POSITION PAPER

IAP Position Paper on Burden of Mumps in India and Vaccination Strategies

VIPIN M VASHISHTHA, *SANGEETA YADAV, #AASHIMA DABAS, CP BANSAL, ROHIT C AGARWAL, VIJAY N YEWALE, NAVEEN THACKER, SS KAMATH AND PRAVIN J MEHTA

*From the Indian Academy of Pediatrics, Advisory Committee on Vaccines and Immunization Practices (ACVIP); and Departments of Pediatrics, *Maulana Azad Medical College and #University College of Medical Sciences, New Delhi; India.*

Correspondence to: Dr Vipin M Vashishtha, Convener, IAP Advisory Committee on Vaccines and Immunization Practices, Mangla Hospital and Research Center, Shakti Chowk, Bijnor, Uttar Pradesh 246 701, India. vipinipsita@gmail.com

Justification: Mumps, despite being a widely prevalent disease in the country, is considered as an insignificant public health problem mainly because of poor documentation of clinical cases and lack of published studies. In the absence of adequate published data on disease burden, Government of India has recently decided to introduce measles-rubella (MR) vaccine in its National Immunization Program and neglected mumps component.

Process: Following an IAP ACVIP meeting on December 6 and 7, 2014, a detailed review of burden of mumps in India along with vaccination strategies to control the disease was prepared. The draft was circulated amongst the members of the committee for review and approval. Revised final draft was later approved by IAP executive board in January 2015.

Objectives: To provide a review of community burden of mumps in India; and to discuss the vaccination strategies to impress upon policymakers to include mumps vaccination in National immunization program.

Recommendations : A total of 14 studies and two media reports on mumps outbreak were retrieved. The outbreaks were reported from all the regions of the country. Mumps meningoencephalitis was responsible for 2.3% to 14.6% of all investigated hospitalized acute encephalitis syndrome or viral encephalitis cases in different studies. Data from Infectious Disease Surveillance (ID Surv) portal of IAP and Integrated Disease Surveillance Program (IDSP) of Government of India (GoI) were also reviewed. While a total of 1052 cases were reported by the IDSurv, IDSP had investigated 72 outbreaks with 1564 cases in 14 states during different time periods. Genotypes G (subtype G2) and C were found to be main genotypes of the mumps virus circulating in the country. Three studies studied serological status of young children and adolescents against mumps, and found susceptibility rates ranging from 32% to 80% in different age groups.

Conclusions: Mumps poses a significant disease burden in India. This calls for inclusion of mumps vaccine in the National immunization program.

Keywords*: Epidemiology, Measles-mumps-Rubella vaccine, National immunization program, Prevention.*

The Government of India (GoI) has announced its decision to include rubella vaccine in form of a bivalent Measles-Rubella (MR) vaccine in its Universal Immunization Program (UIP) [1]. The two-dose MR vaccine shall be provided at 9 months in place of stand-alone measles vaccine, and at 16-24 months along with first booster of Diphtheria-Tetanus-Pertussis (DTP) vaccine [2]. The Indian Academy of Pediatrics (IAP) has argued very strongly for the inclusion of Measles-Mumps-Rubella (MMR) vaccine instead of MR vaccine, because it considers the burden of mumps is also significant, and the same logistics can take care of three instead of two vaccine preventable diseases (VPDs) [2]. The main reasons why GoI has not considered mumps for inclusion in UIP are: the disease is not considered a serious public health issue, lack of published data on the community burden of mumps, and lastly the higher cost of the MMR vaccine in comparison to MR vaccine [3]. The Academy believes that the burden of mumps is significant and merits control strategies at national level. However, lack of published studies hampers efforts to launch nation-wide preventive strategies. Use of MR vaccine in place of MMR vaccine is considered a 'missed opportunity' to target a significant VPD that also has significant teratogenic effects on the developing fetus. The main objective of this paper is to provide a review of community burden of mumps in India along with discussion on vaccination strategies to control the mumps disease.

BURDEN OF MUMPS DISEASE

Background

Mumps remains a prevalent viral disease with more than 90% cases going unreported. The 'classic' mumps illness is characterized by fever and swelling of the parotid gland(s) that affects children and adolescents, and may lead to serious complications. However, only half of infected subjects develop classical disease, and about 30% of the infections are asymptomatic; a significant

number of infections are atypical (without parotitis) [4]. Acute meningoencephalitis, the commonest serious complication seen in children and adolescents, occurs in 1-10% of patients with mumps parotitis, but only 40-50% of patients with mumps meningoencephalitis, confirmed by serology or virus isolation, have parotitis [5].

