

Correspondence

Introducing pentavalent vaccine in EPI in India: issues involved

Sir,

“When we know how to prevent torment, but don't, we become tormenters” (Primo Levi)

The Editorial by Lone and Puliye¹ contains several factual errors. It exhibits a time warp, citing old information but not its new details and a disregard for truth by arguments taken out of context. It contains statements that have been disproved. The idea of pentavalent vaccine has ‘technical’ elements – the epidemiological need to introduce hepatitis B (HB) vaccine and *Haemophilus influenzae b* (Hib) vaccine in the Universal Immunisation Programme (UIP) and a ‘programmatic’ element -- the option to give them separately from diphtheria, whole-cell-pertussis (wP) and tetanus (DwPT) vaccine (9 injections per child) versus in combination (pentavalent vaccine) to simplify the vaccination procedure (3 injections).

The National Technical Advisory Group on Immunisation (NTAGI) is an instrument established by the Ministry of Health in 2002 for making available evidence-based technical recommendations to, and to monitor their implementation by, the Immunisation Division that manages the UIP^{2,3}. About a decade ago Government of India (GoI) had decided, rightly, to roll out HB vaccine in UIP. It was later endorsed by NTAGI. Regarding Hib vaccine, NTAGI appointed a subcommittee of experts for detailed deliberations⁴. It was convened by an officer of Indian Council of Medical Research (ICMR)⁴. NTAGI received, reviewed and endorsed the subcommittee recommendations to add Hib vaccine also in UIP.

The Editorial argues that disease burdens and mortality due to pneumonia and meningitis are too low in India to deserve prevention by national vaccination programme using Hib component. In support, data from an ICMR-sponsored study in Vellore (part of a

multi-centre study) were provided. A careful reading of the Editorial shows that this view is contrived and not genuine or consistent with data. For comparison, data from Apache Reservation, Texas and The Gambia were included as examples of high disease burden areas¹. Although they show striking similarities with the Vellore data, information was distorted to argue the opposite. It stated: “The [Vellore] study showed that the incidence of all-cause pneumonia was 30 per 1000 children under five and mortality was 0.3 per 1000 children under five. Thus mortality is 50 times lower than 14 per 1000 projected by the UNICEF for India.” That the 30/1000 (equal to 3000/100,000) were not the total pneumonia but only ‘hospitalized pneumonia’ and that it was among under-2 children were suppressed. If we assume conservatively that 20 per cent were due to Hib, the incidence of hospitalized Hib pneumonia in under-2 children would be 600/100,000; the incidence of Hib pneumonia and meningitis in under-2 Apache children was 500-1000/100,000, quite similar. If we add non-hospitalized pneumonia and meningitis in Vellore setting, the burden is enormous. Vellore study site is well-served and not typical of all of India – Vellore data would be underestimating for most other regions. Happily the Editorial states that Hib vaccine was highly effective in all three high disease burden regions. The same is true in Vellore region also⁵.

Even the 0.03 per cent death rate in spite of hospital treatment amounts to 1 per cent case fatality; 50 times higher would be 50 per cent case fatality (~15 deaths/1000) – very likely if untreated. UNICEF projection of 14 deaths due to pneumonia per 1000 under-five children¹ is not at all inconsistent with the ICMR study data – even though they derive through different routes and from different denominators. A recent comprehensive study on cause of death conducted by the Government of India using a sample

