Is it Right Time to Introduce Mumps Vaccine in India's Universal Immunization Program?

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Measles, mumps and rubella are vaccine preventable diseases. However, morbidity and mortality due to these diseases remain largely unnoticed in India. Measles has received much attention; mumps and rubella still need to garner attention. According to the World Health Organization, near-elimination of mumps could be achieved by maintaining high vaccine coverage using a two-dose strategy. However, Government of India has not yet decided on mumps vaccine. In this review, we have reviewed sero-prevalence studies, vaccine studies, outbreak investigations, virus isolation and virus genotyping studies on mumps. Overall, mumps seems to be a significant public health problem in India, but does not garner attention due to the absence of a surveillance and documentation system. Thus, inclusion of mumps antigen in the Universal immunization program would have added advantages, the economic burden imposed by the cost of the vaccine offset by a reduction in disease burden.

Keywords: *Epidemiology, Immunization, Measles-Mumps-Rubella Vaccine, Mumps virus*.

Mumps is an acute viral illness affecting young children, characterized by fever and swelling of the parotid gland(s) and may lead to complications mainly deafness, orchitis, oophoritis, pancreatitis and meningo-encephalitis [1]. Approximately half of the infected individuals develop classical disease. About 15-20% of mumps infections may be asymptomatic while the remaining subjects develop non-specific respiratory symptoms [2]. Historically, mumps has been considered as a disease of children, but over the past two decades, it has been observed in older children and adults in countries where childhood mumps immunization has been in routine use. Mumps re-infection can occur after immunization or sometimes after natural infection [3].

In India, very limited data are available on the epidemiology of mumps. Mumps continues to occur in epidemic proportions in India despite the availability of a safe and effective vaccine. Mumps-containing vaccines have not been included in the Universal Immunization Program (UIP) or National immunization schedule, but are available as optional vaccines. Considering reports on mumps cases or outbreaks and mumps-related complications from different parts of the country, the Indian Academy of Pediatrics (IAP) suggested inclusion of mumps antigen in the form of Measles, Mumps and Rubella (MMR) vaccine, first dose at 9 months and second dose at 16-24 months [4]. The IAP Committee on Immunization has reiterated inclusion of mumps antigen in UIP as MMR vaccine instead of Measles-Rubella (MR) vaccine [5].

For the present review, studies on mumps from India were searched in PubMed, PubMed Central, and Google Scholar. In addition, unpublished research data from annual reports of National Institute of Virology (NIV) Pune, were also accessed.

MUMPS REPORTS FROM INDIA

Mumps outbreaks or sporadic cases have been periodically reported from the States of Kerala, Maharashtra, Gujarat, Karnataka, Punjab, Tamil Nadu, Uttar Pradesh and West Bengal [6-20]. These outbreaks or sporadic cases were confirmed either by clinical presentation or by using serological or molecular tools (***Table* I**). Only ten of these studies confirmed mumps by serological or molecular tools while in the remaining studies, clinical diagnosis was used for confirming mumps. Reports suggest that due to lack of surveillance and documentation systems, the burden of mumps is underestimated in India. Similarly, mumps-associated complications and outcome of patients are not reported systematically.

Genetic characterization of mumps virus is an effective tool to track the transmission of wild types. Reverse transcriptase polymerase chain reaction (RT-