The other complications of mumps include pancreatitis, transverse myelitis, orchitis, oophoritis, deafness, facial palsy, ascending polyradiculitis, cerebellar ataxia, and mastitis [4,5]. The infection in pregnant women may result in spontaneous abortions during first trimester and aqueductal stenosis manifesting as congenital hydrocephalous in the newborn [2,4].

Global burden

The burden of mumps remains high (100-1000 cases/ 100000 population) in countries which do not offer routine mumps vaccination, with epidemic peaks every 2-5 years [4,6]. Of late, there has been resurgence of mumps even in countries using mumps vaccine in their national immunization programs (NIPs) [7-9]. According to a recent study by Global Infectious Disease and Epidemiology Online Network (GIDEON) which covers 12,102 outbreaks of 215 infectious diseases involving 44 million cases in 219 countries between 1980 and 2013, mumps has emerged a notable 'newcomer' amongst human-specific infections in the last decade [10]. According to WHO, Southeast Asia Region (SEAR) reported 36,352 cases of mumps in 2013 [11], but there is no information on the cases reported from India.

Burden of mumps in India

Mumps, despite being a widely prevalent disease all over the country, is considered as an insignificant public health problem in India, mainly because of poor documentation of clinical cases and lack of published studies. There is no nationally representative data on incidence of the disease. In fact, no attempt is being made so far to collect and review even the available data through various avenues. This review is an attempt to fill this void.

Search strategy: A thorough search using appropriate terms was conducted through PubMed, Google Scholar, Google, EMBASE, and other search engines. References cited in review articles and case reports were also reviewed. Virus isolation and genotyping studies on mumps virus from institutes like National Institute of Virology, Pune and Postgraduate Institute of Medical and Educational Research, Chandigarh were also studied. Studies citing virological investigations of acute encephalitis syndrome (AES) and acute febrile encephalopathy or viral meningoencephalitis were also included. VPD surveillance portals like IDSurv and IDSP were searched to collect data on sporadic cases and outbreaks of mumps. Google books on mumps and newspaper articles publishing outbreaks of mumps disease were also scanned.

Serological susceptibility: Three studies, two from Northern [12,13] and one from Southern India [14] studied serological status of young children and adolescents against mumps. In first study, almost 60% of children were found to be susceptible to the mumps virus [12]. In the other study by the same researchers, around 80% and 70% mumps susceptibility rates in children aged 9-10 months and 15-18 months, respectively were noted [13]. A study among from 790 students from Manipal reported 32% susceptibility to mumps [14].

Outbreak investigations and virological studies of AES cases: A total of 14 publications in various journals, and two media reports on mumps outbreak were retrieved. ***Table* I** presents a summary of investigations of the mumps outbreaks in different regions along with some studies that had identified mumps virus as an etiological agent of AES [15-30]. Few studies from some premiere institutes of the country have attempted isolating circulating genotypes of mumps virus in these outbreaks [21,22,24]. The outbreaks are reported from almost all the regions of the country (***Fig.* 1**) and number of cases ranged from 7 to 301(***Table* I**). Both 'classic' mumps cases with parotitis and mumps meningoencephalitis are described. Among the studies conducted on hospitalized individuals with AES and acute febrile encephalopathy, mumps contributed 2.3% to 14.6% of all investigated AES or viral encephalitis cases [27-30] (***Table* I**).

The study of different circulating genotypes of mumps virus in the community is a useful tool for identifying transmission pathways and describing mumps epidemiology. There are 12 mumps genotypes (A–N), and only one distinct serotype of mumps virus [31]. The studies conducted on genotyping of circulating mumps virus found genotypes G (subtype G2) and C prevalent in the studied outbreaks [21,22,24]. In one report, two different genotypes, G and C were described to be simultaneously circulating in two nearby villages of the same district [22].

