

Original Article

## Mumps antibody in the Thai population 17 years after the universal measles mumps rubella vaccination program

Varisara Ngaovithunvong<sup>1</sup>, Nasamon Wanlapakorn<sup>1</sup>, Lita Tesapirat<sup>1</sup>, Narrissara Suratannon<sup>2</sup>, Yong Poovorawan<sup>1</sup>

<sup>1</sup> Center of Excellence in Clinical Virology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Pathumwan, Bangkok, Thailand

<sup>2</sup> Division of Allergy and Immunology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Pathumwan, Bangkok, Thailand

### Abstract

**Introduction:** mumps vaccination implementation in the form of MMR – measles, mumps, and rubella) in Thailand for first-grade school students since 1997 and for infants 9–12 months of age since 2010 resulted in a dramatic decline in the incidence of and deaths from mumps. However, there has been a resurgence of mumps outbreaks in Thailand, even in vaccinated populations.

**Methodology:** We aimed to determine the current seroprevalence of IgG antibodies to mumps in those 0–60 years of age from four different geographic areas of Thailand, and compare the results with our previous serosurvey in 2004.

**Results:** Seropositivity rates in children 0–7 years of age increased significantly from 45.8% in 2004 to 72.3% in 2014 after the launch of the MMR vaccine for infants. In the 8–14-year age group who had received one dose of mumps vaccination, the seropositivity rate was 66.7%. In the 15–19-year age group the seropositivity rate was the lowest, at 52.5%.

**Discussion:** Our findings correspond well with the vaccination schedules, as the highest seropositivity rate was found in children between 0 and 7 years of age. For those older than 7, there was a decline in seropositivity rate despite good vaccine coverage and reached its lowest in the 15–19-year age group. This suggested that certain population groups might be incompletely vaccinated, or the humoral immunity provided by vaccination gradually declined over time.

**Conclusions:** We recommend a booster dose of MMR vaccine for Thai adolescents in order to prevent future mumps outbreaks.

**Key words:** mumps; seroprevalence; EPI; Thailand

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### Introduction

Humans are the only hosts for the mumps virus, a non-segmented RNA virus from the *Paramyxoviridae* family. Mumps is usually transmitted through respiratory droplets [1], and the clinical spectrum varies from no symptoms to serious systemic organ involvement [1]. The classic symptoms are swelling of the parotid or salivary glands and fever. More severe symptoms and complications include meningitis, encephalitis, pancreatitis, myocarditis, and orchitis leading to infertility [2,3]. These complications commonly occur in adolescents and adults [4]. Moreover, infected pregnant women can suffer from spontaneous abortion, especially during the first trimester [1].

Countries with national MMR (measles, mumps, and rubella) immunization programs have seen a lower than average annual incidence of mumps, with an 88%–

99% reduction compared to the pre-vaccination era [1]. However, there has been a resurgence of mumps outbreaks in both developed and developing countries, even in vaccinated populations [3,5,6]. In the United States, after a dramatic decrease in mumps cases from > 100 to < 0.1 per 100,000 population as a result of universal vaccination since 1967 [7], several outbreaks with hundreds of patients affected have been reported yearly since 2006 [8]. The main affected populations were adolescents who had received two doses of MMR vaccine over more than 10 years. This raised concerns about a lack of long-term immunity against mumps after the two-dose vaccination [2,5].

In Thailand, in the pre-vaccination era, the incidence of mumps ranged from 20 to 70 cases per 100,000 population per year [9]. The largest mumps outbreak, which occurred in 1995/1996, mainly affected children 5–9 years (280 cases/100,000), 10–14

