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Correspondence

Issue raised about incomplete reporting of research in press releases

We would like to comment on several issues raised in the correspondence entitled "Incomplete reporting of research in press releases: Et tu, WHO?"[1] that we believe significantly misinterpret the results of Bangladeshi[2] and Indonesian[3] studies of the Hib conjugate vaccines. The authors state, "The authors observed statistical significance in the sub-group that received only two dose of vaccine" and suggest that because the effect was seen with two doses, it is not relevant[1]. However, the specific Hib conjugate vaccine used in the study, PRP-T, is well known for being effective at preventing disease after two doses in infancy. During the introduction of Hib-PRP-T in African countries two doses of the vaccine effectively prevented 87 to 97 per cent of invasive Hib disease[4-7], while immunogenicity studies in Indian and the Philippines demonstrated strong antibody responses after 2 doses[8,9]. Hib effectiveness with two doses is excellent news for regions of India with poor immunization coverage; even children who are partially vaccinated will be afforded protection.

Throughout the letter, the authors misrepresent the concept of statistical significance, repeatedly insisting that results that are not statistically significant are not valid, suggesting that non statistically significant results invalidate the statistically significant results of a study. This is simply not the case: while non significant results on their own are not conclusive, they provide supportive data if the trend and magnitude are similar. This was clearly seen in Bangladesh: the point estimates for efficacy against radiologically-confirmed pneumonia in children receiving ≥2 or 3 doses of Hib vaccine ranged from 15 to 44 per cent depending on whether the controls used were hospital or community based[2]. Of the 12 pneumonia comparisons, 7 were statistically significant, with significance seen in analyses of both community and hospital controls. The same was true with Hib meningitis and purulent meningitis: the estimates for efficacy vary from 65 to 93 per cent and 40 to 83 per cent, respectively, with statistically significant results found in each category. The Hib vaccine is clearly effective against radiographically confirmed pneumonia and meningitis in Bangladesh, with both statistical evidence and supportive evidence from non statistically significant results which support this conclusion[2].

In their discussion of the Indonesian study, authors chose to focus on a single result of this study while disregarding more statistically sound data. An increase of 89 (95% CI: -71, 248) cases of radiologically confirmed pneumonia was seen per 100,000 child years in fully vaccinated children. However, this effect was compensated by a reduction in the incidence of clinical pneumonia of 1,467 per 100,000 (95% CI: -60, 2994), a drop of 129 per 100,000 (95% CI: -6.7, 265) of admissions for meningitis or seizure, and a 45 (3.9 to 86) per 100,000 decrease in probable or confirmed bacterial meningitis.

The authors' main contention that these studies "argue against the vaccine" is false. Both studies demonstrate efficacy against meningitis, and fit well with results seen in numerous other studies from around the world. The results of these studies in context with other studies from low and middle-income countries are shown in Table I for easy comparison. The proportion of pneumonia prevented by Hib may vary depending upon the magnitude of respiratory viral outbreaks. Nevertheless it is estimated that Hib vaccine will prevent a significant proportion of all severe pneumonias (Tables II & III).

Hib vaccine prevents 14 to 83 per cent of purulent meningitis[2,3,5,7,10-12], with the median study estimate being 44 per cent. Over the last year, we took part in active surveillance for bacterial meningitis pathogens at our hospitals (Institute of Child Health, Chennai and Kalawati Saran Children Hospital, New Delhi).

Table I. Summary of global studies demonstrating impact of Hib vaccine against purulent/probable meningitis

Location	% Reduction (95% CI)		Study type
Argentina[10]: Elizalde	55	(27, 68)	Introduction
Argentina[10]: San Isidro	44	(10, 65)	Introduction
Bangladesh[2]: *High estimate*	83	(24, 96)	Case-control
Bangladesh[2]: *Low estimate*	40	(-138, 85)	Case-control
Ghana[11]	43	(n/a)	Introduction
Indonesia[3]	57	(n/a)	Randomised control trial
Malawi[7]	36	(n/a)	Introduction
Rwanda[12]	52	(5, 75)	Introduction
South Africa[10]	14	(-20, 38)	Introduction
Uganda[5]	53	(11, 68)	Introduction

n/a - confidence interval not given in text
Superscript numerals denote reference nos.

Table II. Impact of Hib vaccine against radiologically confirmed pneumonia

Location	% Reduction (95% CI)		Study type
Bangladesh[2]: *High estimate*	44	(16, 63)	Case-control
Bangladesh[2]: *Low estimate*	15	(-9, 33)	Case-control
Brazil[13]	31	(-9, 57)	Case-control
Chile[14]	22	(-7, 43)	Randomised control trial
Gambia[15]	22	(2, 39)	Randomised control trial
Indonesia[3]	-12	(-36, 8)	Randomised control trial
Global[16]	21	(3, 36)	Meta-analysis

Superscript numerals denote reference nos.

Table III. Impact of Hib vaccine against clinical pneumonia

Location	% Reduction (95% CI)		Study type
Gambia[15]	7.7	(-4, 18)	Randomised control trial
Indonesia[3]	4	(0, 8)	Randomised control trial
Global[16]	5	(1, 9)	Meta-analysis

Superscript numerals denote reference nos.

