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Early disappearance of maternal anti-measles, mumps, rubella, and varicella antibodies in Indian infants

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ABSTRACT

Background: Immunization of children with vaccines against Measles, Mumps, Rubella, and Varicella (MMRV) is practiced globally with varied recommendations. In India, measles vaccine is administered alone or as MMR at 9 months age. Varicella vaccine is not routinely used. Immunization age is a function of disappearance of maternal antibodies and natural exposure of the children to the pathogens. In view of the measles-WHO-initiative, we aimed to assess if the current immunization age for measles is still valid. In addition, the kinetics of IgG and IgM antibodies against rubella, mumps and varicella viruses was also examined.

Methods: This cross-sectional study was conducted at a tertiary care hospital in Pune, India. A total of 600 children, 150 each in 6-month/9-month (no vaccination) and 12-month/15-month (minimum 4 weeks post-measles-vaccine) cohorts were included. History of these infections and birth status (term/preterm) was recorded. All serum samples were screened for IgG-anti-MMRV-antibodies while IgG-positives were tested for specific IgM antibodies (ELISA).

Results: At 6-months, the prevalence of MMRV antibodies was 4.7%, 2.7%, 10.7%, 5.3% respectively depicting disappearance of maternal antibodies in majority of the children. Birth status did not influence antibody positivity. Despite vaccination at ~9-months, >25% children were still susceptible to measles virus at the age of 12/15-months. The ratio of clinical:subclinical infections was 4:10 (measles) and 12:1 (varicella). All the mumps/rubella IgM positives (1 and 2 respectively) represented subclinical infections.

Conclusion: Demonstration of early disappearance of maternal antibodies against MMRV viruses leading to the risk of these infections at an early age emphasize need for early immunization of Indian children. Suboptimal response to measles vaccine needs to be seriously addressed especially in view of the WHO's initiative for measles eradication.

1. Introduction

Measles, mumps, rubella, and varicella (MMRV) are vaccine-preventable viral diseases causing significant morbidity and mortality in children and are associated with potentially life-threatening complications [1]. Childhood immunization remains the best global option to save our children from dreaded diseases. It is estimated that immunization has averted 2–3 million global deaths annually [2,3]. Recently, the World Health Organization (WHO) ranked India as one of the top ten countries with highest incidence of measles and rubella [4]. An estimated 56,302 (one year, 2017) and 1231 (two years, 2016–18) cases of measles and rubella respectively were reported from India. Based on literature survey, Indian Academy of Pediatrics (IAP) concluded that mumps poses a significant disease burden in India [5]. The global annual disease burden of varicella is estimated to be 140 million cases, 4·2 million severe complications, and 4200 deaths as per the WHO position paper [6]. Although the exact disease burden in India is not known, varicella presents a significant threat from a public health perspective. Frequent varicella outbreaks are reported from India as vaccination is not part of the national immunization policy [7].

During the first year of life, maternal antibodies transferred during pregnancy provide primary protection against infections. The

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half-life of transferred IgG is 35–40 days, and hence time-dependent decay depends on antibody status of the mother. While determining suitable primary vaccination age, the window between disappearance of maternal antibodies and exposure to infection is kept at minimum, depending on the antibody positivity rates in mothers and children. Immature immune system is an important concern. The first measles vaccine is given at 9-months of age as per the Extended Program of Immunization (EPI), India and second dose is recommended at 16–24 months of age. IAP recommends three doses of MMR vaccine, at 9-months, 15–18 months, and between 4 and 6 years of age [8], while varicella vaccine is recommended as two-dose schedule starting at 15-months of age.

The appropriate age for immunization with different vaccines is a function of epidemiology of the infection. The presence and titers of pathogen-specific maternal antibodies, interference of maternal antibodies in vaccine-induced immune response and degree of circulation of the infectious agent are key determinants influencing decisions for determining appropriate age. To ensure continued suitability of vaccination age, antibody profiles of mothers and infants need to be determined from time to time. A few earlier studies examined MMR antibody seropositivity in Indian infants [9–13], with fewer reporting varicella antibody prevalence [14]. However, in view of the Measles-initiative of WHO, it becomes imperative to assess if current childhood immunization strategies for measles or MMR/MMRV vaccination need suitable modifications. To understand Indian scenario, we conducted a study at Pune, a city from western India with an estimated population of 6,275,748 in 2018 [15].