Infectious Disease Surveillance (IDSurv) portal of IAP: Mumps is one of the ten infectious diseases included in the web-based infectious disease surveillance system (IDSurv) launched by IAP [32]. Passive reporting of the cases is done by IAP-member pediatricians based in different cities and towns of the country. ***Table* II** presents key features of reported cases during two different periods. The data shows that majority of the reported mumps cases are above 5 year of age, and are

TABLE I SUMMARY OF PUBLISHED STUDIES EVALUATING OUTBREAKS OF MUMPS AND ACUTE ENCEPHALITIS SYNDROME (AES) IN INDIA

Study [*Ref.*]	*Time period*	*Place*	*Clinical profile*	*Vaccination status*
Studies reporting on Mumps outbreak				
Geeta, *et al*. [15]	1999- 2003	Calicut, Kerala	301 children admitted with mumps, 58% in 5-9 year old.	Not mentioned
John TJ [16]	Jan-Mar 2002	Thiruvananthapuram, Kerala	179 cases; 98 were in age group 5-9	Not mentioned
Ghatage , *et al*.[17]	Dec2005-2006	Sangli, Maharashtra	10 cases with mumps meningo-encephalitis, age group 3-13 yr	9/10 received single dose of MMR at 15-18 months age
Vandana, *et al*. [18]	2005	Manipal, Karnataka	8 cases of atypical mumps, 50% between 5-13 yr of age	All unimmunized
Arshad , *et al*. [19]	2007-2011	Pulwama, South Kashmir, J&K	55 cases of parotitis in age group of 4-12 yrs	All unimmunized
Saha, *et al*.[20]	2009	Kolkata, WB	104 cases, attack rate 4.7%, the highest and lowest being in 6-10 years (11.7%) and above 15 years (0.9%), respectively	Not mentioned
*Malayan *et al*. [21]	2011- 2012	Chennai, TN	56 patients, 39 from pediatric age group (<18 yrs)	30 out of 56 were vaccinated; status of 26 patients unknown
*Vaidya, *et al*. [22]	March 2012	Osmanabad, Maharashtra	village: 91 mumps cases, Aspinga 74% in 5-14 yrs. Pimpla village: 51 cases, 84.3% in 5-14 yrs.	All unimmunized
Samuel , *et al*. [23]	February 2012	Ludhiana, Punjab	7 cases of mumps among 200 dental students of dentistry with average age was 22.57 years (22-24 years)	All immunized
*Mishra, *et al*. [24]	August 2011	Fatehgarh Sahib, Punjab	20 school children with mean age 9.7 yrs mostly females (91%),	All unimmunized
**Amrita KR [25]	January 2012	Ernakulam district, Kerala	95 cases among school children	Not mentioned
*Ghai A [26]	Aug-Sept 2013	Mohali, Punjab	23 of the 49 children at Government Elementary School	Not mentioned
Virological studies of AES cases				
Kumar, *et al*. [27]	1985 -1988	Lucknow, UP	5 (2.3%) cases of mumps encephalo-pathy out of 215 AES cases	Not mentioned
Karmarkar, *et al*. [28]	Feb- 2004-2005	New Delhi	6 (14.6%) cases of mumps meningo-encephalitis out of 41 cases of viral encephalitis	Not mentioned
Beig, *et al*. [29]	2004- 2006	Aligarh, UP	9 (10.5%) of meningo-encephalitis out of 87 cases of acute encephalitis	Not mentioned
Jain, *et al*. [30]	January 2011 to December 2012	Lucknow, UP	138 (8.7%) of meningo-encephalitis out of total 1578 cases of AES >1 yr old, 13 (9.4%) died and 7 left with neuro-logical disability.	Not mentioned

***Genotype studies; ****Media reports; AES: Acute encephalitis syndrome.*

unimmunized. The reported mumps cases reflect significant burden of the disease in the community; they either exceed or equal the overall measles cases reported during these time periods. The cases reported through this site represent both sporadic and outbreak cases occurring throughout the year. However, the reported cases represent only a 'tip of the iceberg' since out of 23,000 members, only less than 10% are reporting to this site. Further, the number of the members regularly reporting is very less.

