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Correspondence

Introducing pentavalent vaccine in EPI in India: A counsel for prudence in interpreting scientific literature

Sir,

Lone *et al*[1], have cautioned about the introduction of pentavalent vaccine, that also includes vaccine against Haemophilus influenzae type b (Hib), citing several studies in support of the lower Hib disease burden in India, which stems from errors in interpretation of scientific literature. Authors have chosen to quote the result (obtained through RTI) of an ICMR study[2] as ''incidence of all-cause pneumonia was 30 per 1000 children under-five and mortality was 0.3 per 1000 children under-five in Anaicut block, Vellore' and compared it with UNICEF's estimations. However, there are several anomalies in their interpretations.

Firstly, ICMR study[2] estimate is about 'incidence of severe clinical pneumonia in 2 months to less than two-year-old children' rather than 'incidence of all cause pneumonia in children less than 5 years' as is mentioned in their editorial. Incidence of all-cause pneumonia is estimated to be ten times the incidence of severe clinical pneumonia[3]. Hence the incidence of all cause pneumonia in the stated study would be at least around 300 per 1000 children in the age group of 2 month to 2 years in the study area. ICMR study had information on mortality of children in 2 months to less than 2 years of age at the time of discharge from the study hospitals and it did not include those who may have died at home after discharge or those who had pneumonia but were not admitted in the study hospitals. Moreover, if a child was admitted to a study hospital with severe pneumonia, he/she was treated with appropriate antibiotics and hence his/her chances of survival increased manifold as compared to children who may not have received treatment with appropriate antibiotics at home or at other health facilities. Further, enhanced surveillance was set up in the study blocks by especially recruited community volunteers for the study to create awareness among the parents about the symptoms and signs of pneumonia so that they can avail appropriate treatment at the earliest. For ethical reason special efforts were also made in the study area to facilitate referral transport and treatment to reduce mortality due to pneumonia among children enrolled in the study, which is usually not the case in the general population. However, parents continued to exercise their choice of either not taking any treatment or choosing treatment from other sources than the study hospitals. The objective of the ICMR study was to ascertain the feasibility of doing a Hib probe study to estimate the Hib vaccine preventable disease burden. It was not specifically set up to estimate mortality due to pneumonia among the under-five-children. Hence, comparison of ICMR study data with UNICEF's estimates of childhood mortality due to pneumonia is not justified. UNICEF's estimates of childhood mortality due to pneumonia (14/1000 under-five-children) is comparable to the results of two other studies[4]. Child Health Epidemiology Reference Group (CHERG) had estimated around 43 million cases and 4,08,000 deaths due to pneumonia in India based upon categories of risk factors for childhood clinical pneumonia in community[5]. Based on these statistics, we estimate the incidence and under-5 mortality due to pneumonia to be 275 per 1000 under-five children and 16 per 1000 live births respectively. The Million Death Study (MDS), using verbal autopsy method to ascertain cause of death for 12,260 child (1-59 months) deaths, has also estimated 3,69,000 deaths due to pneumonia in India in 2005[6]. A lung puncture study using countercurrent immunoelectrophoresis technique (CIE), done among children admitted with severe acute lower respiratory infection (SALRI) at Postgraduate Institute of Medical Education & Research (PGIMER) Chandigarh, found *Haemophilus influenzae* in 15.8 per cent cases[7]. It is estimated that Hib is responsible for 13-19 per cent of pneumonia and lower lung disease[8-11]. Hence, incidence

of Hib pneumonia will be about 44/1000 children in less than 5 yr olds, leading to about 6,88,000 cases of Hib pneumonia in India every year.

Lone *et al*[1] have quoted Vellore study[12] in support of their contention that there is very low incidence of Hib meningitis in India. However, the authors of this study conclude that the incidence of Hib meningitis found in Vellore (7.1, 95% CI: 3.1-14) is the minimal estimate for the region due to passive hospital based nature of surveillance in this study. This reason is also substantiated by findings from Lombok study where only about 28 per cent of the Hib meningitis cases could be detected through hospital-based passive surveillance[13]. Black *et al*[14] have estimated 31,607 deaths attributable to meningitis in India after taking into account cases currently prevented by the Hib vaccination (Hib vaccine is available and used in India). Assuming 16.7 per cent meningitis deaths due to Hib[13], and 25 per cent case fatality rate for Hib meningitis[15-16], the annual number of cases and deaths due to Hib meningitis among under-5 yr old children in the Indian birth cohort of 27 million will be 21,113 and 5,278 respectively.