2. Materials and methods

2.1. Participant enrollment

This cross-sectional study was conducted at Bharati Hospital and Research Center, a tertiary care hospital affiliated with Bharati Vidyapeeth (Deemed To Be University) Medical College, Pune, India and was approved by the "Institutional Ethics Committee". The study population included children aged 6, 9, 12 and 15-months (±1 month for all ages). These included children aged (1) 9-months without any prior measles or measles-mumps-rubella (MMR) vaccination, (2) 15-months without prior varicella vaccination, and (3) 12 and 15-months who received measles vaccine at least 4-weeks prior to enrollment. A total of 600 participants were enrolled in the four age cohorts: 150 each in 6-month, 9-month, 12-month, and 15-month. Written informed consent was obtained from parents before performing any study-related procedures. Demographic and baseline characteristics of the study population were noted.

Participants who received immunoglobulins within 6-months or immunosuppressants/immune-modifying drugs since birth were excluded. Known or suspected congenital or acquired immunodeficiency and symptoms of acute illness at the time of enrollment were other reasons for exclusion. Enrollment was postponed for participants with an axillary temperature ≥38 °C/100.4 °F. Children in care (institutions or orphanages) were also excluded. For determining prevalence of mumps and rubella antibodies at 12- and 15-months age, 291/300 children were considered as 9 children had received MMR vaccine prior to enrollment.

2.2. Detection of MMRV infections

History of (H/O) clinical disease was elicited from mothers of the children by direct questioning. For ~75% of children, detailed clinical records since birth were available and examined for required information. In the absence of vaccination against Mumps, Rubella and Varicella (except 9 receiving MMR vaccine), and measles till the age of 9 months, detection of virus-specific IgM was considered as an indicator of recent exposure to the corresponding virus. The samples collected at the age of 12 and 15-months were obtained ~12 and 24-weeks post-measles immunization respectively. Previously, two different studies detected IgM antibodies in 10% and 0% children investigated at 12–15 weeks post-immunization with live attenuated measles vaccine [16]. Taken together, IgM positivity at 15-months was attributed to subclinical infection, while that at 12-months could have been due to vaccine or natural exposure to the virus.

2.3. Laboratory investigations

Blood samples were collected from all participants. Serum was separated from the samples and stored at −20 °C till testing. All serum samples were screened and tested for IgG antibodies against measles, mumps, rubella, and varicella using ELISA (Euroimmun, Germany). IgG antibody positives were quantitated to determine the levels of seroprotection. Seroprotection levels were defined as:

- Antibody titers ≥150 mIU/ml for measles
- Antibody titers ≥231 U/ml for mumps
- Antibody titers ≥4 IU/ml for rubella
- Antibody titers ≥50 mIU/ml for varicella

For measles, all IgG positive samples till the age of 9-months and a representative number from 12-months (n = 88) and 15-months (n = 105) cohort were tested for IgM antibodies. For MRV, all the IgG-positive samples were tested for IgM.

2.4. Statistical analysis

Quantitative analysis was performed using SPSS software, version 25.0. Mean and standard deviation were calculated for continuous data. Chi-square test was used to compare qualitative data. Yate's correction was applied wherever necessary.

3. Results

3.1. Characteristics of the study population

Table 1 describes the study population. Overall gender distribution in the study was almost equal, with a male to female ratio of 1:0.9. The mean birth weight varied from 2.43 (±0.7) to 2.63 (±0.6) kg. The proportion of preterm infants varied from 13.3% (15-months) to 29.3% (6-months). Overall, mothers of 60 (10%) participants had history of (H/O) measles, and 256 (42.7%) had H/O varicella infection at any point during their lifetime. None of the mothers reported rubella, and mumps was reported only by 5 (0.8%) mothers. About 50% of mothers reported receiving measles vaccine during childhood as part of national immunization program; 39.2% were unaware of their vaccination status. Clinical measles was reported in 9 (1.5%) children: 5 from 12-month cohort and 4 from 15-month cohort, all prior to vaccination. Mumps and rubella were not reported by any participant. H/O varicella was elicited in a total of 12 (2.0%) participants from all four cohorts.

3.2. MMRV seroprevalence with respect to birth status

We first determined MMRV IgG positivity in children born term or preterm (Table 2). No significant difference was noted when antibody positivity against a virus was compared at the same age

Table 1
Characteristics of the study population.

