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Background

Meningococcal disease continues to be a major cause of childhood morbidity and mortality worldwide. The annual number of cases is conservatively estimated to be 1.2 million with at least 135,000 related deaths [1]. The majority of the deaths occur in developing countries. The area most significantly affected stretches across sub-Saharan Africa and has become known as the "meningitis belt" (Figure 1). Cyclic epidemics occur in this region every 5-12 years and exhibit a marked seasonality [2,3].

The incidence rate in epidemic years can reach 1000 per 100,000 population [4]. It has been estimated that since 1988 there have been over one million cases of meningitis in Africa [5]. The largest epidemic occurred in 1996–1997 across Africa, causing over 250,000 cases and 25,000 deaths. In recent years the reported number of meningitis cases has been increasing, with 41,526 cases in 2006, 45,997 in 2007, and 88,199 cases in 2009. This may reflect a new epidemic wave in sub-Saharan Africa [5].

The main etiological agents for bacterial meningitis are Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitidis [6]. Recently, the incidence of Haemophilus influenzae meningitis has declined following the introduction of the Haemophi(and)Tl uneetion of the

immunity [14] and the vaccine response with repeated

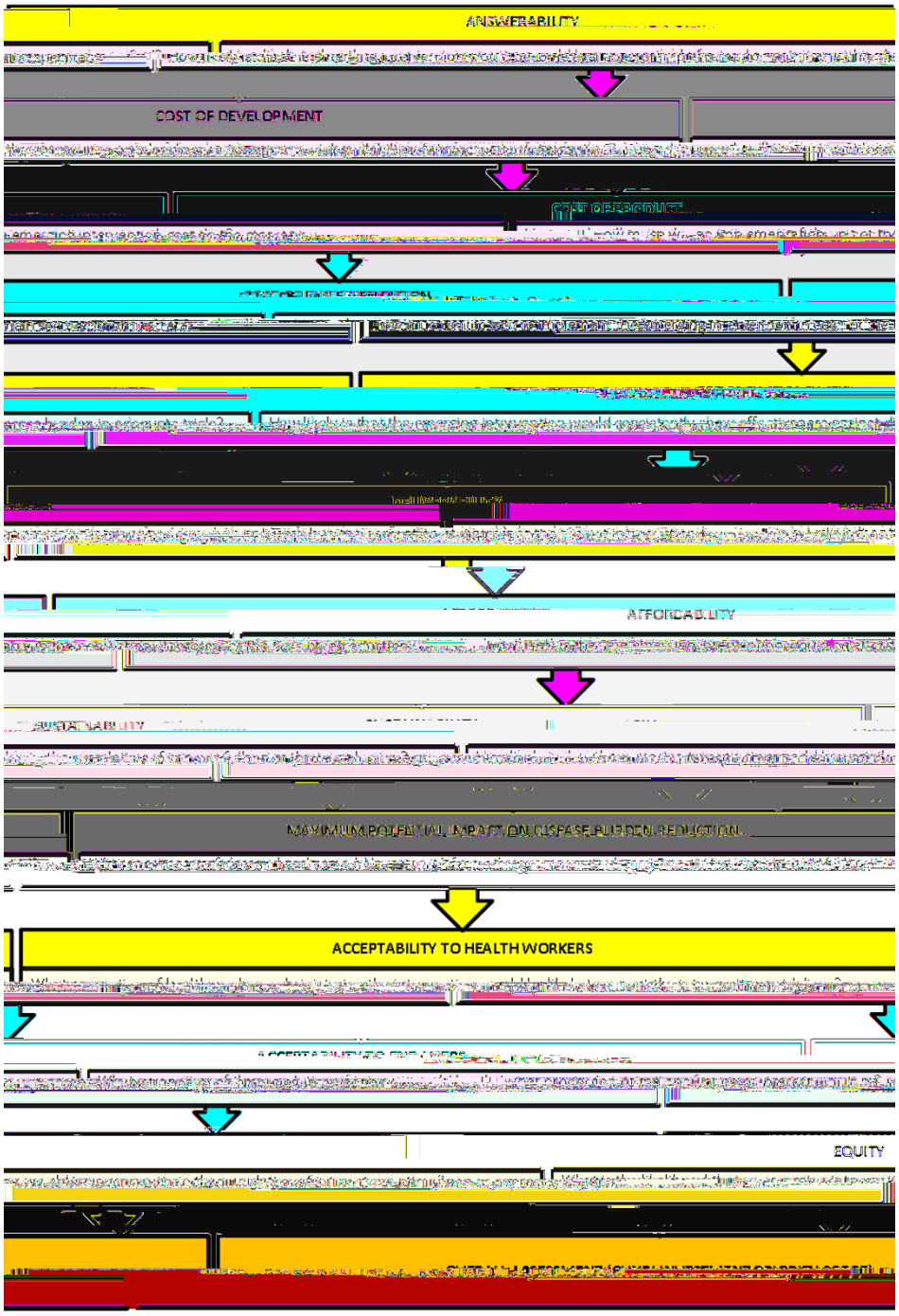


Figure 2 A summary of Stage I of the CHNRI process of an evaluation of emerging intervention (a systematic review of the key CHNRI criteria).

Answerability

The conjugate vaccine boosts immunogenicity by transforming the vaccine from T-cell independent to T-cell dependant, thus allowing for priming of immunological memory and increasing immunogenicity in infants [3]. Conjugate vaccine technology has made significant advances in the past two decades [15] Hib conjugate vaccine was first licensed in 1987 followed by MenC conjugate in 1999 and pneumococcal conjugate (PCV7) vaccine in 2000 [29]. These conjugate vaccines were found to be safe and immunogenic in infants. The efficacy of these conjugate vaccines has demonstrated that the principle that the immunogenicity of bacterial cell surface polysaccharides can be improved by conjugating