years (128 cases/100,000), and 0–4 years (126 cases/100,000) of age [10,11]. In 1997, a first dose of mumps vaccine was incorporated into the national immunization program for Thai children in the form of MMR (Urabe strains of mumps virus) [12]. This was a school-based service that offered one dose of MMR vaccine to first-grade students 6–7 years of age. The incidence of mumps decreased dramatically after universal vaccination, but still ranged between 10 and 30 cases per 100,000 population, as shown in Figure 1. In 2010, the national immunization program re-evaluated the vaccination schedules and replaced the measles vaccine with the MMR vaccine (Jeryl-Lynn strains of mumps virus) for Thai infants 9–12 months of age in order to prevent mumps at an early age and for better protection, with two doses of vaccine, as summarized in Figure 1. Based on the Bureau of General Communicable Disease survey, the coverage of mumps vaccination in 6–7-year-old school students regularly surveyed since 2004 was > 90%, and in infants surveyed in 2013 was as high as 98.7%. Although the incidence of mumps in recent years has gradually decreased [9], the majority of the affected population was recent vaccinees – children 5–9, 0–4, and 10–14 years of age. Thailand has now incorporated two doses of mumps vaccine into the Expanded Program of Immunization (EPI), but a booster dose for adolescents who have received only one dose of mumps vaccine since childhood could be another strategy to reduce outbreaks among young adults. Our objectives were to survey the seroprevalence of mumps IgG antibodies among the Thai population in order to guide vaccination strategies, aiming at better protection and prevention of mumps outbreaks in Thailand.

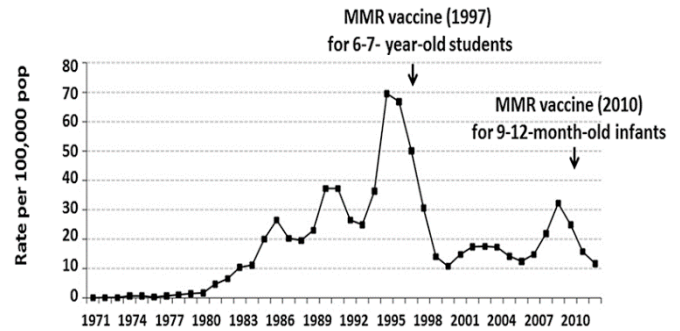
**Methodology**

The research protocol was approved by the institutional review board of the Faculty of Medicine, Chulalongkorn University (IRB No. 154/58), and conducted in accordance with the Declaration of Helsinki. The sera were obtained from the remainder of the project, *The impact of the universal hepatitis B immunization program into newborns as part of EPI* (IRB No. 419/56). Written informed consent and approval for using the sera for further analysis were obtained from study participants or their parents.

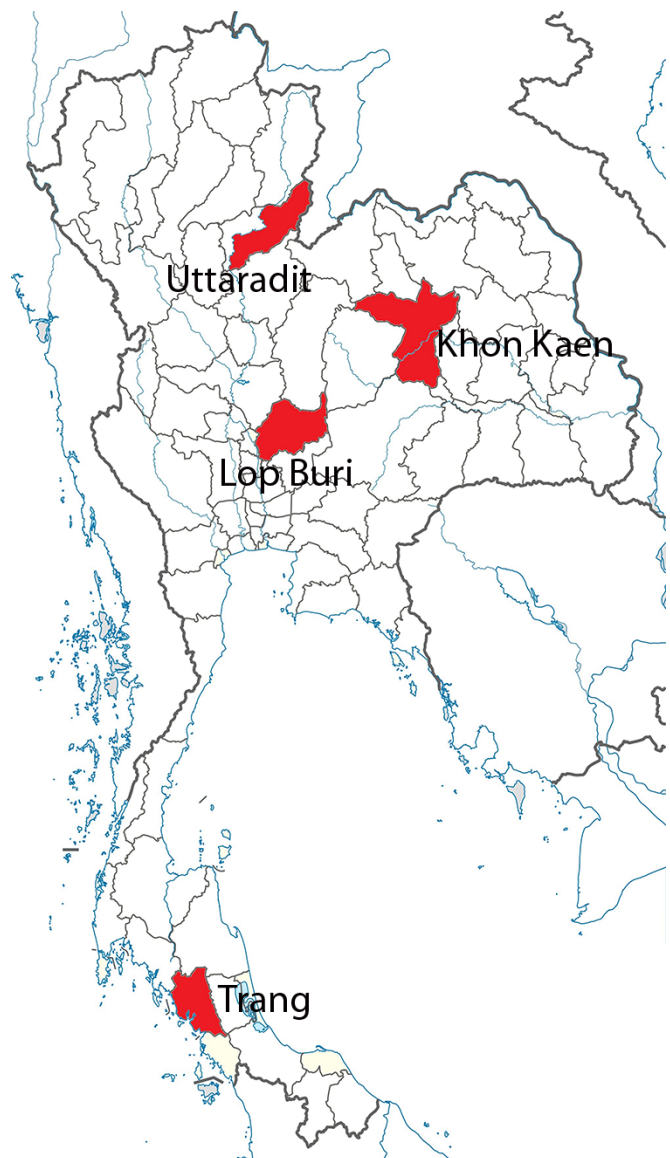
*Study area and population*

Originally, sera with data on age and gender were taken randomly from approximately 6,000 patients residing in seven provinces from different geographic areas of the country for the study on impact of hepatitis

