

2-16-2016

Conjugate Haemophilus influenzae type b vaccines for sickle cell disease.

Slimane Allali

Necker Hospital for Sick Children

Martin Chalumeau

Sorbonne Paris Cite

Odile Launay

Sorbonne Paris Cite

Samir K. Ballas

Thomas Jefferson University, samir.ballas@jefferson.edu

Mariane de Montalembert

Necker Hospital for Sick Children

[Let us know how access to this document benefits you](#)

Follow this and additional works at: http://jdc.jefferson.edu/cardeza_foundation Part of the [Hematology Commons](#)

Recommended Citation

Allali, Slimane; Chalumeau, Martin; Launay, Odile; Ballas, Samir K.; and de Montalembert, Mariane, "Conjugate Haemophilus influenzae type b vaccines for sickle cell disease." (2016). *Cardeza Foundation for Hematologic Research*. Paper 36.
http://jdc.jefferson.edu/cardeza_foundation/36



Cochrane
Library

Cochrane Database of Systematic Reviews

Conjugate Haemophilus influenzae type b vaccines for sickle cell disease (Review)

Allali S, Chalumeau M, Launay O, Ballas SK, de Montalembert M

Allali S, Chalumeau M, Launay O, Ballas SK, de Montalembert M.
Conjugate #Haemophilus influenzae type b vaccines for sickle cell disease.
Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD011199.
DOI: 10.1002/14651858.CD011199.pub2.

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	4
METHODS	4
RESULTS	6
DISCUSSION	7
AUTHORS' CONCLUSIONS	8
ACKNOWLEDGEMENTS	8
REFERENCES	9
CHARACTERISTICS OF STUDIES	11
DATA AND ANALYSES	13
APPENDICES	13
CONTRIBUTIONS OF AUTHORS	14
DECLARATIONS OF INTEREST	15
SOURCES OF SUPPORT	15
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	15

[Intervention Review]

Conjugate *Haemophilus influenzae* type b vaccines for sickle cell disease

Slimane Allali¹, Martin Chalumeau², Odile Launay³, Samir K Ballas⁴, Mariane de Montalembert¹

¹Department of General Pediatrics, Necker Hospital for Sick Children, Paris, France. ²Obstetrical, Perinatal and Pediatric Epidemiology Research Team (EPOPÉ), Centre de Recherche Épidémiologie et Statistique Sorbonne Paris Cité (CRESS), Inserm UMR1153, Paris Descartes University, Paris, France. ³INSERM CIC 1417 of Vaccinology Cochin Pasteur, Sorbonne Paris Cité, Université Paris Descartes, Paris, France. ⁴Cardeza Foundation for Hematologic Research, Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, USA

Contact address: Mariane de Montalembert, Department of General Pediatrics, Necker Hospital for Sick Children, 149 rue de Sevres, Paris, 75015, France. mariane.demontal@nck.aphp.fr.

Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.

Publication status and date: New, published in Issue 2, 2016.

Review content assessed as up-to-date: 28 January 2016.

Citation: Allali S, Chalumeau M, Launay O, Ballas SK, de Montalembert M. Conjugate *Haemophilus influenzae* type b vaccines for sickle cell disease. *Cochrane Database of Systematic Reviews* 2016, Issue 2. Art. No.: CD011199. DOI: 10.1002/14651858.CD011199.pub2.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

People affected with sickle cell disease are at high risk of infection from *Haemophilus influenzae* type b. Before the implementation of *Haemophilus influenzae* type b conjugate vaccination in high-income countries, this was responsible for a high mortality rate in children under five years of age. In African countries, where coverage of this vaccination is still extremely low, *Haemophilus influenzae* type b remains one of the most common cause of bacteraemias in children with sickle cell disease. The increased uptake of this conjugate vaccination may substantially improve the survival of children with sickle cell disease.

Objectives

The primary objective was to determine whether *Haemophilus influenzae* type b conjugate vaccines reduce mortality and morbidity in children and adults with sickle cell disease.

The secondary objectives were to assess the following in children and adults with sickle cell disease: the immunogenicity of *Haemophilus influenzae* type b conjugate vaccines; the safety of these vaccines; and any variation in effect according to type of vaccine, mode of administration (separately or in combination with other vaccines), number of doses, and age at first dose.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. We also contacted relevant pharmaceutical companies to identify unpublished trials.

Date of last search: 23 November 2015.

Selection criteria

All randomised and quasi-randomised controlled trials comparing *Haemophilus influenzae* type b conjugate vaccines with placebo or no treatment, or comparing different types of *Haemophilus influenzae* type b conjugate vaccines in people with sickle cell disease.

Conjugate *Haemophilus influenzae* type b vaccines for sickle cell disease (Review)

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Data collection and analysis

No trials of *Haemophilus influenzae* type b conjugate vaccines in people with sickle cell disease were found.

Main results

There is an absence of evidence from randomised controlled trials relating to the subject of this review.

Authors' conclusions

There has been a dramatic decrease in the incidence of invasive *Haemophilus influenzae* type b infections observed in the post-vaccination era in people with sickle cell disease living in high-income countries. Therefore, despite the absence of evidence from randomised controlled trials, it is expected that *Haemophilus influenzae* type b conjugate vaccines may be useful in children affected with sickle cell disease, especially in African countries where there is a high prevalence of the disease. The implementation of childhood immunisation schedules, including universal *Haemophilus influenzae* type b conjugate vaccination, may substantially improve the survival of children with sickle cell disease living in low-income countries. We currently lack data to evaluate the potential effect of *Haemophilus influenzae* type b vaccination among unvaccinated adults with sickle cell disease. Further research should assess the optimal Hib immunisation schedule in children and adults with sickle cell disease.