Integrated Disease Surveillance Program (IDSP): This program, a surveillance system of the Government of

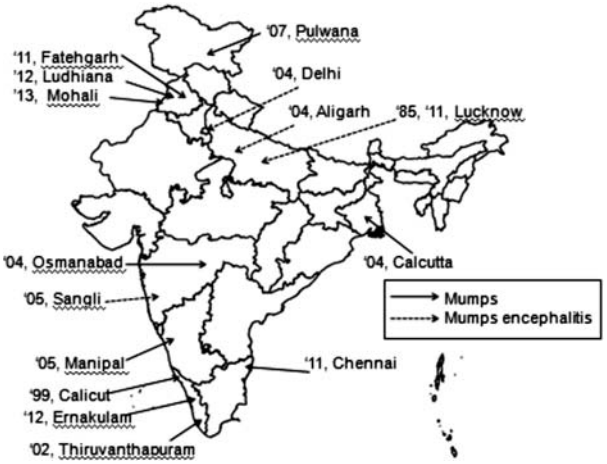

FIG. 1 *Published studies evaluating outbreaks of mumps and mumps menigoencephalitis amongst acute encephalitis syndrome (AES) in India [15-30]. (Values represent year and place).*

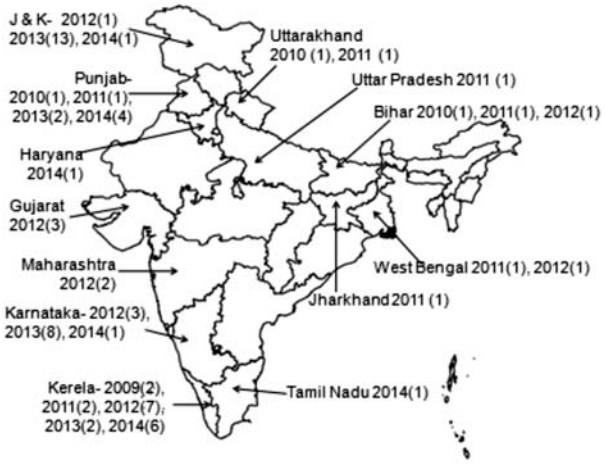

FIG. 2 *Integrated Disease Surveillance Program (IDSP) investigated outbreaks of mumps in India, 2009-2014 [33]. (Year, number of outbreaks in respective year).*

India to detect and respond to disease outbreaks, collects data on epidemic-prone diseases, including mumps, on weekly basis from its reporting units such as health sub-centers, primary health centers, community health centers, hospitals and medical colleges [33]. It has reported and investigated 72 outbreaks of mumps during the period of September 2009 to November 2014 [33]. The outbreaks are reported throughout the year, and from all regions of the country (***Fig.* 2**). A total of 1564 cases were reported in this period. Kerala, Jammu and Kashmir, Punjab, and Karnataka had maximum number of cases (***Fig.* 3**). Some of these outbreaks were also investigated by other researchers and published in journals [19,22,24].

Conclusions: The data presented highlight the fact that mumps contributes significantly to morbidity in children in India. The reported cases of mumps may actually be gross underestimate of actual burden of mumps in the community, as majority are subclinical infections which may go unnoticed and unreported. Also, most of the symptomatic children may not seek health care, and go to faith healers for advice [34], and hence are missed. The above review reflects the burden of only 'classic' mumps and mumps meningoencephalitis, but there is no data on other complications of the disease, including its teratogenic effects.

Vaccination Strategies to Control Mumps

The above review indicates that mumps poses a significant disease burden in India. Both sporadic cases and cyclic outbreaks are regularly reported from all the regions of the country. Safe and efficacious mumps vaccines are available in the country with an indigenous large-scale producer. Near-elimination of mumps could be achieved by adopting and maintaining good coverage of a two-dose strategy in National immunization program [4]. Globally, the incidence of mumps has reduced drastically in countries that have employed mumps vaccination in their immunization schedules. Finland completely eliminated natural transmission of mumps in 1996 [35]. At the end of 2007, 114 countries were administering mumps vaccine, compared with 104 countries at the end of 2002. However, as of 2012, 120 (62%) countries have adopted routine mumps vaccination in their NIPs [36]. The reduction in mumps incidence varies from 88% to 97% in countries adopting single or two doses of vaccine, respectively [6]. A recent

TABLE II IDSURV DATA ON SPORADIC AND OUTBREAK CASES OF MUMPS [32]

