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Original Article

Seroepidemiology of measles in immune generation in Taiwan: Prevalence of neutralizing antibody and immune response to reimmunization

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KEYWORDS
Seroprevalence;
Measles;
Waning immunity;
Neutralizing antibody;
Reimmunization

Abstract *Background:* Secondary vaccine failure was the principal mechanic of measles reemergence in countries with high measles vaccine coverage. The information on neutralizing antibody (nAb) prevalence, epidemiological factors of waned immunity and immune response after reimmunization was essential to measles control but largely lacking in Taiwan.
Methods: The nAb and factors of wanned immunity to measles were evaluated in a cohort of 333 subjects aged 11–30 years in 2010. The longitudinal immune response to reimmunization ($n = 30$) and potential virus exposure ($n = 24$) were assessed in young healthcare workers (HCWs) during a hospital outbreak. The nAb titer was used to define susceptibility to measles disease (<120 mIU/mL) and infection (120–900 mIU/mL).
Results: In the 2010 cohort, the susceptibility to measles diseases and infections was respectively identified in 35 (10.5%) and 226 (67.9%) subjects. A generalized linear model identified earlier ages of first immunization in childhood ($P = 0.0214$) and subjects aged ≥18 years (versus <18 years, $P = 0.0425$) as significant factors associated with lower nAb titers. Reimmunization of 30 seronegative HCWs resulted in seroconversion for all, with nAb titers significantly rising on day 5, peaking on day 15 and declining in month 4 post-immunization. Similar measles-specific IgG levels were observed in 24 seropositive HCWs before and 4 months after measles contact ($P = 0.2352$).

Abbreviations: nAb, Neutralizing antibody; CDC, Centers for Disease Control; PRNT, Plaque-reduction neutralization test; NIIS, National Immunization Information System; HCWs, Healthcare workers; GMTs, Geometric mean titers; CLIA, Chemiluminescent Immunoassay; ELISA, Enzyme-linked immunosorbent assay.

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Conclusion: A lack of protective immunity to measles diseases might be identified in 10% of the Taiwanese population aged 11—30 years and associated with a trend toward earlier ages of the first measles vaccination. The wanned immunity can be boosted promptly by reimmunization but with uncertain durability.

Introduction

Measles is a severe and highly contagious disease that remains common in many parts of the world. A worldwide surge in measles cases occurred in 2018 and 2019, with more than 207,000 measles death in 2019 globally.[1] The largest outbreaks and measles-associated deaths occurred mainly in low- or middle-socioeconomic countries. However, measles cases were also increasingly reported in many high-income countries in Europe, New Zeeland, East Asia, and the United States.[1—4] Although the reported measles cases decreased by more than 80% during the COVID-19 pandemic,[5] it is generally believed that the scale of global measles outbreaks will be huge in the coming years due to that at least 22.3 million children missed their measles vaccine doses in 2020.[6] Measles is still a public health concern for both developing and developed countries for now and for the foreseeable future.

The official adoption of the measles immunization program with a 2-dose schedule at age 9 and 15 months was commenced in 1978 in Taiwan. The latest large-scale outbreak of measles in Taiwan with more than 1000 confirmed cases occurred in 1989. Since 1992, the measles—mumps—rubella (MMR combo) has replaced the second dose of the measles vaccine at age 15 months. The routine administration of a second dose of MMR was commenced in 2001 for the first-grade student at elementary school. Since 2006, Taiwanese children have received their first MMR vaccine at 12—15 months and the booster dose at 5 years of age before entry into primary school. The MMR vaccine deployed in Taiwan was mainly manufactured by MSD (M-M-R® II). The vaccine uptake rate has been maintained at >95% since 1996.[7] Despite the high vaccine coverage rate in Taiwan, it has been demonstrated that the measles-specific IgG antibody would wane significantly after the second dose of vaccination in childhood and reach a low level in teenagers and young adults.[7] The declining humoral immunity resulting in secondary vaccine failure was believed to account for the recent re-emergence of measles in the highly vaccinated young generation.[3] In 2019, multiple measles outbreaks occurred in hospitals and restaurants in Taiwan, and the accumulated indigenous measles cases reached a new high over the past two decades.[8] The observation of secondary vaccine failure leading to the measles outbreak was not confined to Taiwan but also in the US and Canada.[9,10] The alarming occurrence of epidemic measles in the young, immunized generation leads us to suspect that secondary vaccine failure to measles is indeed an important public health threat, especially in countries where measles is considered eliminated, and natural boosters by wild-type viruses are infrequent.