PLAIN LANGUAGE SUMMARY

Vaccines for preventing severe *Haemophilus influenzae* type b (Hib) infections in people with sickle cell disease

Review question

We reviewed the available evidence from randomised controlled trials about how effective and safe *Haemophilus influenzae* type b (Hib) conjugate vaccines are for people with sickle cell disease.

Background

People with sickle cell disease are at high risk of infection from Hib, which was responsible for a high death rate in children under five years of age before Hib conjugate vaccination was introduced in high-income countries. In African countries, where coverage for this vaccination is extremely low, Hib remains one of the most common causes of bacteraemias (bacteria in the blood) in children with sickle cell disease. Another Cochrane review on conjugate vaccines for preventing Hib infections in children under five years of age has shown that Hib conjugate vaccines were safe and effective but it did not specifically look at children with sickle cell disease, who have a high risk of this infection.

Search date

The evidence is current to: 23 November 2015.

Study characteristics

We did not find any randomised controlled trials comparing Hib conjugate vaccines with placebo ('dummy' treatment) or no treatment in people with sickle cell disease.

Key results and quality of the evidence

There are no randomised controlled trials of this vaccine in people with sickle cell disease. However, there has been a dramatic decrease in the occurrence of severe Hib infections in children with sickle cell disease living in high-income countries since the vaccination has been included in childhood immunisation schedules. Therefore, including universal Hib conjugate vaccination in low-income countries may improve the survival of children with sickle cell disease. There is not enough data to allow us to assess the potential effect of Hib vaccination in unvaccinated adults with sickle cell disease. Future trials should assess the ideal Hib immunisation schedule in children and adults with sickle cell disease.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) is a group of genetic haemoglobin disorders, caused by the inheritance of a sickle β globin gene (HbS) from one parent and of another altered β globin gene (HbS, HbC, β -thalassaemia) from the second parent. This includes the homozygous state (SS) as well as compound heterozygous states such as SC, S/ β 0thal, S/ β +thal and SD. Sickle cell trait is defined by inheritance of a single sickle β globin gene and confers some type of protection against falciparum malaria. Therefore, SCD is particularly frequent among people originating from the highly malarious regions, especially Sub-Saharan Africa (where 85% of all SCD occurs) (Modell 2008), India, the Middle East and the Mediterranean region. Due to human migration, the sickle β globin gene has been spread widely throughout the world (Davies 1997) with over 300,000 homozygous (SS) neonates born per year (Piel 2013), making SCD a global public health issue recognised by the United Nations (UN) and the World Health Organization (WHO). The disease is responsible for chronic haemolysis, resistance to nitric oxide (NO) bioactivity, small vessel obstruction, ischaemia-reperfusion injury and increased susceptibility to infections (Overturf 1999).

In low-income countries, SCD is associated with a very high early-life mortality rate, especially in Africa (Rahimy 2003), where it contributes to 5% of deaths in children under five years of age (WHO 2006a). Invasive bacterial infections are responsible for a substantial percentage of the high mortality rate and it was estimated that half of the patients in Sub-Saharan Africa die of infection before the age of five years (Fleming 1989). In high-income countries, such as the USA, before the implementation of early screening and prevention programs (prophylactic penicillin, immunization), bacterial infections were also a major cause of mortality and morbidity in SCD, particularly in early childhood (Gill 1995).

Children affected with SCD are at high risk of infection from encapsulated bacteria, especially *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) (Powars 1983; Ward 1976), the incidence of invasive pneumococcal infection being the highest (Zarkowsky 1986). The main reason for this predisposition is that they may develop asplenia or hyposplenia as early as three months of age with a loss of splenic function beginning before 12 months of age in more than 80% of infants (Rogers 2011). By two years of age, half of the children affected with SCD have functional asplenia (Pearson 1985). The other known immunopathologic mechanisms contributing to an increased vulnerability to encapsulated bacteria in children affected with SCD are defects in the adaptive immune system with dysfunctional immunoglobulin G (IgG) and immunoglobulin M (IgM) antibody responses, defects in alterna-

tive pathway fixation of complement and defective opsonisation (Booth 2010; Overturf 1999).

Studies performed before systematic implementation of Hib conjugate vaccination showed that 90% of all invasive *Haemophilus influenzae* infections in children were due to Hib (Anderson 1995; Asensi 1995). This bacteria is an important cause of meningitis, septicaemia, pneumonia, and other invasive diseases, such as epiglottitis, cellulitis, arthritis, osteomyelitis, and pericarditis. In the pre-vaccination era, it has been estimated to have caused two to three millions cases of serious diseases and more than half a million deaths annually worldwide (Peltola 2000).

Historically, Hib was responsible for a high mortality rate in children with SCD under five years of age (Zarkowsky 1986) and in the early 1980s, in the USA, a four-fold increased risk of *Haemophilus*

infl uenzae septicaemia in children with SCD under nine years of age was observed (Powars 1983). In a study following 694 children enrolled at less than six months of age between 1978 and 1988 in the USA, the mortality was of two out of 10 cases of Hib bacteraemia (Gill 1995). Since the introduction of Hib conjugate vaccination, a dramatic decrease in the incidence of invasive Hib infections has been observed in the USA with no cases

of *Haemophilus infl uenzae* bacteraemia in a retrospective study reviewing the medical records of 815 children with SCD followed at the Children's Hospital of Philadelphia from 2000 to 2010 (Ellison 2013). However, this evolution has not been observed on the African continent, where Hib remains one of the most common organisms involved in bacteraemias in children affected with SCD, accounting for 12% to 19% of cases (Kizito 2007; Williams 2009). This may be due to an extremely low coverage for Hib vaccination, which remains below 10% in children with SCD in many different African countries (Nacoulma 2006).