it with a protein carrier. Thus the development of the emerging MC conjugate vaccines is building on an established technology which has been shown to be successful.

The currently available MenC conjugate vaccines were first introduced in the UK in November 1999. Two different conjugated MenC conjugate vaccines were developed using CRM197 and one with tetanus toxoid as the carrier proteins [2]. These vaccines were licensed on the basis of immunogenicity and safety data but without a formal efficacy study. Studies reviewing the impact of MenC conjugate vaccines reported short term efficacy of 97% for teenagers and 92% for toddlers in England [30]. One year following introduction of these vaccines a 66% decrease in

The panel was very optimistic (score over 85%) about the ability of a monovalent conjugate vaccine against MenA to satisfy the criteria of answerability (Figure 4) while they were somewhat less optimistic (score about 75%) in the case of multivalent MC conjugate vaccines (Figure 5).

Efficacy and effectiveness

Monovalent Conjugate Vaccine against Serogroup A

A serogroup A meningococcal conjugate vaccine using tetanus toxoid as a carrier protein (PsA-TT conjugate vaccine) (MenAfrivax) has been developed at the Serum Institute of India Ltd. (SIIL) using a new licensed conjugation technique from the Center for Biologics Evaluation and Research/Food and Drug Administration (CBER/FDA, MD, USA) [33]. The vaccine demonstrated higher serum bactericidal antibody (SBA) than the PS-only vaccine in animal studies [34]. The first Phase I clinical trial was carried out in India among 18-35 year old healthy volunteers and results of the study showed PsA-TT to be safe, immunogenic and able to demonstrate long term functional antibody titers in adults (Figure 6) [35].