Time period	*Total number of cases*	*Profile of cases*	*Vaccination status*	*Severity*
Jan 16, 2011 - Dec 16, 2013	808(7.6% of all the reported VPDs)	477 (59.1%) above 5 yr of age; 221 (27.4%) between 3-5 yr; 109 (13.5%) below 3 yr	84% unimmunized	6% hospitalized (with complications)
Nov 21, 2014 - Feb 20, 2015	244 (9.0 % of all the reported VPDs)	143 (58.6%) above 5 yr of age; 75 (30.7%) between 3-5 yr; 26 (10.7%) below 3 yr	61% unimmunized	All outpatient cases without any mortality

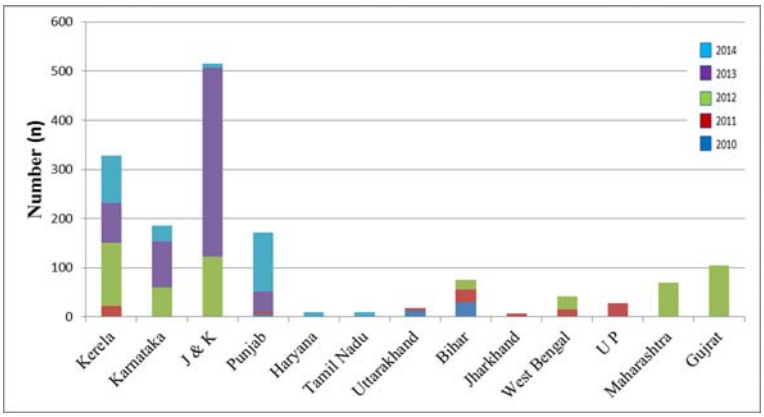

FIG. 3 *Year- and state-wise representation of number of cases investigated by Integrated Disease Surveillance Program (IDSP) in different mumps outbreaks in India, 2010-2014 [33]. (See color image at website)*

meta-analysis in China found the overall vaccine effectiveness for mumps-containing vaccine (either one dose or two doses) to be 85% (95% CI 76%-90%) from cohort studies and 88% (95% CI 82%-92%) from case-control studies [37]. According to the WHO, vaccination strategies targeting mumps control should be closely integrated with existing measles elimination and rubella control [4]. A high coverage with the mumps vaccine is required to offset any undesirable epidemiological shift of the disease to older age groups with resultant higher rates of serious disease and complications.

Efficacy and effectiveness of mumps vaccines: At least 13 different strains of mumps virus, including Jeryl-Lynn, Leningrad-3, Leningrad-Zagreb and Urabe Am9 are used for the development of live attenuated mumps vaccines around the world. Though their protective efficacy and effectiveness vary to some extent, but overall they can protect about 80% of recipients [38]. Most of the strains result in ≥90% seroconversion and/or short-term protective efficacy after administration of single dose, but the long term effectiveness of one dose is reported to be much lower (60-90%) [4]. The Jeryl–Lynn (Priorix by GSK) and Leningrad–Zagreb (Tresivac by Serum Institute of India) strains are used in the production of mumps vaccines available in India. According to a recent Cochrane review analyzing data from 64 MMR vaccine studies, the effectiveness of one dose of MMR in preventing clinical mumps was found to be 69%-81% for Jeryl- Lynn-containing vaccines and 70%-75% for Urabe AM9-containing vaccines [39]. The effectiveness of other mumps vaccine strains is difficult to determine, owing to more limited use and fewer studies. However, few older studies evaluated effectiveness of Leningrad-3 and Leningrad–Zagreb strains in Russia and Yugoslavia, respectively, reported comparable rates of around 91-99% for the former and 97-100% for the latter [38].

There is no effectiveness data available from India since mumps is not part of NIP and only few states and Union Territories are providing mumps vaccine in form of MMR vaccine [2]. Though the MMR vaccine is offered by private sector, the coverage and field-efficacy data are not available. Yadav, *et al*. [13] reported high mumps seropositivity rates (96-100%) with use of single dose of MMR vaccine in Delhi children. In another Indian study conducted amongst 1-10 year old children in Pune, a single dose of MMR (with Leningrad-Zagreb mumps virus strain) was able to maintain mumps-specific IgG (seropositivity rate) in 95% after 6 years [40]. On the other hand, in a study from Chennai, mumps component in the MMR vaccine was found to have low seropositivity; only 15% of vaccinees with a single dose of MMR tested positive for mumps-specific IgG [41].

