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Correspondence

Hepatitis B in India: Systematic review & report of the 'IMA sub-committee on immunization'

Sir,

The National President of the Indian Medical Association (IMA) (2005-2006) Dr Sudipto Roy set up a sub-committee on childhood immunization in India, under the chairmanship of Professor S.K. Mittal with a view to advise policy. This report refers to the sub-committee's findings on the issue of hepatitis B vaccination in India.

A pilot study was undertaken in 15 selected cities and 32 districts in 17 States of the country in 1996, to study the impact of administration of hepatitis B vaccination[1,2]. On September 6, 2005 the Minister of Health said that the pilot project was highly effective and the vaccine was to be brought under the national immunization programme; to be administered with DPT at the 6th 10th and 14th week of life[3].

The sub-committee looked at the various issues involved, namely the magnitude of the problem of hepatitis B in India, (specifically the chronic carrier rate in the country and the number of deaths from the disease each year), the evidence supporting different vaccination schedules and finally the evidence of the success of the pilot project.

To arrive at an 'evidence-based conclusion' the sub-committee undertook a systematic review of the literature and meta-analysis of the data. The findings of the systematic review were circulated among stakeholders, experts and researchers spanning several specialties including paediatrics, gastroenterology, public health, biostatistics and the social sciences. Besides researchers, Dr P. M. Bhargava, Vice Chairman of the National Knowledge Commission, representatives of the Indian Academy of Pediatrics, the WHO and UNICEF were invited. They were asked to enlarge the evidence-base with articles that had not been retrieved in the search of the electronic databases and the hand searched reviews and linked cross references. A national level consultation of all these experts was held at Delhi on May 14, 2006. We here report the conclusions of the systematic search and the consultation.

Hepatitis B chronic carrier rate : On meta-analysis, the point prevalence of hepatitis B in non tribal populations was found to be 2.1 per cent (95% CI 1.8 to 2.5) and this corresponded to a chronic carrier rate of 1.7 per cent. Among tribal populations the point prevalence was 19.4 (CI 15.3 to 23.5) in the groups studied and this corresponded to a chronic carrier rate of 15.5 per cent. Details of the systematic review and meta-analysis of prevalence data were published elsewhere[4].

Conclusion : A chronic carrier rate less than 2 per cent suggests that India is a country with low endemicity[5]. However, tribal populations in Madhya Pradesh and the Andamans have a much higher endemicity rate. The sub-committee recommended that this group needs special attention to study the epidemiology of infection and its consequences. The likely impact of immunizations in this indigenous population must be evaluated before any recommendations for vaccination is made.

Deaths due to hepatitis B: Review of available evidence: The majority of hepatitis B carriers go through life unaware of their HBsAg status and unaffected by it. A small minority develops fulminant hepatic failure[6]. Some develop chronic active hepatitis, cirrhosis and hepatocellular carcinoma (HCC). In India, in the absence of a surveillance system to track chronic liver disease, the incidence of hepatocellular carcinoma (due to hepatitis B) is a surrogate measure of the magnitude of the problem of chronic liver disease caused by the virus. The consensus statement of the Indian Association for Study of the Liver (INASL)[7] used deaths from HCC

as denominator when looking at 'cost per life saved,' suggesting that HCC is the predominant cause of death from hepatitis B.

The National Cancer Registries maintained by the Indian Council of Medical Research (ICMR) records all deaths from cancer in well defined areas and looks at liver cancer as a proportion of deaths from all cancers. Analysis shows that HCC forms 1.6 per cent of all cancers in the country. Approximately 773,000 deaths in the country are due to cancer[8]. About 11000 deaths in the country are due to HCC and of that, 5000 are due to hepatitis B[8]. Confusion has arisen because of an alternate estimate of 'over 184,000' deaths from hepatitis B in India[7,9]. The error in these estimates has been acknowledged in both the journals[10, 11].

There have been attempts to use iterative mathematical models like the Markov model; employing values for transition-states from other countries, but such studies have not been included here as they reflect the mortality in the countries from where the transition-state data have been extracted[6,12].

