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Commentary

Time to re-think measles vaccination schedule in India

The Immunisation Division of the Department of Family Welfare, Ministry of Health and Family Welfare (MoHFW), Government of India, manages the Universal Immunization Programme (UIP) with the mandate to vaccinate annually about 125 million under-five children including 26 million infants. In spite of it being a massive undertaking, the largest of its kind in the world, the Immunisation Division does not have either an epidemiology wing to measure the impact of UIP or a research wing to help answer technical questions regarding vaccines, immunization and vaccine-targeted diseases. In the 21st century, the Immunisation Division must have access to epidemiological expertise and research capacity.

The MoHFW now has a Department of Health Research (DHR) since 2007. Therefore, the Ministry is now in a position to commission research in support of UIP. The Immunisation Division ought to identify every question that needs answering through research and the Ministry must commission the DHR to answer it. Effective control and eventual elimination of measles is one goal for which much research is urgently needed. For example, the DHR is currently investigating the aerosol application of measles vaccine to young infants as an additional tool for measles control[1].

Regarding epidemiology support for UIP with regards to measles, there are two requirements – monitoring and laboratory tests. The current level of control in every district and sub-district has to be monitored in real-time, which should not be considered research, but an integral function of UIP itself. Currently the National Polio Surveillance Project is helping in the detection and diagnosis of measles and rubella outbreaks in selected States[2], but project sustainability and district level national coverage of all States will require a visionary design for re-engineering UIP. Epidemiological monitoring must not be confined to measles, but should also cover all currently targeted diseases for control through vaccinations. The best approach will be to create a Department of Public Health in MoHFW[3] and embed UIP within it. The public health infrastructure will also be able to conduct district level diseases surveillance exploring the epidemiology of diseases against which vaccines are available but not yet included in the UIP. Moreover, the required laboratory service support can be created in the public health infrastructure instead of positioning it in a vertical design, as is currently practiced by other disease control programmes, such as those against tuberculosis, malaria and AIDS each with its own laboratory network. Indeed, these vertical programmes remain vertical and not integrated because of the lack of a public health infrastructure to subsume all of them[3].

In 1978, when India adopted the Expanded Programme on Immunization (EPI) promoted by the World Health Organization (WHO), measles vaccine was excluded under the mistaken belief that it was not a common problem. In the absence of surveillance of vaccine-preventable diseases or epidemiological investigations by the EPI, the importance of measles remained unrecognized until sufficient data accumulated through other sources. Research reports and advocacy papers from Vellore had brought out the importance of measles vaccination even before the EPI was launched[4,5]. The need to vaccinate infants at 9 months of age was identified, guiding the global EPI on measles vaccination schedule[4,5]. Measles caused death of about 3 per cent of rural and 1 per cent of urban under-five children, for which reason the highest priority was recommended for measles prevention[6-8]. Annual pulse immunization, a simplified vaccine schedule, was shown to be highly effective in controlling measles in a rural community[9].

Tamil Nadu independently introduced measles vaccination in 1980, with special central government permission to use the not-yet licensed vaccine, and by obtaining several millions of measles vaccine doses as a gift from the Rotary International[10]. Based on the Tamil Nadu experience of the ready acceptance of measles vaccine by the community, in 1985 it was licensed in India and introduced nationally in a phased manner under the 7th five-year Plan, until it reached all districts by 1990. EPI was then renamed UIP.

During outbreaks even young infants were at risk for severe disease; hence it was important to vaccinate at the earliest, but maternal antibody interfered with immune response[6,11,12]. The choice of 9 months was to balance the tension between the need for early protection and the advantage of delaying it for best vaccine efficacy[11,12]. The highest seroconversion rate and antibody titre were obtained when measles vaccine was given at or after 12 months of age[12,13]. Vaccinated at 9 months 10-15 per cent infants will fail to seroconvert, whereas >95 per cent would seroconvert if vaccinated at 12 months and 98 per cent if vaccinated at 15 months[12-14].

In late 1990s vaccine-preventable diseases were under surveillance in one district in Kerala and important information on measles had emerged; the majority of measles cases were in school age children, mostly among recipients of one dose at 9 months[15]. Several recent reports on measles in India have highlighted the upward age-shift of measles cases due to, and the continued occurrence of measles in spite of, immunization at 9 months of age[15-17]. Measles continues to occur partly due to inadequate coverage with one dose and partly due to single-dose vaccine failure. To remedy this, in 2010 the Immunisation Division has begun implementing a second dose of measles vaccine either through immunisation delivery channel or through State-wide campaigns.

