Immunogenicity and Safety of a Heptavalent (Diphtheria, Tetanus, Pertussis, Hepatitis B, Poliomyelitis, *Haemophilus influenzae* b, and Meningococcal Serogroup C) Vaccine

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Summary

In this open, phase II, randomized study, 480 infants from Germany, France and Canada received the heptavalent vaccine (Hepta group) or hexavalent and monovalent meningococcal serogroup C control vaccines (HexaMenC group) co-administered with a 13-valent pneumococcal conjugate vaccine at 2, 4 and 12 months of age. Immunogenicity was measured 1 month after the second primary dose, and before and 1 month after the booster dose. Non-inferiority of immune responses to meningococcal serogroup C (MenC) and *Haemophilus influenzae* b (Hib) induced by 2-dose primary vaccination with the heptavalent vaccine *versus* control vaccines was demonstrated. In exploratory analyses, post-primary and post-booster functional antibody geometric mean titers against MenC tended to be lower (1119.5 *vs* 3200.5; 2653.8 *vs* 6028.4) and antibody geometric mean concentrations against Hib higher (1.594 *vs* 0.671 µg/mL; 17.678 *vs* 13.737 µg/mL) in the Hepta *versus* the HexaMenC group. The heptavalent and control vaccines were immunogenic to all other antigens, although immune responses to poliovirus were lower than expected in both groups. No differences in safety and reactogenicity profiles were detected between groups.

Commentaries

Evidence-based-medicine Viewpoint

Relevance: The ongoing effort to balance introduction of newer vaccines into infant immunization schedules, with simplification of their administration (in terms of dosage volume, number of doses and timing) has resulted in novel multi-antigen combination vaccines in recent years. The simplest combinations include extemporaneous combination of different antigens for simultaneous administration; while more complex formulations include chemical combination of various antigens of one or multiple pathogenic organisms. Either way, combination vaccines have to demonstrate sufficient immunogenicity (ability to stimulate the immune system to generate antibodies against each antigen in the combination), safety (the combination must not result in greater severity or frequency of undesirable effects), and feasibility for use (acceptable dosage volume, incorporation into existing immunization schedules, etc). The vaccine antigens are expected to target infectious diseases of public health importance (in terms of burden of disease, morbidity/ mortality, cost burden etc). In some developed countries, meningococcal serotype C (MenC) disease matches these criteria, and MenC vaccination is recommended, either as a separate injection with other routine infant vaccinations or a licensed combination with Hib vaccine. In such settings, there are efforts to increase coverage of MenC vaccination without extra injections; hence combinations with MenC are now being developed and tested. A previous trial comparing a heptavalent combination (pentavalent DTaP-HBV-IPV combined with Hib-MenC) against separate injections of hexavalent vaccine (DTaP-HBV-IPV-Hib) coadministered with monovalent MenC vaccine – given through a 3+1 schedule (3 primary doses at 2,3,4 mo age and a booster at 12 mo) – demonstrated comparable effects in healthy infants [1]. The present study [2] is a further step to simplify vaccination using a 2+1 schedule (2 primary doses at 2 and 4 mo, followed by booster at 12 mo), comparing the novel heptavalent combination (*Intervention*) versus the licensed hexavalent vaccine + MenC administered separately (*Comparison*), in terms of immunogenicity and safety (*Outcomes*) in healthy infants (*Population*).

Critical appraisal: The study [2] was designed as a multi-country (*n*=3), multi-center (*n*=33) trial, funded and conducted by a vaccine manufacturing company

with a global presence. Standard inclusion and exclusion criteria were applied. Baseline characteristics showed that the two groups had similar gender ratio, ethnicity and age at administration of first dose. However, no other demographic characteristics have been described. The investigators designed this as a non-inferiority trial calculating the sample size to demonstrate the upper bound of the 95% CI of the difference between comparison and intervention arm to be less than 10% for the immune response to Hib and MenC components of the vaccine (primary outcome). However, for some obscure reason, the non-inferiority data are only presented in online supplementary tables, and not in the paper itself.

Critical appraisal of the trial using the Cochrane Risk of Bias tool [3] suggests that the randomization sequence was adequately generated (using a central internet-based system). A minimization procedure was used, wherein the chance of assignment to a particular group varies on the basis of assignment of previous participants in order to ensure minimum imbalance between groups. However, concealment of allocation has not been explicitly described. For practical reasons, the trial was unblinded since the heptavalent vaccine group received one injection at each visit whereas the comparison group received two injections. This can create bias among parents who were responsible for reporting local and systemic adverse events. However, laboratory personnel who performed tests to establish immunogenicity were blinded to the allocation. The investigators enrolled a total of 480 infants of which 408 (85%) were included in the analysis of the primary outcome. The respective percentages in the intervention and comparison arms were 90% and 80%, suggesting a differential attrition rate that has not been explained or explored. There was further attrition in both arms for outcomes measured following the booster dose. The authors used *per protocol* analysis rather than the expected intention-to-treat analysis. All relevant outcomes were included in the trial and there was no selectiveness of reporting. The trial had a somewhat complex set of outcomes that included markers of immunogenicity to each of the components in the combination vaccine, as well as safety parameters. Overall, the trial had moderate risk of bias.