Plaque-reduction neutralization test (PRNT) measuring antibodies with neutralizing ability (nAb) was considered the most sensitive, reliable criteria and the gold standard for defining susceptibility to measles.[11—14] A PRNT titer >120 mIU/mL was considered a threshold of protection from typical measles based on the finding of a measles outbreak in Boston in 1985.[14] In that outbreak, Chen et al. reported that the measles cases meeting the CDC case definition of fever, rash, and ≥1 of cough, coryza, and conjunctivitis were identified in 88.9% (8/9) of subjects with a preexposure PRNT titer of ≤120 but in none of 71 subjects with a preexposure titer of >120. In the same study, 63.6% of subjects with a preexposure PRNT titer of 216—874 had ≥ four-fold increase (seroconversion) in postexposure antibody titers, and many of them had at least one symptom of measles, indicating subclinical or paucisymptomatic infection. None of the subjects with a preexposure titer of ≥1052 had seroconversion. A PRNT titer of 120 has since been wildly adopted as a correlate of protection from classic measles illness, whereas a PRNT titer in the range of 120 and 900 has been considered partly protective from typical measles but vulnerable to measle virus infection.[11,12]

The seroprevalence level determinant using the PRNT was critical information for measles control but mainly lacking for the contemporary Taiwanese population. Factors associated with absent humoral immunity to measles and the dynamic changes of anti-measles antibodies after exposure to the virus or reimmunization were unavailable for the young people who had been fully immunized in childhood. The study utilized the RPNT measuring nAb against measles and aimed to provide information on the seroepidemiology of measles in Taiwan. The information provided in this study will be invaluable in shaping the strategy of measles immunization against the re-emergent disease.

Methods

Ethics statement

For the longitudinal evaluation of the kinetics of antibodies against measles in the hospital outbreak, written informed consent was obtained from all participants. The serosurvey during the hospital outbreak and the serosurvey using residual serum samples in the 2010 serum cohort were reviewed and approved by the ethical committee in the Chang Gung Memorial Hospital (IRB No. 201800744A3).

Settings

2010 serum cohort

In 2010, we conducted a seroprevalence study to estimate the incidence and severity of the pandemic H1N1 in 2009 in Taiwan.[15] A total of 1558 serum samples from civilians of all ages residing in four regions of Taiwan were obtained from September to October of 2010 with a multi-stratified design. The serum samples were stored at −80 °C after the survey. To understand the seroepidemiology and factors associated with measles immunity in the immune generation in Taiwan, 333 (83.5%) of 399 subjects aged 11—30 years with residual serum samples were selected from the 2010 blood cohort (Fig. 1). Subjects young than 18 years old were defined as adolescents. In collaboration with Taiwan CDC, the past immunization history against measles, if available, was obtained from the National Immunization Information System (NIIS) database.

Serosurvey during a hospital cluster

A hospital cluster of measles occurred in northern Taiwan in 2018, which involved four laboratory-confirmed cases and approximately 1000 close contacts.[2,3] As part of the infection control measures to mitigate the outbreak, the serostatus defined by measles-specific IgG was determined in all contacts and a dose of MMR combo vaccine was administered to the seronegative HCWs. During the outbreak, 34 HCWs including 24 seropositive contacts and 10 seronegative contacts were invited for serosurveys four months after exposure to the measles cases or booster vaccination (Fig. 1). Another 20 seronegative employees were invited for a longitudinal serosurvey in five-time points on day 0 (day of immunization), day 5, day 10, day 15 and day 30 post-immunization.

Detection of measles-specific binding antibodies

Measles-specific IgG and IgM antibodies were determined using the commercial measles IgG Chemiluminescent Immunoassay (CLIA kit, DiaSorin, Saluggia, Italy) and measles IgM enzyme-linked immunosorbent assay (ELISA) kit (Euroimmun, Lübeck, Germany or NovaTec Immundiagnostica, Germany), respectively. Results of IgG tests were expressed as AU/ml and interpreted as negative (<16.5 AU/ml), and positive (≥ 16.5 AU/ml). The sensitivity and specificity of this test were 94.7% and 97.4%, respectively, according to the manufacturer.