registration process has estimated that 22 per cent of under-5 deaths in India are attributable to pneumonia⁶. The ICMR-supported multi-centre study report has recently been published; incidence of severe pneumonia in under-2 age was in the range of 27 to 80 per 1000 child-years (2700-8000/100,000)⁷. Risk of pneumonia will continue during 2-4 yr of age, for the total burden in under-5 children, but it was not measured in the study. Incidence of clinical meningitis was in the range of 19-24 per 1000 child years, 17-29 per cent of which was purulent⁷. Extrapolated, there are about 500 cases of purulent meningitis per 100,000 per year. If we assume a third to half are due to Hib, then the frequency is 170-250/100,000 which is no different from that of The Gambia (200/100,000) or the Apache Reservation. In Texas it was said to be only 109/100,000¹. The burden of pneumonia and meningitis in India is enormous and even higher than in some of the high burden regions selected for comparison. It is disingenuous to try to argue that mortality in under-5 children in India due to bacterial pneumonia and meningitis is negligible and does not deserve preventive interventions. Inclusion of Hib vaccine in UIP was qualified in the Editorial as "profligate exercise in futility"¹, whereas in reality it is an unavoidable necessity.

The argument that "Hib disease has little potential for pandemic"¹, hence there is no need for universal immunization, reveals gross ignorance of infectious disease epidemiology. Hib infection is highly contagious and 'ubiquitous' - pandemics occur only with novel pathogens against which large segments of world population are immunologically naive. The epidemiology of Hib disease is closer to that of diphtheria, polio, pertussis and measles – against which immunization is universally practiced, than to any pandemic-prone disease. The "harmless nasopharyngeal colonization" of Hib stated in the Editorial¹ is virtually no different from colonization by *Corynebacterium diphtheriae* or poliovirus, as harm comes only when infection or toxin crosses barriers and causes disease. Colonization is the most important risk factor and a pre-requisite for disease for them including Hib. Hib vaccination protects from invasive disease by preventing blood stream invasion from mucosal surface, and, from pneumonia by preventing mucosal extension to lungs. Such protection occurs in the vaccinated; herd effect of vaccination programme reduces the risk/rate of colonization among the unvaccinated. Hib vaccine offers higher herd effect than almost any other vaccine in current use. Where Hib vaccination coverage reached >70 per cent, Hib disease has virtually disappeared⁸.

The programmatic option of the pentavalent vaccine was considered and recommended by the NTAGI subcommittee. The liquid formulation was chosen as it will simplify both staff training and vaccine delivery, as it will replace DwPT vaccine. NTAGI endorsed the recommendation. Liquid pentavalent vaccine is manufactured by two Indian companies and both are WHO prequalified. Thus India has access to indigenous quality products at prices substantially lower than in international market. There are established mechanisms under the National Regulatory Authority (NRA) to ensure and assure quality. There are purchasing mechanisms in the Immunisation Division to prevent profiteering by vaccine marketers.

Dr Puliyeel has been arguing in various forums against the introduction of HB and Hib vaccines in UIP, including in 4 meetings referred to below. Since they will be introduced as pentavalent, the 'counsel for caution' is a single stroke against both the vaccines. The Hib antigen in the pentavalent formulation is as *effective* as when given separately, contrary to the claim by Lone and Puliyeel¹. Their error arises from selective reading, outdated citation and incomplete understanding of vaccine immunology and epidemiology. Although there had been old reports showing marginal and inconsequential reduction of *antibody level* induced by Hib antigen after giving some pentavalent products [with acellular pertussis (aP) component and aluminium hydroxide adjuvant], subsequent evidence showed that it does not translate either to lower *effectiveness* (clinical protection) or even to reduced *immunogenic vaccine efficacy* in terms of proportion of children immunologically responding with adequate antibody levels – particularly if the adjuvant is replaced with aluminium phosphate. This phenomenon did not apply to pentavalent vaccines with wP component. In vaccination programmes effectiveness is the desired outcome. The implicit aspersion cast on Indian NRA that it allows an inferior product is unfair.