A Phase II clinical trial in Mali and Gambia evaluate the immunogenicity and safety of a single injection of PsA-TT vaccine in young children compared to a licensed meningococcal ACWY polysaccharide vaccine (PsACWY) and a licensed Hib conjugate vaccine (Figure 6). The preliminary results showed 96% of the subjects in PsA-TT group had a four-fold increase in rSBA titer from week 0 to 4 as compared to 64% in the ACWY PS group and 36% in Hib group [36]. A Phase II/III clinical trial with 909 subjects of 2-29 year olds was carried out in Mali, Senegal, and the Gambia comparing the immunogenicity and long-term persistence of antibodies of a single dose of the PsA-TT vaccine with that of PsACWY. The preliminary findings were presented at International Pathogenic Neisseria Conference in 2008 which concluded that the PsA-TT vaccine is safe and consistently induced higher immune responses with respect to the licensed tetravalent polysaccharide vaccine. The immune response as measured by the MenA IgG ELISA concentrations ≥ 2 μg/mL was 100% (CI 99-100) in PsA-TT group and 88% (CI84-92) in the PsACWY group [37,38]. Preliminary results of similar Phase 2/3 study in India in healthy children of 2–10 years of age showed that the vaccine was safe and highly immunogenic [39]. Two Phase 3 clinical trials are currently being carried out in India and Mali to evaluate the safety and immunogenicity of a single dose of the PsA-TT vaccine [40].

Based on these, the experts were very optimistic (score over 85%) regarding the likelihood of efficacy of the monovalent conjugate vaccine against meningitis (Figure 4).

Multivalent Vaccines against Serogroup A and W-135

The two currently available meningococcal conjugate vaccines in developed world that target both MenA and MenW-135 along with serogroup C and Y are Menactra and Menveo.

Menactra (Meningococcal ACWY-diphtheria vaccine; MenACYW-D; Sanofi Pasteur) is a quadrivalent meningococcal protein–polysaccharide conjugate vaccine licensed for use in the United States for routine vaccination of 11–12 years old and for increased risk of invasive meningococcal disease (IMD) of 2–55 years old for both Canada and USA.

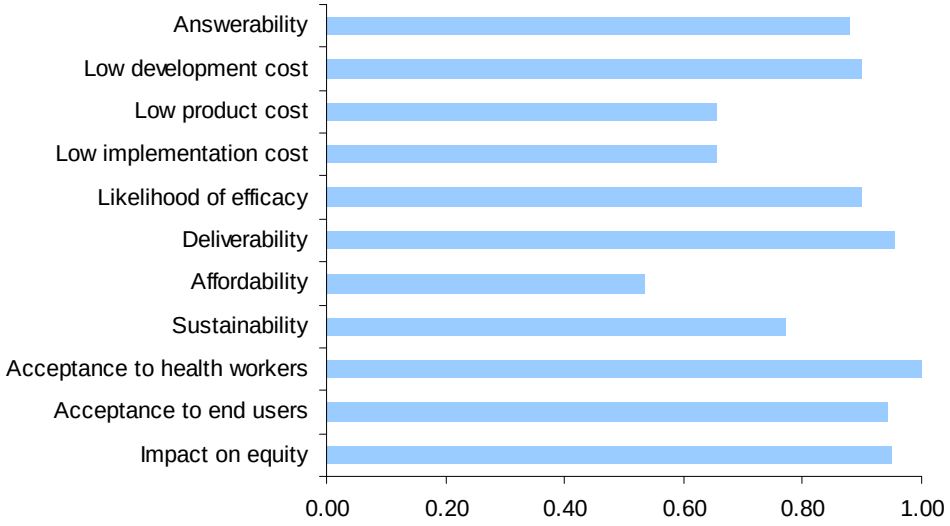
Menveo is a quadrivalent glycoconjugate vaccine, (MenACWY-CRM, Novartis Vaccines), formulated from oligosaccharides of MenA (10 g) and of Men C, W-135 and Y (5 g of each) and covalently linked to the diphtheria mutant toxin carrier protein, CRM197. In early 2010, the vaccine received approval from the Federal Drug Administration and European Medicines Agency for use among teenagers and adults.

These vaccines offer protection against four of the five most common meningococcal serogroups: A, C, Y and W-135.

