' or where the trial did not address the outcome. We will judge as 'high risk', for example, where there had been no blinding or incomplete blinding, and the outcome assessment was likely to be influenced by this; or where blinding of key trial participants and personnel was attempted, but likely that it was broken.

4. Handling of withdrawals and losses

The authors will grade this as 'low risk'), 'unclear risk', or 'high risk' of bias. This will be according to whether:
a. there will be a clear description given of the difference between the two groups of losses to follow-up and;
b. reasons will be given why participants withdrew or were lost to follow-up (attrition bias).
Studies including 90% or more of randomized participants in the analysis shall be graded as 'low risk' and studies with less than 90% in the analysis, will be graded as 'high risk', and 'unclear risk' if it is not reported. Reasons for withdrawal or loss to follow-up will be explored and presented in additional tables.

5. Selective outcome reporting

We planned to assess this as 'low risk', 'unclear risk', or 'high risk' of bias. Those assessed as 'low risk' will to include, for example, where the trial protocol is available and where all the pre-specified outcomes have been reported in the pre-specified way. We will assess as 'unclear risk' where there is insufficient information to permit judgement of 'low risk' or 'high risk'. We will judge as 'high risk', for example, where not all of the trial's pre-specified primary outcomes have been reported; and where one or more reported primary outcomes where not pre-specified (unless clear justification provided).

6. Other sources of potential bias

We planned to state any important concerns about bias not addressed in the other domains in the tool.

Measures of treatment effect

For the dichotomous outcome variables of each individual study (e.g. acute morbidity from salmonella infection (any cause); mortality; chronic complications (any cause); serum opsonic activity; limitation of physical or role activity; absence from school or work), we will calculate the odds ratio (OR). The authors also plan to report count data during the effective period of the vaccine as the endpoint may occur more than once. We will also calculate the summary weighted odds ratios and 95% confidence intervals (CIs) (fixed-effect model) using the Review Manager software (RevMan 2014). Numbers-needed-to-treat (NNT) and their 95% CIs will be calculated from the pooled OR and its 95% CI for a specific baseline risk, which is the sum of all the events in the control groups (in all studies) divided by the total participant numbers in control groups in all studies using an online calculator (Cates 2003).
For continuous outcomes (antibody levels; frequency of bodily pains; frequency of hospitalisation), we will record the mean relative change from baseline for each group or mean post-treatment or post-intervention values and standard deviation. If standard errors are reported, we will calculate the standard deviations. We will

then calculate a pooled estimate of treatment effect by the mean difference and 95% CI (fixed-effect model) again using Review Manager (RevMan 2014).

Dealing with missing data

If data are missing from the published studies, then the authors will contact the study investigators for clarification.

Assessment of heterogeneity

The authors plan to assess clinical heterogeneity by examining the characteristics of the studies; the similarity between the types of participants, the interventions and the outcomes. We will assess statistical heterogeneity using a chi-squared test in addition to the I^2 test, where I^2 values over 50% indicate moderate to high heterogeneity (Higgins 2003).

Assessment of reporting biases

If the authors identify sufficient RCTs, we will to attempt to assess publication bias using a funnel plot (Egger 1997). If asymmetry is found, we intend to investigate the reasons for this.

Data synthesis

We will only pool the results of any clinically and statistically homogeneous trials to provide estimates of the efficacy of the interventions if the studies have similar interventions received by similar participants.

For meta-analysis of quantitative data the authors will use the fixed-effect model for homogeneous data sets. If we establish that there is significant heterogeneity between the studies, to take this into account we will use the random-effects model.

Subgroup analysis and investigation of heterogeneity

If we find heterogeneity and sufficient studies are included, the authors intend investigate the causes further. We plan to perform subgroup analysis and investigate heterogeneity (clinical, methodological and statistical) among the different subgroups. Such groups will include:

1. sickle cell anaemia versus sickle cell beta-0;
2. sickle cell SC versus sickle cell SD;
3. sickle cell beta-0 versus sickle cell beta-+;
4. children versus adults;
5. tropical versus temperate environment.

Sensitivity analysis

If there are sufficient studies for inclusion, we plan to conduct sensitivity analyses to assess the robustness of the review's results by repeating the analysis with the following adjustments: exclusion of studies with unclear or inadequate allocation concealment; and unclear or no blinding. In addition, we may undertake sensitivity analyses to examine the effect of randomisation, blind outcome assessment and completeness of follow-up.