To cover the immunity gap inevitably created by the 9-month schedule, a second dose of measles vaccine was recommended, universally, by WHO[18]. The Indian Academy of Pediatrics (IAP) recommends a dose of measles-mumps-rubella vaccine (MMR) at 15-18 months of age, fulfilling the need for a second dose of measles vaccine[19]. The Delhi Government has adopted this recommendation for children in Delhi[20]. In the rest of the country, UIP practices the single dose schedule, although moves are afoot to offer a second dose either in age-based schedule or by vaccination campaign covering a broad age range in all States.

Gomber and colleagues[20] measured the immunity prevalence in children in Delhi who had earlier received 2 doses of vaccine, first at 9 months and the second (as MMR) in the second year of life, as reported in this issue. Only 20 per cent of children had adequate antibody levels. This finding raises serious concerns regarding the adequacy of the currently used 2-dose schedule, when the first dose is given at 9 months[20]. In an earlier multi-centre study of the response to the second dose (as MMR), it had elicited response in 100 per cent[21]. With such contradictory and widely varying effect of the second dose of measles vaccine given as MMR, the Immunisation Division will do well to commission an evaluation of the response to a second dose of measles vaccine in all regions of the country.

The multi-centre study measured antibody when the peak was expected post-vaccination, whereas the Delhi study measured it a few years later[20,21]. Could the variant results between the two studies be explained by the time gap of testing, or could it be related to different geographic locations? Do infants respond well to the second dose, but lose antibody titres later on? While the Division expands the second dose schedule to increasing populations, we need evidence that the track is right. Investigations are of the utmost urgency and DHR should be charged with this mission.

Three lines of studies are essential. First, how sure are we that the potency of measles or MMR vaccine made available through UIP or private market is well preserved? The potency of vaccine should be tested and certified adequate before it is used for measuring immune response. Guidelines for ensuring that loss of potency will not vitiate measurement of immune responses are needed. Most of the studies cited here had the flaw of not checking and confirming adequate potency of the vaccine. Investigators had obtained measles or MMR vaccine from the market; how sure are we that such vaccines are of good potency? Obviously, guidelines are also necessary in UIP for random collection to check potency at the end user level.

The second line is to detect and monitor geographic variations of immune responses, if any, to the first and second doses. In one study, the antibody prevalence after one dose at 9 months was 50 per cent at Indore, 82 per cent at Pune and 93 per cent at Mumbai[21]. Since the measurements were done in one laboratory the results are surprisingly at variance according to geography. In another study in Vellore, at 4 yr, 66 per cent of children who had received a dose of measles

vaccine at 9 months had protective antibody levels[22]. Two factors could affect the antibody prevalence in children who got only one dose of measles vaccine at 9 months. One is the height of maternal antibody in the local community; higher the level, lower will the seroconversion frequency be. Secondly, if measles virus continued to circulate, then subclinical infection could have enhanced the antibody prevalence.

The third line is to measure, in different geographic regions, the possible adverse effect of the 9-months measles dose on the response frequency to the second dose and even a third dose. The interactions between passive maternal antibody and measles virus, wild and vaccine, is complex[23-25]. It would be reasonable to assume that the higher the maternal antibody, the greater its influence on the immune response to the first dose of vaccine including the blunting of subsequent response to the second dose; the study by Gomber *et al*[20] suggests that such interference continues even for a third dose given at 4-6 yr of life. However, this assumption must be investigated so that the Immunisation Division will know how to modify the measles vaccine schedule by geography, if found necessary.

Gomber and colleagues attempted to cover the immunity gap remaining even after a second dose, by giving a third dose (as MMR), at the age of 4-6 yr[20]. The Indian Academy of Pediatrics recommends a third dose, but apparently without evidence of its need or of its effect[19]. The expectation would be that at this age immune responses to measles vaccine would be 100 per cent. In the study by Gomber *et al*, in Delhi, the dose-specific response rate was only 65 per cent, for an overall antibody prevalence of 72 per cent after 3 doses of measles vaccine[20]. Obviously this is unexpectedly low and this phenomenon deserves urgent investigation to determine if this finding is confirmable in further studies first in Delhi and also in other regions. Such investigation will be best performed in tandem with the third line described above.

It is quite likely that if vaccination coverage with the first dose is well above 90 per cent and if the second dose coverage also reaches such high level, any immunological disadvantages will be smoothened out for epidemiological vaccine effectiveness. However, until these are reached we need the best measles vaccine schedule for the individual child, since the primary purpose of vaccination is to protect the individual child. Protection should be robust enough to prevent disease if and when exposed to measles virus infection at a future date. The presence or absence of protective antibodies at measurable levels after 2 doses does not necessarily tell the whole story of protection against measles in vaccinated children. In one study in Senegal, up to 50 per cent of vaccinated but seronegative children had sufficient immunity to prevent clinical disease during a measles outbreak[26]. It was very likely that low antibody levels, below the lowest dilution tested, were enough for protection in vaccinated children. Moreover other elements of immunity, such as memory B cells or immune T cells, have a role in protection in spite of waning antibody levels.