Safety of mumps vaccines: Overall, all the available mumps strains are considered safe; only mild adverse reactions are noted. Few cases of mild, self-limiting aseptic meningitis have been reported following the use of the Urabe Am9, Leningrad–Zagreb, Hoshino, Torii and Miyahara strains [4]. The highest risk of association with aseptic meningitis was observed within the 3rd week after immunization with Urabe-strain (RR14.3; 95% CI 7.9, 25.7), and within the 3rd (RR 22.5; 95% CI 11.8, 42.9) or 5th (RR 15.6; 95% CI 10.3, 24.2) week after immunization with the Leningrad-Zagreb strain [38]. Very low rates of aseptic meningitis cases have been associated with the use of the Jeryl–Lynn and RIT4385 strains [4]. However, due to the variability of the methods used in the different studies, no clear conclusion can be drawn on the differences in risk for aseptic meningitis among various strains, and in 2006 the WHO Global Advisory Committee on Vaccine Safety (GACVS) concluded that in terms of safety, all mumps vaccine preparations are acceptable for use in immunization programmes [4].

TABLE III SUMMARY OF STUDIES EVALUATING OUTBREAKS OF MUMPS GLOBALLY, 2000-2012.

Researcher	*Place, Year*	*Clinical profile*	*Vaccination status*
Sane, *et al*. [48]	Netherlands, 2009-2012	Annual incidence per 100,000- 4.5 in 13-17-year age group, 21.4 in 18-25-year age group	All vaccinated. 67.7% received two doses
Walker, *et al*. [49]	Scotland, 2010-2011	119 cases. Median age 20 yr	44.5% received single dose, 27.7% received two doses
Nelson, *et al*. [50]	Guam, US, 2010	505 cases. School age children	93% received two doses
Bangor-Jones, *et al*. [51]	Western Australia, 2007-2008	183 cases. 54% less than 20 yr	67% received single dose, 52% two doses
Gonzalez, *et al*. [52]	Spain, 2008	116 cases over 7 months. 68.9% school age	Vaccine coverage >90% with two dose effectiveness as 99%
Dayan, *et al*. [53]	United States, 2006	6584 mumps cases- 83% college students	63% vaccinated: 10% single and 53% two doses
Cohen, *et al*. [54]	England, 2004	312 cases. Age 2-12 yr	Vaccine effectiveness 88% for single dose and 96% for two doses
Hindeyeh, *et al*. [55]	Palestine, 2004-2005	3871 mumps cases (parotitis). 76.3% in 5-15 yr age group	Vaccination coverage >85%.
Reaney, *et al*. [56]	Ireland, 2000	332 cases positive, 95% in 9-19 yr age	55% had received one dose, 1% two doses

Recent resurgence of mumps among vaccinated individuals: A resurgence of mumps after a single vaccine dose has been seen globally [42,43], following which a second dose of mumps vaccine was introduced at 4-5 years [44,45], preferably in combination with measles and rubella vaccines. The effectiveness of two doses is estimated to be between 69% and 95% [39,46,47]. However, despite reasonable vaccine effectiveness, outbreaks of mumps have been reported globally, mainly in older children (***Table* III**) [48-56].

Causes of resurgence and waning of immunity: Primary vaccine failure is unlikely to be a cause of these outbreaks in vaccinated individuals. Low coverage and use of single dose of mumps may have been contributing factors in some outbreaks, but outbreaks are reported even amongst vaccinees with two doses and with good coverage. Hence, there is definite waning of protective immunity following either single or two doses of mumps vaccination. However, waning after two doses is not as dramatic as after single dose [38].

Waning of immunity following large-scale mumps vaccination in few industrialized countries can be attributed to lack of natural boosting due to highly successful vaccination programs. With near elimination of mumps in several countries that have achieved high levels of two-dose vaccine coverage, opportunities for boosting are limited. Another reason could be poor B-cell memory responses induced by mumps strain present in MMR vaccine. In a study, it was shown that measles virus in MMR vaccine induced 3-fold higher levels of virus-specific antibody-secreting cells than mumps virus [57]. Other possible explanations could be high population density and contact rates in colleges and universities, as well as antigenic differences between the vaccine strain and the wild-type strain, possibly permitting immune escape [38,41]. To counteract occurrence of outbreaks amongst highly vaccinated individuals, a third dose of mumps vaccine is being contemplated, though the current evidence for its use is still lacking [58]. Further, adding third dose may not be cost-effective as far as mumps control is concerned.