Plaque reduction neutralization test (PRNT)

Neutralizing antibody titers against measles were measured in the serum sample by the plaque reduction neutralization test (PRNT). Briefly, Sera heat-inactivated at 56 °C for 30 min was diluted serially 4-fold from 1/4 to 1/4096 (6 dilutions) and mixed with 30 mL of measles virus (20—40 PFU/well) at room temperature for 90 min in a 96-well plate. Then, 50 mL of the mixtures were transferred to 24-well plates and incubated with 1 mL cell suspension (4×10^5 cells/ml) at 37 °C in 5% CO_2 for 2—3 h. The medium was removed, and 1 mL overlay medium was added to each well. After 7 days of incubation at 37 °C in 5% CO_2, the cell monolayers were fixed with 5% formalin and stained with crystal violet, and the number of plaques in each well was counted. A titration of measles international standard serum (the World Health Organization third international standard anti-measles serum, coded 97/648, supplied by the National Institute for Biological Standards and Control, South Mimms, United Kingdom) was used as control. The 50% reduction point of virus growth was calculated using the Karber formula and, by comparing it with the standard serum, neutralizing antibody titers were converted to mIU/ml.

Serologic correlate of protection for measles

According to the study by Chen et al.,[14] a PRNT titer <120 mIU/mL was defined as vulnerable to typical measles illness, whereas a PRNT titer of 120—900 mIU/mL was considered protective from typical measles illness but vulnerable to measles virus infections. A PRNT titer >900 mIU/mL was considered completely protected from measles virus infection in this study.

Virus

Low passage Edmonston wild-type measles virus (ATCC® VR-24™, American Type Culture Collection, Rockville, Md.) was used as a challenge virus and passaged once more in Vero cell (ATCC CCL-81) to produce the working virus stock. Working virus stock was harvested when the cytopathic effect spread to involve about 80% of the monolayer (5—7 days) and titrated as previously described.[16] The virus dilution that gave 25—35 plaques per well was noted and used in PRNT. The multiplicity of infection of the virus stock was determined by standard assays.[17]

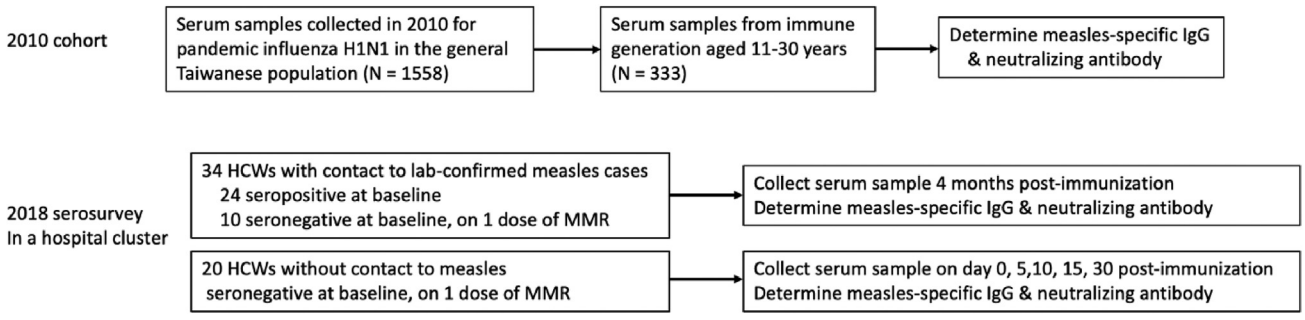

Figure 1. Scheme of study design.

Statistical analyses

Statistical analysis and graph constructions were performed using SAS software (version 9.3; SAS Institute, Inc., Cary, NC) and Prism software (version 5.0; GraphPad Software Inc., San Diego, CA). A generalized linear model using the *glm* function in SAS was used to test the significance of the epidemiological factors including the age, gender, age of the very first measles immunization, and the city of residence, associated with the trend of PRNT titers in the 2010 serum cohort. The paired T-test was used for the survey during the hospital outbreak to compare immune responses at different time points after vaccination or contact with confirmed measles cases. Geometric mean titers (GMTs) were calculated using log-transformed individual titers and were reported as back-transformed titers. Statistical significance was defined as $P < 0.05$.