Again, contrary to the claim that it is unsafe, pentavalent (in rich countries with DaPT, in low income countries with DwPT) or even hexavalent (with inactivated poliovirus vaccine) vaccines are safe and currently used in over 150 countries. Do the authors believe in Indian exclusivism -- unique physiological advantages against diseases and excessive vulnerability to vaccine adverse reactions? The Ministry has initiated a system of AEFI monitoring but it has yet to become functionally efficient enough to detect all signals and to investigate causality. At the global level, the Global

Advisory Committee on Vaccine Safety (GACVS), an independent watch-dog group, monitors AEFI signals and advises the World Health Organization (WHO) on vaccine safety^{9,10}. The Editorial highlights the report of deaths in children given pentavalent vaccine in Sri Lanka, but fails to complete the story that the national expert advisory group had cleared the vaccine which has been reintroduced without problem. GACVS had concluded that the pentavalent vaccines did not cause death but are safe. Harping on the signals (found to be false alarm) and hiding the final outcome is unethical science writing. The implicit aspersion that Indian NRA continues to allow marketing of a killer vaccine is preposterous.

NTAGI was pleased that India was finally moving out of the rut of over 3 decades giving only the original 6 antigens of EPI established in 1974 - whereas other countries had introduced HB vaccine in the 1980s and 1990s and Hib vaccine in the 1990s and 2000s. Progress was slowly being made until the meeting on December 14, 2009, referred to in the Editorial¹. The Health Secretary-cum-Chairperson of NTAGI was in the chair. Selected individuals (members and non-members of NTAGI and the subcommittee) had been called to that meeting, to hear that the earlier approval of the NTAGI recommendations by the previous NTAGI Chairman was no longer valid and will be re-examined¹. Puliyl argued vigorously against inclusion of HB and Hib vaccines in UIP. The chair requested the Secretary, Department of Health Research (DHR), also present, to get the NTAGI recommendations reviewed; thus an *ad hoc* procedure was made to override the *established* mechanism, a process that might be justified in very exceptional circumstances but we did not hear any compelling reason to invoke such a mechanism.

Puliyl asked why data from the preparatory phase of the ICMR-sponsored multi-centre Hib vaccine 'probe' study were not examined by the subcommittee. Members of the subcommittee clarified that: the subcommittee had invited the investigators from all centres to present their results; and the data, still incomplete from cleaning, analysis, interpretation and writing up, had been discussed first in a special meeting in ICMR in January 2008 and again in the NTAGI subcommittee in April 2008⁴. This information is contained in Reference No. 3 in the Editorial itself. We were under the impression that the misunderstanding had been cleared up, but knew we were mistaken when we read the same allegation repeated in writing in a

reputed journal¹¹; once again it has been refuted, in writing¹². The Editorial repeats the allegation and adds in support that "the chairperson of NTAGI admitted that results from ... multi-center study were reviewed by the subcommittee, but it was left out from the report"¹. But the present chairperson of NTAGI was not in charge when the subcommittee met⁴. Repeating the allegation for the third time in the Editorial, ignoring evidence to the contrary, appears to be a calculated attempt to malign the subcommittee and NTAGI as a means to prevent the inclusion of HB and Hib vaccines in UIP^{1,4,11,12}.

Now we have reached a realm wherein 'suspicion' and 'belief' rather than 'evidence' are at play. It explains why the WHO experts had to be pictured as 'less than honest' and NTAGI and its subcommittee had to be depicted as selectively using data to make recommendations that did not convince one or two individuals, themselves blatantly using means that they are accusing others of¹. Their goal seems to be to prevent the inclusion of HB and Hib vaccines in UIP, to achieve which no holds – such as unfounded allegations, distortion of data and veiled personal vilification - appear to be barred. We do not know the fundamental reason why they are against inclusion of HB and Hib vaccines in the UIP – it is not science or evidence. Is the reason a 'belief system' that goes against all modern vaccines? Truth seems to be the casualty and innocent children, who will not be protected against rampant HB virus infection and its sinister consequences and against tragic Hib invasive and mucosal diseases, are the victims.