TABLE I MUMPS REPORTS FROM DIFFERENT PARTS OF THE COUNTRY

Study Year	*District, State*	*Age Group (Years)*	*No of cases*	*Serolological confirmation*	*Molecular confirmation*	*Year, Reference*
1969	Vellore, Tamil Nadu	5-11	66†	Yes; 1/66	No	*1969 [17]
1999-2003	Calicut, Kerala	1-12	301	No	No	2004 [7]
2002	Thiruvananthapuram, Kerala	1-14	183	No	No	2004 [6]
2004-2006	Aligarh,Uttar Pradesh	0.5-12	87†	Yes; 2/87	No	*2010 [18]
2005	Manipal, Karnataka	5-13	8‡	Yes; 8/8	No	2010 [10]
2005-2006	Sangli, Maharashtra	3-13	10	No	No	*2007 [8]
2009	Kolkata,West Bengal	0->15	104	No	No	2012 [6]
2011	Fatehgarh Sahib, Punjab	6-12	20	Yes; 9/19	Yes; 7/19	2013 [12]
2011-2012	Chennai, Tamil Nadu	0-45	56	Yes; 48 /56	Yes; 3 /5	2012 [15]
2011-2012	Chennai, Tamil Nadu	5-11	5	Yes; 5 /5	Yes; 5 /5	2013 [16]
2012	Ludhiana, Punjab	22-24	7††	No	No	2014 [14]
2012	Osmanabad, Maharashtra	0-65	142	Yes; 44/62	Yes; 23/28	*2013 [9]
2009-2014	Country wide Data by IDSP	0-15	1564	No	No	2015 [5, 20]
2014	Davangere, Karnataka	1-15	31	Yes; 18/31	Yes; 2/31	2015 [11]
2015	Tapi, Gujarat	5-13	9	Yes; 8/9	No	NIV Data Unpublished
2015	Pune, Maharashtra	0-15	35	Yes; 23/35	No	NIV Data Unpublished
2011-2013	Country wide Data by IAP#	0-15	808	No	No	2015 [5,20]
2014- 2015	Country wide Data by IAP (72 Outbreaks)		0-15	520	No	2015 [5,20]

**Studies reported viral encephalitis; #10% of IAP Pediatricians had provided data; †Encephalitis; ‡Atypical mumps; ††Dentistry students.*

PCR) test, based on small hydrophotic gene of mumps virus, has been used to generate global sequence database [21]. Recently, WHO has updated mumps virus nomenclature to 12 genotypes *viz*. A, B, C, D, F, G, H, I, J, K, L and N. To date, 46 mumps virus sequences are available from India (***Web Fig.* 1**). Circulation of C genotype strains have been reported from the States of Maharashtra, Karnataka and Tamil Nadu and a circulation of mumps genotypes G from Maharashtra and Punjab [9,11,12,15,16]. Additional efforts are required to strengthen molecular surveillance of mumps virus in India. The complete genome sequence of Indian mumps strains and its cross-neutralization studies may be useful to facilitate the introduction of mumps containing vaccine in the country.

SERO-PREVALENCE STUDIES

Limited studies are available on sero-prevalence of mumps in India. The first serological survey was performed on 285 serum samples collected during 1964, and tested by both complement fixation test (*n*=180) and hemagglutination-inhibition test (*n*=105) [22]. Serum samples were collected from the local blood donors aged 20–30 years and clinical cases aged between 18–20 years. Study documented relatively low mumps positivity (*i.e.* 13.3% by complement fixation test and 38.1% by hemagglutination-inhibition test) in the healthy blood donors from Pune, India.

A cross-sectional study was performed on 321 serum samples to detect mumps-specific antibodies in the children below 5 years, and also to assess the optimum age for the MMR vaccination [23]. Result showed 53.3% sero-positivity for mumps in children aged <9 months, 20.3% for age 9-12 months, and 40% for 2-year-olds. Mean antibody levels for mumps were low between 9 months to 2 years with a slight rise by five years. Thus, Chakravarti, *et al*. [23] suggested that a large number of children may be at risk by the age of 9 months, and MMR vaccination at this age may be beneficial**.**

The sero-prevalence study conducted in Health Sciences students (*n*=790, 18-25 years old enrolled during November 2008 to August 2011) from Manipal University revealed that about 32% of them were susceptible to mumps [24]. Amongst the MMR vaccinated group, 34.7% were susceptible to mumps, indicating likely waning immunity after single dose of mumps- containing vaccine. Hence, such population may be at risk for mumps infection during their training.

The serum samples (*n*=86, age 7 mo-27 y) referred for laboratory diagnosis of measles or rubella during

2013-14 were tested for the presence of mumps IgG antibody (samples were used for an assay development project). Overall 45.3% samples showed presence of mumps-specific IgG antibody, suggesting that over half of these were susceptible to mumps infection. Mumps IgG antibody seropositivity was 39.1% in <15 year-olds (NIV Pune Data).

Above mentioned studies suggest that seropositivity for mumps among Indian population is low, and large group of the population remains susceptible. Thus, studies on age-specific sero-prevalence of mumps are required to formulate mumps vaccine policy. In conclusion, limited seroprevalence data are available for mumps from different parts of the country due to which accurate proportion of susceptible population in the rural and urban settings is not available.