Results

2010 serum cohort

Among 333 subjects, 204 (61.3%) were female and 77 (23.1%) were teenagers younger than 18 years old. The distribution of nAb titers, GMTs, and seroprotective rates among all ages

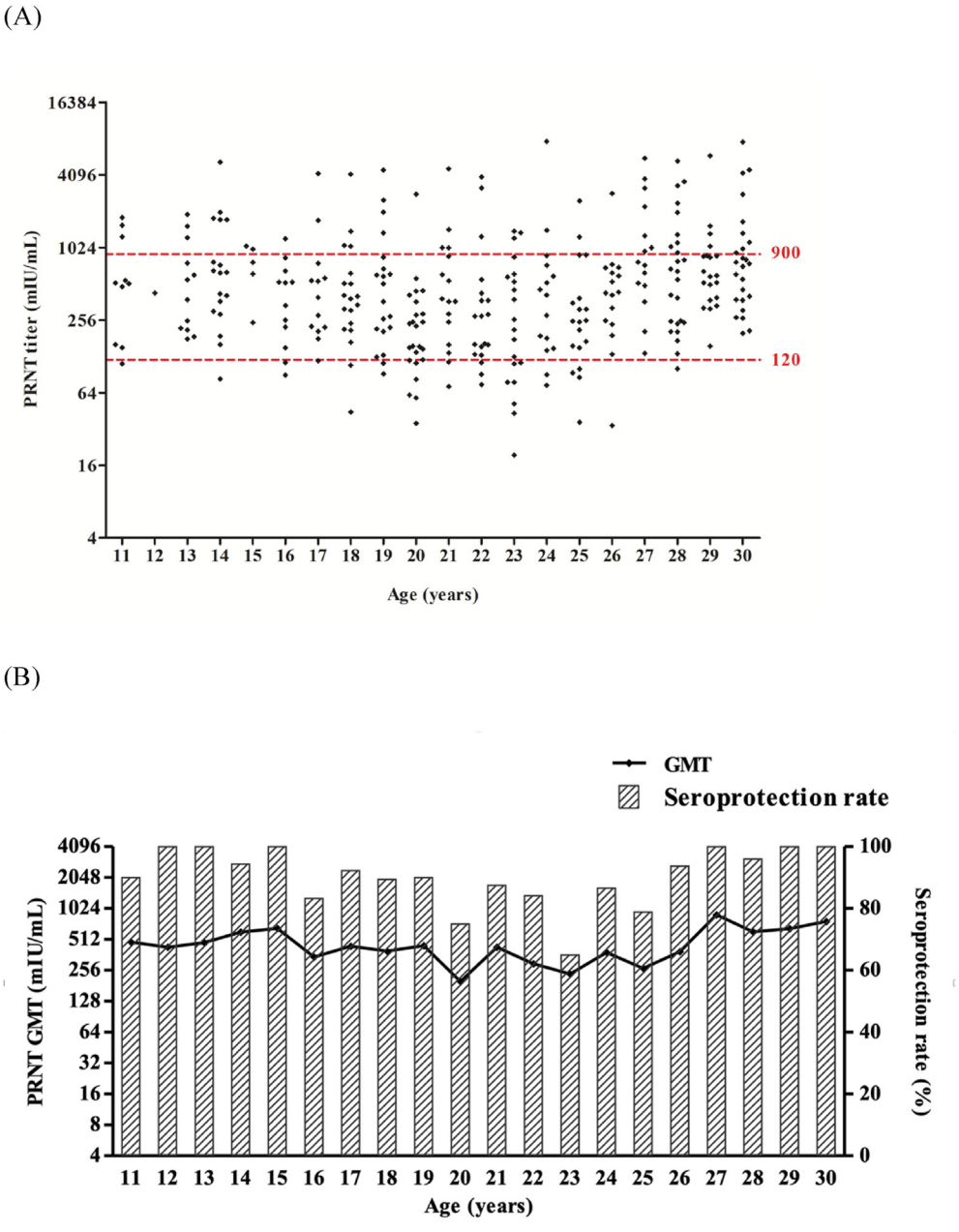

Figure 2. Distribution of neutralizing antibody (nAb) titers by plaque reduction neutralization test (PRNT) against measles in 333 subjects aged 11—30 years old in Taiwan. (A) Age-specific distribution of nAb titers (B) Age-specific seroprotective rate (>120 mIU/mL) and geometric mean titers.

Table 1 Distributions of serostatus of measles defined by measles-specific IgG with CLIA method and neutralizing antibody with PRNT methods in 333 adolescents and young adults in Taiwan in 2010.