Description of the intervention

Since the 1970s, Hib vaccinations have been used to protect children and adults affected with SCD (Pearson 1977); Hib polysaccharide vaccines, consisting of the type b capsular polysaccharide, polyribosylribitol phosphate (PRP), were first available but had a weak immunogenicity when administered under two years of age (Rubin 1989). This was probably because bacterial polysaccharides do not generate memory responses in B cells. Yet, those with SCD younger than two years of age have the highest risk of fulminant infections related to encapsulated bacteria. Since the 1990s, Hib conjugate vaccines have been available; these were created by covalently attaching the PRP to a protein carrier, resulting in a T-cell-dependant immune response with the production of high-affinity antibodies and the formation of memory B cells. Therefore, Hib conjugate vaccines have a much better immunogenicity than Hib polysaccharide vaccines (Frank 1988) and are consid-

ered as safe and highly immunogenic in children with SCD (de Montalembert 1993; Goldblatt 1996; Kaplan 1992; Rubin 1992). Hib conjugate vaccines are routinely administered to all infants living in high-income countries, including those with SCD, with catch-up vaccination until five years of age; and the WHO recommends that they should be included in all routine infant immunization programs all over the world. However, immunization against Hib has reached only a fraction of the children living in low-income countries (WHO 2006b) and therefore, the burden of Hib disease is much more significant in those countries, especially in Africa (Watt 2009). Four different Hib conjugate vaccines have been licensed, differing by the type of protein carrier (tetanus toxoid for PRP-T which is the most widely used, non-toxic mutant diphtheria toxin for HbOC, outer membrane protein of *Neisseria meningitidis* for PRP-OMP and diphtheria toxoid for PRP-D which is no longer used in young infants because of its poor immunogenicity). They can be administered separately or in combination with other vaccines. Different immunization schedules exist. The schedule recommended by the WHO consists in a three-dose primary series, including a first dose which may be given to infants as young as six weeks of age, and a second and third doses at four-to-eight-week intervals along with diphtheria-tetanus-pertussis (DTP). If given, the booster dose should be administered between 12 months and 18 months of age (WHO 2006b). In the USA, the schedule recommended by the Advisory Committee on Immunization Practices (Briere 2014) includes a primary series at two, four and six months of age (the dose at age six months being not indicated if PRP-OMP is used at two and four months of age), a booster dose at age 12 months to 15 months and an additional dose for unvaccinated or partially vaccinated persons aged five years or older who have a high-risk condition, including SCD.

How the intervention might work

A Cochrane review has shown that Hib conjugate vaccines were safe and effective in preventing Hib diseases in children under five years of age (Swingler 2009).

Immunization with Hib conjugate vaccines is considered to have largely controlled infections caused by this pathogen in SCD children living in high-income countries (Ellison 2013; Overturf 1999).

Why it is important to do this review

The Cochrane review on conjugate vaccines for preventing Hib infections in children aged less than five years did not undertake a specific analysis of a subgroup of children with SCD (Swingler 2009). Considering that the risk of severe Hib infections is extremely high in children with SCD, and by analogy with pneumococcal conjugate vaccines, whose immunogenicity has been

demonstrated in people with SCD (Davies 2004), it justifies a specific review of this highly-exposed population.

In unvaccinated, or partially vaccinated, children aged five years or older who have high risk conditions, including SCD, it is recommended to administer one dose of Hib vaccine (Briere 2014). However, there is no published systematic review on Hib vaccines in children older than five years or in adults and therefore, in some clinical guidelines, administration of a single dose of Hib vaccine in unvaccinated adults with SCD is recommended (Briere 2014; Sickle Cell Society 2008), while it is not mentioned in others (NIH 2002).

This review is motivated by the fact that there is no published systematic review on Hib vaccines in children or adults with SCD and yet the benefit could be very different in this population, notably because of the high risk reduction. Such a review could help produce evidence-based recommendations and argue that the implementation of the recommended universal childhood immunisation program, including Hib conjugate vaccination, should be a public health priority in low-income countries, especially in African countries, where it could substantially affect the survival of children with SCD.

OBJECTIVES

Primary objective

To determine whether Hib conjugate vaccines reduce Hib mortality and morbidity in children (aged under 18 years) and adults (aged 18 years and over) with SCD.

Secondary objectives

1. To assess the immunogenicity of Hib conjugate vaccines in children and adults with SCD.
2. To assess the safety of Hib conjugate vaccines in children and adults with SCD.
3. To determine any variation in effect according to type of vaccine, mode of administration (separately or in combination with other vaccines), number of doses, and age at first dose.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs.

Types of participants

People of all ages and both sexes affected with SCD of all types including SS, SC, S/ β_0 thal, S/ β_+ thal and other combinations such as Hb SD or Hb SO (confirmed by high performance liquid chromatography, Hb electrophoresis and sickle solubility test with family studies or DNA tests), regardless of the setting.

Types of interventions

Comparisons of all the available Hib conjugate vaccines with placebo or no treatment.
Comparison between different types of Hib conjugate vaccines.

Types of outcome measures

Primary outcomes

1. Mortality from Hib infections
2. Overall mortality
3. Acute morbidity from Hib infections (e.g. vaso-occlusive, hyperhaemolytic and sequestration crises, septicaemia, meningitis, pneumonia, acute chest syndrome, epiglottitis, cellulitis, arthritis, osteomyelitis, pericarditis).

Secondary outcomes

1. Immunogenicity of Hib conjugate vaccines (e.g. antibody levels and serum opsonic activity in order to assess the biologic function of the antibody)
2. Adverse events related to the vaccines (e.g. redness, swelling, fever, pain, vaso-occlusive crisis, irritability, drowsiness, loss of appetite, vomiting)
3. Standard 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) frequency of absence from school
 - vi) lost time at work
 - vii) frequency of hospitalisation
 - viii) any other relevant measures reported

Search methods for identification of studies

Electronic searches

The review authors searched for relevant trials from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register using the terms: sickle cell AND *influenza*.

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 is 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 Module](#).

Date of the most recent search of the Group's Haemoglobinopathies Trials Register: 23 November 2015.

