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# Status of Measles Antibody Protection and Immune Memory Evaluation for Teenagers in Taiwan

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## ABSTRACT

Measles virus is a highly contagious virus that can still cause death in developing or unvaccinated countries. The Taiwanese government fully implemented the measles vaccine in 1978. Due to the high vaccinated rate of measles vaccination and the high development of medical care, measles cases have fallen sharply. However, World Health Organization statistics report also pointed out that the number of global measles cases increased by more than 110,000 in 2018, and 89 measles confirmed cases were discovered in Taiwan in the first five months of 2019. The measles antibody efficacy data of 969 healthy MV-vaccinated adolescents were collected and analyzed. This study explores the proportion of effective measles antibody protection in MV-vaccinated generations born in the period between 1998 and 2002 to their age of 16 and 17-years-old. Overall, the prevalence of measles antibody was 57.48% to their aged 16 years and 6 months to 17 years and 5 months old. This study observed the rate of measles antibody protection in modern adolescents is not sufficient even in the country with a high level of vaccination coverage; this may explain the possibility of measles outbreak and can be a basis for future evaluation of adult measles vaccination policy.

**Keywords:** Measles vaccination, Measles antibody, Antibody protection efficacy, Long-term memory immunity

## INTRODUCTION

The measles virus (MV) belongs to the paramyxoviridae family, and humans are the only natural host. It is transmitted through the nasal secretion from an infected host. Measles is a highly contagious, acute viral disease that causes complications in approximately 5-10% of patients, including otitis media, pneumonia, and encephalitis, and may even cause serious complications [1-3]. In Taiwan, the current implementation of universal routine vaccination programs with measles-containing vaccines has dramatically reduced the incidence of these diseases and their associated mortality and morbidity [4-6]. Despite the availability of a safe and effective measles vaccine, MV remains a major global health concern with high morbidity and mortality rates worldwide, and caused approximately 164,000 deaths in 2008 [7,8].

Before the measles vaccine was implemented in 1963, more than 99% of the people were infected, and from 1953 to 1961, there were approximately 700 to 900 measles deaths in each year in Taiwan [9,10-12].The measles vaccine became available in Taiwan in 1968 and was fully implemented by the Taiwanese government in 1978. Until January 2006, the measles vaccination was replaced by the measles–mumps–rubella (MMR) vaccine [13]. In Taiwan, the current routine vaccination policy for children suggests that a dose of MMR vaccine should be administered twice at the age of 1 year and 5 year [14,15]. Both the measles and MMR vaccines are attenuated vaccines, and the antigen-specific antibodies are produced approximately one week following the first dose, and the effectiveness of the vaccines can reach more than 95% following the second dose, thus achieving herd immunity. According to a report by the Ministry of Health and Welfare, the annual completion rate of the measles vaccine and MMR vaccination in Taiwan exceeded 97.64% after 2000; although the completion rate of the children of foreign residents was lower, it still reached 96.04% [16,17]. Measles is a category 2 legal infectious disease, and the infection must be notified within 24 hours of symptom presentation [17].

Since 1990, there have been only a few measles cases in Taiwan because of extensive vaccination; in 2000, local measles was also eradicated in the United States [18,19]. However, sporadic measles outbreaks still occur, mainly among unvaccinated populations and international travelers visiting measles-endemic countries. For example, in Romania, since the MMR vaccine was introduced in 2004, three outbreaks of measles have occurred between 2004 and 2016, and 64 deaths were confirmed in 2016. In this outbreak, the Romanian national surveillance system was notified of 17,533 measles cases, 93% of which were unvaccinated. In 2016, the measles outbreak in Romania was a consequence of insufficient vaccine coverage; therefore, the Romanian government should take more measures to improve surveillance performance and achieve high routine MMR vaccination coverage [20]. Measles reemerged in a nationwide outbreak in Bulgaria between 2009 and 2011 that affected 24,364 persons.