A randomized controlled trial was conducted among 11-18 years old comparing the immunogenecity of Menactra with Menomune (PSV-4; A/C/Y/W-135; Sanofi Pasteur Inc), a licensed tetravalent polysaccharide vaccine (Figure 6). The findings of the study showed a high percentage of subjects with fourfold or greater rise in serum bactericidal activity for all four antigens (the seropositivity was measured by Serum Bactericidal Assay with baby rabbit complement (rSBA)). The respective seroresponse rate in Menactra and Menomune for MenA, MenC, MenY and MenW-135 are presented in

group [46]. A new Quadrivalent Meningococcal (A, C, Y and W-135) Tetanus Protein Conjugate Vaccine (TetraMen-T) is in late stages of development from Sanofi Aventis (http://clinicaltrials.gov/ct2/show/NCT01049035) and a quadrivalent Meningococcal (A, C, Y, W-TT) Protein Conjugate Vaccine from GSK nearing licensure [47-49].

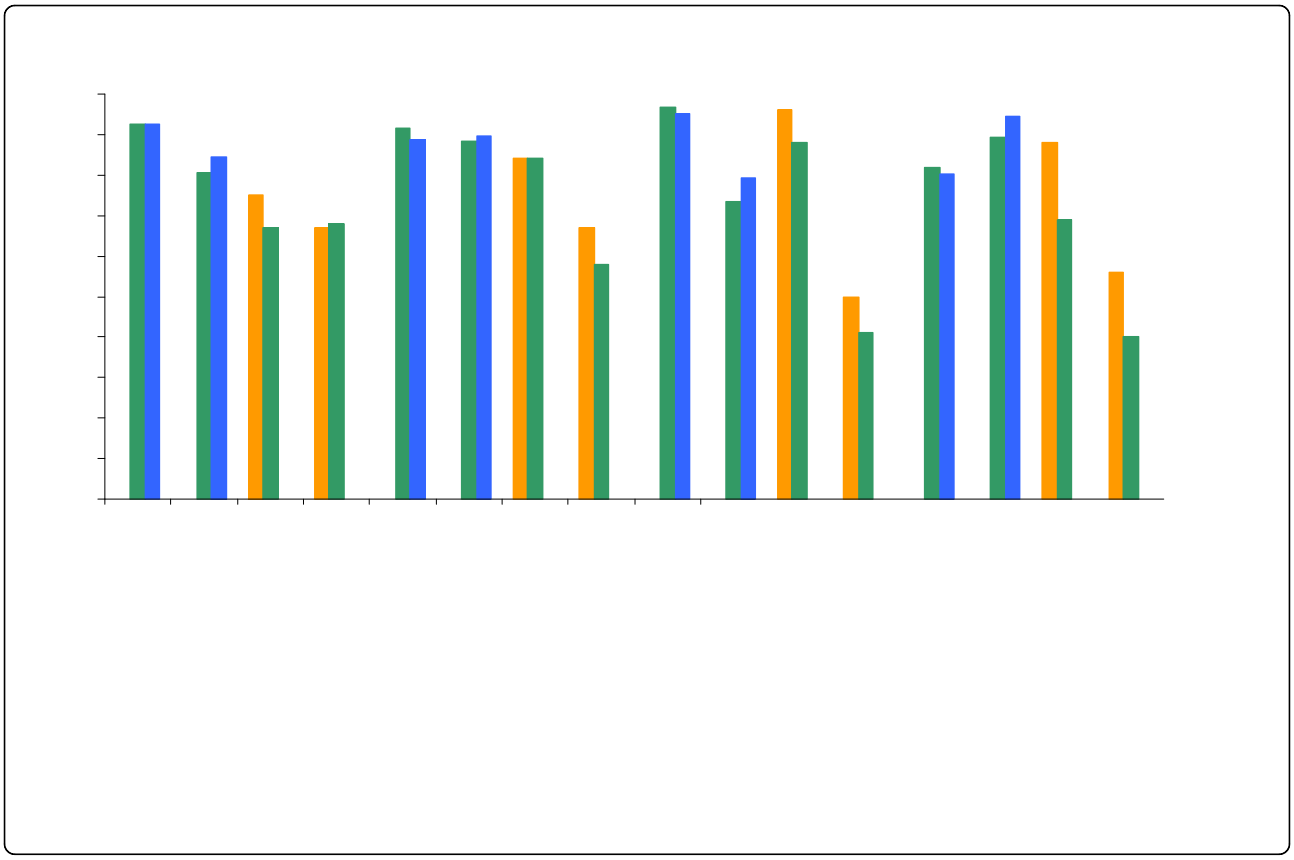
A novel heptavalent vaccine targeting Neisseria meningitidis serogroups A and C along with diphtheria, tetanus, whole cell pertussis-hepatitis B