As India is on the threshold of accelerated measles mortality reduction and is getting prepared to enter the measles elimination era, the measles immunization schedule has to be re-examined and modified if necessary, based on research evidence, as suggested above.

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References

1. *http://www.who.int/vaccine_research/documents/Session2_HeRe_Gre_presen.pdf*, accessed on July 17, 2011.
2. *http://www.npspindia.org/download/Measles%20Guide.pdf*, accessed on July 17, 2011.
3. John TJ, Muliyil J. Public health is infrastructure for human development. *Indian J Med Res* 2009; *130* : 9-11.
4. John TJ, Jesudoss ES. A survey of measles antibody in children. *Indian Pediatr* 1973; *10* : 65-6.
5. John TJ, Devarajan LV. Priority for measles vaccine. *Indian Pediatr* 1973; *10* : 57-8.
6. John TJ, Joseph A, George TI, Radhakrishnan J, Singh RPD, George K. The epidemiology and prevention of measles in rural south India. *Indian J Med Res* 1980; *72* : 153-8.
7. John TJ, Steinhoff MC. Appropriate strategy for immunization of children in India. 4. Measles and its control, priority number one. *Indian J Pediatr* 1982; *49* : 303-10.
8. John TJ. Measles in India, a neglected problem. *Indian J Pediatr* 1983; *50* : 399-403.
9. John TJ, Ray M, Steinhoff MC. The control of measles by annual pulse immunization. *Am J Dis Child* 1984; *138* : 299-300.
10. Ramchandar AK, editors. *Rotary International. A history (1929-2007) of District 3220*. Available from: *http://www.rotaryfirst100.org/districts/districts/3230/3230disthist.pdf*, accessed on July 17, 2011.

11. John TJ. The optimum age for measles vaccination. *Indian Pediatr* 1982; *19* : 455-6.
12. Job JS, John TJ, Joseph A. Antibody response to measles immunization in India. *Bull World Health Organ* 1984; *62* : 737-41.
13. Singh R, John TJ, Cherian T, Raghupathy P. Immune response to measles mumps & rubella vaccine at 9, 12 & 15 months of age. *Indian J Med Res* 1994; *100* : 155-9.
14. Singh J, Dutta KK. Measles vaccine efficacy in India: A review. *J Commun Dis* 1997; *29* : 47-56.
15. John TJ, Rajappan K, Arjunan KK. Communicable diseases monitored by disease surveillance in Kottayam district, Kerala state, India. *Indian J Med Res* 2004; *120* : 86-93.
16. Bhaskaran P, Balakrishna N, Goud BN, Sukanya M. Post vaccination scenario of measles. A retrospective analysis. *Natl Med J India* 1999; *12* : 111-2.
17. Sharma MK, Bhatia V, Swamy HM. Outbreak of measles in a slum of Chandigarh. *Indian J Med Sci* 2004; *58* : 47-53.
18. World Health Orgnization. Measles vaccine: WHO Position Paper. *Wkly Epidemiol Rec* 2004; *79* : 131-42.
19. *http://www.iapindia.org/immunisation/immunisation-schedule,* accessed on July 17, 2011.
20. Gomber S, Arora SK, Das S, Ramachandran VG. Immune response to second dose of MMR vaccine in Indian children. *Indian J Med Res* 2011; *134* : 302-6.
21. Bhargava I, Chapparwal BC, Phadke MA, Irani SF, Chapparwal D, Dhorje S, *et al*. Imunogenicity and reactogenicity of indigenously produced MMR vaccine. *Indian Pediatr* 1995; *32* : 983-8.
22. John S, Lalitha G, George K, Joseph A. Serological response to early measles vaccination. *J Trop Pediatr* 2004; *50* : 175-7.
23. Wilkins J, Wehrle PF. Additional evidence against measles vaccine administration to infants less than 12 months of age. *J Paediatr* 1979; *94* : 865-9.
24. Stetler HC, Orenstein WA, Bernier RH, Herrmann KL, Sirotkin B, Hopfensperger D, *et al*. Impact of revaccinating children who initially received measles vaccine before 10 months of age. *Pediatrics* 1986; *77* : 471-6.
25. Cherian T, Joseph A, John TJ. Low antibody response in infants with measles and children with subclinical measles virus infection. *J Trop Med Hyg* 1984; *87* : 27-31.
26. Samb B, Aaby P, Whittle HC, Seck AM, Rahman S, Bennet J, *et al*. Serological status and measles attack rates among vaccinated and unvaccinated children in rural Senegal. *Pediatr Infect Dis J* 1995; *14* : 203-9.