**Figure 1.** Reported cases of mumps per 100,000 population by year, Thailand, 1971-2013



**Figure 2.** Map of Thailand showing provinces from which serum samples were taken.



B immunization. Then, a total of 545 samples were randomly selected for analysis of mumps IgG from four provinces, Uthairat, Lopburi, Khon Kaen, and Trang, to represent the north, central, northeastern, and southern regions of Thailand, respectively (Figure 2). The participants were healthy people with no recent hospitalization for critical illnesses and no clinical signs of HIV infection or other immunodeficiency disorders. They were also not receiving any immunosuppressive therapy at the time of the study.

*Seroprevalence assay*

Serum samples were analyzed for mumps IgG antibody using Ag-coated 96-well microplate enzyme-linked immunosorbent assay (Anti-Mumps Virus ELISA (IgG); Euroimmun, Lübeck, Germany), according to the manufacturer’s instructions. The result was measured in relative units (RU/mL) compared to the recommended cut-off at 20 RU/mL. The lower detection limit of the anti-mumps virus ELISA (IgG) is 0.3 RU/mL. Samples  $\geq 20$  RU/mL were considered seropositive. Titers  $> 100$  RU/mL were considered strongly positive, between 50 and 100 RU/mL moderately positive, and between 20 and 50 RU/mL slightly positive.

*Analysis of data*

The analysis was conducted by dividing the serum samples into eight age groups to illustrate the characteristics of MMR seropositivity rates. Data were analyzed using the value of IgG concentration, expressed as RU/mL. Geometric mean titers (GMTs)

were used and calculated for subjects with detectable antibodies. The proportions of the population that tested positive in accordance with the suggested cut-off value for anti-mumps IgG were calculated in percentages for three categories, including age, gender, and province. Using the Chi-squared test,  $p \leq 0.05$  was considered statistically significant.

**Results**

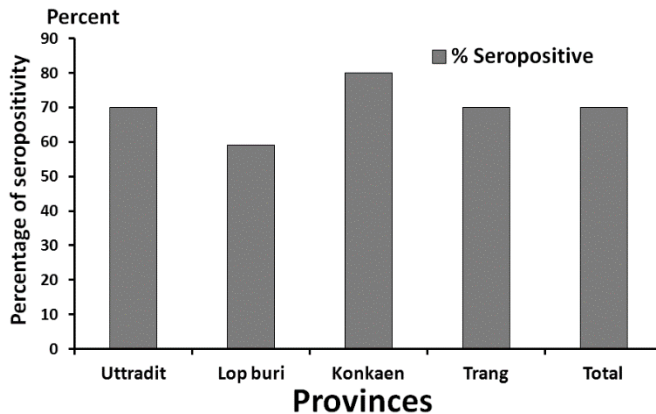
A total of 545 serum samples were tested for the presence of mumps IgG antibodies. Percentage of seropositive samples and GMTs by age group compared with the data reported from 2004 [12] are shown in Table 1. In general, 70% of the population (383/545) was seropositive. The lowest seropositivity rate of 52.5% was found in the 15–19-year age group; the second lowest was in the 8–14-year group, at 66.7%. In other age groups, the seropositivity rate ranged between 69% and 75%. The seropositivity rate was significantly lower in the 2014 survey than in the 2004 survey in every age group except the 0–7-year age group ( $p \leq 0.05$ ). For the nationwide comparison, Khon Kaen province (representing the northeast region) had a seropositivity rate of 81%, Uthairat 71%, Trang 70%, and Lopburi 59%, as shown in Figure 3. The seropositivity rate of Khon Kaen province was comparable to that of Uthairat but was significantly higher than that of Lopburi ( $p < 0.001$ ) and Trang ( $p = 0.046$ ). The seropositivity rate of Uthairat province was also significantly higher than that of Lopburi ( $p = 0.022$ ). There was no statistically significant difference in seropositivity between males and females. The