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Most cases (73%) were among children less than 15 years old. Of those who were 1–14 years old, 22% were unvaccinated and 70% had received one dose of a measles-containing vaccine. Twenty-four cases of measles-related deaths were reported, and the outbreak of measles in Bulgaria was caused by insufficient vaccination protection [21]. On August 26, 2011, the Los Angeles County Department of Public Health was notified of suspected measles in a refugee from Burma who had arrived in Los Angeles, California; this case expanded the measles survey of individuals in the area and no secondary cases were identified. This outbreak emphasizes the importance of maintaining a high level of vaccination coverage and high vigilance for measles in the United States, particularly among incoming international travelers [22]. Although the implementation of universal routine vaccination programs with measles-containing vaccines has dramatically reduced the incidence of MV, World Health Organization (WHO) statistics indicated that there were approximately 60,000 cases of measles worldwide in 2011 and more than 110,000 measles cases worldwide in 2018 (Lin). In the first half of 2019, the global rate of measles infection was increasing and outbreaks were reported in several countries, such as the Philippines, Vietnam, Thailand, Japan, and the United States and in Europe [23].

Most studies on the protective effectiveness of the measles vaccine have been horizontal interval studies evaluating and statistically analyzing the reason, number, and patterns of infections at times of epidemic outbreaks [24-26]. The Global Measles Elimination Strategy Program achieved and maintained high population immunity by increasing the completion rate of two measles-containing measles-related vaccines. However, the persistence of measles-specific immunity to measles among individuals being vaccinated remains an unsolved problem [22-25]. This study attempts to understand the proportion of effective measles antibody protection in adolescent populations through analysis of a measles antibodies database from the vaccination generation and observation of the immune memory of modern adolescents to provide a basis for future adult measles vaccination policy evaluation.

## MATERIALS AND METHODS

### Samples

MV is highly contagious through the nasal secretions of the infected population; before undertaking an internship, second-year students in the nursing department of a regional teaching hospital in Taiwan are required to undergo a measles antibody examination. If the concentration of the measles antibody is not sufficient for protection, then the individual student must be vaccinated before the internship to reduce the risk of contracting a measles infection. In this study, the measles antibody efficacy data of adolescents, namely nursing college students in Taiwan, were collected from 2015 to 2019.

### Statistical analyses

All data were statistically analyzed using JMP software version 10.0 (SAS Institute Inc., Cary, NC, USA). No measles cases were identified, and the measles antibody efficacy of all individuals being vaccinated was used for univariate statistical analysis with the chi-square test. A two-tailed P value of less than 0.05 was considered statistically significant.

## RESULTS

A total of 969 adolescents were enrolled, and individuals included in the study were categorized according to the demographic characteristics of the cohort for the birth year Table 1. The relative age of detection ranged from 16 years and 6 months to 17 years and 5 months. In Taiwan, most of the students in the nursing department were women. Demographic characteristics of the study participants revealed that the proportion of male students was low, with only 9.49% of the 969 participants being men Table 1.

**Table 1:** Demographic characteristics of the cohort for the birth year.

| Birth Year | 1998 | 1999 | 2000 | 2001 | 2002 | N |
|---|---|---|---|---|---|---|
| Male | 5 | 7 | 36 | 28 | 16 | 92 |
| Female | 51 | 79 | 234 | 294 | 219 | 877 |
| N | 56 | 86 | 270 | 322 | 235 | 969 |

For the MV-vaccinated generations born in the period between 1998 and 2002 to their age of 16 and 17-years-old, their measles antibody status are shown in Table 2. For the 56 individuals of the MV-vaccinated generation who were born in 1998 and screened in May 2015, the seropositivity rate was 62.50%. For the 86 individuals of the MV-vaccinated generation who were born in 1999 and screened in May 2016, the seropositivity rate was 52.33%. For the 270 individuals of the MV-vaccinated generation who were born in 2000 and screened in May 2017, the seropositivity rate was 56.30%. For the 322 individuals of the MV-vaccinated generation who were born in 2001 and screened in May 2018, the seropositivity rate was 59.63%. For the 235 individuals of the MV-vaccinated generation who were born in 2002 and screened in May 2019, the seropositivity rate was 56.60%. Overall, the seropositivity rate for antimeasles antibody remained approximately 57.48% for vaccinated individuals born in the period from 1998 to 2002 who were 16 or 17 years old Table 2. The results indicated that throughout the 15 years after vaccination, the seropositivity rates for antimeasles antibody remained approximately 52.33%-62.50%, and there was no significant difference in the efficacy of measles antibody protection between the five different birth year generations ($P>0.05$, Table 3). The differences in measles antibody protection in terms of gender revealed that the seropositivity rates for antimeasles antibody remained higher (65.22%) in male adolescents than in female adolescents (56.67%). The total number of men was 92 in this study; therefore, a significant difference in gender could not be determined ($P=0.111$, Supplementary Table 1).