RESULTS

Description of studies

No randomised control trials were identified which are eligible for inclusion in the review.

Risk of bias in included studies

No trials were identified which were eligible for inclusion in the review.

Effects of interventions

No eligible trials were found assessing the effects of interventions.

DISCUSSION

As invasive salmonella infection with complications such as septicaemia, meningitis, osteomyelitis and septic arthritis are a major challenge in the management of people with sickle cell especially in children, it is surprising that there are no randomized control trials on salmonella vaccines among people with sickle cell disease (SCD). Demonstrable efficacy is between 50% and 70% for oral Ty21a and Vi capsular polysaccharide vaccines, both of which are recommended by the World Health Organisation (WHO) for children over two years of age and young adults in endemic areas (WHO 2008). None of the randomized controlled trials (RCTs) on salmonella vaccines reported the effectiveness of the vaccines on SCD as a group. In Tajikistan, mass immunisation was suggested as a useful measure in controlling multidrug-resistant typhoid fever epidemics (Tarr 1999). In Vietnam, V1 polysaccharide vaccine was adopted for mass immunisation in children three to 10 years of age (DeRoeck 2004). While individuals with SCD are a group of people that should benefit from the use of salmonella vaccines, this review unfortunately did not identify any studies that could be synthesized to enable an evidence-based decision to be made on its use among people with SCD.

In non-endemic countries, salmonella vaccines are recommended for people travelling to areas where the risk of exposure to serotype

typhi is recognised, people with intimate exposure to a documented typhoid fever carrier and laboratory workers with frequent contact with serotype typhi (WHO 2008). Authorities in the USA also recommend it for people living in typhoid endemic areas outside of the USA (CDC 1990). The situation is, however, different in developing countries as the vaccine is not on the routine immunization schedule of the various national programs on immunization and its introduction to the national programs on immunization is not even being considered.

However, considering the fact that salmonella septicaemia, osteomyelitis and septic arthritis are real issues to contend with in people suffering from SCD, especially in resource poor countries (Adeyokunnu 1980; Ebong 1986; Wright 1997), it is logical to expect that use of salmonella vaccines could benefit this group of individuals. Moreso, evidence has shown that pneumococcal conjugate vaccines have been shown to be useful in another Cochrane Review (Davies 2004) and *Haemophillus influenza* vaccine is also given routinely to people with SCD in some settings. Unlike pneumococcal infection where prophylactic measures such as pneumococcal conjugate vaccines and penicillin are available, there are no prophylactic measures against salmonella infections.

Current efforts to control salmonella invasive disease is focused on improvements in water quality and sanitation and also health education. Training of health professionals in diagnosis and treatment especially in endemic countries are other efforts aimed at controlling the condition (WHO 2008).

The absence of studies suggests that this is an area where evidence is needed to inform the scientific community as to the benefit or otherwise of this intervention tool in the battle against invasive salmonella infections among individuals with SCD. This may partly be explained by the fact that sickle cell anaemia is not prevalent in Asian countries with high burden of typhoid disease (Ochiai 2008). This review has thus shown that there is a gap in knowledge about this potentially important intervention strategy that could be useful to a group of patients. In the absence of relevant studies on this topic, no conclusions can be made on the use of salmonella vaccines among people with SCD.

AUTHORS' CONCLUSIONS

Implications for practice

No RCTs of salmonella vaccines for invasive disease in people with SCD were found for inclusion in this review. Thus, there is no level of evidence on which to recommend routine use of salmonella vaccines for people with SCD. Therefore, the choice whether to use salmonella vaccines or not is limited to the opinions of individual clinicians and to evidence presented in non-randomized studies.

Implications for research

This systematic review has identified the need for well-designed, adequately-powered RCTs to assess the benefits and risks of use of salmonella vaccines as a means of reducing acute morbidity and decreasing mortality from salmonella infection in people with SCD.