Timing and scheduling of mumps vaccine: IAP has recently revised its recommendations on MMR vaccination with first dose at 9 months in place of stand-alone measles vaccine, and second at 15 months of age [59]. The timing of the first dose was initially advocated beyond 12 months due to possible interference by maternal antibodies. However, as per Indian data, a significant part of the infant population remains susceptible to mumps [13]. Wang, *et al*. [60] found 60-63% seroprevalence rates in Chinese infants. The seropositivity increased to 92% at 2-4 year after vaccination, but declined again at 5-9 years [60]. Furthermore, the new recommendations also conform to the SAGE guidelines [61], which include (*i*) for countries introducing or using rubella vaccine, it must be given in combination with the first dose of measles containing vaccine (MCV) (as MR or MMR); (*ii*) in countries using rubella containing vaccine (RCV) and a two-dose schedule of MCV, both doses should be of the same

formulation [61]. There are many studies, both from India and from other countries, demonstrating efficacy and safety of MMR vaccine given at 9 month of age and comparable seroconversion rates were seen at 9 months and 12-15 months across different studies, implying minimum risk of interference of maternal antibodies [13, 62-67]. Redd, *et al*. [68] reported that response to mumps strain varied little by age of the child or birth year of the child's mother when immune responses to MMR vaccine given at 9, 12 or 15 months were compared [68]. Among 240 Indian children who received MMR at 9-10 months or 15-18 months of age, seroconversion of mumps was comparable in both groups (100% and 96%, respectively) [13]. Additionally, lowering the age of first dose would have better outreach [2]. Therefore administering the first dose before 12 months may be a prudent choice.

Cost-effectiveness analysis: Data from industrialized countries have proved the cost-effectiveness of mumps when translated to reduced school- and work-absenteeism and reduction in associated long term complications and costs of associated hospitalization. As per an economic analysis of mumps vaccination in US, the average cost per case of mumps prevented was $3614, which was greater than costs incurred with prevention of single measles case ($2207). The total annual costs averted by MMR vaccination was $ 7,878,378,382 with a benefit-to- cost ratio of 0.49 [69]. Similarly, the additional benefit of routine mumps vaccination exceeded additional costs of vaccine in a cost-effectiveness analysis in Japan [70]. There is no detailed cost-effectiveness analysis available for India.

CONCLUSIONS

IAP Committee on Immunization reiterates its firm stand that mumps is a serious public health concern in India and the disease should be targeted for control [2]. Control of mumps can be linked to existing measles elimination and rubella control strategies. The Committee believes that the move would not entail too much of extra economic burden to the government considering the fact that mumps vaccination can piggy-back on the existing measles and rubella vaccination without employing extra logistics. Realizing the significant community-burden of the disease in the community, the move should prove to be a cost-effective exercise. It is high time that the government realizes the current burden of mumps and need of mass vaccination for its prevention and control. With the availability of a safe, effective, indigenous and cost-effective vaccine, mumps should be immediately included in the UIP as MMR vaccine in place of MR vaccine. Further, there is an urgent need of initiating surveillance of clinical cases of mumps all over the country and it should be declared as a 'notifiable' disease in India. The immunization coverage should be monitored, all outbreaks should be investigated, and routine mumps surveillance should be set up to evaluate the impact of vaccination.

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ANNEXURE

Writing committee: Vipin M Vashishtha, Sangeeta Yadav*, Aashima Dabas*, CP Bansal, Rohit C Agarwal, Vijay N Yewale, Naveen Thacker, Sachindanand Kamath, Pravin J Mehta.

IAP Advisory Committee on Vaccines & Immunization Practices, 2013-14: ***Office-bearers:*** CP Bansal (Chairperson), Rohit Agarwal (Co-chairperson), Vijay Yewale (Co-chairperson), Vipin M Vashishtha (Convener), Pravin J Mehta (IAP Coordinator), ***Members:*** Shashi Vani, Anuradha Bose, Ajay Kalra, AK Patwari, Surjit Singh; ***Consultants:*** Naveen Thacker, NK Arora, Rajesh Kumar, HPS Sachdev, VG Ramchandran, Ajay Gambhir; ***Rapporteur:*** Panna Choudhury.

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** Invited experts (outside of IAP ACVIP)*

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