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Original Article

Humoral immunity to mumps in a highly vaccinated population in Taiwan

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Abstract *Background:* A resurgence of mumps was noted recently and outbreaks were increasingly reported in populations with high vaccine coverage. We aimed to evaluate the seroprevalence to mumps in Taiwan, where a two-dose childhood mumps-containing vaccine program, with a high coverage rate, had been implemented for >20 years.
Methods: The anti-mumps IgG was determined in 3552 participants of all ages in Taiwan. The age-specific seropositivity rates were calculated and the sociodemographic variables associated with the seronegative sera were analyzed with a logistic regression method.
Results: The overall seroprevalence to mumps was 71%, with a higher rate in adults ≥19 years old than in the pediatric population <19 years old (80.4% versus 62.0%, $P < 0.0001$). In participants aged 2–20 years, who had been given at least one mumps-containing vaccine, the seropositivity fluctuated across different age subgroups and the lowest rate (36.8%) occurred in the 17–18 years age group. The multivariate analysis identified age within 17–18 years (adjusted odds ratio [aOR] 8.598, 95% confidence interval [CI] 2.990–24.722, $P < 0.0001$), within 19–20 years (aOR 5.076, 95% CI 1.702–15.133, $P = 0.0080$), and being a resident of the suburban area of northern Taiwan (aOR 1.089, 95% CI 0.823–1.414, $P = 0.0008$) as independent factors associated with an increased risk of seronegative sera.

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Conclusion: The seropositivity to mumps was unexpectedly low in highly vaccinated generations, and with a significant geographical discrepancy in Taiwan, which may have been responsible for the sustained reports of mumps cases in Taiwan.

Introduction

Mumps is an acute systemic disease, characterized by the swelling of the parotid gland, accompanied by fever, headache, malaise, and myalgia. This disease is caused by a single-stranded RNA virus belonging to the Paramyxoviridae family. Most patients recover from the disease without any complications. However, some patients with mumps can have complications including aseptic meningitis, encephalitis, orchitis, oophoritis, pancreatitis, deafness, carditis, and nephritis.[1] Owing to the measles-mumps-rubella (MMR) vaccination program, the incidence of mumps declined dramatically in many countries around the world.[1–3] In 1992, the Taiwanese government started routine MMR vaccinations with a one-dose schedule, administered at 15 months of age. In 2001, children started to receive the second dose of the MMR vaccine before entering primary school. Nowadays, the official vaccination schedule for mumps consists of two doses of the MMR vaccine, with the first dose to be given between 12 and 15 months of age and a second dose at the beginning of primary school. The uptake rate of the MMR vaccination in Taiwan has been maintained at more than 95% for the past two decades.[4,5]

A resurgence of mumps has occurred in recent years and outbreaks have been increasingly reported among highly vaccinated populations in many countries.[6–10] In Taiwan, despite the high coverage rate of the MMR vaccine, approximately 770 to 1202 cases of mumps were reported to the Taiwan Centers for Disease Control (CDC) in the past decade. Most of the reported cases were children younger than 15 years of age.[5] The seroprevalence of mumps in the general population and the factors associated with the seronegative participants remain largely unknown. As such, 3552 Taiwanese volunteers were enrolled into our study, to determine the humoral immunities to a variety of vaccine-preventable diseases, including mumps. The study was aimed to evaluate the seroprevalence to mumps and to identify the sociodemographic factors associated with seronegative participants, under the high coverage rate of MMR vaccination, for more than 20 years in Taiwan.

Methods

Ethics statement

This study was approved by the institutional review boards of Chang Gung Memorial Hospital in 2007. Written informed consent was obtained from the adult participants and from the parents or legal guardians of the juvenile participants before enrollment in the study.