Parameter	Age in months				Total
	Six	Nine	Twelve	Fifteen	
Number	150	150	150	150	600
Term, preterm (% preterm)	106, 44 (29.3)	115, 35 (23.3)	127, 23 (15.3)	130, 20 (13.3)	478, 122 (20.3)
Male: female	–	–	–	–	1:0.9
H/O clinical measles	0	0	5*	4*	9*
H/O clinical mumps	0	0	0	0	0
H/O clinical rubella	0	0	0	0	0
H/O clinical varicella	1	2	4	5	12

* All before measles vaccination.

Table 2
Comparison of IgG-anti-measles, mumps, rubella and varicella antibody prevalence among preterm and term children.*

	Age in months IgG antibody positive/No tested (%; CI_{95}**)			
	Six	Nine	Twelve	Fifteen
Measles, preterm	1/44 (2.3; 0–6.7)	2/35 (5.7; 0–13.4)	19/23 (82.6; 67.1–98.1)	18/20 (90; 76.8–103.1)
Measles, term	6/106 (5.7; 1.3–10.1)	2/115 (1.7; 0–4.1)	92/127 (72.4; 64.7–80.2)	94/130 (72.3; 64.6–80)
Mumps, preterm	2/44 (4.5; 0–10.7)	3/35 (8.6; 0–17.8)	1/23 (4.3; 0–12.7)	2/20 (10; 0–23.1)
Mumps, term	2/106 (1.9; 0–4.5)	9/115 (7.8; 2.9–12.7)	5/121(4.1; 0.6–7.7)	16/127 (12.6; 6.8–18.4)
Rubella, preterm	2/44 (4.5; 0–10.7)	2/35 (5.7; 0–13.4)	0/23 (0)	2/20 (10; 0–23.1)
Rubella, term	14/106 (13.2; 6.8–19.6)	4/115 (3.5; 0.1–6.8)	7/121(5.8; 1.6–9.9)	11/127 (8.7; 3.8–13.5)
Varicella, preterm	1/44 (2.3; 0–6.7)	0/35 (0)	0/23 (0)	1/20 (5; 0–14.5)
Varicella, term	7/106 (6.6; 1.9–11.3)	3/115(2.6; 0–5.5)	6/127 (4.7; 1–8.4)	8/130 (6.1; 2–10.3)

* No significant difference in MMRV antibody positivity when preterm and term infants were compared at the same age for individual viruses.
** CI_{95}: 95% confidence interval.

($p > 0.1$ for all). For further analysis, preterm and term groups in the same age-group were clubbed.

3.3. Kinetics of IgG and IgM antibody positivity

Table 3 depicts age-dependent antibody positivity against different viruses. To differentiate between maternally transferred and infection acquired antibodies, we tested all IgG-positives for IgM antibodies against respective viruses.

3.3.1. Measles

At 6-months, only 4.7% (7/150) infants were IgG-anti-measles positive that was further reduced to 2.7% at 9-months (Table 3). Of the 150 children each in 12 and 15-months age-groups, 291 children had received measles vaccine as part of national immunization program, while 9 children were immunized with MMR vaccine. Subsequently, 74% (12-months, geometric mean titer, GMT = 222.1) and 74.7% (15-months, GMT = 260.2) immunized children were positive for IgG-anti-measles indicative of response to the vaccine. Thus, at the age of 12- and 15-months, >25% children were still susceptible to measles virus.

Next, we tested IgG antibody positive samples for evidence of recent virus exposure i.e. IgM positivity (Table 3). Till 9-months age, none of the IgG-positive children were reactive for IgM-anti-measles. At 12- and 15-months age, we could detect IgM in 12.5% (11/88) and 9.5% (10/105) of the IgG-positives respectively.