Measles specific IgG titers (AU/mL) by CLIA	Neutralizing antibody titers (mIU/mL) by PRNT			
	Negative, <120	Positive, 120–900	Positive, >900	Total
Negative, <16.5	26	67	1	94 (28.2%)
Positive, ≥16.5	9	159	71	239 (71.8%)
Total	35 (10.5%)	226 (67.9%)	72 (21.6%)	333

of the 333 subjects are shown in Fig. 2 and Table 1. The PRNT identified 35 (10.5%) and 226 (67.9%) subjects respectively vulnerable to measles diseases (nAb <120 mIU/mL) and measles virus infection (nAb of 120–900 mIU/mL) (Table 1). The serostatus defined by nAb was significantly associated with the city of residence ($P = 0.0006$) but not with the genders, ages, and ages of first childhood immunization against measles (Table 2). A potential role of the age factor in the nAb titer to measles was supported by the finding that the GMT of nAb was higher in adolescents than in adults with approach the borderline of significance (483.2 mIU/mL versus 415.0 mIU/mL, $P = 0.0582$, Table 2). A similar observation was made on the age of first childhood immunization against measles. The seronegative subjects (titer <120 mIU/mL) were more commonly to be immunized at the age of 270–360 days after birth whereas the subjects with infection-protective nAb (titer >900 mIU/mL) were more commonly to be immunized at a later age at > 360 days (Table 2). The GMT was also higher in those immunized at elder age >360 days than those at 270–360 days (455.8 mIU/mL versus 396.4 mIU/mL) though without statistical significance ($P = 0.6341$).

To evaluate the effect of the age and age of the first immunization more robustly on measles immunity, a generalized linear model was built on a continuous outcome, the nAb, which confirmed an increasing trend of nAb titers toward the later age of childhood immunization (Table 3 and Fig. 3, $P = 0.0214$). The model also illustrated a significant elevation of nAb titers in adolescents than in adults ($P = 0.0425$). The significance of the city of residence was lost in the multivariate analysis.

Serosurvey during a hospital outbreak

Of 24 seropositive subjects who had contact with the measles cases, the GMTs of measles-specific IgG did not significantly alter four months after contact (Fig. 4A). All 24 subjects were negative for IgM in the follow-up serosurvey.

Among 30 seronegative subjects on booster vaccination, 10 had contact to the measles cases but none developed clinical measles disease. A significant and continuing elevation of measles-specific IgG levels was identified on day 10 and day 15 post-MMR immunization (Fig. 4B). The

Table 2 Serostatus and the geometric mean of neutralizing titers of measles in subjects of different residences, gender, ages, and ages of childhood immunization against measles.

Factor	Neutralizing antibody against measles by PRNT					
	Serostatus				GMT, mIU/mL	
	Negative (<120 mIU/mL)	Disease protective (120–900 mIU/mL)	Infection protective (>900 mIU/mL)	*P*	(95% CL)	*P*
City of residence						
Taipei, N (%), n = 89	17 (19.1)	61 (68.5)	11 (12.4)	.0006	227.1 (223.9–343.0)	<.0001
Tainan, N (%), n = 107	7 (6.54)	67 (62.6)	33 (30.8)		576.6 (472.8–703.1)	
Taoyuan, N (%), n = 106	11 (10.4)	70 (66.0)	25 (23.6)		473.3 (382.6–585.5)	
New Taipei, N (%), n = 31	0 (0)	28 (90.4)	3 (9.68)		396.2 (306.6–511.9)	
Gender						
Female, N (%), n = 204	21 (10.3)	139 (68.1)	44 (21.6)	.9852	434.1 (377.3–499.5)	.2168
Male, N (%), n = 129	14 (10.9)	87 (67.4)	28 (21.7)		423.2 (347.4–515.7)	
Ages, mean (SD)	21.9 (3.54)	22.5 (5.63)	23.0 (6.47)	.6140	…	…
Age group						
Adolescents (<18 years), N (%), n = 77	5 (6.49)	53 (68.8)	19 (24.7)	.3709	483.2 (393.0–594.3)	.0582
Adults (≥18 years), N (%), n = 256	30 (11.7)	173 (67.6)	53 (20.7)		415.0 (362.4–475.3)	
Age of 1st measles vaccination						
Median age in days (range), n = 100	300.5 (283–367)	289.5 (266–690)	296.5 (273–426)	.9039	…	…
270–360 days, N (%), n = 86	9 (10.5)	59 (68.6)	18 (20.9)	.8010	396.4 (321.0–489.6)	.6341
>360 days, N (%), n = 13	1 (7.69)	8 (61.5)	4 (30.8)		455.8 (254.4–816.8)	

Abbreviations: PRNT, plaque-reduction neutralization test; GMT, geometric mean titer.

Table 3 Multivariate analysis of demographic and environmental factors associated with neutralizing titers against measles in the young Taiwanese population aged 11—30 years in 2010 by a generalized linear model (GLM).