Conclusion: Hepatocellular carcinoma is rare in India and constitutes only 1.6 per cent of all cancers. The estimated annual deaths attributable to hepatocellular carcinoma due to hepatitis B is approximately 5000.

Evidence supporting different vaccination schedules

The original, universally recommended, hepatitis B vaccination schedule was three doses at 0, 1 and 6 months. This is based on the fact that a limited number of recipients seroconvert following the first dose, thereby necessitating a closely spaced second dose. With this, there is a high seroprevalence but low antibody titre, necessitating a third dose spaced further apart[13]. All scientifically governed variations in hepatitis B vaccination schedule follow this principle[14,15]; the Advisory Committee on Immunization Practices (ACIP) of the American Academy of Pediatrics recommended a minimum gap of eight weeks between the second and third doses and at least 16 wk between the first and third doses, clarifying further that the final (third) dose should be administered only beyond 24 wk of age[16,17]. This is the basis for using the 2, 4 and 6 month schedule in USA since perinatal transmission is not a problem there. In effect, even the 0, 6 and 14 wk schedule in the Indian context, does not meet this principle.

Critics of this argument cite a number of studies that have shown good sero-conversion with closely spaced schedules as well[18]. But these studies measure antibodies four to eight weeks after the third dose and the long-term efficacy is unknown[19-23]. Also, many of these studies have used a fourth dose usually several months later[24-27], which is a useful option but increases the cost by one-third.

A careful search of literature using the search strategy of the Cochrane Hepato-Biliary Group revealed 1187 references through PubMed, 897 references in the Cochrane Controlled Trials Register and additional 190 references in LILACS, but there is no study showing that the abbreviated schedule as proposed for India (6,10 and 14 wk) is protective in the long-term.

Studies looking at burden of vertical and horizontal transmission to determine importance of the birth dose: Nayak *et al*[28] suggested that 30 per cent of chronic carriers get infected vertically and remaining get infection horizontally from those who got it vertically. Others have used these data to suggest that, as nearly 70 per cent carriers get infection horizontally, immunization at birth is not crucial[29]. They however overlook the fact the immunization coverage is unlikely to be complete, and those who get infection vertically are a threat to others who are not immunized. Immunization at birth overcomes this problem.

Conclusion: Although papers from Taiwan[30-34], China[35], Iran[36], Italy[37-39], Thailand[40], Andamans India[41] and Nigeria[42] showed reduction in carrier rate after universal immunization starting at birth, we found no papers where immunization starting at 6 wk has been proven efficacious

Evidence of the success of the pilot project

Carrier rate in pilot area (against historic controls): What is the carrier rate among children less than 5 yr, in cities where the pilot study was conducted compared to the carrier rate before the introduction of this prophylaxis? Systematic search yielded only one paper from tribals in Andamans, and they were vaccinated at birth[41].

Carrier rate in those immunized starting at 6 wk: What is the carrier rate among children vaccinated at 6, 10 and 14 wk in the pilot area compared to those who received the birth dose? This would help answer the question about the importance of the first dose within 48 h of birth. Systematic search yielded no papers that answer that research question.

Carrier rate in those immunized (compared to those not immunized) in the pilot areas : This would be more

useful than using historic controls. There were no papers.

Vaccine uptake in the pilot project areas : We have one study from East Delhi that reports that the coverage with hepatitis B was 14 per cent - only marginally more than the baseline 9 per cent before the vaccine was made available, free of cost, by the Global Alliance for Vaccine and Immunization (GAVI)[43]. Another study from Delhi found coverage of 19 to 21.6 per cent[1].

What else is known from the pilot study? : We know Rs. 270 million were spent on this pilot project, perhaps the only real mark of success of the programme.

Conclusion : There is no evidence that the pilot project was a success.

The sub-committee therefore recommends that epidemiological studies be done in the areas of the pilot project to see the numbers who were vaccinated, the carrier rate among those vaccinated and those not vaccinated and looking at carrier rate in the sub-group vaccinated at birth and those vaccinated starting at 6 wk.

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