Searching other resources

The review authors planned to review the bibliographic references of all retrieved articles and to contact authors in an attempt to identify additional reports of trials. They also attempted to identify unpublished trials by contacting pharmaceutical companies.

Data collection and analysis

Selection of studies

Two review authors, Mariane de Montalembert (MdM) and Slimane Allali (SA), independently assessed trials for inclusion in the review. This was done by firstly examining titles and abstracts of records retrieved from the search and excluding irrelevant reports; and secondly, by examining each full-text of the remaining potentially relevant reports to determine eligibility. There was no disagreement on the suitability of a trial for inclusion.

Data extraction and management

Two review authors (MdM and SA) planned to independently extract the data from the included trials using a data extraction form (collecting information on trial methods, participants, intervention, control and outcomes). The review authors planned to resolve any disagreements by discussion with a third author, Martin Chalumeau (MC). If possible, they planned to extract data for primary outcomes and quality of life measures at one, three, six, 12 months and annually thereafter. They planned to extract immunogenicity measures four weeks after vaccination, as well as adverse events occurring up to 72 hours after vaccination. If any

outcome data had been recorded at other time points, then the review authors would have considered examining these as well.

Assessment of risk of bias in included studies

Two review authors (Mm and SA) planned to independently assess the risk of bias of each trial by evaluating selection bias (sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (unavailable outcome data) and reporting bias, according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). They planned to use Cochrane's tool for assessing the risk of bias and to resolve any disagreements between authors by discussion with a third author (MC).

Measures of treatment effect

For dichotomous outcome data (e.g. mortality from Hib infections, overall mortality, acute morbidity from Hib infections, limitation in physical activity) the review authors planned to calculate the risk ratio (RR), the number needed to treat (NNT) and their 95% confidence intervals (95% CI).

For continuous outcome data (e.g. antibody levels, frequency of bodily pain) they planned to calculate a mean difference (MD) or if different scales were used to evaluate the same outcome, a standardised mean difference (SMD), both with their corresponding 95% CI.

Unit of analysis issues

For the primary outcomes measured longitudinally at different time points, the review authors planned to perform a separate analysis at each time point in order to avoid a unit-of-analysis error.

If cluster-randomised trials had been available, the review authors would have conducted the analysis at the same level as the allocation, using a summary measurement from each cluster.

Dealing with missing data

If important data had been missing from the included trials, the review authors would have tried to obtain these through contact with trial investigators. If these data had remained unavailable, they would have considered the potential effects of missing data on the results of the review. If the review authors had assumed data were missing at random, they would have ignored these and they would have based their analyses on the available data.

Assessment of heterogeneity

The review authors planned to test for heterogeneity between trials by using the Chi^2 test (significance set at $P < 0.10$). In addition to this, they planned to assess the quantity of inconsistency across trials in a meta-analysis by using the I^2 statistic (I^2 values greater than 50% indicating substantial statistical heterogeneity). They also planned to assess heterogeneity through a visual examination of the combined data presented in the forest plots.

Assessment of reporting biases

If the review authors had included more than 10 trials in the review, they would have tried to identify reporting biases by using a funnel plot (Egger 1997). If asymmetry had been present, they would have explored possible causes including publication bias, high risk of bias, and true heterogeneity.

Data synthesis

The review authors planned to carry out statistical analysis to compare Hib conjugate vaccines with placebo or no treatment using the Cochrane Review Manager software (RevMan 2014).

If they had found no substantial heterogeneity (as defined above) between the trials, they would have performed meta-analyses using a fixed-effect model. Otherwise they would have used a random-effects model.

Subgroup analysis and investigation of heterogeneity

If the review authors had been able to include sufficient data, they would have investigated statistically significant heterogeneity identified by performing subgroup analyses according to:

- age at first vaccination (under five years of age versus five years and over);
- type of vaccine;
- number of doses;
- setting (high-income versus low-income countries).

Sensitivity analysis

If the review authors had included an appropriate number of trials in the review, they would have performed sensitivity analyses in order to assess the robustness of the review's results by repeating the analysis after exclusion of the trials which:

1. utilised quasi-randomisation methods;
2. were assessed as having an overall high risk of bias.

RESULTS

Description of studies

Results of the search

Three individual primary trials were identified by the electronic searches (Ambrosino 1986; Frank 1988; Souza 2010); no further trials were identified by contacting authors and pharmaceutical companies.

Included studies

No trials were included in the review.

Excluded studies

One trial was excluded because it did not deal with Hib but with influenza vaccines (Souza 2010); one trial was excluded because it dealt with passive immunization against Hib (Ambrosino 1986); and one was considered more closely for inclusion, but it was excluded since it compared immunogenicity between a Hib conjugate vaccine (PRP-D) and a Hib polysaccharide vaccine (PRP) (Frank 1988). Therefore, no trials were included in the review.

Risk of bias in included studies

No trials were included in the review.

Effects of interventions

No trials were included in the review.

DISCUSSION

Summary of main results

No randomised controlled trials (RCTs) comparing Hib conjugate vaccines with placebo or no treatment in people with sickle cell disease (SCD) were identified in our systematic review. Thus, it is not possible to answer our review question using results issued from trials with the highest level of evidence, although other sources of evidence may be helpful.

Overall completeness and applicability of evidence

No trials were included in the review.

Quality of the evidence

No trials were included in the review.

Potential biases in the review process

There may be some publication bias in the review process given trials with negative results are less likely to be published; but no additional unpublished trials were identified by contacting authors and pharmaceutical companies.

