PERSPECTIVE

Commitment of Measles Elimination by 2020: Challenges in India

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The eleven member states of World Health Organization South-East Asia Region committed to eliminate measles by 2020. In phased manner, Government of India is working on this goal, and has introduced two-dose strategy for measles vaccine in the routine immunization. Molecular epidemiology of measles in India has been considerably growing that would be useful for understanding the circulation of wild type measles in pre- and post-elimination period. However, importations of cases from other countries may be likely. This article describes major challenges to achieve the measles elimination goal in India.

Keywords: *Disease eradication, Essential immunization, Measles-Mumps-Rubella vaccine.*

Measles elimination means absence of endemic measles transmission or no more cases of measles caused by indigenous virus in a defined geographical area, for ≥12 months in the presence of a well-performing surveillance system. Recently, the eleven member states of World Health Organization South-East Asia Region (WHO SEAR) have committed to eliminate measles by 2020 at the 66th session of the WHO regional committee [1]. As per WHO's recommendation, all available measles vaccines are safe, effective and protect equally well against all wild type measles genotypes [2]. In the phased manner, the Government of India (GoI) is working for measles elimination. GoI introduced second dose of measles in 2010, and recently announced to introduce the rubella vaccine in its Universal Immunization Program (UIP) [3]. Indian Academy of Pediatrics (IAP) supports elimination of measles and rubella but also of mumps in the form of two doses of affordable measles-mumps-rubella (MMR) vaccine [4].

Measles is reported to be cause of considerable morbidity and mortality in India. In 2005, an estimated 92000 deaths occurred in India due to measles, predominantly in children aged less than 5 years. Estimates from year 2008 indicate that 77% of global measles mortality was in the WHO SEAR, the majority from India. An update on 1st dose of measles-containing vaccine coverage, progress in implementing a 2nd dose of measles-containing vaccine coverage and measles outbreak surveillance activities was conducted during years 2006 to 2010 in the eight Indian States [5]. This report highlights that the pace of implementation of measles mortality reduction is variable across the States.

A model to estimate the progress made towards the global measles-mortality reduction goal emphasizes need to intensify control measures and further commitments on the political/financial issues [6]. Updated estimates of measles case fatality rates (CFR) are critical for monitoring progress towards measles elimination goals. A retrospective cohort study to estimate measles CFR and its risk factors for measles death in the State of Bihar has been recently reported [7]. Report indicates higher CFR in the children less than 5 years of age (1.22%), and amongst children belonging to scheduled castes/tribes (1.72%). A review of Indian community-based measles CFR studies conducted between year 1975 and 2008 indicates significantly higher CFR in rural population, and further emphasizes to enhance measles vaccine coverage and routine supplementation of vitamin A in the outbreak settings [8]. Recent estimates indicate that over 100,000 children died due to measles in India during 2005 [9]. The majority of measles deaths occurred in the States of Uttar Pradesh, Bihar and Madhya Pradesh. Estimate also shows that girls were at higher risk of mortality compared to boys. All these reports show need of supplementary immunization activity in the high burden districts.

The feasibility of measles elimination and the possible challenges in India to achieve this important goal have been described earlier [10]. This review also describes the National Technical Advisory Group of India's (NTAGI) strategies on routine measles vaccine coverage and introduction of supplementary immunization activity (SIA) in a phased manner. However, measles-mortality reduction remains the top

priority. The Government of India had introduced two-dose strategy for measles vaccine in the UIP [11]. As per the revised routine immunization schedule, every child should get two doses of measles vaccine: first at the age of 9-12 months and 2nd at the age of 16-24 months. If a child missed any of these doses, these can be offered up to 5 years of age maintaining a gap of at least 4 weeks between the doses. Recent reports [12,13] on the measles outbreak investigations indicate need to improve measles vaccine coverage and community participation. Use of vitamin A during outbreak management and supplemental immunization is essential to improve the control measures in the outbreak settings [14]. Vitamin A deficiency contributes to delayed recovery and high rate of post-measles complications. The beneficial effect of two doses of vitamin A during treatment of measles is well established, and WHO recommends administration of vitamin A to all patients with measles [2].

Between January 2013 and June 2014, Maharashtra State health agencies have investigated 197 suspected measles outbreaks in the 28 districts. Of these outbreaks, 138 were confirmed as measles, 18 were confirmed as rubella, 31 were mixed outbreaks, and nine outbreaks remained unconfirmed (Unpublished data). During this investigation, few adult measles cases were also reported; majority were among unimmunized. Recently, three outbreaks of measles in adults (medical cadets, medical students and nursing students) were reported from the State of Maharashtra, Karnataka and Andhra Pradesh. The possibility of shift in age for measles is likely, necessitating further such studies. Primary vaccine failure or waning immunity in adults may also be the likely cause. In the developed countries, measles outbreak-based (or case-based) surveillance coupled with genotyping of virus strains have generated data for tracking the transmission routes, documenting the elimination of endemic virus strains, and indicating any risk groups.