The trial had several methodological refinements, including multiple quality control measures for laboratory tests of immunogenicity (such as testing in duplicate for borderline results, re-testing of samples for selected outcomes showing unexpected results, use of reference laboratory and procedures). The investigators used internationally accepted correlates of protection for each of the antigens in the vaccines. For immunogenic response to MenC, they measured antibodies to both rabbit and human complement; and also calculated an additional measure *viz* titer ≥1:128 for both. Likewise for Hib, they measured percentage of vaccinees with antibody levels higher than 0.15 µg/ml and 1.0 µg/ml correlating with short and long term protection, respectively. They also measured antibodies to each of the 13 components of the Pneumococcocal conjugate vaccine administered concomitantly with the trial vaccines.

However some important issues have not been addressed adequately. For example, it is unclear whether the comparison group received both vaccines in different limbs or at different sites in the same limb. This has great relevance in the evaluation of reactogenicity, since each injection has the potential to independently cause local side effects. Therefore, we would expect the local adverse events in the comparison arm to have a denominator that is double that of the single heptavalent vaccine injection. However this has not been done. The definitions of the local adverse events have not been described, although each event was graded on a 3-point scale and criteria for only grade 3 are mentioned. Further, there is no description of direct observation for local adverse events by trial investigators for 30-60 minutes (which is standard practice even after routine vaccination). Even the process of obtaining the data for 'solicited' adverse events is unclear. For example, this could be done through daily telephonic contact with the family, or a personal daily home visit. It is possible that irrespective of the method used, data collection was highly sensitive since very high proportion of infants in both arms appear to have developed local adverse events. On the other hand, if these high proportions do not reflect overly sensitive reporting, the high adverse event rates raise safety concerns. The investigators have not addressed this issue. Additionally, it would have been useful to study the adverse event rate after each dose of vaccine; and also whether any of the infants developed some events after every dose. These also have not been studied.

In terms of immunogenicity, the investigators focused exclusively on the issue of comparability between the two arms. However analysis of the percentage of infants with antibodies below the conventional protective levels **(*Table* 1)** raises some interesting points. For all the antigens (except tetanus), antibody levels had declined below the protective threshold by the age of 12 months. This suggests that a significant proportion of infants were unprotected (hence susceptible to disease) at some time point between 5 and 12 months. This observation calls for

TABLE I PROPORTION OF VACCINEES WITH ANTIBODY LEVELS BELOW THE CONVENTIONAL PROTECTIVE LEVELS, AT DIFFERENT TIME POINTS

	Intervention arm (%)			*Comparison arm (%)*		
	Post primary	*Pre-booster*	*Post-booster*	*Post primary*	*Pre-booster*	*Post-booster*
MenC SBA <1:8	1.9	8.2	0.5	0.5	19.4	0
Anti-PRP <0.15µg/ml	5.6	26.4	0	15.7	36.9	0
Anti-PRP <1.0µg/ml	38.0	83.8	1.0	63.2	86.7	5.6
Anti-T <0.1 IU/ml	0	4.1	0	0	9.7	0
Anti-D <0.1 IU/ml	0.5	27.4	0	0.4	13.3	0
Anti-pertactin < 5 ELISA U/ml	0.5	34.5	0	0.5	27.6	0
Anti-FHA < 5 ELISA U/ml	0	0.5	0	0	0.5	0
Anti-PT < 5 ELISA U/ml	0	29.5	0.5	0	21.1	0.5
Anti HBs <10mIU/ml	1.4	9.6	1.0	0.5	4.8	0.2
Anti-poliovirus 1 <1:8	14.3	55.2	4.7	12.0	47.9	1.6
Anti-poliovirus 2 <1:8	18.9	52.5	1.6	23.1	48.9	1.6
Anti-poliovirus 3 <1:8	13.8	47.5	1.6	9.6	42.6	2.1

comparison with responses following a three-dose primary series, and also careful monitoring of the vaccinated infants for detection of diseases caused by the respective pathogens. Neither has been done in this study. Additionally, there appear to be significant differences between the two arms with respect to the pre-booster antibody levels. For example, in the case of MenC and tetanus, more than twice the number of infants in the comparison arm has antibodies below the protective level compared to the intervention arm. The reverse appears to be true for diphtheria, hepatitis B, and two of the three pertussis antigens. These issues and possible implications have not been elaborated in the paper. In contrast, the investigators noted that almost half the vaccinated infants in both arms had inadequate protection to all three strains of poliovirus, although these were comparable between the arms. This is also cause for concern.