Agreements and disagreements with other studies or reviews

The Cochrane review on conjugate vaccines for preventing Hib infections in children aged less than five years has shown that Hib conjugate vaccines were safe and effective in preventing Hib diseases (Swingler 2009). In this review, the effect size was major with a relative risk for invasive Hib disease of 0.20 (95% confidence interval 0.07 to 0.54). How could the results of this review be related to people with SCD in particular? First, the baseline risk is probably different and much higher among people with SCD than in the general population. It has been reported in the early 1980s in the USA that there was a four-fold increased risk of *Haemophilus influenzae* septicaemia in children with SCD under nine years of age (Powars 1983); but we do not know the relative burden of invasive Hib disease in people with SCD living in low-income countries. However, it has been shown in a recent review, including 33 studies from Africa with data on SCD and bacterial disease, that those with invasive Hib disease had a 13- to 17-times greater odds of having SCD than controls (Ramakrishnan 2010). Thus, if a complete vaccination offers the same protection against Hib among people with SCD, the effect size would be much higher. Secondly, SCD modifies host response to pathogens and concerns may rise on host response to vaccines and consequently on their efficacy. However, vaccine-induced protection is usually evaluated by the immunogenicity and although dysfunctional IgG and IgM antibody response has been reported in people with SCD (Overturf 1999), Hib conjugate vaccines seem to be highly immunogenic in this population (de Montalembert 1993; Goldblatt 1996; Kaplan 1992; Rubin 1992) with IgG titers comparable to those obtained in healthy children. By analogy, the immunogenicity of pneumococcal conjugate vaccines has also been demonstrated in people with SCD (Davies 2004). The dramatic decrease in the incidence of severe Hib infections in people with SCD living in high-income countries in the post-vaccination era cannot be explained only by herd immunity since Hib strains are still circulating and are responsible for meningitis in individuals with an incomplete vaccination schedule and in those affected with immunological deficiency, but not in those with SCD (Pop-Jora 2008). The condition is not considered a risk factor for Hib conjugate vaccine failure in childhood (Heath 2000). Thirdly, the sa-

fety of Hib conjugate vaccines in people with SCD may be questioned. No serious adverse effects, but some essentially mild local reactions, fever, irritability and crying were reported in the trials (a total of 257,000 infants) included in the above-mentioned Cochrane review (Swingler 2009), but the adverse effects related to vaccines might be more severe in people with SCD. However, Hib conjugate vaccines are considered to be safe in people with SCD (de Montalembert 1993; Rubin 1992) and only mild local reactions, pain and fever have been reported. To date, no important adverse effects have been reported in people with SCD by the Vaccine Safety Datalink, which started in 1990 and the pharmacovigilance data in high-income countries are reassuring. In a randomised controlled trial, in an unselected population of 42,848 infants at two, three and four months of age, in Gambia (where SCD prevalence is 1% (Grosse 2011)), a Hib PRP-T conjugate vaccine mixed with diphtheria-tetanus-pertussis (DTP) was compared to DTP alone. In this trial, no serious adverse effects were reported across the whole population, and it is thus probable that around 200 children with SCD received Hib conjugate vaccine without any serious adverse effect (Mulholland 1997).

Thus, given a highest baseline risk, a good serological responsiveness, observational data from high income countries and lack of concerns on safety, Hib conjugate vaccines in people with SCD are probably at least as effective and as safe as in the general population.

In unvaccinated adults affected with SCD, we ignore the baseline risk for Hib infections and consequently there is no consensus on Hib conjugate vaccination in this population. In the general population, Hib vaccination is not recommended for unvaccinated adults and children aged more than five years because, in the pre-vaccination era, invasive Hib disease affected almost exclusively children aged less than five years (Peltola 2000). Healthy, unvaccinated adults have protective immunity against Hib due to natural anti-Hib antibodies that may have been induced by exposure to some common environmental bacteria that carry antigens cross-reacting with PRP (Nix 2012). However, in high-income countries, in the post-vaccination era, Hib cases no longer occur in vaccinated children but a few cases now occur in adults with low Hib antibody levels and co-morbidities, including asplenia (Collins 2013). Hib conjugate vaccines seem to have a high immunogenicity in asplenic adults (Meerveld-Eggink 2011) and are considered as safe and effective in splenectomized and non-splenectomized adults with thalassemia (Cimaz 2001) and in the elderly (Lottenbach 2004). These findings suggest that unvaccinated adults with SCD might benefit from Hib conjugate vaccination to achieve protective immunity but we lack data to evaluate the potential effect of Hib vaccination in this population in high or low-income countries.

The correct implementation of universal Hib conjugate vaccination into routine childhood immunisation schedules has largely

controlled Hib infections in SCD children living in high-income countries and it may improve the survival of children with SCD living in low-income countries, especially in African countries where vaccination reaches only a fraction of them (Nacoulma 2006) and where Hib remains one of the most common organisms, responsible for invasive infections in SCD children (Kizito 2007; Williams 2009).

AUTHORS' CONCLUSIONS

Implications for practice

No RCTs comparing Hib conjugate vaccines with placebo or no treatment in people with SCD were found for inclusion in this review. However, since safety and efficacy of Hib conjugate vaccines have been shown by the Cochrane review on conjugate vaccines for preventing Hib infections in children aged less than five years, and given a highest baseline risk of Hib infections in people with SCD, a high immunogenicity of Hib conjugate vaccines, dramatic observational data from high-income countries in the post-vaccination era and lack of concerns on safety, it is reasonable to expect that Hib conjugate vaccines could particularly benefit children affected with SCD. The implementation of childhood immunisation schedules including universal Hib conjugate vaccination may improve the survival of children with SCD and should be a public health priority in low-income countries. We lack data to evaluate the potential effect of Hib vaccination among unvaccinated adults with SCD.

Implications for research

The proven efficacy and safety of Hib conjugate vaccines in non-SCD individuals, the reassuring immunogenicity and safety data in those affected with SCD and the fact that invasive Hib infections have become extremely rare in people with SCD living in high-income countries following the introduction of Hib conjugate vaccination into routine childhood immunisation schedules, are sufficient to preclude controlled trials comparing Hib conjugate vaccines with placebo in people with SCD. Further investigations (especially comparing immunogenicity of different Hib vaccination schedules in the short, medium and long term) are required to assess the optimal Hib immunisation schedule in children and adults with SCD.