Study population

The selection of the study region and the recruitment of participants are described elsewhere.[4] Briefly, a multi-stratified design was used to sample the general population residing in 4 regions of Taiwan, including the metropolitan area of northern Taiwan, the suburban area of northern Taiwan, central Taiwan, and southern Taiwan. Four townships were randomly selected in each region and a total of 16 townships were included in this serosurvey. A total of 20 age groups were pre-determined (Supplementary Table 1). In each of the sampled townships, age-stratified sampling was conducted using the volunteer-based population. From August to December 2007, participants visiting the official health center for an extended program of immunization or for a routine health checkup were invited to donate their serum samples. A questionnaire-based interview was used to collect the demographic and anthropometric data of the participants. Questionnaires including age, sex, residing region, marriage status, occupation, education, socioeconomic status, information regarding immigration, underlying diseases, and history of vaccinations, were collected. The sample size determination in each age group was in accordance with the method described elsewhere.[4] All data was digitalized without identifying personal information, before statistical analysis.

Antibody test

Serum samples were stored at −20 °C before testing. We used the RIDASCREEN® Mumps Virus IgG test (R-Biopharm AG, Darmstadt, Germany) to determine IgG antibodies against mumps. Sera were tested in accordance with the instructions of the manufacturers. A titer >24.0 U/mL was considered seropositive, and a titer <14.0 U/mL was considered seronegative. Antibody titers within 14.0–24.0 U/mL were considered equivocal. The sensitivity and specificity of this test was reported to be 98.2% and 94.7%, respectively.

Statistical methods

Log-transformed individual titers were used to calculate geometric mean titers (GMT) for all participants, irrespective of serostatus. The GMT was then reported as back-transformed titers. Univariate analysis was used to identify the risk factors associated with the absence of mumps immunity. Pearson's chi-squared or Fisher's exact 2-tailed test was used to examine nominal data and a value of $P < 0.05$ was considered statistically significant. The independent

predictors for the absence of mumps immunity were identified by using multiple logistic regression analysis for the significant risk factors on the univariate analysis. SAS version 9.3 (SAS Institute, Cary, NC, USA) was used for the statistical analysis.

Results

Demographics

Between August and December 2007, a total of 3552 participants were recruited to this study. Of these, 2126 (59.9%) participants were female and 1822 (51.3%) were children (<19 years old). Newly arrived immigrants comprised a small group, accounting for 1.65% (47 participants) of all participants. The detailed distributions of demographics, socioeconomic characteristics, and details on the mumps vaccination doses as reported by the patient are displayed in Supplementary Table 1. The total vaccination doses, conducted under national programs based on age subgroups, are displayed at the bottom of Fig. 1.

Overall and age-specific seroprevalence

At a positive cut-off of >24.0 U/mL, the overall seroprevalence of mumps was 71.0% in this serosurvey. The seropositivity rate was significantly higher in the adult population aged 19 years or older than in the pediatric population aged younger than 19 years (80.4% versus 62.0%, $P < 0.0001$). Female participants also had a higher seropositivity rate than male participants (74.9% versus 65.1%, $P < 0.0001$). The participants from the metropolitan area of northern Taiwan and central Taiwan had higher seropositivity rates (80.8% for both) than those from southern Taiwan (70.2%) and from a suburban area of northern Taiwan (61.4%, $P < 0.0001$ for geographic difference).

The detailed age-specific seroprevalence is displayed in Fig. 1. A fluctuation of age-specific seropositivity was identified in children and young adults. The seropositivity rate increased from 11.4% in infants of less than one year old to 34.3% in children in their second year of life. At the third year of life (aged 2 years), the first universal MMR vaccine had been administered to most of the children and the seropositivity rate increased to 66.9%. The seropositivity rate was stable in children aged 2—4 years, and a level of 66.0%—66.9% was maintained. The seropositive rate decreased slightly at the age of 5—6 years and increased to the peak level (79.4%) at the age of 7—8 years, when the second universal MMR vaccine was given before their entry into elementary school. Thereafter, the seropositivity rate declined with advancing age, reaching the lowest point of 36.8% in adolescents aged 17—18 years. In the adult population, the seropositive rates were generally high and levels of 79.8%—87.3% were maintained in the participants older than 20 years of age. The young adults aged 19—20 years had a significantly lower seropositivity rate than those in the older population, namely those older than 20 years (59.3% versus 83.2%, $P < 0.0001$).