In India, data on the circulation of measles strains was generated during 2005-10 by establishing national network (*i.e.* MeaslesNetIndia) of 27 centers and sentinel practitioners in 21 States and 2 Union Territories of India [15]. Phylogenetic studies revealed circulation of measles genotype D4 and D8 strains. This project has created support and capabilities for countrywide measles molecular surveillance. Measles genotype D7 was detected from two classical measles cases from the Chennai and Pune cities, and in a fulminant SSPE case from the Bangalaru city [16]; circulation of this genotype was not detected afterwards. Molecular studies from the States of Uttar Pradesh [17,18] and Tamil Nadu [19] indicate presence of measles genotype D8 strains. India's measles virus sequencing data now cover different regions of the country (***Table* I**). Recently, circulation of measles genotype B3 was reported from Thiruvananthapuram, Kerala [20] indicating either importation from other countries or unidentified indigenous measles strain. Thus, studies on the genetic and antigenic properties of circulating wild type viruses will be important in context of measles elimination.

A longitudinal follow-up study conducted during 1995 shows that measles containing vaccine (MMR) had excellent immunogenicity, low reactogenicity and good seroconversion rate (75% to 100%) in previously vaccinated children [21]. The persistence of measles IgG antibodies was studied up to 6 years post-vaccination, that revealed 88% measles seropositivity, and suggests 2nd dose of measles for the boost-up [22]. A study

TABLE I MEASLES VIRUS STRAINS DETECTED IN DIFFERENT PARTS OF THE COUNTRY (1996-2014)

State/Union Territory	*Genotype D4*	*Genotype D8*	*Total*
Andaman and Nicobar	-	7	7
Andhra Pradesh	7	15	22
Arunachal Pradesh	12	7	19
Assam	1	7	8
Bihar	1	5	6
Chattisgarh	-	2	2
Delhi	-	9	9
Gujarat	10	2	12
Haryana	-	2	2
Himachal Pradesh	2	-	2
Jammu and Kashmir	8	-	8
Jharkhand	1	-	1
Karnataka	11	21	32
Kerala	-	4	4
Madhya Pradesh	3	-	3
Maharashtra	32	49	81
Manipur	-	4	4
Meghalaya	-	1	1
Nagaland	-	6	6
Odisha	-	3	3
Rajasthan	2	5	7
Sikkim	6	1	7
Tamil Nadu	9	48	57
Tripura	-	1	1
Uttar Pradesh	3	44	47
Uttarakhand	5	6	11
West Bengal	-	4	4
Total	113	253	366

conducted on 84 children (aged 4-6 years) from the State of Delhi shows increased seropositivity for measles (21.4 to 72.6%), mumps (87.4 to 100%) and rubella (75.7 to 100%) after introduction of 2nd dose of MMR vaccine [23]. However, large-scale studies are necessary to understand the level of sero-protection, and ultimately to understand the impact of measles immunization.

Limited sero-epidemiological studies on measles are available from India. The prevalence of serological susceptibility to measles was 9.5% in 790 health science students [24]. Additional efforts are needed to generate more information to understand the real impact of measles immunization. For the large-scale studies, alternative neutralization assays that utilize a 96-well tissue culture plate format would be preferred [25]. However, commercially available more rapid enzyme linked immunosorbent assays (EIA) do not differentiate neutralizing and non-neutralizing antibodies. For the characterization of vaccine or wild type-induced immune response, rapid and reliable neutralization tests are essential. Therefore, the focus reduction neutralization tests (FRNT) for measles, mumps and rubella viruses have been developed [26].

The major challenges to achieve measles elimination goal in India are as follows:

Vaccine Procurement and Supply

WHO estimates shows that US$ 800 million are required for the SEAR to achieve the target of measles elimination before 2020. Thus, for the procurement of measles vaccine, there is a need to find funding source from the State Governments, Central Government and other national or international agencies. Similarly, efforts are required to tie up with the vaccine manufacturers for adequate and timely vaccine supply. Maintenance of cold chain during the transportation and vaccine storage facilities may be the key issue in the South-East Asian countries. Similarly, adequate supply of syringes and needles, and their proper disposal is an important issue.

Efforts to Maintain High Vaccine Coverage

The prime target is to achieve >95% population immunity with high vaccine coverage by two doses of measles and/or by supplementary immunization activities. For this, trained staff would be required for vaccine delivery, and to mobilize the community participation. More attention is needed in the tribal areas, hilly regions, and migrant population.

Active Surveillance

In order to succeed, country must plan a surveillance system that detects all cases of measles. For this purpose, a case-based measles surveillance needs to be established, and if possible, laboratory confirmation of the representative cases/circulating wild type viruses should be undertaken. Few States have already established measles outbreak-based surveillance system and in near future, these States may enter into the case-based surveillance. To date, GoI have not introduced the measles case-based surveillance. However, States that can utilize their existing surveillance system (like Integrated Disease Surveillance Program or National Polio Surveillance Project network) may enter into a measles case-based surveillance.

Strengthening of Laboratory Facilities

To strengthen laboratory capacities, WHO has recognized 11 national laboratories (MeaslesLabNet) in different States of India. These laboratories perform serological (IgM antibody detection) and molecular testing (measles virus detection and genotyping). For the measles virus sequencing, PCR products have been referred to the Reference laboratory at NIV Pune. As work load increases, there is need to create more laboratories without compromising on the WHO's accreditation criteria. Recently, Indian Council of Medical Research have identified 150 virus diagnostic laboratories across the country, and attempts are going on to strengthen them. These laboratories can be included in the MeaslesLabNet for the measles and rubella diagnosis. Role of laboratories is crucial in documenting interruption of endemic transmission of the circulating (indigenous) measles viruses.

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