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Reply

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Sir: In response to the comments of Drs Kaplan and Heyse, we would start by stressing that this was an exploratory trial designed to assess the immunogenicity of the four Hib vaccines and their respective reactogenicity. Such preliminary studies typically have no *a priori* endpoints (i.e. a post-hoc type analysis) and as such the statistical findings are considered to be descriptive and the differences are suggestive of trends. Furthermore, we believe that Journal readers are familiar with statistical methodology and will view the results within the confines of the statistical methodology. In addition, while accepting that this is indeed an exploratory trial, we feel that there is obvious benefit to the medical community of publishing such preliminary results. This was in fact reflected in the comments of one of the reviewers of the original manuscript: ''this manuscript covers an important topic in modern vaccine development''. The reviewer describes the study & concludes ''taking into account that in the near future IPV will be in the primary vaccine to prevent polio, at least in European countries, the authors describe an attractive and important way to achieve high acceptance and sufficient immune responses with a new multivalent childhood vaccine. Thus, in this reviewer's opinion the data reported are up-to-date and important for a broad paediatric community''.

Regarding the statistical analysis based on diary cards, we agree that the analysis of incidence of symptoms per all doses would indeed favour the Hib vaccines given as three doses over Pedvax Hib, which is given as two doses. Therefore, if this is the case, the most pragmatic approach would be to present the incidence of symptoms per subject, which considers the full burden of the symptoms over the full vaccination course. Therefore we have conducted the per subject analysis and in brief, comparing the least (Hiberix) and most (Pedvax Hib) reactogenic vaccines the results are as follows: pain 9.1% (95% CI 5.7–13.8) versus 30% (21.6–39.5), redness 31.1% (25.0–37.6) versus 59.1% (49.3–68.4), swelling 14.6% (10.2–20.0) versus 36.4% (27.4–46.1), fever 17.8% (13.0–23.5) versus 24.5% (16.8–33.7), respectively. However, what is important to note is that the trend is still the same (as suggested by the non overlap of 95% CI): Pedvax is still markedly more reactogenic, when given as two doses, than the other three Hib vaccines, which are administered as a three dose course. Regarding Dr Kaplan's observation that ''later doses generally produce fewer injection site reactions'' (therefore bias Pedvax), this appears not to be the case. The incidence of swelling and redness increases with successive dose which would bias against the three dose vaccines and although the incidence of pain does decreases after successive doses, it is still markedly higher in the group receiving Pedvax Hib. Furthermore, contrary to Dr Kaplan's remark, the impact of the DTPa-HBV-IPV vaccine on reactogenicity is discussed in the paper. We concluded that the majority of general symptoms associated with vaccination are attributable to DTPa containing vaccine, because the incidences are similar to those reported for DTPa and DTPw vaccines [1], therefore we concluded that the Hib vaccine has little or no impact on the incidence of general symptoms. This is further substantiated by the similarity of the incidences of general reactions seen between groups. As the DTPa-HBV-IPV and Hib vaccines are administered at different sites, such discussion on local site reactions would not be relevant.

In answer to the specific points addressed to the Hib response by Drs Kaplan and Heyse, firstly we would point out that as DTP and IPV are mandatory paediatric requirements that share the same administration schedule as Hib, it would be unethical not to administer these vaccines together. Secondly, we also point out that there would only be a need for a control group receiving only Hib vaccine if the primary conclusion was to determine whether there was interference of the Hib response by co-administering with DTPa-HBV-IPV. However, this was neither a primary conclusion nor objective. As described in the statistical section, the study assessed the differences in immunogenicity and reactogenicity between the four study groups. However, an observation as to the Hib response is made in the Conclusion section of the Abstract as follows ''there does not appear to be any interference with the immune response when commercially *Haemophilus influenzae* type b conjugate vaccines are concomitantly administered with a candidate diphtheria-tetanus-acellular-hepatitis B inactivated polio virus vaccine as separate injections''. This comes from the observation made in the discussion section that ''the immunogenicity of all four vaccines was good, all but 1 of the 508 subjects having detectable antibodies above the 0.15 μg/ml cut-off. This value is also a reference for ''protective'' anti-PRP titres against Hib disease.'' Therefore it would seem that with such a high degree of seroprotection achieved there is no problem with co-administering any of the four commercial Hib vaccines with the DTPa-HBV-IPV combined vaccine.

We of course also note Dr Kaplan's two other points regarding the non-blinding of the study and the non adjustment for multiple comparisons, but as mentioned earlier, this was an exploratory study. Furthermore, we understand from the sponsors that a much larger trial with a similar design has recently been conducted and publication of these results will help confirm these preliminary observations.

Reference

1. Pichichero ME, Christy C, Decker MD, Steinhoff MC, Edwards K, Rennels MB, Anderson EL, Englund JA (1995) Defining the key parameters for comparing reactions among acellular and whole-cell pertussis vaccines. Pediatrics 96: 588–592

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