Of the 9 children giving H/O clinical measles before vaccination (5 and 4 at the ages of 12- and 15-months respectively, Fig. 1), one was negative for IgG-anti-measles when tested at 12-months age questioning validity of the history. Of the remaining 8 children, two were positive for IgM (both 12-months age), and four (1 at 12-months and 3 at 15-months age) circulated very high titers (2319, 4286, 4140 & >5000) of IgG indicative of exposure to the virus. The IgG titers were low in two children (299.4, 12-months and 301.4, 15-months). In addition, we detected IgM in 21 children (11 and 10 respectively at 12- and 15-months age), without clinical disease. IgM positivity at ~24-weeks post-vaccination in these children at the age of 15-months reflected subclinical measles infection (Fig. 1). Thus, the ratio of clinical:subclinical measles infection in this age group was 4:10 (1:2.5). At 12-months age, IgM induction could have been due to vaccine or natural exposure. In the absence of longitudinal follow-up of the same child, it is not

Table 3
Age-dependent IgG-anti-MMRV positivity and proportion of virus-specific IgM-positives among respective IgG-positive children.

	Age in months antibody positive/no tested (%; CI_{95}*)							
	Six		Nine		Twelve		Fifteen	
	IgG	IgM	IgG	IgM	IgG	IgM	IgG	IgM
Measles	7/150 (4.7; 1.3–8)	0/7	4/150 (2.7; 0.1–5.2)	0/4	111/150 (74.0; 67–81)	11/88 (12.5; 5.6–19.4)	112/150 (74.7; 67.7–81.6)	10/105 (9.5; 3.9–15.1)
Mumps	4/150 (2.7; 0.1–5.2)	0/4	12/150 (8; 3.7–12.3)	1/12 (8.3; 0–24)	6/144 (4.2; 0.9–7.4)	0/6	18/147 (14.2; 6.9–17.5)	0/18
Rubella	16/150 (10.7; 5.7–15.6)	0/16	6/150 (4; 0.9–7.1)	0/6	7/144 (4.9; 1.3–8.3)	1/7 (14.3; 0–40.2)	13/147 (8.8; 4.2–13.4)	1/13 (7.7; 0–22.2)
Varicella	8/150 (5.3; 1.7–8.9)	1/8 (12.5; 0–35.4)	3/150 (2; 0–4.2)	2/3 (66.7; 13.3–120)	6/150 (4; 0.9–7.1)	3/6 (50; 10–90)	9/150 (6; 2.2–9.8)	1/9 (11.1; 0–31.6)

* CI_{95}: 95% confidence interval.

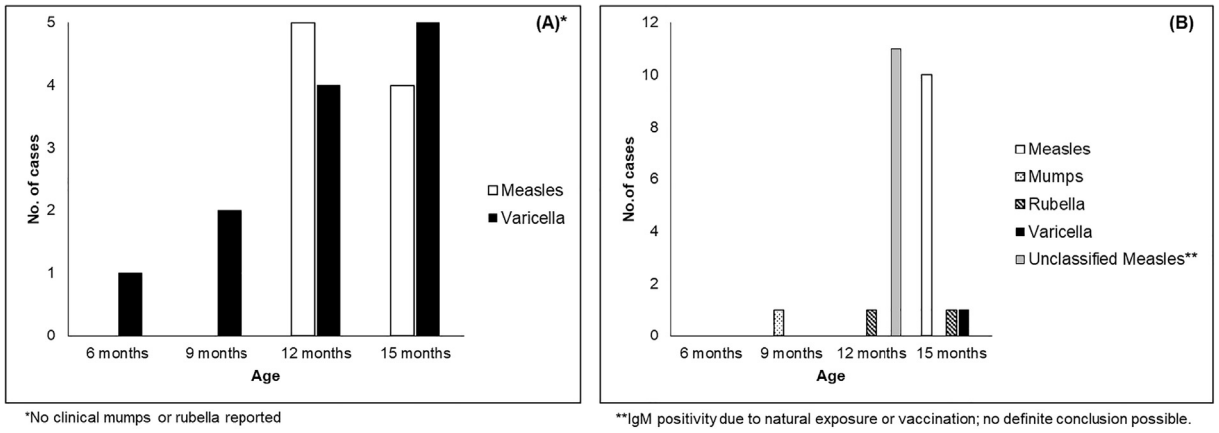

Fig. 1. Prevalence of (A) clinical and (B) subclinical infections of Measles, Mumps, Rubella and Varicella in children aged 6, 9, 12 and 15 months.

possible to differentiate between such antibodies. Importantly, none of the immunized children developed clinical disease. IgM antibodies were not detected in the 23 vaccine non-responders (IgG-negatives) tested.