As requested by the chair of NTAGI the Secretary DHR held meetings on January 18, February 16, and March 24, 2010 and discussed the issues threadbare, and patiently listened to repetitive arguments by Puliyl not to introduce HB and Hib vaccines in UIP. The conclusions and recommendations, by overwhelming majority but not by consensus with Puliyl present, essentially endorsed the NTAGI recommendations for universalizing HB and Hib vaccinations beginning from selected States. Neither the subcommittee nor NTAGI had erred in their judgment regarding the 2 vaccines or the liquid pentavalent vaccine.

We add, that the Invasive Bacterial Infection Surveillance (IBIS) study found prevalence of Hib confined to under-5 children (predominantly in under-2, while the denominator included all age groups, thus

creating the illusion of low overall prevalence); Hib is one of the 2 commonest causes of bacterial meningitis in that age group in India; natural immunity to Hib is a universal phenomenon, not exclusive to India (which explains why serious Hib disease is mostly in under-2 and not beyond 5 yr); invasive Hib diseases are meningitis and bacteraemic febrile illnesses while pneumonia results from mucosal extension instead of blood stream invasion, but with overlaps; strain-replacement is not a reason for not using Hib vaccine (the country wherein this was suggested continues to use the vaccine); and sovereign nations must make autonomous choices based on epidemiology, economics and ethics. The decision-making processes should be systematic and transparent.

The 2009 election manifesto of the Indian National Congress promised "health security for all" which has to be fulfilled by the Health Ministry¹³. As far as UIP is concerned, 'health security' includes protection of all children from all vaccine-preventable diseases. NTAGI had recommended that the Ministry should re-engineer UIP - to ensure >95 per cent coverage with vaccines on time in all districts and sub-districts, to establish case-based surveillance of all vaccine-preventable diseases, to create adequate numbers of posts of officers to help achieve the above, to shift from ritualistic giving of vaccines to effective disease control, to create robust mechanisms for monitoring vaccine safety and effectiveness – in short, to establish a 21st century model of EPI, vastly superior to the 1974 WHO model that India has even today. This should be the priority function of the Immunisation Division and the Health Ministry.

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Authors' response

We thank Drs Jacob John and Jayaprakash Muliylil for responding to our editorial¹. They begin their letter with a quote from Primo Levi "When we know how to prevent torment, but don't, we become tormentors." We agree with the saying wholeheartedly. There is only a slight difference in the interpretation of torment. We will attempt to deal with all the substantive issues raised, in the response below.

1. We need to clarify here that the editorial was written after the meeting with the Health Secretary on December 14, 2009, referred to by the correspondents in paragraph 9 of their letter. Prior to this meeting, we had obtained the results of the multi-center study of the ICMR (study done from July 2005 to December 2006) through a request under the 'Right to Information Act (RTI)'. We presented the RTI data at the meeting with the Health Secretary. The main submission was that the data from this multi-center ICMR study were deliberately left out of the NTAGI report² because it did not support the need for vaccination. Members of the NTAGI present at this meeting did not deny that they had access to the data when the NTAGI report recommending the vaccine was drafted. It was under these circumstances that the Chair took the extraordinary action of asking for the NTAGI report to be reviewed.

The correspondents say we have made this allegation a 'second time' in Indian Pediatrics (IP)³. Actually the 'allegation in Indian Pediatrics (IP)' was sent first, soon after the NTAGI report was published in November 2009, well before the December 14, 2009 meeting with the Health Secretary. Pertinently, NTAGI authors did not respond to that letter, in spite of repeated reminders from the Editor. In the end, our letter was published in IP in June 2010 without a NTAGI response. The authors (JJ & JM) say they have refuted our IP letter in writing and in spite of that, we have made the allegation a 'third time' in this editorial published in the IJMR in July 2010. We must point out respectfully that the reference they give of 'refuting in writing' (Reference 11 in their letter) is an article that has not been published (even as we write this reply in August 2010). Perhaps it was written after our IP letter appeared on June 17, 2010³. Admittedly we do not have any powers of clairvoyance. We could have known in December 2009 (when we were asked to write the Editorial) what the authors will write 6 months later in June 2010. It seems evident that all this mock indignation is aimed at altering this record of events retrospectively, to shore up the reputation of the NTAGI.