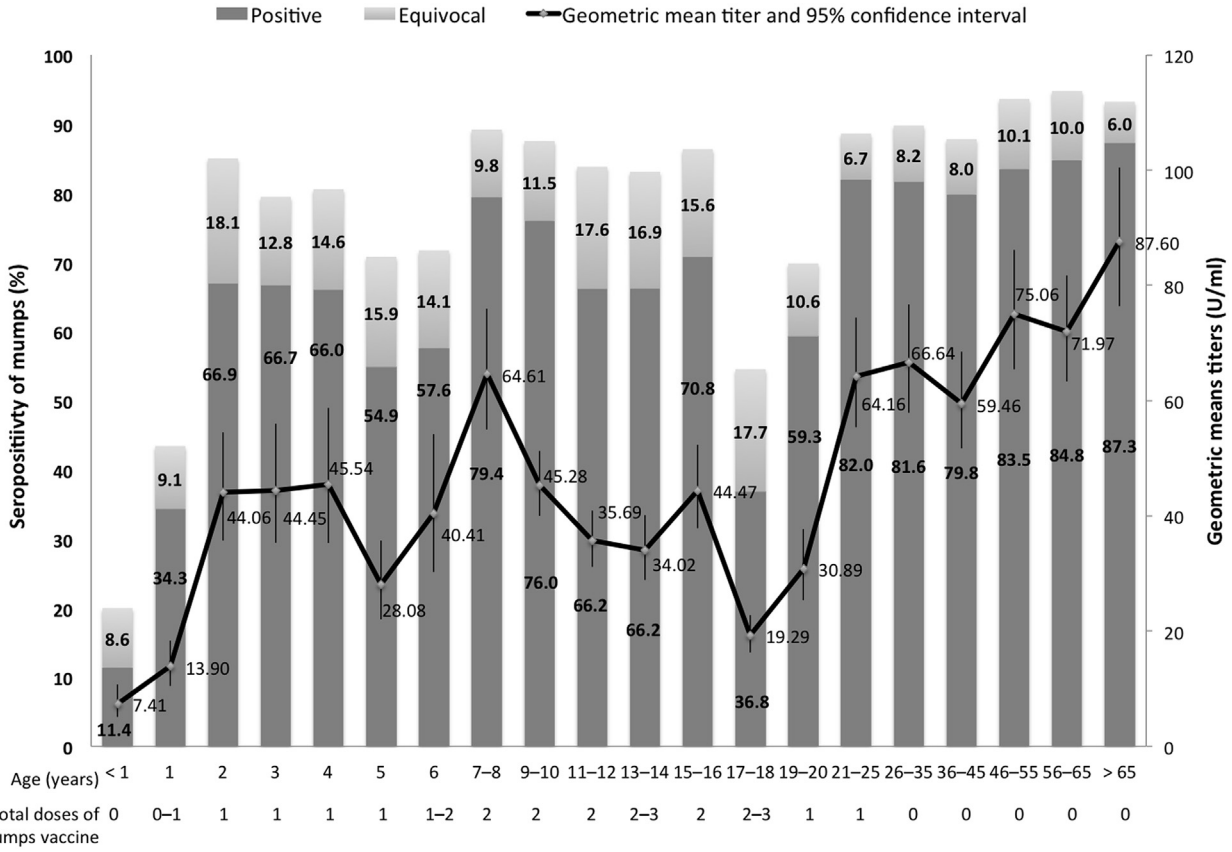

Figure 1. The age-specific seropositivity to mumps and geometric mean titers in 3552 volunteer participants in Taiwan.