Comparison of absolute concentration of antibodies in the two arms raises another interesting pattern. Inter-arm levels seem comparable for pertussis (all three antigens) and poliovirus (all three strains). The intervention group had significantly higher antibody levels against Hib and tetanus at all three time points and lower antibody levels at all time-points for diphtheria and hepatitis B. For MenC, the intervention arm had lower antibody concentrations following the primary and booster doses, but higher levels just prior to the booster. The implications of these differences have also not been described.

Although the data are not highlighted, it appears that infants in both arms had inadequate protection to 2 of the 13 serotypes in the multivalent Pneumococcal conjugate vaccine administered with the trial vaccines.

Extendibility: There are several reasons why the trial results are not applicable to the Indian setting. Besides being a phase II trial, the target disease (MenC) is currently not considered a public health problem in India necessitating universal vaccination. In our setting, the six diseases targeted in the EPI continue to remain public health challenges, necessitating that any new vaccine must ensure serological (and preferably protective) efficacy against them. Therefore, the inadequate response to poliovirus strains and rapid waning of the antibodies to D and P are cause for concern. In the Indian context, the differences in burden of disease, baseline vaccination rate, vaccination schedule, number of doses in the primary course, and age at booster vaccination are also significant.

Conclusions: This clinical trial suggests that although the sero-efficacy and safety of a heptavalent vaccine incorporating MenC administered in a 2+1 schedule, is comparable to the simultaneous administration of a licensed hexavalent + monovalent Men C vaccine (in a developed country context), there are several gaps that require to be addressed before the vaccine and schedule can be routinely used.

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Public Health Perspective

Combination vaccines have benefits to the public health system of any nation. The major advantage of this combination vaccine is reduced requirement of separate injection for meningococcal vaccine antigen compared to hexavalent vaccine, that will aid in improving compliance with the vaccine schedule apart from added benefit of providing protection against target diseases. However, the authors have not mentioned the non-inferiority margin that was aimed to be detected by the sample included in the study, and the adequacy of current sample size seems to be questionable [4]. Thus statistically, the results presented could not be commented for achieving non-inferiority of meningococcal vaccine component compared to control vaccines. Also, the included trial sites were chosen from developed nations (Germany, France, Canada), thus limiting the generalizability of the findings to developing nations.

The epidemiology and circulation of meningococcal serogroups varies by different countries of the world, and thus the vaccine type requirements will also vary in different parts as recommended by Global Meningococcal Initiative [5]. In South-East Asian countries, including India, there is need for detailed epidemiological assessment of meningococcal disease burden including invasive meningococcal disease. In India, the predominant meningococcal serogroup reported in epidemics is A, and thus any future vaccine that will have to be used, should provide protection against capsular group A meningococci. Prevention experience of handling serogroup A has been documented successfully from African meningitis belt through use of monovalent conjugate vaccine manufactured at Serum Institute of India [6].

The investigational heptavalent vaccine and comparator hexavalent vaccine had also included injectable polio virus, and this is of interest to nations that have recently eliminated polio virus from local circulation like India. In the next phase of polio eradication efforts, introduction of IPV is of immense value, particularly for responding to impending threat of circulating vaccine derived polioviruses [7]. Though the investigational combination vaccine induced lower immunity against polioviruses as compared to hexavalent vaccine, there exists scope of introducing IPV as part of combination vaccines. India has introduced pentavalent vaccines in many states as part of Universal Immunization Schedule (UIP); future research is imperative to add more antigens to the combination vaccine to ease the vaccine delivery in routine public health system of the country.

Also pertinent to note here is the vaccine schedule utilized for administering the heptavalent vaccine (2-4-12) that varies from country's current UIP pentavalent vaccine/ DPT vaccine (1.5-2.5-3.5) primary schedule. Future trials of Indian relevance should dwell into developing vaccines following similar schedules for better introduction and acceptance by the public health system. Further efficacy and effectiveness vaccine trials of combination vaccines from Indian settings, considering local epidemiology with added component of economics, will be critical before any decisions can be made about their utility to routine public health immunization programs.

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Pediatrician's Viewpoint

Pentavalent and hexavalent vaccines containing DaPT/ IPV/Hib and DaPT/IPV/HBV/Hib vaccines are routinely used in many countries in the world. Invasive meningococcal disease caused by serogroup C is commonly encountered in Europe and Canada, and monovalent conjugate vaccine against it has been in use in the National schedule of many European countries and in Canada.

This study concludes that the experimental heptavalent vaccine is non-inferior to the control vaccine in achieving the primary outcome as immunogenicity and safety of conjugate meningococcal C and Hib vaccine. However, there was lower than expected level of immunogenicity against polio vaccine in both the groups but still above the protective range.

The new Heptavalent vaccine would be an excellent armamentarium in immunization program of countries where Meningococcal C disease is still a major public health problem. However, in Indian context this new combination shall have practically no role as group A meningococcal disease causes almost all cases of invasive disease.

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