When the birthplace of the adolescents was used as the basis for classification, the proportions of adolescents in a few birth countries were extremely small; therefore, the statistics were not sufficiently reliable for analysis. Therefore, the difference in the seropositivity rates of measles antibodies in the birthplace is not shown in the table. According to the preliminary observation, we observed that only seven teenagers were born in Taipei City and that all of them were seropositive (100.00%). There were four adolescents born in the Hualien county, and only one of them was seropositive for the measles antibody (25.00%). Three of the adolescents were born in Taoyuan county, and one of them was seropositive (33.33%); moreover, 34 adolescents were born in the Yunlin county, of whom 14 were seropositive for

**Table 2:** The seropositivity rate for antimeasles antibody status for adolescents.

| Birth Year | Assay time | Anti-measles antbody N (%) | | N |
|---|---|---|---|---|
| | | Sero-Negative (-) | Sero-Positive (+) | |
| 1998 | 2015/05 | 21 (37.50%) | 35 (62.50%) | 56 |
| 1999 | 2016/05 | 41 (47.67%) | 45 (52.33%) | 86 |
| 2000 | 2017/05 | 118 (43.70%) | 152 (56.30%) | 270 |
| 2001 | 2018/05 | 130 (40.37%) | 192 (59.63%) | 322 |
| 2002 | 2019/05 | 102 (43.40%) | 133 (56.60%) | 235 |
| Total Number | | 412 (42.52%) | 557 (57.48%) | 969 |

**Table 3:** Comparison of the birth year in the differences of measles immunological memory antibody.

| | | | Anti-measles antbody (+) | | | | |
|---|---|---|---|---|---|---|---|
| | | Birth Year | 1998 | 1999 | 2000 | 2001 | 2002 |
| | Birth Year | Percentage (%) | 62.50 % | 52.33 % | 56.30 % | 59.63 % | 56.60 % |
| Anti-measles antbody (+) | 1998 | 62.50% | | 0.232 | 0.394 | 0.689 | 0.423 |
| | 1999 | 52.33% | 0.232 | | 0.517 | 0.225 | 0.494 |
| | 2000 | 56.30% | 0.394 | 0.517 | | 0.415 | 0.946 |
| | 2001 | 59.63% | 0.689 | 0.255 | 0.415 | | 0.476 |
| | 2002 | 56.60% | 0.423 | 0.494 | 0.946 | 0.476 | |

measles (41.18%). The seropositivity rates of measles antibody in adolescents in the other counties of Taiwan were greater than 50%.

## DISCUSSION

Measles is a highly contagious disease. From 1990 to 2018, the annual number of confirmed measles cases was less than 50 in Taiwan; however, from January 2019 to May 2019, the number of confirmed measles cases exceeded 80. Most deaths due to measles were formerly caused by pneumonia and encephalitis in cases of underdeveloped medical resources; however, most current cases are caused by overseas immigration in Taiwan, and there have been no deaths due to measles in Taiwan since 2000 [25]. The measles cases between 2001 and 2015 were analyzed according to the infected area, and 37% of the measles cases were determined to be caused by overseas immigration [22]. From Jan 2019 to May 2019, 33.71% of the 89 confirmed measles cases were overseas immigration cases and 47.19% of cases were persons infected directly or indirectly from immigration into Taiwan [24].

