

## Editorial

### **Introducing pentavalent vaccine in the EPI in India: A counsel for caution**

The story of how pharmaceutical companies influenced scientists and official agencies like the World Health Organization (WHO) in the recent swine flu scare<sup>1</sup> and the saga of the undeclared conflicts of interests of members of the WHO's Strategic Advisory Group of Experts<sup>2</sup> has set off alarm bells around the world. When trusted advisors are less than honest, the potential for harm is great, and the feeling of betrayal is poignant.

A similar feeling of sadness and betrayal was evoked by the report of National Technical Advisory Group on Immunization (NTAGI) sub-committee on *Haemophilus influenzae* B (Hib) published recently<sup>3</sup>. On December 14, 2009, the Health Secretary chaired a meeting to discuss the policy framework for vaccine preventable disease in the country. Invited to this meeting were the chairperson, vice-chairperson and Indian Academy of Pediatrics representative to the NTAGI Hib sub-committee. Data from an ICMR study in Anaicut block of Vellore, obtained under the Right to Information Act were presented. The 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<sup>4</sup>. It was additionally pointed out that even if mortality was assumed to be as high as 10 per cent (instead of 0.7% observed in the study), there would be 3 deaths per 1000 children under-five. This study data undercut one of the main points in the sales pitch for introducing 2 vaccines - the pneumococcal conjugate vaccine and the Hib vaccine in India. Members of the NTAGI were asked why the data on pneumonia were not included in the NATGI report when it had selectively quoted nasopharyngeal-carrier data from the same study. The Chairperson of NTAGI admitted that the results from Anaicut and also that from Kolkata and Chandigarh

in this multi-center study were reviewed by the sub-committee, but it was left out from the report.

#### **WHO directive on Hib**

The latest WHO position paper on Hib says 'Hib vaccine should be included in all routine immunization programmes'<sup>5</sup>. This suggests that Hib vaccine should be included in the immunization programme universally, irrespective of an individual country's disease burden, not withstanding of natural immunity attained within the country against the disease, and not taking into account the rights of sovereign States to decide how they use their limited resources. The mandate and wisdom of issuing such a directive, for a disease that has little potential of becoming a pandemic, needs to be questioned.

The directive has come after a number of failed attempts to convince the scientific community of the need for this vaccine in Asia<sup>6,7</sup>. We present this as a case study on the visible and invisible pressures brought to bear on governments to deploy expensive new vaccines.

#### **Invasive Hib in pre-vaccination era**

There is a clear distinction between invasive Hib disease (resulting in pneumonia and meningitis) on the one hand and harmless nasopharyngeal colonization on the other. The incidence of invasive disease was 500-1000 per 100,000 children under-2 in the Apache reservation and this came down to 22 per 100,000 after immunization<sup>8</sup>. In Dallas county, Texas, it was 109 per 100,000 children under-5<sup>9</sup>. In Gambia, incidence of Hib meningitis was 200 per 100,000 infants and it fell to 21 with immunization<sup>8</sup>. On the other hand, the incidence of invasive disease in Asia, even without immunization was reported as 3 to 9 per 100,000 children-under-5<sup>10,11</sup>.

### **IBIS (Invasive Bacterial Infections Surveillance) study (India)**

It has been suggested that the low incidence of invasive disease in Asia may be due to early exposure to other bacteria with cross reactive antigens<sup>12,13</sup>. Others deny the incidence of Hib in Asia is low and suggest that this is a wrong impression resulting from the use of inappropriate culture plates<sup>14</sup>. However, the IBIS Group using appropriate culture techniques, working in 6 large referral hospitals over 4 yr (1993-1997), came up with only 125 positive cultures<sup>15</sup>. To explain this low culture yield the IBIS group speculated that all cases of meningitis may not had access to the hospitals. They recommended that community based studies must be done<sup>15</sup>.

### **Community study of Hib meningitis (India)**

A community based study looking for Hib meningitis followed (1997-1999). It showed the Hib meningitis incidence of 0.007 per cent<sup>12</sup>. In 2002, Dr Thomas Cherian, who is now the WHO Co-ordinator of EPI, wrote that based on the available data, Hib vaccine could not be recommended for routine use in India<sup>16</sup>.

Prior antibiotic use and problems with transport of CSF specimens were then blamed for the poor yield in cultures<sup>12</sup>. This led investigators to undertake 'probe studies' to identify reduction in disease burden after immunization<sup>17</sup>.

### **Asian probe studies**

The probe trial in Indonesia from December 1998 to December 2002 found more cases of pneumonia admitted to hospital among those vaccinated and meningitis admissions were not reduced significantly either<sup>18</sup>.

A case-control study on the effectiveness of Hib vaccine in Bangladesh (June 2000 to September 2003) found no significant vaccine effectiveness after 3 doses of vaccine when either radiologically confirmed pneumonia or meningitis were compared with matched community controls<sup>19</sup>. Data dredging and post-hoc analysis found statistical significance in vaccine effectiveness against pneumonia after two doses of vaccine. It is recommended that the results of post-hoc analysis should be explicitly labelled 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<sup>20</sup>. This was not done in the original report nor

has this been explained in the various discourses on this paper.

### **Strain replacement with invasive nonserotypable *H. influenzae* disease**

The wisdom of having introduced Hib in the West is now being questioned. The vaccine has effectively reduced the incidence of Hib disease. However, there has been a proportionate increase in non-Hib strains, of *H. influenzae*, including non-serotypeable strains, causing invasive disease in the post-Hib vaccine era<sup>21,22</sup>.

### **Vaccine efficacy of pentavalent formulation**

The NTAGI has recommended that Hib vaccine be introduced in India as pentavalent vaccine combined with DPT and hepatitis B. A Cochrane meta-analysis has however, shown that the combination is less effective than the vaccines given separately<sup>23</sup>. It is not used for primary immunization in many countries and the experience with this is therefore limited<sup>24</sup>.

### **Coincidental side-effects: cause and effect relation not proven yet**

**Deaths as side effect:** Pentavalent vaccine was introduced in the national immunization programme in Sri Lanka in January 2008 but after several thousand doses were administered, it was withdrawn in April 2008 because of 25 serious adverse reactions that included 5 deaths. A WHO expert panel investigated the adverse effects and deaths and in its report said that the vaccine was 'unlikely' to have caused the adverse events. It states that although it was not certain if the vaccine was responsible, the committee could not declare categorically that the pattern of adverse events was unrelated to the vaccine and conclusive evidence regarding an alternate cause of the events and outcome was lacking<sup>25</sup>. This nuanced WHO report was misleadingly summarized to suggest that 'investigations conducted by WHO did not reveal any causal association between the events and the Hib containing vaccine'<sup>26</sup>. Pentavalent vaccine was then introduced in national immunization programme of Bhutan in July 2009. Within 2 months, after 8 deaths, the vaccine was withdrawn in that country<sup>27</sup>. The NTAGI has not yet withdrawn its recommendation, nor has the Drug Controller of India sent out advisory asking doctors to look out for these rare adverse events. The jury is still out on the evidence about side effects but parents may like to know the odds of benefits and harms.

### Justification for introducing Hib in the National Immunization Programme

The equity argument is often brought up. It is said the vaccine is given by private practitioners to their well-to-do clientele and it is the responsibility of government to make it available to the poor. Introduction of this vaccine in the national programme in the face of proven low incidence of invasive disease, absence of benefit from Hib vaccination demonstrated in the probe studies from Asia and the evidence of strain replacement in the West, appears to be a profligate exercise in futility.

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