MUMPS-CONTAINING VACCINE STUDIES

A few mumps vaccine studies were available from India. The sero-conversion rates in MMR-vaccinated children at 9, 12 and 15 months of age were assessed to understand the optimum age for the vaccination [25]. The pre-immunization results showed that levels of mumps maternal antibody were detectable by hemagglutination inhibition up to 9 months in all infants. An evidence for subclinical infection was found in 19-31% infants by the age of 15 months. The response to mumps antigen was also higher (92%) at 12 months than at 9 months (75%). Vaccine failure was less frequent at 12 months than at 9 months. Singh, *et al*. [25] suggested that a better response to the MMR vaccine can be achieved at or after 12 months of age. A longitudinal follow-up was performed to study the immunogenicity and reactogenecity of the indigenously produced MMR vaccine [26]. Results indicated boost in the mumps IgG antibody positivity from 12% to 92% indicating an excellent immunogenicity and low reactogenicity with some adverse side effects.

A study was performed to assess the serological status of measles, mumps and rubella in young children, and to evaluate the seroconversion of MMR vaccine at 9 and 15 months of age [27]. Of 120 infants (age 9-10 mo), 80% were sero-negative for mumps. However, 100% mumps sero-positivity was observed at 6-8 weeks post-vaccination. Amongst children aged 15-18 months, 70% were sero-negative, and 96% of them showed mumps sero-positivity after 6-8 weeks of vaccination. The antibody levels in Indian girls were measured after 6 years of MMR vaccination [28]. Results showed 95% seropositivity for mumps specific IgG antibodies (geometric mean titres 1.4, 95% CI 1.3-1.5). A prospective study was carried out to assess the extent of seroprotection against measles, mumps and rubella in the measles or MMR-vaccinated children (age 4-6 y), and also the immune response after 2nd dose of MMR was assessed after 4-6 weeks of vaccination [29]. The pre-vaccination seropositivity of 103 children was 87.4% for mumps, and seropositivity increased to 100% in 84 children who were followed. The geometric mean titers for all three antigens were significantly increased in post-vaccinated serum samples. Similar studies are necessary to document long-term persistence of antibodies in the Indian population.

A study was performed to investigate mumps infection in MMR-vaccinated and non-vaccinated populations in Chennai, India [30]. Blood samples were collected from the suspected mumps cases (n=74, 56.7% <12-year-old), and tested for the presence of mumps specific IgM antibody, IgG antibody against measles, mumps and rubella viruses by enzyme-linked immunoassay (EIA). Altogether, 67 (91%) patients had received minimum one dose of MMR vaccine. All the 67 vaccinated cases had parotitis, and presence of mumps virus specific IgM antibodies. However, only 10 (15%) were positive for IgG antibodies. All samples were positive for rubella and measles IgG antibodies. Similar instances have been reported from other countries where mumps vaccine is in routine use. Another preliminary study was performed on 12 participants who received one dose and 91 participants who received two doses of MMR vaccine [31]. Result showed the low seropositivity for mumps IgG antibodies compared to measles and rubella IgG antibodies. However, large-scale studies are essential to understand the mumps immune response in the vaccinated population.

Above studies indicate that mumps-containing vaccine provides good sero-conversion amongst the vaccinated subjects, but two doses of vaccine are crucial to boost the circulating antibodies. The data on mumps vaccine effectiveness are not available from India as mumps is not part of UIP, except few States and Union Territories.

MEASUREMENT OF IMMUNE RESPONSE

The protective neutralizing antibody titer for mumps is not well-defined, and therefore characterization of immune response to mumps virus in immunized population (pre- and post-vaccination) or natural infection is very important. Plaque reduction neutralization test (PRNT) measures the functional antibody (of any class) by *in vitro* virus neutralization, and is considered as the 'gold-standard' assay for assessing the serological correlates of protection. However, PRNT is technically demanding, not easy to

automate, and has limitations for screening the large numbers of sera needed for epidemiological investigations. PRNTs require 6-7 days for completion. For large-scale studies, alternative neutralization assays like focus reduction neutralization test (FRNT) would be preferred [32]. However, commercially available more rapid EIA did not differentiate neutralizing and non-neutralizing antibody. Therefore, a cell culture-based rapid and reliable immuno-colorimetric assay (ICA) was established for detection of measles, mumps and rubella viruses [33]. Use of ICA have been documented on 35 virus isolates, three vaccine strains and clinical specimens collected from the suspected measles and mumps cases. Furthermore, an application of ICA in a neutralization test (*i.e.*, FRNT) was documented and may be useful for the sero-epidemiological, cross-neutralization and pre/post-vaccine studies.