3.3.2. Mumps and rubella

The lowest IgG antibody positivity for mumps (2.7%, Table 3) and rubella (4%, Table 3) was seen at the age of 6- and 9-months respectively. At the age of 15-months, 14.2% and 8.8% children respectively were positive for IgG-mumps and rubella, suggestive of natural exposure to these viruses. None of these children reported clinical disease (Fig. 1). Appearance of IgM started at 9-months for mumps (1/12 IgG-anti-mumps positives) and at 12-months for rubella (1/7 IgG-anti-rubella positives). None of the mumps or rubella IgM-positives developed clinical disease and remained subclinical (Fig. 1). Of the 9 children receiving MMR vaccine, seroconversion was observed in 8 children each for measles, mumps and rubella.

3.3.3. Varicella

Maternal anti-varicella antibodies were observed in 5.3% (8/150) children at the age of 6-months, reducing to 2% (3/150) at the age of 9-months (Table 3). Natural exposure to this virus was seen as early as 6-months, peak IgM positivity being at 9-months. H/O clinical varicella was recorded in 12/600 (2%) children at 5–14 months age (Fig. 1), and all circulated very high titers of IgG-anti-varicella antibodies (2966–5000). The samples collected at 3–8 weeks (n = 7) following the clinical disease were positive for the IgM-anti-varicella antibodies while those collected after 10->20 weeks were IgM negative (n = 5). None of the IgG-anti-varicella positive children without H/O of clinical varicella were identified as IgM-anti-varicella positive. Subclinical infection was recorded in one child of 15-months age (IgG positivity in the absence of H/O clinical disease) (Fig. 1). Importantly, the sibling of this child had H/O varicella infection few months back.

Overall, at the age of 6-months, majority (>90%) of the infants were seronegative for MMRV antibodies and hence susceptible to these infections, if exposed.

4. Discussion

This study deals with two important issues in relation to childhood immunizations in India: (1) revisiting recommended ages for immunization with MMRV vaccines and, (2) assessment of immune response to measles vaccine, the disease to be eradicated globally.

Assessment of maternal antibodies was based on the antibody status of children at the age of 6-months. Birth status (full term or preterm) did not influence antibody positivity at this age (Table 2). At birth, a significantly less transfer of maternal antibodies was observed in preterm babies in Netherlands [17]. The important finding of this study is that at the age of 6-months, >95% (measles and mumps) and ≥90% (rubella and varicella) children were susceptible and could be infected, if exposed. With such high antibody negativity at the age of 6-months, it is pertinent to note that 9 children gave H/O measles disease, all before vaccination, emphasizing need for an early immunization than the current recommended age. In this connection, recent findings from two tertiary care hospitals are noteworthy. Of the 149 laboratory-confirmed measles cases from south India, 47% were <9-months, 3 (2%) being within 28 days. Importantly, 25% of the eligible cases (>9-months) did not receive vaccine while another 25% developed disease despite immunization [18]. In western India, 45/584 admitted measles cases were <9-months, mortality in <6-months and 6–9 months being 17% and 7% respectively [19].

Of the 21 IgM-positives detected among IgG-reactives, we could attribute subclinical infection to 10 children at the age of 15-months. As IgM positivity at 12-months could have been due to natural exposure to the virus and/or vaccination, a definite conclusion could not be drawn. It is not clear if the subclinical infections were breakthrough infections after vaccination, or vaccine was administered after subclinical infection at an early age. Of note, no clinical disease was recorded in the immunized population. In view of (1) clinical disease before vaccination at 9-months and (2) possibility of transmission of measles virus from children with subclinical infection, it would be desirable to administer first dose of the vaccine at 5–6 months and second dose at 12-months age. Currently, the second dose is recommended at 16–24 months.

Detection and persistence of maternal antibodies is a function of the antibody positivity/titers of the mother at the time of delivery. The exposure of mothers to different pathogens varies with changing trends in epidemiology of a particular agent. A study from Netherlands revealed that transfer of maternal antibodies from vaccinated mothers was much lower than from mothers with natural exposure to the virus [20]. As far as India is concerned, measles vaccine was added in the national immunization program in 1985 and a booster at 16–24 months was recommended in 2010. Though information on the ages of mothers of the infants included in this study is not available, a substantial proportion of women delivering in 2017 may have been vaccinated leading to a rapid decline in anti-measles antibodies at the age of 6-months. Though our study is restricted to one study site, with the enhanced vaccine coverage, one would expect similar situation in other areas as well.