The GMTs among the age subgroups generally followed the trend of age-specific seroprevalence, with the highest GMT value (64.61 U/mL) occurring at 7—8 years of age and the lowest GMT value (19.29 U/mL) at 17—18 years of age in the pediatric participants. In adult participants, the GMT increased with advancing age, from 30.89 U/mL in the participants aged 19—20 years to 87.6 U/mL in the participants aged 65 years or older.

Factors associated with seronegative sera in the vaccinated age group

The variation of age-specific seropositivity and unexpectedly low seropositivity in certain age subgroups occurred in children and young adults. To explore the associated factors, we analyzed the characteristics of 1887 participants aged 2—20 years. Within this group, 405 (21.5%) were seronegative for mumps (antibody titer $<$ 14.0 U/mL) although 1 to 3 doses of mumps vaccine had been administered (Fig. 1). The participants in this subpopulation from the metropolitan area of northern Taiwan had the highest seropositivity rate (78.0%), followed by central Taiwan (69.3%), southern Taiwan (64.0%), and finally the suburban area of northern Taiwan (55.9%) (Fig. 2 and Table 1). Univariate analysis further identified the age groups ($P < 0.0001$), education level ($P < 0.0001$), and vaccination against mumps ($P < 0.0001$) as significant factors associated with the seronegative sera (Table 1). The multivariate analysis, using a logistic regression model, identified that the age subgroups 17—18 years (aOR 8.598, 95% CI 2.990—24.722, $P < 0.0001$), 19—20 years (aOR 5.076, 95% CI 1.702—15.133, $P = 0.0080$) and residence within the suburban area of northern Taiwan (aOR 1.089, 95% CI 0.823—1.414, $P = 0.0008$), were associated with an increased risk of seronegative sera (Table 1).

Discussion

Results from the current study demonstrated a substantial fluctuation in the seropositivity of mumps among different age groups in children and young adults. This result has not been previously observed in similar seroepidemiological studies of mumps in several European countries.[11,12] Mumps immunization at age 15 months has been included in the national vaccination program since 1992 in Taiwan. Two additional MMR catch-up campaigns were carried out in 1992—1994 and 2001—2004, and targeted children born between 1976 and 1990 (age 7 to 15-year-old school students) and 1989 and 1994 (age 7 to 12-year-old school students), respectively.[4] Accordingly, the participants aged 17—20 years in this study should have received at least one dose of mumps-containing vaccine. The extremely low seropositivity in the age subgroup 17—18 years was especially noteworthy, given that 2 to 3 doses of mumps vaccine had been administered to the participants in this age subgroup (Fig. 1). Vaccine failure is not a likely explanation for the low rate, given the high seropositivity (79.4%, Fig. 1) and GMT (64.61 U/m) in participants aged 7—8 years after a booster dose of MMR vaccine. Waning humoral immunity to mumps appears to be the most plausible explanation for