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* *Indicates the major publication for the study*

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. LILACS Search Strategy

Search carried out 18 April 2011 and repeated on 17 May 2013 and 26 June 2014.
Searched for all years using advanced form: http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=A

LINE 1

(sickle or anemia falciforme anemia de celulas falciformes or drepanocitosis or "SICKLE" or "SICKLE CELL HEMOGLOBIN C DISEASE" or "SICKLE CELL HEMOGLOBIN C DISEASE/" or "SICKLE CELL HEMOGLOBIN C DISEASE/BL" or "SICKLE CELL HEMOGLOBIN C DISEASE/CO" or "SICKLE CELL HEMOGLOBIN C DISEASE/DI" or "SICKLE CELL HEMOGLOBIN C DISEASE/DT" or "SICKLE CELL HEMOGLOBIN C DISEASE/EP" or "SICKLE CELL HEMOGLOBIN C DISEASE/ET" or "SICKLE CELL HEMOGLOBIN C DISEASE/GE" or "SICKLE CELL HEMOGLOBIN C DISEASE/MI" or "SICKLE CELL HEMOGLOBIN C DISEASE/PA" or "SICKLE CELL HEMOGLOBIN C DISEASE/PC" or "SICKLE CELL HEMOGLOBIN C DISEASE/PP" or "SICKLE CELL HEMOGLOBIN C DISEASE/TH" or "SICKLE CELL HEMOGLOBIN C DISEASE/UR" or "SICKLECELL" or "ANEMIA, SICKLE CELL" or "ANEMIA, SICKLE CELL/" or "ANEMIA, SICKLE CELL/AN" or "ANEMIA, SICKLE CELL/BL" or "ANEMIA, SICKLE CELL/CL" or "ANEMIA, SICKLE CELL/CN" or "ANEMIA, SICKLE CELL/CO" or "ANEMIA, SICKLE CELL/DI" or "ANEMIA, SICKLE CELL/DT" or "ANEMIA, SICKLE CELL/EH" or "ANEMIA, SICKLE CELL/EN" or "ANEMIA, SICKLE CELL/EP" or "ANEMIA, SICKLE CELL/ET" or "ANEMIA, SICKLE CELL/GE" or "ANEMIA, SICKLE CELL/HI" or "ANEMIA, SICKLE CELL/IM" or "ANEMIA, SICKLE CELL/ME" or "ANEMIA, SICKLE CELL/MI" or "ANEMIA, SICKLE CELL/MO" or "ANEMIA, SICKLE CELL/NU" or "ANEMIA, SICKLE CELL/PA" or "ANEMIA, SICKLE CELL/PC" or "ANEMIA, SICKLE CELL/PP" or "ANEMIA, SICKLE CELL/PX" or "ANEMIA, SICKLE CELL/RI" or "ANEMIA, SICKLE CELL/SU" or "ANEMIA, SICKLE CELL/TH" or "ANEMIA, SICKLE CELL/UR" or "ANEMIA, SICKLE CELL/US" or "HEMOGLOBIN S DISEASE" or "HEMOGLOBIN S DISEASE/" or "HEMOGLOBIN S DISEASE/AN" or "HEMOGLOBIN S DISEASE/BL" or "HEMOGLOBIN S DISEASE/CL" or "HEMOGLOBIN S DISEASE/CN" or "HEMOGLOBIN S DISEASE/CO" or "HEMOGLOBIN S DISEASE/DI" or "HEMOGLOBIN S DISEASE/DT" or "HEMOGLOBIN S DISEASE/EH" or "HEMOGLOBIN S DISEASE/EN" or "HEMOGLOBIN S DISEASE/EP" or "HEMOGLOBIN S DISEASE/ET" or "HEMOGLOBIN S DISEASE/GE" or "HEMOGLOBIN S DISEASE/HI" or "HEMOGLOBIN S DISEASE/IM" or "HEMOGLOBIN S DISEASE/ME" or "HEMOGLOBIN S DISEASE/MI" or "HEMOGLOBIN S DISEASE/MO" or "HEMOGLOBIN S DISEASE/NU" or "HEMOGLOBIN S DISEASE/PA" or "HEMOGLOBIN S DISEASE/PC" or "HEMOGLOBIN S DISEASE/PP" or "HEMOGLOBIN S DISEASE/PX" or "HEMOGLOBIN S DISEASE/RI" or "HEMOGLOBIN S DISEASE/SU" or "HEMOGLOBIN S DISEASE/TH" or "HEMOGLOBIN S DISEASE/UR" or "HEMOGLOBIN S DISEASE/US" or "HEMOGLOBIN SC DISEASE" or "HEMOGLOBIN SC DISEASE/" or "HEMOGLOBIN SC DISEASE/BL" or "HEMOGLOBIN SC DISEASE/CO" or "HEMOGLOBIN SC DISEASE/DI" or "HEMOGLOBIN SC DISEASE/DT" or "HEMOGLOBIN SC DISEASE/EP" or "HEMOGLOBIN SC DISEASE/ET" or "HEMOGLOBIN SC DISEASE/GE" or "HEMOGLOBIN SC DISEASE/MI" or "HEMOGLOBIN SC DISEASE/PA" or "HEMOGLOBIN SC DISEASE/PC" or "HEMOGLOBIN SC DISEASE/PP" or "HEMOGLOBIN SC DISEASE/TH" or "HEMOGLOBIN SC DISEASE/UR")