We would like to point out here that seropositivity rates at 9–10 months are similar when a previous multicenter study [14] conducted during 2009–11 (IgG-anti-MMR positivity in <2.7%, and 2.7–8.3% for varicella) is compared with the present study.

The current measles vaccine policy is based on the observation of superior seroconversion when maternal antibodies have waned and hence recommended at 9-months. However, several developing countries have recorded early disappearance of maternal anti-measles antibodies questioning suitability of 9-month age for vaccination [21–24]. Taken together, there is a definite need to review and lower vaccination age with special reference to the WHO initiative. Importantly, early vaccination at the age of 4.5 months was not associated with a higher risk of adverse events such as fever, rash, and convulsions within the first 2 weeks [25].

Measles vaccine was shown to have beneficial protective role in reducing mortality from other childhood infections in Guinea-Bissau [26]. Of note, neonatal vitamin A supplementation negatively influenced the reduction in measles vaccine associated mortality. Subsequently, the vaccine was associated with reduction in all-cause hospitalizations and general morbidity [25,27]. Interestingly, vaccination in the presence of maternal antibodies (two doses, one at 4–6 months and 2nd at 9–12 months) was found to be superior in offering this non-specific protective effect than in the absence of such antibodies [28]. Such studies have not been conducted in India. Nonetheless, it seems that the concern about lower response to measles vaccination in the presence of maternal antibodies can be addressed by the suggested two-dose schedule.

Lower measles antibody response to the vaccine (≈75%) is of concern because the prevalence of positive IgG measles antibodies found in the study in individuals aged 12–15 months was lower than the prevalence of 89–91% associated with herd immunity [29]. Based on the 2008 Indian District Level Health Survey, Awofeso et al documented that only 72.4% infants from the surveyed Indian population received measles vaccine of which only 30% received the vaccine at the age of 9-months [30]. In our cohort, the age at vaccination varied from 9 to 15 months. Comparison of antibody responses of Indian children to early immunization (age 6–8 months) with those vaccinated at recommended age revealed that both schedules led to suboptimal responses in providing protection for the first 5 years, and requirement of second dose was obvious [31]. Overall, special efforts need to be undertaken to ensure adequate coverage and seroconversion following vaccination. This study included 9 children immunized with MMR vaccine, 8 seroconverting to all the three vaccine components. Though the number is small, utility of this vaccine is evident.

For rubella, mumps and varicella, the policy of vaccination with MMR/MMRV vaccines varies in different countries. Short duration of maternal antibody-associated protection was recorded in Netherlands (~3-months) and Belgium (~2-months) [20,22]. In the absence of samples collected from infants <6-months age, we cannot determine the earliest age with maximum disappearance of maternal antibodies. A similar recent study from Turkey observed that 75% (measles), 85.4% (mumps), 76.8% (rubella) and 82.9% (varicella) children were susceptible at the age of 6-months [32]. Overall, there is a definite requirement of earlier protection of infants from these diseases.

Subclinical rubella and mumps infections (IgM positivity) were seen at 9- and 12-months respectively. No clinical disease was recorded. On the contrary, clinical varicella was predominant in the study population (5–14 months age, n = 12) with a single subclinical infection in a sibling of a clinical varicella patient. An inverse relationship of maternal anti-VZV antibodies and varicella disease severity in infants is noteworthy [33]. Virus transmission from usually unrecognized subclinical infections remains a point of concern when eradication of diseases is desired.

Being a cross-sectional design, our study has certain limitations. In the absence of longitudinal follow-up of children, it was not possible to differentiate between measles vaccine and infection-induced IgM antibodies at the age of 12-months and hence diagnosis of subclinical infection remained questionable. Nonetheless, detection of virus-specific IgM and/or high titer IgG antibodies in the presence or absence of clinical disease could distinguish between clinical and subclinical infections with mumps, rubella and varicella viruses at all ages, and measles at 15-months age i.e ~6-months post-immunization.

In conclusion, we demonstrate early disappearance of maternal antibodies against MMRV viruses leading to the risk of these infections at an early age. It would be prudent to undertake a multicenter follow-up study that would help the policy makers to reconsider the current vaccination age. Suboptimal response to measles vaccine needs to be seriously addressed especially in view of the WHO's initiative for measles eradication.

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Conflict of interest

The authors declare no conflict of interest.

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