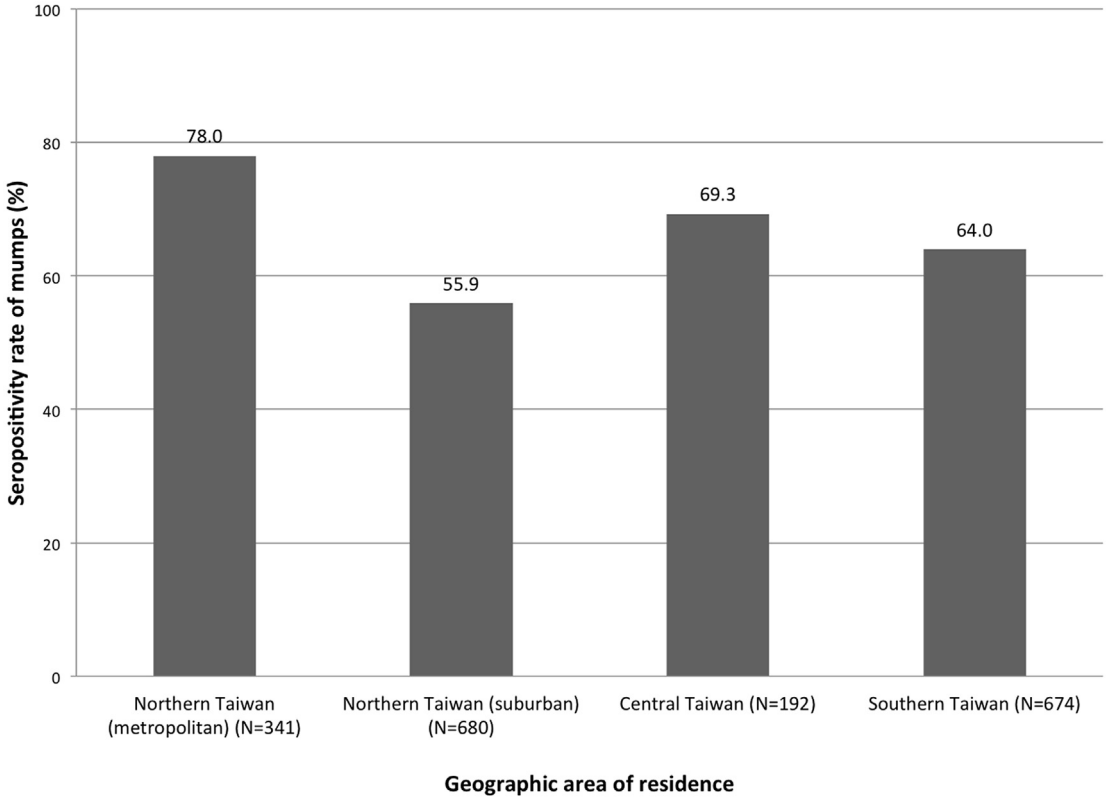

Figure 2. The geographic distribution of seropositivity of mumps in vaccinated population aged 2—20 years in Taiwan.

Table 1 Factors associated with absence of mumps immunity in 1887 participants aged 2—20 years in Taiwan, 2007.

