Indian Conjugate Vi Typhoid Vaccine: Do We Have Enough Evidence?

Recently, advertisements of the so called first Indian Vi conjugate typhoid vaccine (Vi conjugated with Tetanus Toxoid as carrier–Pedatyph^{R}) appeared in Indian Pediatrics. However do we have enough data to start using it? After going through available data on conjugate Vi vaccines in general, another Vi conjugate vaccine (Vi conjugated with the non toxic recombinant exotoxin A of the *Pseudomonas aeruginosa* as carrier–Vi-rEPA) which has been tested in field efficacy trials and data available from the product monograph of Pedatyph^{R}, I have following points to ponder(1-5):

Serologic correlates of protection: Unlike many vaccine preventable diseases, serologic correlates of protection are not available for typhoid disease or typhoid vaccines. Hence, even though typically more than 90% of vaccinees achieve seroconversion after unconjugated Vi vaccine, efficacy is actually 50-70% in field efficacy trials(1). Thus one necessarily needs field efficacy trials to conclude the protection provided by any typhoid vaccine and can not rely on immunogenicity data alone. While field efficacy trials have been conducted for Vi-rEPA vaccine, no such clinical efficacy trials have been conducted for Pedatyph^{R}. The vaccine is licensed based only on immunogenicity data, that too only a single study involving few hundred Indian subjects (Product Monograph, BioMed Pvt. Ltd.).

Field efficacy of Vi conjugate vaccines: Szu, *et al*.(2) successfully conjugated Vi antigen with the non toxic recombinant exotoxin A of the *Pseudomonas aeruginosa* leading to the development of the vaccine Vi-rEPA, field efficacy for which has been shown to be nearly 93% at 27 months follow up using 2 doses in children of 2-4 years of age(2,3). However this vaccine is different from Pedatyph^{R} where Vi is conjugated using tetanus toxoid as carrier protein. Hence, one can not presume or extrapolate similar efficacy using different conjugate carriers and techniques. Even for Vi-rEPA vaccine, there is no efficacy data in children below 2 years leave aside infants as young as 3 months and yet Pedatyph^{R} is recommended for use from 3 months of age onwards.

Bridging studies: One can bridge the immunogenicity data of a new vaccine with the efficacy data of an existing vaccine, provided one tests the new vaccine in the same population using same antibody testing technique as was applicable for the existing vaccine. However, this can not be applied to Pedatyph^{R} for two reasons. First of all, serologic correlates of protection are not known for Vi typhoid vaccines, and hence one can not extrapolate efficacy of Vi-rEPA vaccine (for which efficacy data are available) with the Pedatyph^{R} vaccine (for which only immunogenicity data are available). Secondly, these two vaccines are made using different carrier proteins and different conjugate techniques, and are tested in different population using different techniques for testing antibody levels; Pedatyph^{R} is tested in Indian population whereas it is compared for efficacy with Vi-rEPA vaccine which was tested in Vietnam and using different technique for measuring antibody levels. Just to compare, from our Hib experience we know that all Hib conjugate vaccines did not compare in efficacy e.g. PRP-D Hib conjugate vaccine had inferior efficacy than PRP-T vaccine.

Pedatyph^{R} data and product monograph: The only study done on Pedatyph^{R} vaccine is on 169 Indian subjects > 12 weeks old for safety and 145 for immunogenicity, compared to a control group of 37 children > 2 years old given Vi vaccine studied for safety and 29 for immunogenicity; totally unmatched for number of subjects (and obviously for the age group). To best of my knowledge, the study is neither published in peer reviewed journal nor available for critical review. The only source of data is the product monograph and even there the data available is

piecemeal and not complete. The safety and immunogenicity data are not available for the subjects receiving unconjugated Vi vaccine (control) arm for comparison with those receiving Pedatyph^{R} vaccine. Again, one is misled to believe that Pedatyph^{R} vaccine is same as the Vi-rEPA vaccine by repeated highlighting the work done by Szu, *et al.*(2) and Kossaczka, *et al.*(3) (which is for Vi-rEPA vaccine), stating field efficacy data of Vi-rEPA vaccine (which is different from Pedatyph^{R} and then linking it to Pedatyph^{R} which in fact is totally different vaccine then the Vi-rEPA.

To conclude, it will be more reassuring to have direct clinical efficacy data with Pedatyph^{R} which will make us more confident to use the vaccine in our day to day practice.

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Conjugate Typhoid Vaccine(s) in the Indian Context

The recent conference presentations and advertisements for 'indigenous' conjugate typhoid vaccine prompt the following considerations.

IS TYPHOID A SIGNIFICANT PUBLIC HEALTH PROBLEM IN INDIA TO MERIT VACCINATION?

(*a*) It is usually taken for granted that typhoid is a major public health problem in developing countries. However, careful analysis of data from current(1) and previous studies(2) shows that the absolute incidence of blood-culture proven typhoid episodes is only about 0.2% per year and, it contributes to a very small proportion of the total febrile episodes across all age groups (***Table* I**). This is a very important observation because vaccination can/will protect only against typhoid episodes and not febrile episodes believed to be typhoid and/or loosely labelled 'enteric fever' and treated as typhoid.

(*b*) Increasing antibiotic resistance(3) is often cited to emphasize the public health significance of typhoid. However, the latest multi-centric international study reported resistance in India to

TABLE I SIGNIFICANCE OF TYPHOID IN INDIA

Age-group	Febrile episodes/ 100,000/y	Typhoid episodes/ 100,000/y	Contribution of typhoid episodes among total febrile episodes
< 2 years	13920	89.2	0.64%
2-4 years	12040	340.1	2.82%
5-15 years	9490	493.5	5.2%
> 16 years	6620	119.7	11.7%
Overall	7690	214.2	2.79%

Data from the latest multicentric study (*1*)