Factor	Sum of squares	Least square means	F value	P value
City of residence	5.5429	1.8476	2.17	.0967
Gender	2.2562	2.2562	2.65	.1069
Age group (adolescents versus adults)	3.6005	3.6005	4.23	.0425
Ages of first immunization against measles	4.6637	4.6637	5.48	.0214

GMT was further increased on day 30 (79.4 AU/mL) though of no significant difference when compared to that on day 15 (60.5 AU/mL, $P = 0.1071$, Supplementary Table 1). The GMT at four months was lower than that at day 30 post-immunization (Fig. 4B).

The nAb changes post-immunization was very much like that of the IgG binding antibody (Fig. 4C). However, the significant elevation of nAb titer was identified earlier than that of binding IgG. At day 5 post-immunization, there has been a significant increase of GMT to 316.3 mIU/mL from 226.2 at baseline ($P = 0.0028$). The nAb reached the plateau at day 15—30 (titers, 1556.1—1763.0 mIU/mL) but declined to 506.6 mIU/mL at four months post-immunization.

Of all 30 seronegative subjects, positive measles-specific IgM with low titer (12.9, positive cutoff ≥11) was identified in only one 28-year-old female nurse at follow-up survey who had IgG seroconversion from <5 AU/mL to 31.7 AU/mL after vaccination (Supplementary Table 1).

Suboptimal performance of measles-specific IgG in defining serostatus of measles

Of 100 serum samples collected at 5 time points among 20 HCWs on MMR vaccination, the measles-specific IgG titers were only modestly correlated with nAb ($r = .51208$, $P < 0.0001$ by Pearson correlation, Fig. 5). The measurement of the measles-specific IgG in the serum samples in the 2010 cohort disclosed a seronegative rate of 28.2% (94/333). The sensitivity and specificity of measles-specific IgG were respectively 77.2% (230/298) and 74.3% (26/35) when nAb at a cutoff of 120 mIU/mL was used as standard (Table 1).

Discussion

Our previous seroprevalence study in 2007 disclosed an unexpectedly low (50—60%) protective immunity to measles in the young Taiwanese population.[7] Based on the finding, it was anticipated that measles outbreaks would occur in the new generation if cases were imported from the endemic countries. As predicted, multiple measles clusters occurred in 2018 and 2019 in Taiwan, and young adults were the population affected. However, it was noteworthy that the outbreaks were occurring on a relatively small scale.[3] The limited transmission of measles among the young population with only 50—60% seropositivity for anti-measles IgG antibodies was unexpected, given the highly contagious nature

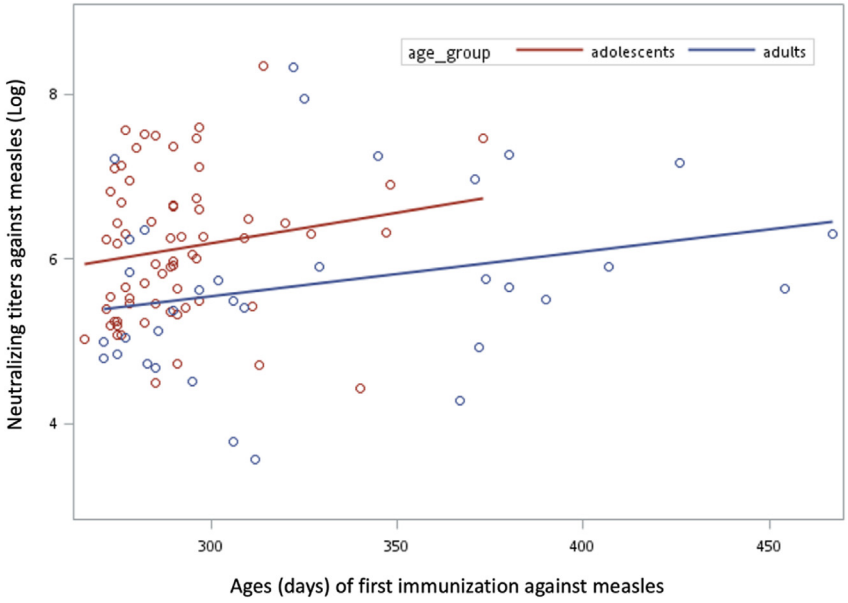

Figure 3. Association of neutralizing titers against measles and the ages of first measles-containing immunization in childhood in 100 subjects. There was a significant and increasing trend of neutralizing titers in subjects with first immunization at a later age ($P = 0.0214$) and higher PRNT in adolescents compared to adult subjects ($P = 0.0425$).