Recently, the cross-neutralization studies were performed using a panel of serum samples that challenged with two wild types i.e. genotypes C and G and Leningrad-Zagreb vaccine strain *i.e.* genotype N [34]. Result showed all serum samples obtained from naturally infected or unimmunized individuals effectively neutralize mumps wild types and a vaccine strain. However, significantly lower level of FRNT titers was noted to wild types than to vaccine strain [34]. Limited data are available on mumps immune response studies (*i.e.* vaccine or wild type virus induced) from India. Thus, characterization of mumps immune response in the vaccinated population should be undertaken using well-validated IgG antibody EIA or neutralization tests.

CONCLUSIONS

Many outbreak reports, three sero-prevalence studies and seven vaccine studies on mumps are available from different parts of the country. In addition IAP web-based system and Integrated Disease Surveillance Program (IDSP) network reported 2892 mumps cases between September 2009 and May 2015. This review highlights that mumps is a public health problem in India; however, inadequate data from different parts of the country underestimate the true extent of the burden. It has been observed that there is no uniformity in the methodology of surveillance, serological testing algorithm, attempt for virus isolation, and use of available molecular tools and sequencing. Limited information is available about the seasonality of mumps cases in the country. Circulation of two mumps viruses (i.e. genotypes C and G) were reported from India; more genotyping studies are necessary to understand other indigenous mumps virus circulation if any. Inclusion of mumps antigen in the UIP would have added advantages; the economic burden imposed by the cost of the vaccine is likely to be offset by a reduction in disease burden and related complications.

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REFERENCES

1. Hviid A, Rubin S, Mühlemann K. Mumps. Lancet. 2008;371:932-44.
2. Philip RN, Reinhard KR, Lackman DB. Observations on a mumps epidemic in a "virgin" population. 1958. Am J Epidemiol. 1995;142:233-53.
3. Dayan GH, Rubin S. Mumps outbreaks in vaccinated populations: are available mumps vaccines effective enough to prevent outbreaks? Clin Infect Dis. 2008;47:1458-67.
4. Vashishtha VM, Yewale VN, Bansal CP, Mehta PJ. IAP perspectives on measles and rubella elimination strategies. Indian Pediatr. 2014;51:719-22.
5. Vashishtha VM, Yadav S, Dabas A, Bansal CP, Agarwal RC, Yewale VN, *et al.* IAP Position Paper on burden of mumps in India and vaccination strategies. Indian Pediatr. 2015;52:505-14.
6. John TJ. An outbreak of mumps in Thiruvananthapuram district. Indian Pediatr. 2004;41:298-300.
7. Geeta MG, Kumar PK. Mumps— need for urgent action. Indian Pediatr. 2004;41:1181-2.
8. Ghatage ST, Kakade GM. An outbreak of mumps meningoencephalitis in Sangli district. Indian Pediatr. 2007;44:235.
9. Vaidya SR, Chowdhury DT, Kumbhar NS, Tomar R, Kamble MB, Kazi MI. Circulation of two mumps virus genotypes in an unimmunized population in India. J Med Virol. 2013;85:1426-32.
10. Vandana KE, Arunkumar G, Bairy I. Role of laboratory in rapid diagnosis of atypical mumps. Braz J Infect Dis. 2010;14:201-2.
11. Raut CG, Sinha DP, Jayaprakash H, Hanumiah H, Manjunatha MJ. Mumps disease outbreak in Davangere district of Karnataka, India. Indian J Med Microbiol. 2015;33:378-82.
12. Mishra B, Pujhari SK, Dhiman V, Mahalakshmi P, Bharadwaj A, Pokhrel S, *et al.* Genotyping and subtyping of mumps virus isolates from the Indian subcontinent. Arch Virol. 2013;158:2359-63.
13. Bhatnagar N, Kaur R, Gupta M, Sharma D. Introducing combined measles, mumps and rubella vaccine in Chandigarh, India: Issues and concerns. Indian Pediatr. 2014;51:441-3.
14. Samuel CJ, Thomas AM, Bhatia D. Mumps outbreak in dental care providers in a North Indian dental college. CHRISMED J Health Res. 2014;1:216-7. Available from: *http://www.cjhr.org/text.asp?2014/1/3/216/* Accessed June 8, 2015.
15. Malayan J, Warrier A, Ramanan PV, Reddy SN, Manickan E. Unnoticeable mumps infection in India: Does MMR vaccine protect against circulating mumps