ACKNOWLEDGEMENTS

We wish to thank Pr Dominique Gendrel for commenting on the discussion of this review.

REFERENCES

References to studies excluded from this review

Ambrosino 1986 *{published data only}*

Ambrosino DM, Landesman SH, Gorham CC, Siber GR. Passive immunization against disease due to Haemophilus influenzae type b: concentrations of antibody to capsular polysaccharide in high-risk children. *Journal of Infectious Diseases* 1986;**153**(1):1–7. [CENTRAL: 40950; CRS: 5500100000000249; PUBMED: 3484503]

Frank 1988 *{published data only}*

Frank AL, Labotka RJ, Rao S, Frisone LR, McVerry PH, Samuelson JS, et al. Haemophilus influenzae type b immunization of children with sickle cell diseases. *Pediatrics* 1988;**82**(4):571–5. [CENTRAL: 56056; CRS: 5500100000000364; EMBASE: 1988237622; PUBMED: 3262857]

Souza 2010 *{published data only}*

Souza AR, Braga JA, de Paiva TM, Loggetto SR, Azevedo RS, Weckx LY. Immunogenicity and tolerability of a virosome influenza vaccine compared to split influenza vaccine in patients with sickle cell anemia. *Vaccine* 2010;**28**(4):1117–20. [PUBMED: 20116631]

Additional references

Anderson 1995

Anderson EC, Begg NT, Crawshaw SC, Hargreaves RM, Howard AJ, Slack MP. Epidemiology of invasive Haemophilus influenzae infections in England and Wales in the pre-vaccination era (1990–2). *Epidemiology and Infection* 1995;**115**(1):89–100. [PUBMED: 7641841]

Asensi 1995

Asensi F, Otero MC, Perez-Tamarit D, Miranda J, Pico L, Nieto A. Economic aspects of a general vaccination against invasive disease caused by Haemophilus influenzae type b (Hib) via the experience of the Children's Hospital La Fe, Valencia, Spain. *Vaccine* 1995;**13**(16):1563–6. [PUBMED: 8578843]

Booth 2010

Booth C, Inusa B, Obaro SK. Infection in sickle cell disease: a review. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2010;**14**(1):e2–e12. [PUBMED: 19497774]

Briere 2014

Briere EC, Rubin L, Moro PL, Cohn A, Clark T, Messonnier N. Prevention and control of haemophilus influenzae type b disease: recommendations of the advisory committee on immunization practices (ACIP). *MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control* 2014;**63**(RR-01):1–14. [PUBMED: 24572654]

Cimaz 2001

Cimaz R, Mensi C, D'Angelo E, Fantola E, Milone V, Biasio LR, et al. Safety and immunogenicity of a conjugate vaccine against Haemophilus influenzae type b in splenectomized

and nonsplenectomized patients with Cooley anemia. *Journal of Infectious Diseases* 2001;**183**(12):1819–21. [PUBMED: 11372038]

Collins 2013

Collins S, Ramsay M, Campbell H, Slack MP, Ladhani SN. Invasive Haemophilus influenzae type b disease in England and Wales: who is at risk after 2 decades of routine childhood vaccination?. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2013;**57**(12):1715–21. [PUBMED: 24076970]

Davies 1997

Davies SC, Oni L. Management of patients with sickle cell disease. *BMJ (Clinical research ed.)* 1997;**315**(7109):656–60. [PUBMED: 9310570]

Davies 2004

Davies EG, Riddington C, Lottenberg R, Dower N. Pneumococcal vaccines for sickle cell disease. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [DOI: 10.1002/14651858.CD003885.pub2; PUBMED: 14974042]

de Montalembert 1993

de Montalembert M, Begue P, Fritzell B, Houmeau P. Immunogenicity and tolerability of Haemophilus b-tetanus protein conjugate (PRP-T) in children with sickle cell anemia [Immunogenicite et tolerance du vaccin anti-Haemophilus b conjugue a la proteine tetanique (PRP-T) chez l'enfant drepanocytaire.]. *Archives Francaises de Pediatrie* 1993;**50**(10):863–6. [PUBMED: 8053763]

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed.)* 1997;**315**(7109):629–34. [PUBMED: 9310563]

Ellison 2013

Ellison AM, Ota KV, McGowan KL, Smith-Whitley K. Epidemiology of bloodstream infections in children with sickle cell disease. *The Pediatric Infectious Disease Journal* 2013;**32**(5):560–3. [PUBMED: 23340560]

Fleming 1989

Fleming AF. The presentation, management and prevention of crisis in sickle cell disease in Africa. *Blood Reviews* 1989;**3**(1):18–28. [PUBMED: 2650773]

Gill 1995

Gill FM, Sleeper LA, Weiner SJ, Brown AK, Bellevue R, Grover R, et al. Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative Study of Sickle Cell Disease. *Blood* 1995;**86**(2):776–83. [PUBMED: 7606007]

Goldblatt 1996

Goldblatt D, Johnson M, Evans J. Antibody responses to Haemophilus influenzae type b conjugate vaccine in sickle cell disease. *Archives of Disease in Childhood* 1996;**75**(2):159–61. [PUBMED: 8869201]

Grosse 2011

Grosse SD, Odamé I, Atrash HK, Amendah DD, Piel FB, Williams TN. Sick cell disease in Africa: a neglected cause of early childhood mortality. *American Journal of Preventive Medicine* 2011;**41**(6 Suppl 4):S398–405. [PUBMED: 22099364]

Heath 2000

Heath PT, Booy R, Griffiths H, Clutterbuck E, Azzopardi HJ, Slack MP, et al. Clinical and immunological risk factors associated with Haemophilus influenzae type b conjugate vaccine failure in childhood. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 2000;**31**(4):973–80. [PUBMED: 11049779]

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011. Available from www.cochrane-handbook.org.