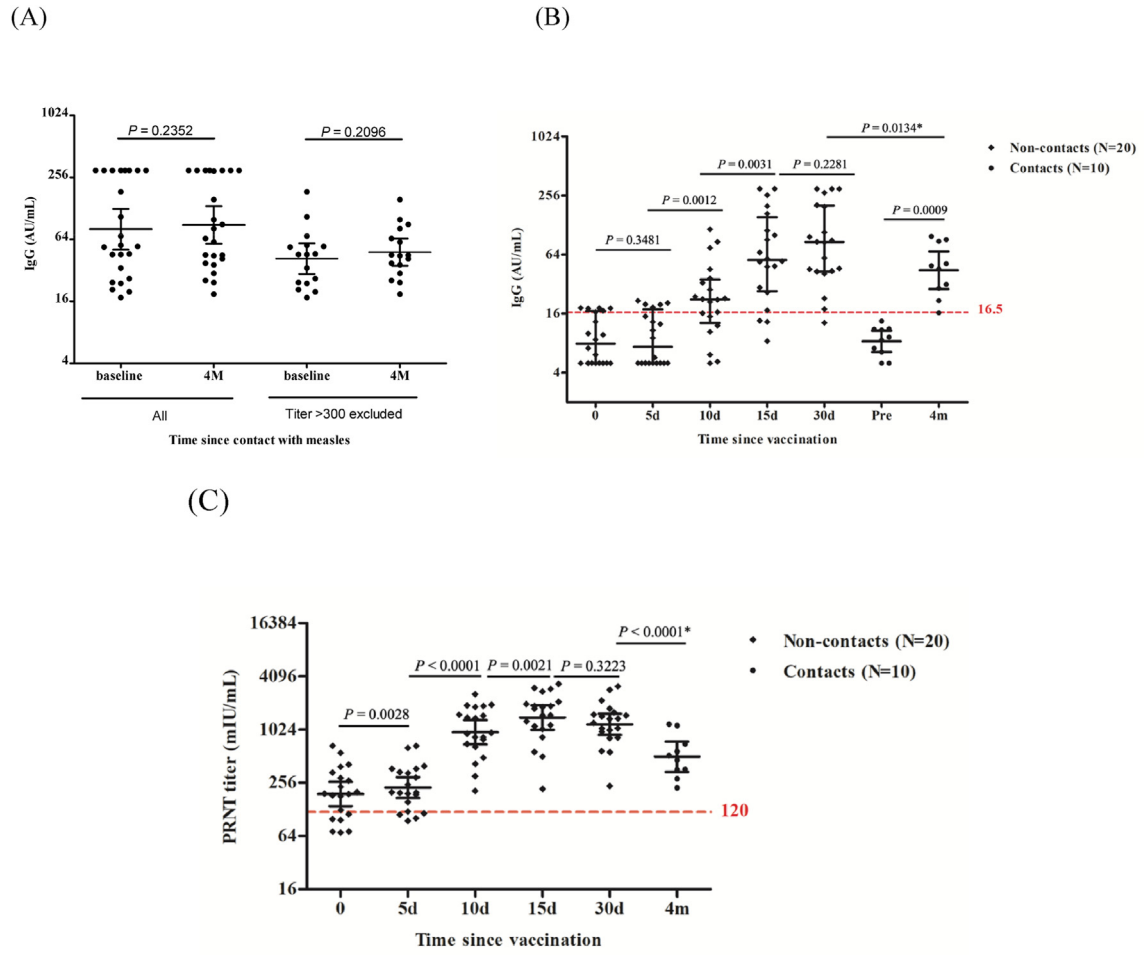

Figure 4. Dynamic change of measles antibodies in 54 healthcare workers (HCWs) during a hospital cluster in 2018. Measles-specific IgG titers at baseline and four months apart in 24 seropositive HCWs with contact to laboratory-confirmed measles cases (A). Measles specific-IgG titers within one month of booster immunization in 20 seronegative HCWs. IgG titer at baseline and four months apart are shown for 10 seronegative HCWs who had contacted to measles and received booster vaccination (B). Neutralizing antibody titers within one month of booster immunization in 20 seronegative HCWs. Neutralizing antibody titers four months apart are shown for 10 seronegative HCWs who had contracted to measles and received booster vaccination (C). The significance of the difference in titers between time points was evaluated with paired t-test if not otherwise indicated. * Two-sample t-test.