virus genotype C? World Academy of Science, Engineering & Technology 2012;6:1365-71.
16. Jeevan M, Sambantham S, Thangam M. Characterisation of mumps virus genotype C among patients with mumps in India. Indian J Med Microbiol. 2013;31:290-2.
17. Carey DE, Myers RM, Webb JK. Search for herpes simplex, mumps and lymphocytic choriomeningitis associated with central nervous system disease at Vellore, Southern India. Indian J Med Res. 1969;57:567-8.
18. Beig FK, Malik A, Rizvi M, Acharya D, Khare S. Etiology and clinico-epidemiological profile of acute viral encephalitis in children of western Uttar Pradesh, India. Int J Infect Dis. 2010;14:e141-6.
19. Saha I, Haldar D, Paul B, Shrivastava P, Das DK, Pal M, *et al*. An epidemiological investigation of mumps outbreak in a slum of Kolkata. J Commun Dis. 2012;44:29-36.
20. Infectious Disease Surveillance (IDsurv) by Indian Academy of Pediatrics. Available from: *http://www.idsurv.org.* Accessed June 08, 2015.
21. World Health Organization. Mumps virus nomenclature update: 2012. Wkly Epidemiol Rec Wkly Epidemiol Rec. 2012;87:217-24.
22. Waller SO, Rai J, Bannerjee AK. A serological survey of mumps. Indian J Med Res. 1965;53:819-21.
23. Chakravarti A, Yadav S, Berry N, Rastogi A, Mathur MD. Evaluation of serological status of rubella and mumps in children below five years. Indian J Med Res.1999;110:1-3.
24. Arunkumar G, Vandana KE, Sathiakumar N. Prevalence of measles, mumps, rubella, and varicella susceptibility among health science students in a University in India. Am J Ind Med. 2013;56:58-64.
25. Singh R, John TJ, Cherian T, Raghupathy P. Immune response to measles, mumps and rubella vaccine at 9, 12 & 15 months of age. Indian J Med Res. 1994;100:155-9.
26. Bhargava I, Chhaparwal BC, Phadke MA, Irani SF, Chhaparwal D, Dhorje S, *et al.* Immunogenicity and reactogenicity of indigenously produced MMR vaccine. Indian Pediatr. 1995;32:983-8.
27. Yadav S, Thukral R, Chakarvarti A. Comparative evaluation of measles, mumps and rubella vaccine at 9 & 15 months of age. Indian J Med Res. 2003;118:183-6.
28. Raut SK, Kulkarni PS, Phadke MA, Jadhav SS, Kapre SV, Dhere RM, *et al.* Persistence of antibodies induced by measles-mumps-rubella vaccine in children in India. Clin Vaccine Immunol. 2007;14:1370-1.
29. 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.
30. Malaiyan J, Menon T. Low vaccine efficacy of mumps component among MMR vaccine recipients in Chennai, India. Indian J Med Res. 2014a;139:773-5.
31. Malaiyan J, Duraipandian T, Warrier A, Menon T. Low rate of seropositivity (IgG) to mumps component in MMR vaccinees in Chennai, South India. Indian J Med Res. 2014;139:949-51.
32. Vaidya SR, Brown DW, Jin L, Samuel D, Andrews N, Brown KE. Development of a focus reduction neutralization test (FRNT) for detection of mumps virus neutralizing antibodies. J Virol Methods. 2010;163:153-6.
33. Vaidya SR, Kumbhar NS, Bhide VS. Detection of measles, mumps and rubella viruses by immuno-colorimetric assay and its application in focus reduction neutralization tests. Microbiol Immunol. 2014;58:666-74.
34. Vaidya SR, Dvivedi GM, Jadhav SM. Cross-neutralization between three mumps viruses and mapping of hemagglutinin-neuraminidase (HN) epitopes. Indian J Med Res. 2016;143:37-42.