The WHO reported that more than 93% of the total population that received the measles vaccine can account for the herd immunity of the population [26-30]. The United States vaccination requirements ensured that students were protected from the vaccine-preventable diseases in the 2017-18 school year. Median vaccination coverage was 94.3% for two doses of MMR, preventing measles outbreaks such as in the cases of Romania, Bulgaria, and Brazil, which were caused by insufficient vaccine coverage. However, insufficient vaccine coverage is not the cause of measles among Taiwanese people or the increase in measles outbreaks [28-31]. For Taiwanese people with high vaccine coverage, the reason for measles outbreaks is possibly because the measles vaccinator has lost the specific immune memory through time against the measles, resulting in no antibody production or insufficient antibody concentration to protect them from measles.

The purpose of vaccination is to induce adaptive immunity, mainly through the cooperation of T cells and B cells to produce specific antibodies. The measles vaccine is a live-attenuated vaccine. Following vaccination, the vaccine does not cause the disease; instead, the vaccinated individual produces memory B cells and long-lived plasma cells (LLPCs) to maintain specific immune memory for MV [32]. One report revealed that the administration of 1 or 2 doses of MMR-containing vaccines to children in their second year of life induced antibody responses against MVs that persisted up to 10 years post-vaccination ( ≥ 93.4%). Kennedy et al., examined changes in the markers of the measles immunity at two time points, approximately 7 and 17 years after the two-dose MMR-II (R) vaccination, in a cohort of 98 healthy adults [33]. Their results indicated that for both mumps and measles, neutralizing antibody titres were fairly low and may have already declined, considering the amount of time since vaccination [32]. The data used in the present study tracked the seroprevalence of antimeasles antibodies in adolescents aged 16 to 17 years in Taiwan, and the seroprevalence of antimeasles antibodies was noted to have decreased to 57% (Table 2). Our data indicated that the long-term immune memory against the measles vaccine may be insufficient for ensuring protection for more than 16 years and that the specific immune outcomes of individuals may wane at different rates.

LLPCs, mainly present in the bone marrow, can sustain antibody release without needing to rebind to the special antigen [16]. Prolonged humoral immune dependence on the continued titre of the specific antibodies provided by LLPCs. After most children in Taiwan receive the measles vaccination, they are not re-infected or stimulated by the measles antigen until their adolescence. It can be inferred that the adolescents in this study maintained an effective measles antibody concentration in the blood and appeared to mainly rely on the sustained release of antibodies from LLPCs. In this study, 969 adolescents were born between 1998 and 2002, and the seroprevalence of antimeasles antibodies decreased to 57% in their teenage. These data highlight our

currently incomplete protective immune responses to measles for adolescents or the necessity of measles revaccination.

This study has some limitations. First, we only collected the measles antibody data of second-year students in the nursing department of college. In this study, more measles antibody data was available for female adolescents than for male adolescents. Previous reports have indicated that gender may be a reason for the differences in vaccine efficacy and cellular immune response. We suggest that future research focus on differences in gender, measles antibody protection, and immune memory. Second, according to statistics reported by the Ministry of Health and Welfare, the annual MMR vaccination coverage in Taiwan between 2015 and 2017 exceeded 98%. However, from the classification of adolescent birthplaces, we discovered that measles seropositive adolescents from the remote countryside were probably low. We suggest that future experimental research explore the differences in vaccine coverage rate among regions in Taiwan.

## CONCLUSION

The activation process of humoral immunity by vaccines and long-term immunity memory is crucial for immune protection and persistence; however, it is still not fully understood. The seroprevalence of antimeasles antibodies in adolescents provides useful information for researchers explore the lifetime and physiological changes in their LLPCs. The WPRO measles epidemic from 2010 to 2016, the most dangerous threat for measles in Asia, included China, the Philippines, and Vietnam. In recent years, the number of international travelers and new foreign residents has increased and measles antibodies in the 20-40 years age group have declined. This study also serves as a reminder to international travelers, pregnant women, medical staff, and infant care staff to take initiative for ensuring effective antibody protection in the body or boost measles vaccination to reduce the risk of MV infection.

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