Factor[a]	Univariate analysis			Multivariate analysis		
	Subject with antibody titer <14.0 U/mL (N = 405) n (%)	Participants with antibody titer >14.0 U/mL (N = 1482) n (%)	*P*	Adjusted odds ratio	95% confidence interval	*P*
Age group (in years)			<0.0001			
2	19 (4.69)	108 (7.29)		0.881	0.351—2.212	0.0348
3	24 (5.93)	93 (6.28)		1.220	0.351—2.212	0.2417
4	20 (4.94)	83 (5.60)		1.381	0.492—3.028	0.4291
5	33 (8.15)	80 (5.40)		2.188	0.554—3.440	0.5008
6	26 (6.42)	66 (4.45)		2.213	0.931—5.142	0.4452
7—8	22 (5.43)	182 (12.3)		Referent	Referent	…
9—10	27 (6.67)	190 (12.8)		1.142	1.028—4.767	0.1234
11—12	33 (8.15)	171 (11.5)		1.61	0.873—2.969	0.6727
13—14	25 (6.17)	123 (8.30)		1.458	0.586—3.628	0.5483
15—16	21 (5.19)	133 (8.97)		1.308	0.48—3.563	0.3702
17—18	95 (23.5)	114 (7.69)		8.598	2.99—24.722	<0.0001
19—20	60 (14.8)	139 (9.38)		5.076	1.702—15.133	0.008
Female sex	211 (52.1)	818 (55.2)	0.2673	…	…	…
Geographic area			<0.0001			
Northern Taiwan (Metropolitan)	44 (10.9)	297 (20.0)		0.525	0.357—0.771	0.0053
Northern Taiwan (Suburban)	171 (42.2)	509 (34.4)		1.089	0.823—1.414	0.0008
Central Taiwan	36 (8.89)	156 (10.5)		0.628	0.404—0.976	0.1910
Southern Taiwan	154 (38.0)	520 (35.1)		Referent	Referent	…
Newly arrived immigrants	1 (0.3)	13 (1.08)	0.3257	…		
Marriage status			0.0862	…		
Single	389 (98.7)	1410 (98.5)				
Married	2 (0.51)	20 (1.40)				
Divorced/Separated	2 (0.51)	1 (0.07)				
Widowed	1 (0.25)	1 (0.07)				
Education level			<0.0001			
Not formally educated	112 (28.3)	383 (26.5)		2.398	0.813—7.077	0.1351
Elementary school	79 (20.0)	525 (36.3)		1.343	0.500—3.602	0.7259
Junior high school	43 (10.9)	194 (13.4)		1.571	0.690—3.579	0.7869
Senior high school	78 (19.7)	160 (11.1)		1.370	0.860—2.182	0.7782
College or graduate school	84 (21.2)	184 (12.7)		Referent	Referent	…
Drug abuse	3 (0.75)	7 (0.49)	0.4596	…		
Smoking habit	12 (2.99)	29 (2.0)	0.2491	…		
Alcohol consumption			0.4225	…		
< 12 episodes in life	308 (89.0)	1163 (91.3)				
< 12 episodes in recent 1 year	34 (9.83)	98 (7.69)				
> 12 episodes in recent 1 year	4 (1.16)	13 (1.02)				
Diabetes	0 (0)	1 (0.07)	1.0000	…		
Chronic liver disease	3 (0.74)	2 (0.14)	0.0702	…		
Chronic lung disease	10 (2.48)	45 (3.07)	0.6201	…		
Vaccination against mumps			<0.0001			
None	178 (44.5)	711 (49.0)		Referent		
One dose	71 (17.8)	350 (24.1)		1.089	0.749—1.584	0.8559
Two doses	135 (33.8)	363 (25.0)		0.938	0.634—1.389	0.1966
Unknown	16 (4.00)	26 (1.79)		1.542	0.730—3.256	0.2325

[a] Missing value was identified in 61 participants for marriage, 45 participants for education level, 47 participants for drug abuse, 37 participants for smoking, 267 participants for alcohol consumption, 6 participants for diabetes, 12 participants for chronic liver disease, 16 participants for chronic renal disease and 37 participants for vaccination against mumps.

this observation. This conclusion is supported by the finding that the GMT of mumps also declined from 64.61 U/mL to 19.29 U/mL in participants aged 7—18 years. We observed a similar situation with measles immunity within the Taiwanese population. The seropositivity of measles can decline to as low as 50% in young adults aged 21—25 years, who had received 3 doses of measles-containing vaccine during their school years.[4] The data taken together strongly

suggests that humoral immunity induced by live vaccines at childhood, including measles and mumps antibodies, does not provide lifelong immunity, but can wane rapidly to an extremely low level by adolescence and young adulthood. This situation can be especially apparent in populations lacking boosters derived from natural infections.