Kaplan 1992

Kaplan SL, Duckett T, Mahoney DH Jr, Kennedy LL, Dukes CM, Schaffer DM, et al. Immunogenicity of Haemophilus influenzae type b polysaccharide-tetanus protein conjugate vaccine in children with sickle hemoglobinopathy or malignancies, and after systemic Haemophilus influenzae type b infection. *Journal of Pediatrics* 1992;**120**(3):367–70. [PUBMED: 1538281]

Kizito 2007

Kizito ME, Mworoti E, Ndugwa C, Serjeant GR. Bacteraemia in homozygous sickle cell disease in Africa: is pneumococcal prophylaxis justified?. *Archives of Disease in Childhood* 2007;**92**(1):21–3. [PUBMED: 16531454]

Lottenbach 2004

Lottenbach KR, Granoff DM, Barenkamp SJ, Powers DC, Kennedy D, Irby-Moore S, et al. Safety and immunogenicity of haemophilus influenzae type B polysaccharide or conjugate vaccines in an elderly adult population. *Journal of the American Geriatrics Society* 2004;**52**(11):1883–7. [PUBMED: 15507066]

Meerveld-Eggink 2011

Meerveld-Eggink A, de Weerd O, van Velzen-Blad H, Biesma DH, Rijkers GT. Response to conjugate pneumococcal and Haemophilus influenzae type b vaccines in asplenic patients. *Vaccine* 2011;**29**(4):675–80. [PUBMED: 21115060]

Modell 2008

Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. *Bulletin of the World Health Organization* 2008;**86**(6):480–7. [PUBMED: 18568278]

Mulholland 1997

Mulholland K, Hilton S, Adegbola R, Usen S, Oparaugo A, Omosigbo C, et al. Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate vaccine [corrected] for prevention of pneumonia and meningitis in Gambian infants. *Lancet* 1997;**349**(9060):1191–7. [PUBMED: 9130939]

Nacoulma 2006

Nacoulma EW, Kam L, Gue EE, Kafando E, Ayerouere J, Blot I. Vaccination status of children with sickle cell disease in Ouagadougou (Burkina Faso) [Evaluation du statut vaccinal de l'enfant drepanocytaire de la ville de Ouagadougou (Burkina Faso)]. *Sante (Montrouge, France)* 2006;**16**(3):155–60. [PUBMED: 17284390]

NIH 2002

National Institutes of Health, National Heart, Lung, and Blood Institute, Division of Blood Diseases and Resources. The Management of Sickle Cell Disease. NIH Publication No. 02-2117 2002 June.

Nix 2012

Nix EB, Hawdon N, Gravelle S, Biman B, Brigden M, Malik S, et al. Risk of invasive Haemophilus influenzae type b (Hib) disease in adults with secondary immunodeficiency in the post-Hib vaccine era. *Clinical and Vaccine Immunology: CVI* 2012;**19**(5):766–71. [PUBMED: 22398246]

Overturf 1999

Overturf GD. Infections and immunizations of children with sickle cell disease. *Advances in Pediatric Infectious Diseases* 1999;**14**:191–218. [PUBMED: 10079855]

Pearson 1977

Pearson HA. Sick cell anemia and severe infections due to encapsulated bacteria. *The Journal of Infectious Diseases* 1977;**136** Suppl:S25–30. [PUBMED: 330779]

Pearson 1985

Pearson HA, Gallagher D, Chilcote R, Sullivan E, Wilimas J, Espeland M, et al. Developmental pattern of splenic dysfunction in sickle cell disorders. *Pediatrics* 1985;**76**(3):392–7. [PUBMED: 2412200]

Peltola 2000

Peltola H. Worldwide Haemophilus influenzae type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. *Clinical Microbiology Reviews* 2000;**13**(2):302–17. [PUBMED: 10756001]

Piel 2013

Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. *Lancet* 2013;**381**(9861):142–51. [PUBMED: 23103089]

Pop-Jora 2008

Pop-Jora D, Dabernat H, Levy C, Lecuyer A, Cohen R, Grimpel E. [Surveillance of Haemophilus Influenzae meningitis in children in France, 2001–2006] [Surveillance des meningites a Haemophilus Influenzae de l'enfant en France, 2001–2006.]. *Archives de Pediatrie: organe officiel de la Societe francaise de pediatrie* 2008;**15** Suppl 3:S148–53. [PUBMED: 19268245]

Powars 1983

Powars D, Overturf G, Turner E. Is there an increased risk of Haemophilus influenzae septicemia in children with sickle

