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Reply to Letter to the Editor

Response to: A Phase III open-label, randomized, active controlled clinical study to assess safety, immunogenicity and lot-to-lot consistency of a bovine-human reassortant pentavalent rotavirus vaccine in Indian infants

To the Editor,

We have read the article with interest and we welcome the arrival of new rotavirus vaccines to address the partly unmet medical need to protect children against rotavirus in the developing world. A broader offer from multiple vaccine manufacturers should contribute to increasing both the vaccination coverage and supply reliability in these geographic areas.

However, the accurate generation and presentation of data and evidence pertaining to all available vaccines should be constantly pursued. This objective was not met in the study by Rathi *et al.* [1] Specifically, three elements in the study design corresponding to the immunogenicity assessment have not been handled in a way to allow any valid or objective comparison between Rotasiil and Rotarix: immunogenic assay, timing of blood sampling and seropositivity threshold.

- Firstly, the measurement of immune responses of two vaccines that are conceptually different from each other in their antigenic composition require vaccine-specific assays. In this study, the authors did not use the appropriate immunogenic assays validated by each of the vaccine manufacturers. In this regard, the recent publication by Libster and collaborators [2] demonstrated that one vaccine elicited different seropositivity rates when different vaccine antigens were used (homologous versus heterologous).

- Secondly, using different blood sampling timing for each vaccine (four weeks after the last dose of active vaccination for Rotasiil versus eight weeks for Rotarix) is a methodological error in the immunogenicity evaluation. Indeed, the impact of post-vaccination blood sampling timepoint on antibody titers and subsequent seropositivity rates has been previously highlighted [3]. Moreover, information on timing of blood sampling for Rotarix is only provided in the last paragraph of the discussion. While the authors acknowledge these two points in the discussion (use of the same immunological assay despite antigenic differences and different timepoints for blood sampling), the bias in the immunogenicity assessment leads to an unbalanced comparison of the vaccines and to subsequent erroneous conclusions. It is also worth mentioning that while the authors reported immunogenicity data obtained for Rotarix in an Indian study [4], they failed to point out the discrepancy between their results and the results from that study.

- Thirdly, no details are given in the immunogenicity section nor in any supplementary material regarding the assay used and how the 20 U/mL cut-off was defined for the immune responses induced by Rotasiil. The 20 U/mL cut-off was indeed established only for Rotarix by Cheuvart *et al.* [5].

The lack of sound scientific design does not permit a comparison of the immunogenicity results between Rotasiil and Rotarix. The authors' discussion of the limitations does not mitigate the erroneous data comparison in the immunogenicity results which may, in their presentation, most likely lead to invalid conclusions on the immune response profile of the Rotarix vaccine. We hence ask the authors to withdraw the immunogenicity data of Rotarix and its comparison with Rotasiil, in each of their occurrence: abstract, results section including table and discussion.

Conflict of interest

Paul Gillard and Bernd Benninghoff are employed by and hold shares in the GSK group of companies.

References

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