Contrary to observations in children and young adults, the seroprevalence rate was generally high in adults without mumps immunization. The GMT of the mumps antibody continued to increase in participants with advancing age. The finding was consistent with another serosurveillance study using convenient serum samples collected in 1999 in Taiwan, which disclosed high seropositivity rates (78.2%—85.5%) of mumps in participants aged 23—50 years.[13] The indirect exposure to vaccine strains through immunized children may be contributable to the high seropositivity in the adults, especially elderly. However, we are more willing to believe that the data indicated a higher rate and longer duration of seropositivity, induced by natural infection, compared to that generated by immunization. Indeed, the higher seropositivity in elder than in young population was also evident in many once prevalent but now vaccine-preventable transmissible diseases, including measles and human papillomavirus.[4,14] Once the immunity to mumps was established by immunization in a majority of citizens, the population immunity would inevitably be reduced and outbreaks could increasingly occur. Indeed, this consideration is supported by increasing reports of mumps outbreaks in recent years in the US and in Europe, both with high MMR vaccine coverage.[3,6,7,10,15,16] Most of the outbreaks occurred in schools and universities, which suggests the potential impact of a relatively low seroprevalence rate and rapidly waning immunity from immunization in more recent generations. The widely adopted two-dose scheduled MMR vaccination might not be sufficient to interrupt the transmission of mumps in communities. Although it has been suggested that the third dose of the vaccine can be used for controlling a mumps outbreak,[9] no consensus has been reached on the routine use of the third dose of MMR vaccine in adolescents or young adults. Continuing surveillance of mumps activities and comprehensive studies on population immunity against mumps, and in different ethnic groups, will be needed to address this issue.

It was intriguing to note that the seropositivity differed significantly in participants from distinct geographical areas. The vaccine uptake rate was universally high in all regions in Taiwan and was unlikely to explain the particularly low seroprevalence (55.9%, Fig. 2) in the suburban area of northern Taiwan. Sampling bias may be a plausible explanation due to the use of volunteer-based participants. However, we believe that the chance of severe bias is minimal and our data accurately reflects the real condition in this region. Indeed, in a study characterizing the suspected mumps cases reported to Taiwan CDC between 2006 and 2011 (a period beginning 1 year before our study and running for 4 years afterwards), the investigators found that a majority (56%) of the mumps cases were from northern Taiwan.[17] The finding was consistent with the high prevalence of susceptible hosts to mumps in this region.

Characterizations of all study participants revealed that the female participants had significantly higher seropositivity of mumps than male participants. Although the difference was not significant in a multivariate analysis of participants at 2—20 years of age, a trend toward lower seronegativity in females compared to males still existed (20.5% versus 22.6%, Table 1). This observation was supported by a cross-sectional study of children over 15 years of age, who received the MMR vaccine at 12—15 months after birth, which demonstrated that the prevalence of serum IgG antibodies against mumps was significantly higher in girls than in boys.[18] Females generally exhibit a greater humoral and cell-mediated immune response to vaccines compared to males.[19] These sex-based immune response differences may also be attributable to hormonal influences along with genetic and epigenetic factors.[20,21]

There were limitations in this study. First, a major limitation was the use of volunteer participants as opposed to randomized samples in the estimation of seroprevalence of mumps. It is possible that the estimation of immunity to mumps might be secondary to a low coverage rate of immunization caused by a sampling bias. However, we consider this was less likely to be the case. Using the same sera from the same participants, we had also determined antibody titers against another vaccine-preventable disease, rubella. The serosurvey of rubella demonstrated extremely high rates of seropositivity across all age groups, including the pediatric population. The rubella virus has not been circulating in Taiwan for more than two decades and the last outbreak occurred in 1992. The seropositive cases in the pediatric population (<19 years) would have acquired immunity exclusively by immunization. Rubella seroprevalence data supported the high coverage rate of MMR immunization in children and adolescents in this cohort. Second, the suspected mumps cases reported to the Taiwan CDC were not routinely confirmed using virologic or serologic methods. We were therefore unable to correlate the seroprevalence data with the age and geographical distributions of confirmed mumps cases in Taiwan.

In conclusion, a declining antibody level to mumps, linked to age and a geographical discrepancy in population immunity, was evident in the younger generation in Taiwan where the childhood MMR vaccine uptake rate was maintained to a high level over the past 20 years. The waning population immunity, possibly linked to immunization, may have played a potential role in the recent mumps outbreaks and the increasing number of reported mumps cases in certain geographical regions. A continuous surveillance program and more detailed immunity studies will be needed to understand the disease burden and possible vaccine-induced immunity to mumps.

Transparency declaration

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jmii.2017.09.001.