virus and Hib (DTPw-HBV/Hib-MenAC) was developed and was found to be safe and efficacious at generating immunological memory, particularly in infants in initial Phase I/II studies (Figure 6). A dose-ranging trial in the Philippines in 524 healthy infants showed that the DTPw-HBV/Hib-MenAC vaccine produced antibody responses comparable to the non-combination vaccines [50]. Another Phase II study on DTPw-HBV/Hib-MenAC in Ghana demonstrated adequate immunogenecity in infants [51]. However, currently there are no plans to take this vaccine forward for registration [52].

No randomized controlled clinical trial has been conducted to evaluate the effectiveness of these multivalent vaccines in developing world settings. Although immunogenicity studies usually can predict short-term effectiveness, the understanding of long-term protection needs well designed effectiveness trials. Moreover studies should be carried out to gather knowledge on link between immunogenicity and impact on nasopharyngeal carriage and herd immunity in the epidemic prone areas.

Based on the available information, the expert group was very optimistic (score over 85%) regarding the



likelihood of efficacy of the multivalent conjugate MC vaccines against meningitis (Figure 5).

Cost, affordability, deliverability and sustainability

The ongoing MenA clinical trials are currently evaluating the efficacy of different schedules of vaccination in infants. The Meningitis Vaccine Project (MVP) proposes delivery of the MenA conjugate vaccine in a two dose schedule, at 14 weeks and 9 months, or as a single dose at 9 months [2]. A catch-up from age 1 to 29 years is planned for each meningitis belt country. This permits incorporation of the vaccine into existing EPI schedules, since it will be given concurrently with the final DPT dose (DTP3) at 14 weeks and with the measles vaccine at 9 months [53]. This should act to promote high coverage of the MenA vaccine without the need to commit very substantial further resources for promotion and delivery of a new immunisation programme. In 2006, the average uptake of the DTP3 vaccine across the African region was 73%, with similar rates of coverage for the measles vaccine [54]. However, this masks pronounced disparities between countries, in the "meningitis belt". For example, Niger achieved <40% coverage for DTP3 while rates in Burkina Faso and the Gambia were >90%, which suggests that approaches to vaccine delivery must be modified in areas where current strategies have low uptake. Such countries may benefit from the implementation of periodic regional campaigns to boost immunisation coverage [54].

Provision of viable vaccines relies on appropriate storage and transport and a functioning "cold-chain". Currently, there is a significant wastage of vaccines in developing countries due to inadequate funding, poor equipment and lack of training of health-care workers [55]. Storage is an important factor to address as the MenA Ps, from which the conjugate is derived has been shown to be the least stable meningococcal Ps [56] and any deviation from the recommended 2-8°C storage temperature [55] could render the vaccine unusable. This is also applies to the multivalent conjugate vaccines.

The greatest barrier to uptake of vaccines by developing countries is cost [57]. The MVP was been granted $70 million by The Gates Foundation [57] and $29.5 million from The Global Alliance for Vaccines and Immunisation (GAVI) [58], which should allow Men A conjugate vaccine to be provided at $0.40 a dose, in agreement with the manufacturer, the Serum Institute of India Limited [3]. Currently the MVP aims to provide the Men A conjugate vaccine at a lower cost through

push financing. MenAfriVac™ has received WHO pre-

presented against a common set of criteria. These scores reflect the "collective optimism" of a panel of experts drawn from varying backgrounds. We have shown that both the monovalent MC conjugate and multivalent MC conjugate vaccines are considered to have the potential to significantly reduce the burden of meningococcal meningitis in children under the age of 5 years. Countries in the meningitis belt in general, and the poorer nations in particular, account for the greatest global burden of disease due to meningitis. An effective vaccine distributed worldwide will reduce that burden, and if delivery is targeted at the poorest areas, the inequity gap in health will also be reduced.

