International Journal of Infectious Diseases (2008) **12**, 278—288

http://intl.elsevierhealth.com/journals/ijid

The development of a new heptavalent diphtheria—tetanus—whole cell pertussis—hepatitis B—*Haemophilus influenzae* type b—*Neisseria meningitidis* serogroups A and C vaccine: a randomized dose-ranging trial of the conjugate vaccine components☆

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Received 19 February 2007; received in revised form 13 July 2007; accepted 1 August 2007
Corresponding Editor: Dean A. Fergusson, Ottawa, Canada

KEYWORDS
Neisseria meningitidis serogroup A;
Neisseria meningitidis serogroup C;
Conjugate vaccine;
Haemophilus influenzae;
Immune memory

Summary
Objective: To assess immunogenicity, antibody persistence, immune memory, and reactogenicity of a novel heptavalent DTPw—HBV/Hib—MenAC (diphtheria, tetanus, whole cell pertussis—hepatitis B virus/*Haemophilus influenzae* type b—*Neisseria meningitidis* serogroups A and C) vaccine.
Design: This was an open, randomized study in the Philippines, with DTPw—HBV/Hib—MenAC administered at 6, 10, and 14 weeks of age. Three different polysaccharide contents of the conjugate vaccine components were assessed with conjugated PRP (polyribosylribitol phosphate), MenA, and MenC polysaccharides at the following doses: 2.5 μg of each, 5 μg of each, or 2.5 μg of PRP and 5 μg each of MenA and MenC. Controls received licensed DTPw—HBV and Hib or DTPw—HBV/Hib and MenC conjugate vaccines separately. Immune memory was evaluated via plain polysaccharide challenge administered to half of the subjects at 10 months of age.
Results: After primary vaccination, at least 97.7% of DTPw—HBV/Hib—MenAC recipients had serum bactericidal antibody (SBA)—MenA and SBA—MenC titers ≥1:8, and at least 99% had anti-PRP

☆ Data from primary and challenge phases of this study were presented as posters at the International Pathogenic Neisseria Conference, Milwaukee, USA, 5—10 September, 2004.

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doi:10.1016/j.ijid.2007.08.007

antibody concentrations $\geq$0.15 μg/ml. Immune responses to DTPw—HBV components were not impaired by the lowest dose of Hib—MenAC vaccine. Plain polysaccharide challenge induced marked increases in Hib, MenA, and MenC antibodies in primed subjects, indicative of immune memory. All of the experimental vaccines were well tolerated.

Conclusion: The lowest dose of DTPw—HBV/Hib—MenAC polysaccharide conjugate vaccine was well tolerated, immunogenic, had good persistence of antibodies, and demonstrated immune memory, and consequently was selected for further development.

Introduction

Neisseria meningitidis causes endemic and epidemic meningococcal disease worldwide with at least 30 000 deaths estimated to occur each year.[1] This figure does not consider the numbers who die in rural areas of Africa and Asia before reaching medical facilities. Mortality in some regions may reach 15% even with treatment, with a much higher proportion of victims left with long-term sequelae including limb loss and neurological deficit.[1,2] Children under 5 years of age are most often affected by endemic disease, while infants under 3 months of age seem to be protected by maternal antibodies.[2]

Although outbreaks due to serogroup C (MenC) and more recently W-135 and serogroup X have been reported in Africa and Asia, serogroup A (MenA) accounts for most meningococcal epidemics and particularly affects countries within the 'meningitis belt' of Africa.[3–8] In Asia, serogroup A has been responsible for three pandemics since the 1960s: the first began in China in the mid 1960s, the second one started in China and Nepal in the 1980s, extending to India, Bhutan, Saudi Arabia, and Yemen, and the third one began in China in 1994 and moved to Mongolia, Russia, and Africa.[9,10] In addition to these pandemics, epidemics have affected Mongolia (1973—74) and Vietnam (1977). More recently, Taiwan reported a re-emergence of MenA cases in 2001; MenA outbreaks also occurred in India and the Philippines in 2005.[9–11]

Endemic disease rates in Africa may be as high as 20/100 000, but during epidemics may reach more than 1000/100 000.[1,2,6] To place this rate in perspective, an overall disease incidence rate of approximately 10/100 000 was observed during the 1999 MenC epidemic in England and Wales prior to the introduction of MenC conjugate vaccines.[12]

Meningococcal polysaccharide vaccines have been available since the 1980s and are effective in preventing disease. However these vaccines do not provide long-term protection, their effect on carriage is minimal, and their use is therefore restricted to epidemic situations.[1,2] Except for serogroup A polysaccharide that induces an immune response in infants under 1 year of age with some evidence of efficacy, meningococcal polysaccharide vaccines are poorly immunogenic in young children under 2 years of age. Furthermore, administration of the MenC polysaccharide is found to cause hyporesponsiveness to subsequent doses of MenC vaccine.[13]

The availability of MenC conjugate vaccines has fundamentally altered the epidemiology of MenC disease in countries where vaccination has been widely implemented.[12,14] The development of an effective MenA conjugate vaccine for infant immunization would enlarge endemic and epidemic invasive meningococcal disease control even further. The World Health Organization (WHO) Expanded Program on Immunization (EPI) currently recommends routine vaccination against diphtheria, tetanus, pertussis, hepatitis B virus (HBV), polio, and *Haemophilus influenzae* type b (Hib) for all infants.[15] Whole-cell pertussis vaccines are most commonly used in less industrialized countries mostly because of lower cost compared to more recent acellular pertussis vaccines. In endemic areas where poliomyelitis has not been eradicated yet, WHO recommends the use of oral polio vaccine (OPV).[16] Combined diphtheria—tetanus—whole-cell pertussis—hepatitis B (DTPw—HBV) and DTPw—HBV/Hib vaccines are now widely used, and their coverage is increasing. The addition of MenA and MenC conjugates to these existing vaccines will promote rapid uptake and high coverage of the new components, while minimizing cost and logistical problems in vaccine delivery.

This study evaluated three novel heptavalent DTPw—HBV/Hib—MenAC combination vaccines that differed in the dose of the Hib—MenAC conjugate component, for use in a three-dose primary schedule during the first year of life.

Methods

Study design and subjects

The study was an open, randomized study in the Philippines, conducted in two phases: primary vaccination (study number: 759346/001) and polysaccharide challenge (study number: 759346/002). The study protocols (NCT00317174) were reviewed and approved by the relevant ethics committee and were conducted according to Good Clinical Practice Guidelines and the Declaration of Helsinki. Written informed consent was obtained from the parent/guardian of every child prior to enrolment in the study.

Healthy infants aged between 6 and 10 weeks at the time of the first vaccination were eligible for inclusion. Subjects were excluded if they had a major congenital defect or serious chronic illness, any confirmed or suspected immunosuppressive or immunodeficient condition, evidence of previous diphtheria, tetanus, pertussis, hepatitis B, Hib, MenA and/or MenC vaccination or disease, any history of allergic reactions to any vaccine component, receipt of any investigational or non-registered drug or vaccine within 30 days before or during the study, or receipt of immunosuppressive or immunoglobulin therapy or blood products before enrolment or during the study. Subjects were also excluded if they had received hepatitis B or Bacille Calmette—Guérin vaccine after the first two weeks of life.

In the primary phase of the study, 525 eligible infants were randomized to one of five groups (1:1:1:1:1). Three groups evaluated different doses of the novel heptavalent vaccine: group 2.5/2.5 received DTPw—HBV/Hib—MenAC containing 2.5 μg each of conjugated PRP (polyribosylribitol phosphate), MenA, and MenC polysaccharides, group 2.5/5