Secondly, authors have pointed out flaws in the Bangladesh study which in fact was not a Hib probe study[17]. They argue that '3-doses of vaccine were ineffective in Bangladesh setting and hence the study investigators resorted to data dredging by presenting results for effectiveness of 2-doses of Hib vaccine'. It needs to be highlighted that rather than a controlled experiment, the Bangladesh study was done in a routine programme setting and had a drop out of 65 per cent from 1st to 3rd dose of Hib vaccine, which has been cited as a limitation of the study. Hence, presentation of effectiveness of 2 doses of Hib is to our understanding appropriate.

Thirdly, a Cochrane review[18] cited in the editorial[1] has been mis-interpreted as they say 'review has shown that the combination of Hib with DPT and HBV is less effective than vaccines given separately' whereas the Cochrane review concedes that "none of the 18 studies had data on clinical outcomes for primary outcome" hence, it was based on immunogenicity trials. Overall, the Cochrane review concludes that "we could not conclude that the immune response elicited by the combined vaccine was different from or equivalent to the separate vaccines". It goes on to state that "the differences rely mostly on one study each" and "no study uses an intention-to-treat analysis and we are uncertain in risk of bias in many of the studies" .

Lastly, we agree with Lone *et al*[1] that Hib disease with its associated risk factors affect the poorest of the poor. Data from India show highly inequitable distribution of infectious diseases among children as well as to access of curative health care[19]. Hence, it is implied that the redistributive effect of Hib vaccine will largely accrue to the poorest sections of society. We think the decision about introduction of pentavalent vaccine in India should be based on a careful review of all available evidence including the cost-effectiveness analysis.

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Authors' response

Sir,

We thank Gupta *et al*[1] for responding to our editorial. Perhaps they have written the letter before the correspondences of Drs Madhavi & Raghuram[2], Drs John & Muliyil[3] and our response appeared in print.

All their questions have been answered in response to the letters above and we will be hard pressed to answer these questions without simply repeating ourselves.

The points they make are:

1. We should not have used under-2 morbidly statistics on the under 5 population. The answer is available in Reference 3. In brief, we did this to show that even after the figures were exaggerated in this manner it still did not come up to the projections of the UNICEF.

2. The Vellore study[4] cannot reflect community morbidity as parents' exercised choice of taking or not taking treatment (notwithstanding the 2-weekly visits by the study teams). Some patients may have died before coming to hospital.

   We have addresses this question in Reference 3. Verbal autopsies were done of all deaths at home precisely to overcome the problem of missing deaths at home.

3. The correspondents[1] make their own estimates from other studies like the Million Death Study.

   As these were not referred to in our editorial and they do not pertinent, we will not discuss the merits of their assumptions in this letter.

4. With regard the Bangladesh 'probe like' study[5], the correspondents think that although the end-point for study was to be measured after 3 doses of vaccine (and there was no benefit), it is appropriate to present effectiveness with 2 doses without using appropriate statistical tests for multiple testing. We respect their right to have their opinion, although it is at variance with standard teachings of statistics.

5. They write that the Cochrane review only concluded "we could not conclude that the immune response elicited by the combined vaccine was different from or equivalent to the separate vaccines". We refer to the next sentence in the authors' conclusions of the Cochrane review for an explanation. They say "The data showed significantly less immunological response for H influenza and hepatitis B, and more local reactions to the injections".

6. The equity argument was addressed in our responses earlier[3]. If the vaccine provides no protection as seen from the Bangladesh study, then it is important that resources are not squandered on the programme. The poor need equity in a number of areas but they do not seek equity in terms of being injected with worthless vaccines.

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