LINE 2

(salmonella or salmonellas "SALMONELLA" or "SALMONELLA INFECTIONS" or "SALMONELLA INFECTIONS/" or "SALMONELLA INFECTIONS/BL" or "SALMONELLA INFECTIONS/CF" or "SALMONELLA INFECTIONS/CI" or "SALMONELLA INFECTIONS/CL" or "SALMONELLA INFECTIONS/CO" or "SALMONELLA INFECTIONS/DI" or "SALMONELLA INFECTIONS/DT" or "SALMONELLA INFECTIONS/EP" or "SALMONELLA INFECTIONS/ET" or "SALMONELLA INFECTIONS/IM" or "SALMONELLA INFECTIONS/ME" or "SALMONELLA INFECTIONS/MI" or "SALMONELLA INFECTIONS/MO" or "SALMONELLA INFECTIONS/PA" or "SALMONELLA INFECTIONS/

PC" or "SALMONELLA INFECTIONS/PP" or "SALMONELLA INFECTIONS/PS" or "SALMONELLA INFECTIONS/RH" or "SALMONELLA INFECTIONS/SU" or "SALMONELLA INFECTIONS/TH" or "SALMONELLA INFECTIONS/TM" or "SALMONELLA INFECTIONS/UR" or "SALMONELLA VACCINES" or "SALMONELLA VACCINES/IM" or "SALMONELLA/" or "SALMONELLA/AE" or "SALMONELLA/AN" or "SALMONELLA/CH" or "SALMONELLA/CL" or "SALMONELLA/CO" or "SALMONELLA/CY" or "SALMONELLA/DE" or "SALMONELLA/GD" or "SALMONELLA/GE" or "SALMONELLA/IM" or "SALMONELLA/IP" or "SALMONELLA/ME" or "SALMONELLA/MI" or "SALMONELLA/PY" or "SALMONELLA/RE" or "SALMONELLA/VI")

WHAT'S NEW

Last assessed as up-to-date: 8 May 2015.

Date	Event	Description
8 May 2015	New search has been performed	A search of the Cochrane Cystic fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register did not identify any potentially relevant trials. A search of LILACS identified seven references, all of which were not eligible for inclusion in any section of the review
8 May 2015	New citation required but conclusions have not changed	The update contains minor changes throughout the text.

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 4, 2009

Date	Event	Description
28 June 2011	New search has been performed	The search of the Group's Haemoglobinopathies trials Register did not identify any potentially eligible trials for inclusion in the review The search of the LIILACS database identified six references, of which none were eligible for inclusion
26 April 2010	New search has been performed	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Friday Odey (FO) drafted the protocol with comments from Uduak Okomo (UO) and Angela Oyo-Ita (AO).

FO acts as guarantor for the review.

DECLARATIONS OF INTEREST

There are no financial conflicts of interest and the authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.

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External sources

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- National Institute for Health Research, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The section of 'Assessment of risk of bias in included studies' has been modified in light of the release of the new RevMan 5.1 software and the publication of the new Cochrane Handbook for Systematic Review of Interventions 5.1 produced by the Cochrane Collaboration.

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia, Sickle Cell [*complications]; Salmonella Infections [*prevention & control]; Salmonella Vaccines [*administration & dosage]

MeSH check words

Humans