**Table 1.** Percentage of seropositive samples and GMTs demonstrated by age group in the 2004 [12] and 2014 surveys.

Age (years)	2004 survey			2014 survey		
	Sample size	SPR; n, % (95% CI)	GMT (95% CI) (U/mL)	Sample size	SPR; n, % (95% CI)	GMT (95% CI) (RU/mL)
0–7	179	82, 45.8% (38.4–53.4)	2.9 (1.7–5.1)	101	73, 72.3% (63.6–81.0)	35.3 (26.6–46.8)
8–14	157	141, 89.8% (83.7–93.9)	77.9 (56.6–107.2)	72	48, 66.7%* (55.8–77.6)	35.7 (27.3–46.7)
15–19	101	86, 85.2% (76.4–91.2)	48.6 (28.3–83.7)	40	21, 52.5%* (37.0–68.0)	23.0 (14.9–35.6)
20–24	89	81, 91.0% (82.6–95.8)	87.8 (55.0–140.2)	31	22, 71.0%* (55.0–87.0)	35.3 (25.7–48.5)
25–29	94	81, 86.2% (77.2–92.1)	55.8 (34.1–91.3)	39	28, 71.8%* (57.7–85.9)	52.6 (37.8–73.2)
30–39	98	89, 90.8% (82.8–95.5)	86.3 (55.2–134.7)	83	58, 69.9%* (60.0–79.8)	37.1 (27.8–49.6)
40–49	95	90, 94.7% (87.6–98.0)	120.4 (88.3–164.3)	90	68, 75.6%* (66.7–84.5)	46.8 (37.5–58.3)
50+	98	93, 94.9% (87.9–98.1)	112.4 (80.2–158.2)	89	65, 73.0%* (63.8–82.2)	40.6 (32.3–51.0)
Total	911	743, 81.5% (79.0–84.0)	–	545	383, 70.3% (66.6–74.0)	36.8 (33.0–41)

GMT: geometric mean titer; SPR: seropositivity rate; \* $p \leq 0.05$ ; Chi-squared test was used to compare seropositivity between year 2014 and 2004 [12].

**Figure 3.** Seropositivity rate of mumps IgG in four regions of Thailand, shown in percentages.



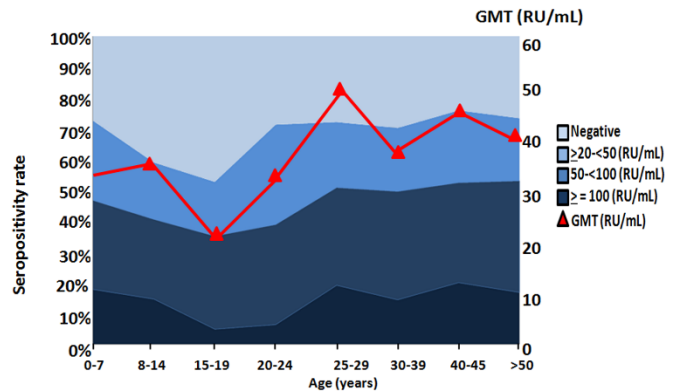
proportions of the population with strongly positive, moderately positive, and mildly positive anti-mumps IgG are shown in Figure 4. The seropositivity rate gradually declined during the first two decades of life and reached its lowest among 15–19-year age group. The GMT also correlated well with the seropositivity rate. In those over 20 years of age, the seropositivity rate was maintained at approximately 70%.

**Discussion**

In this paper, we present a cross-sectional observation of mumps IgG titers 17 years after the national vaccination program, originally targeted at first-grade students between 6 and 7 years of age and 4 years of age after an additional dose of mumps vaccination, was incorporated for infants 9–12 months of age. Our findings correspond well with the vaccination schedules, as the highest seropositivity rate in the present study was found in children between 0 and 7 years of age who had recently received their first dose of mumps vaccine. The seropositivity rate of mumps antibodies in this age group also increased compared to the previous serosurvey in 2004, when no mumps vaccines were given to children under 7 years of age. For those older than 7, this study showed that the seropositivity rate declined despite good vaccine coverage among first-grade students, and reached its lowest in the 15–19-year age group. This suggested that certain population groups might be incompletely vaccinated, and that the humoral immunity provided by vaccination gradually declined over time. The seropositivity rate increased again after 20 years of age, probably as a consequence of natural infection from greater exposure to the surrounding community [13].