- cell anemia?. *Pediatrics* 1983;**71**(6):927–31. [PUBMED: 6602325]
- Rahimy 2003**
Rahimy MC, Gangbo A, Ahouignan G, Adjou R, Deguenon C, Goussanou S, et al. Effect of a comprehensive clinical care program on disease course in severely ill children with sickle cell anemia in a sub-Saharan African setting. *Blood* 2003;**102**(3):834–8. [PUBMED: 12702514]
- Ramakrishnan 2010**
Ramakrishnan M, Moisi JC, Klugman KP, Iglesias JM, Grant LR, Mpoudi-Etame M, et al. Increased risk of invasive bacterial infections in African people with sickle-cell disease: a systematic review and meta-analysis. *The Lancet Infectious Diseases* 2010;**10**(5):329–37. [PUBMED: 20417415]
- RevMan 2014 [Computer program]**
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
- Rogers 2011**
Rogers ZR, Wang WC, Luo Z, Iyer RV, Shalaby-Rana E, Dertinger SD, et al. Biomarkers of splenic function in infants with sickle cell anemia: baseline data from the BABY HUG Trial. *Blood* 2011;**117**(9):2614–7.
- Rubin 1989**
Rubin LG, Voulalas D, Carmody L. Immunization of children with sickle cell disease with Haemophilus influenzae type b polysaccharide vaccine. *Pediatrics* 1989;**84**(3):509–13. [PUBMED: 2788866]
- Rubin 1992**
Rubin LG, Voulalas D, Carmody L. Immunogenicity of Haemophilus influenzae type b conjugate vaccine in children with sickle cell disease. *American Journal of Diseases of Children (1960)* 1992;**146**(3):340–2. [PUBMED: 1543182]
- Sickle Cell Society 2008**
Sickle Cell Society. Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK. <http://sct.screening.nhs.uk/standardsandguidelines> (accessed 30 January 2014).
- Swingler 2009**
Swingler GH, Michaels D, Hussey GG. Conjugate vaccines for preventing Haemophilus influenzae type B infections. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD001729.pub3; PUBMED: 19821280]
- Ward 1976**
Ward J, Smith AL. Hemophilus influenzae bacteremia in children with sickle cell disease. *Journal of Pediatrics* 1976;**88**(2):261–3. [PUBMED: 1082499]
- Watt 2009**
Watt JP, Wolfson LJ, O'Brien KL, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by Haemophilus influenzae type b in children younger than 5 years: global estimates. *Lancet* 2009;**374**(9693):903–11. [PUBMED: 19748399]
- WHO 2006a**
World Health Organization. Sickle-cell anaemia. Report by the Secretariat. Provisional agenda item 11.4 A59/9. Fifty-Ninth World Health Assembly; 2005 May 16–25. 2006.
- WHO 2006b**
World Health Organization. WHO position paper on Haemophilus influenzae type b conjugate vaccines. *Weekly epidemiological record / Health Section of the Secretariat of the League of Nations* 2006;**81**(47):445–52. [PUBMED: 17124755]
- Williams 2009**
Williams TN, Uyoga S, Macharia A, Ndila C, McAuley CF, Opi DH, et al. Bacteraemia in Kenyan children with sickle-cell anaemia: a retrospective cohort and case-control study. *Lancet* 2009;**374**(9698):1364–70. [PUBMED: 19747721]
- Zarkowsky 1986**
Zarkowsky HS, Gallagher D, Gill FM, Wang WC, Falletta JM, Lande WM, et al. Bacteremia in sickle hemoglobinopathies. *Journal of Pediatrics* 1986;**109**(4): 579–85. [PUBMED: 3531449]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ambrosino 1986	Deals with passive immunization against Hib.
Frank 1988	Comparison of a Hib conjugate vaccine (PRP-D) and a Hib polysaccharide vaccine (PRP)
Souza 2010	Does not deal with Hib but with influenza vaccines.

Hib: *Haemophilus influenzae* type b

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. Glossary

Term	Definition
Cellulitis	spreading bacterial infection underneath the skin surface
Chronic haemolysis	chronic destruction of red blood cells
Conjugate vaccine	vaccine containing bacterial capsular polysaccharide joined to a protein to enhance immunogenicity
Encapsulated bacteria	bacteria that have an outer covering made of polysaccharide
Epiglottitis	inflammation of the epiglottis
Fulminant infections	infections coming on suddenly with great severity
Functional asplenia	absence of splenic function due to spontaneous infarction of the spleen
<i>Haemophilus influenzae</i>	Gram-negative, coccobacillary, facultatively anaerobic bacterium that was first described in 1892 by Richard Pfeiffer during an influenza pandemic
Hyposplenia	reduced splenic functioning
IgG	immunoglobulin G
IgM	immunoglobulin M
Immunogenicity	capacity of producing an immune response
Ischaemia-reperfusion injury	tissue damage caused by oxidative stress when blood supply returns to the tissue after a period of ischaemia
Nitric oxide (NO)	soluble gas, continuously synthesized in endothelial cells, whose vasodilator activity is decreased in SCD
Opsonisation	immune process by which a pathogen is targeted for destruction by a phagocyte

(Continued)

Osteomyelitis	infection of the bone
Pericarditis	inflammation of the pericardium
Quasi-randomised controlled trial (quasi-RCT)	trial using a quasi-random method of allocation (such as alternation, date of birth, or hospital number)
Septicaemia	invasion of the bloodstream by bacteria, accompanied by a systemic inflammatory response
Sequela	pathological chronic condition resulting from a disease as a complication of an acute morbidity
Serum opsonic activity	ability of antibodies in blood serum to attach to bacteria to make them more susceptible to destruction by phagocytes

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
TASK	WHO WILL UNDERTAKE THE TASK?
<i>Protocol stage:</i> draft the protocol	M de Montalembert Slimane Allali Martin Chalumeau Odile Launay Samir Ballas
<i>Review stage:</i> select which studies to include (2 + 1 arbiter)	Slimane Allali M de Montalembert Martin Chalumeau
<i>Review stage:</i> extract data from studies (2 people)	Slimane Allali M de Montalembert
<i>Review stage:</i> enter data into RevMan	Slimane Allali
<i>Review stage:</i> carry out the analysis	Slimane Allali Martin Chalumeau
<i>Review stage:</i> interpret the analysis	Slimane Allali M de Montalembert Martin Chalumeau Odile Launay

(Continued)

	Samir Ballas
<i>Review stage:</i> draft the final review	M de Montalembert Slimane Allali Odile Launay Martin Chalumeau Samir Ballas
<i>Update stage:</i> update the review	M de Montalembert Slimane Allali Odile Launay Martin Chalumeau Samir Ballas

DECLARATIONS OF INTEREST

Slimane Allali: none known.

Martin Chalumeau: none known.

Odile Launay: none known.

Samir Ballas: none known.

Mariane de Montalembert: wrote a paper on Hib vaccination in children with sickle cell disease in 1993.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.