For MenA MC conjugate vaccine the experts showed a high level of optimism (~ 90%) for 7 out of the 12 criteria. The expert group felt that the likelihood of efficacy on meningitis was very high (~ 90%) and the maximum potential impact on disease burden was also high. Median potential effectiveness of the vaccines in reduction of overall meningitis mortality was predicted to be 20% (interquartile range 20-40% and min. 8%, max 50%). The MenA conjugate vaccine scored well on answerability, low development cost, likelihood of efficacy against meningitis, deliverability, acceptability to health workers and end users, effect on equity and maximum potential to reduce the burden of mortality due to meningitis. The multivalent vaccines scored similarly well on all criteria except answerability and low development cost. The main concern related to both vaccines was expressed over the cost of product, its affordability and cost of implementation

Both the monovalent and quadrivalent vaccines have been shown to have a good safety profile, with high immunogenicity against MenA and MenW-135 in young children and adults across Phase II/III trials. However it is important that well designed controlled studies are carried out in developing world settings to provide data on effectiveness. Following demonstration of the viability of the MenC conjugate vaccine stored at room temperature, a similar study examining the effect of storage temperature on the new conjugate vaccines would be invaluable. This would potentially allow reassessment of deliverability, particularly to communities with limited cold chain facilities.

The CHNRI methodology was primarily designed to evaluate existing interventions and competing investment priorities for health research. Though we used the CHNRI criteria, we modified it by including systematic review of available literature and not involving all stakeholders (e.g. end-users and health workers). The scores included herewith express the collective opinion of a panel of 20 experts. While there is always an element of uncertainty in predicting impact of interventions which do not exist and have no clinical trial data to support them, we feel that the results would be reproducible with another panel in a different setting. The literature review also had some limitations. Firstly, the literature search was limited to selected databases and to articles published in English. In addition, a variety of key-words yielded results, especially when searching the domains "deliverability" and "equity". Although every effort was made to be inclusive, such a broad range increases the chance of missing information that may be important. Secondly, it was not always possible to find current literature specific to meningococcal vaccines. In these circumstances relevant data on other related vaccines was sought and this may not always be fully appropriate. Finally, due to marketing patents, retrieval of the most recent information on the progress of a vaccine was generally difficult.

Conclusions

With increasing recognition of the burden of meningococcal meningitis, especially during epidemics in Africa, it is vitally important that steps are taken to reduce the morbidity and mortality attributable to this disease. The strengthening of the surveillance system is important to support any vaccination program. The increase in incidence of W135 in recent epidemics raises the question of whether it would be more appropriate to use a multivalent vaccine with A and W135 in the "Meningitis Belt" instead of a monovalent vaccine. New Initiatives are joining MVP to strengthen the international effort to eliminate meningococcal epidemics in Africa. A new international consortium (MenAfriCar) http://www.menafricar.org/ has started working in Africa and aims to study patterns of meningococcal carriage and transmission in this region, as well as documenting the impact of any new MC conjugate vaccine. MenAfriCar aims to further develop regional capacity for delivery of immunization programmes. However, success will rely on concerted and sustained commitment from governments, charities and health care workers to implement those vaccination strategies shown by research to be the most effective and practical/feasible.

Additional material

Additional file 1: Additional search terms

Additional file 2: Questions used in the Phase II CHNRI process

Additional file 3: The clinical trial process

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Authors' contributions
All authors of this research paper have directly participated in the planning, execution, or analysis of the study and have read and approved the submitted version. In particular IR and HC designed the study and directed its implementation, including quality assurance and control. DC and TH were responsible for the acquisition of the data and conducted the literature review. ET, HN, LZ, RF, IL, HLJ, SEA, CBN and RB helped design the study's analytic strategy and prepared the Materials and Methods, Results and Discussion sections of the text. All authors of this research paper have critically revised the manuscript for important intellectual content.

Competing interests
The authors declare that they have no competing interests.

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