In Thailand in 2013, the individuals infected with mumps were children 5–9 years of age (45.74 cases per

**Figure 4.** Seropositivity rate of mumps IgG among all age groups. The red line represented GMTs. The lowest seropositive rate which represented the highest susceptibility was found among the 15-19-year-old age group, followed by 8-14-year-old age group.



100,000 population), followed by children 0–4 years of age (39.51 cases per 100,000 population), and children 10–14 years of age (16.93 cases per 100,000 population) [9]. Based on our 2014 serosurvey, the lowest seropositive rate, which represented the highest susceptibility, was found among the 15–19-year age group, followed by the 8–14-year group. Since the implementation of the MMR vaccine for infants in 2010, we expect that the incidence of mumps in children under 5 years of age will gradually decrease over the next few years. Children over 7 years of age will then be vaccinated with two doses, and this could result in better immunity and protection than with the previous single-dose strategy.

Our study also demonstrated that, in the 0–7-year age group, the seropositivity rate of mumps antibodies increased compared to the previous serosurvey in 2004, when no mumps vaccinations were given to children under 7 years of age. In 2014, the seropositivity rates were < 80% in all age groups, whereas in 2004, most age groups had seropositivity rates > 85%. The GMTs of mumps immunity surveyed in 2014 were also lower than in 2004 for most age groups except the 0–7-year group. A possible reason for this was the different ELISA test and cut-off points used: the previous survey used 12 U/mL as a cut-off for seropositivity, whereas our current study used 20 RU/mL. However, sustainable immunity after 20 years of age in both surveys reflects the antibody persistence after natural infection in the pre-vaccination era.

The effectiveness of one dose of MMR vaccine to mumps was estimated to be as low as 64%, compared with 79% after two doses [14,15]. The benefit of two doses was significantly higher than after one dose [13]. Our study also provides evidence that subjects between



0 and 14 years of age who had received one dose of mumps vaccine had a seropositivity rate of around 66.7%–72.3%. Thailand is now offering two doses of mumps vaccines, and a few years from now, all Thai children will be vaccinated with two doses. Nevertheless, much evidence suggests that there are continual small outbreaks of mumps throughout the world despite two-dose immunization. The reasons for this might be waning of immunity over time, together with a lack of natural boosters in the community [16,17]. A study by LeBaron *et al.* also indicated that 10–15 years after a second booster dose, mumps antibody levels were approximately equivalent to those of the pre-boost titers [16]. Although a recent study suggested that a third dose of vaccine might help prevent outbreaks [17], others have demonstrated that, despite the low level of IgG titers, vaccinated subjects are protected for more than 10–20 years because of the good antigen-specific lymphoproliferative responses [5,13]. Further experiments, such as measuring neutralizing antibody to mumps after the second dose of vaccine, or evaluating the long-term T-cell response, might be useful to define the need for a third or extra dose.

The basic reproductive number ( $R_0$ ) of mumps is 4–7, hence the herd immunity ( $1 - 1/R_0$ ) is approximately 75%–86%. The seropositive rates found among adolescents in our present study were lower than the herd immunity. Reports from several European countries indicate a high incidence of mumps among adolescents and young adults because of environmental factors, such as school or new workplaces [18–20]. This age group was also at higher risk for the complications of mumps, such as orchitis and meningitis. Based on the results of our current study, we advise a booster dose for adolescents to achieve the appropriate level of immunity and prevent an outbreak in this age group.

## Conclusions

We recommend a booster dose of MMR vaccine for Thai adolescents in order to prevent future mumps outbreaks. Seroprevalence surveys of mumps antibodies should also be re-evaluated in the near future when children have been immunized with two doses of MMR, to observe the efficacy of the vaccine.

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**Corresponding author**

Yong Poovorawan  
 Center of Excellence in Clinical Virology  
 Department of Pediatrics, Faculty of Medicine  
 Chulalongkorn University, Bangkok 10330, Thailand  
 Phone: 66 2 256-4909  
 Fax: 66 2 256-4929  
 Email: yong.p@chula.ac.th

**Conflict of interests:** No conflict of interests is declared.