During this time Hib was the most common pathogen identified by latex particle agglutination, accounting for 71 per cent of confirmed bacterial meningitis. In total we found 27 cases of Hib meningitis, 5 of whom died, and 81 cases of purulent meningitis. Based on an efficacy of 44 per cent against purulent meningitis and full vaccination, 36 cases of meningitis would have been prevented. It is likely that all the children who died of Hib meningitis would still be alive today if they had access to Hib vaccine.

India is now a leading producer of Hib vaccine, a vaccine which is being used to protect the children of Pakistan, Nepal, Sri Lanka and Bangladesh against the deadly Hib bacterium. There is enough evidence regarding the efficacy of Hib vaccine for both meningitis and pneumonia[13-16]. It is unfortunate that routine immunization programme has less than adequate coverage in many parts of our country. At the same time we should not deprive the children of our country of the protection offered by this vaccine. The National Technical Advisory Group of Immunization (NTAGI) strongly recommended that Hib vaccine should be introduced in India's UIP[17]. Indian Academy of Pediatrics recommends that Hib vaccine should be given routinely if the parents can afford it[18]. Hib vaccines are widely used in the private sector in India as part of childhood immunization. It is ironic that we allow our children to suffer needlessly when our nation is one of the Hib vaccine suppliers for the world's children. We propose that Hib vaccine be made a part of routine immunization programme in the states with high immunization coverage. If the vaccine is not made part of the National Immunization Programme, only the poorest children, who suffer the highest attack rates of disease, will continue to die from this disease while those who can afford the vaccine are protected.

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Authors' reply

We thank Drs Suresh and Aneja for their interest in our observations about a misleading press release related to the Bangladesh Hib study. We cannot however, agree with their arguments and we will explain why.

Hib disease is rare in Asia as compared to the West and Africa. Studies from India and other Asian countries have all underlined this point[1-6]. An editorial in the *Bulletin of the WHO* had highlighted this, way back in 1999[7]. This is why data from Argentina and Ghana have little relevance for India. However, it is not as if the disease is non existent here. Drs Suresh and Aneja write that they have seen 5 deaths from Hib meningitis. Unfortunately they do not provide a figure which can be used as a denominator to determine the disease burden in the community and as such it cannot help their argument. If the 'population attributable risk' is low and the numbers needed to vaccinate (NNT) is large, disease control with universal vaccination may not be a cost-effective proposition.

The correspondents make four rather unique assertions in their letter:

1. They point out that the Bangladesh study had shown benefit with two doses and this shows that even partially immunized children are protected. They say we ignored this.

   Admittedly we did ignore it, but for good reason. Ninety three per cent of the population under study received the full 3 doses of vaccine. There was no benefit in the population receiving 3 doses, when either radiologically confirmed pneumonia or meningitis was compared with

matched community controls and these were the primary end point for analysis. Data dredging and post-hoc analysis found statistical significance in vaccine effectiveness against pneumonia after two doses of vaccine. Ordinarily there results of post-hoc analysis should be explicitly labeled to avoid misleading readers and unadjusted *P* values must be interpreted in light of the fact that these are a small and selected subset of a potentially large group of *P* values[8]. Post-hoc analysis greatly inflates the total number of statistical tests and necessitates the use of multiple testing procedures to compensate. In the absence of such analysis we ignored the finding. This avoids the bizarre suggestion that partially immunized children are better protected than those fully immunized.

2. The correspondents contend that we misrepresent the 'concept of statistics significance' by insisting that results that are not statistically significant are not valid. This is not true. Results are just as valid regardless of statistical significance. In statistics, a result is called statistically significant if it is unlikely to have occurred by chance. That is the standard interpretation for all scientific data. We will not labour that point. It is not very meaningful to discuss point estimates without providing data on the confidence limits.

3. The correspondents assert that in the Indonesian study, the increase in incidence of radiological pneumonia [89 per 100,000 child years (95% CI -71 to 248)] was *compensated* by a reduction in incidence of clinical pneumonia [1467 per 100000 child years (95% CI -60 to 2994)]. We cannot agree. We insist that neither the increase in radiological pneumonia nor the decrease in clinical pneumonia is statistically significant.

   The Press Release did not bring up the issue of meningitis in the Indonesia study, and as such we did not refer to it. The correspondents suggest that Hib vaccine may be helpful to prevent meningitis. Again this is not borne out by the figures. The vaccine preventable incidence of microbiologically confirmed Hib per 10^5 child-years was 20 (95% CI -0.43 to 40) and of meningitis admissions it was 36 (95% CI -85 to 157)[9]. This suggests that there was no real benefit for the vaccinated compared to placebo recipients.

4. Finally the correspondents assert that Hib is used by some parents of well-to-do families for their children and so the Government of India must provide it free for the poor. Such assertions appear to be in line with the view pushed by manufacturers of the vaccine and others with vested interests. We fail to understand this reasoning.

   The discussion above shows Hib disease is rare in Asia and further that Hib vaccine - for all its cost - is no better than placebo. The poor need equity in a large number of areas but definitely, they are not hankering after the useless vaccines the rich may be taking. To foist this programme on them in the name of equity is a cruel means of siphoning off the limited funds available for the poor, and in its place providing them a service they do not need and which does them no good. When the evidence is so clear, it is the duty of all to protect them and the country from such misuse of resources.

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