2. We concluded the editorial asking for caution based on 3 reasons:

- (i) Proven low incidence of invasive disease (in Asia).
- (ii) Absence of benefit from Hib vaccination demonstrated in probe studies and probe-like studies from Asia.

(iii) Evidence of strain replacement in the West.

Each of the three conditions above would independently be sufficient and compelling reason not to introduce this vaccine.

3. We quoted evidence of low incidence of invasive Hib disease in Asia. The incidence was considered to be low even in the 1990s. We presented pre-vaccination data available in publications prior to 1998, from Apache Reservation, of invasive disease of 500-1000 per 100,000 children under-2 and contrasted this with Asian data of invasive disease of 3 to 9 per 100,000. The methodology used to arrive at these figures is not very clear and so we also provided references of systematic studies done in India from 2000 to 2010 to prove our point. The correspondents use the figures of 'pneumonia from any cause' and 'meningitis from any cause' from the Vellore limb of the ICMR multi-center study and add-on assumptions about what percentage of these pneumonia and meningitis are 'Hib related' and arrive at a figure that matches that of the Apache Reservation. As the assumptions are made by the correspondents, and these were not stated in the Editorial, we will not expend the space allotted for the defense of our editorial to argue those assumptions here.

4. The correspondents do not address the issue of how they support an expensive vaccination programme when it has been shown that the vaccine does not reduce disease burden (when compared with placebo). The story of how GAVI, WHO, USAID, Johns Hopkins and the Hib Initiative, among others, released a misleading press statement to suggest the vaccine was useful has been published in this journal and in the BMJ^{4,5}. In the context of what has been said by Primo Levi: Probe studies show the vaccine does not reduce the torment of disease: the cost of the vaccine may well torment the country.

5. In our editorial we quoted studies from Canada that introduced Hib vaccine over 20 years ago, where *H. influenzae* b has nearly been eradicated but it has been replaced by other strains of invasive *H. influenzae*. The correspondent say that strain replacement is not a reason for not using Hib vaccine in India, because Canada continues to use the vaccine! We find the logic inscrutable. He who rides a tiger is afraid to dismount. Those who witness the predicament of the rider would seldom want to take a ride. The

consequences in these countries that are overrun by non-b *H. influenzae*, if Hib vaccine is withdrawn, will need careful consideration before the vaccine is actually withdrawn. But countries that have not introduced the vaccine - like India, can learn from this history and avoid being condemned to repeat the mistakes.

6. In paragraph 8, the authors say, we have highlighted reports of deaths in children given Pentavalent vaccine in Sri Lanka but fail to complete the story that the Global Advisory Committee on Vaccine safety has concluded the vaccine did not cause death but is safe. As we write, this week's *British Medical Journal* has published how the expert committee actually changed the WHO standard classification of adverse effects following immunization (AEFI) and removed the categories 'Probably related to vaccine' and 'Possibly related to vaccine' from their classification to enable them to declare the deaths were 'unlikely to be related' to vaccine⁶! Another letter in the electronic BMJ shows how 3 children died in Pakistan; one healthy child within 30 min of vaccination and 2 within 12 to 14 h⁷. Two were declared to have died of "sudden death" and the cause of the third was said to be uncertain. The controversy about the changed WHO classification featured in the lay press more than a month ago^{8,9}. As an aftermath of the detection of this subtle change in classification of adverse effects following immunization, which the NTAGI² and the 'Core Committee on Immunization'¹⁰ failed to highlight to the Government, special mention was tabled in the Indian Parliament that the Indian experts must find the cause for deaths in neighbouring countries before recommending the vaccine for India¹¹.

To get back to Primo Levi: Hib vaccine does not reduce the torment of disease and Pentavalent vaccine is associated with 'sudden deaths': Not writing 'a counsel for caution', would be siding with the tormentor.

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