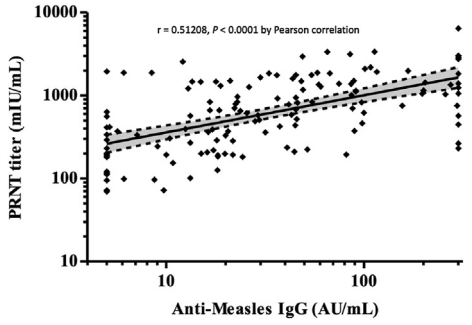

Figure 5. Correlation of measles-specific IgG titers measured by CLIA and neutralizing antibody against measles by PRNT in 100 serum samples from 20 subjects collected in five time points after immunization.

of the virus. The observation raised an important question regarding the correlation between measles-specific IgG antibody levels determined by the ELISA method and the true protection from measles. Results from the current study demonstrated that, when nAb titer by PRNT was considered as standard, measurement of binding IgG antibody levels provided only 77.2% sensitivity in detecting seroprotection to measles diseases. The seronegative rate was reduced from 28.2% by detecting measles-specific IgG to 10% by measuring functional nAb. Further, only a modest correlation was identified between the binding IgG titers and the nAb titers against measles in this study. A similar result (9.7% of seronegativity) was recently reported in young Canadian population aged 12—19 years, though with a PRNT cutoff of <112 mIU/mL defining non-immune.[18] Taken together, our data suggested that the binding antibody IgG would significantly overestimate the seronegativity of measles and was unsuitable for evaluating true protective serologic immunity to measles at the population level.

Although laborious and time-consuming, the measurement of nAb titers was a better method that provided useful and precise estimation regarding the degree of protection from diseases and virus infections.

The age of first childhood immunization against measles has long been known as the most important factor associated with primary measles vaccine failure. An early investigation in the US in the 1970s demonstrated that more than 50% of primary school students being immunized before 9 months of age were seronegative for measles.[19] The seronegative rate largely decreased to $<$10% in those being immunized at $\geq$ 13 months of age. In the current study, the age of first childhood immunization was further identified as a significant factor of nAb titers in the vaccinees in their adolescent and young adulthood with ages 11—30. Consistent with our finding, early measles vaccination before 12 months of age in infants in the Netherlands yielded a long-term decrease in neutralizing antibody response.[20] In Canada, immunization of the first measles vaccine at an early age (i.e., $<$15 months versus $\geq$15 months) was reported to be associated with a greater risk of susceptibility to measles.[10] The first immunization against measles at 12—14 months of age (compared to age $\geq$15 months old) was also identified as a significant factor associated with the absence of measles immunity in young adults in the US.[21] The multiple lines of evidence indicated that the early age of measles vaccination was associated with increased chances of both primary and secondary vaccine failures. Currently, children aged 12 months are officially recommended to receive their first measles-containing vaccine in Taiwan. Postponing the primary measles vaccination to older age (i.e., beyond 15 months old) is a reasonable approach to enhance the population's immunity after childhood and should be considered in the future policy-making of the national vaccination program.

With the population immunity lower than the threshold (95%) of herd immunity against measles, it was intriguing to learn how the population immunity would change after the re-immunization of subjects without seroprotection. Data from the longitudinal serosurvey during the hospital cluster demonstrated that the antibody response was prompt (in 5 days) in the seronegative subjects on reimmunization. The nAb level increased approximately 8 folds 15 days after booster vaccination. To mitigate the measles outbreaks since 2018 in Taiwan, a universal booster dose of MMR vaccine for seronegative healthcare workers was recommended by the Taiwan CDC. For the seronegative adult subjects, reimmunization appeared to be the logical immediate approach to improve the waning immunity. However, the long-term effect of the 3rd measles-containing vaccination remained controversial.[21,22] It was observed in the small subset of subjects in this study that the booster immunity wanned again four months after reimmunization. Further, Taiwan's single measles-containing vaccine booster policy was not widely adopted in most western countries with highly vaccinated populations. A prospective, longitudinal study across multiple years will be needed to evaluate the long-term effect of reimmunization against measles in young adults in Taiwan.

There were limitations to the study. Firstly, the seroprevalence study was conducted using the convenient blood samples collected in 2010. The epidemiological factors associated with the vaccine-induced measles antibody may not be comprehensively collected and controlled. Secondly, the birth cohort for the participants aged 11—30 in 2010 was from 1980 to 1999. The policy of measles vaccination in childhood has been changed since 2006 in Taiwan, and the age of the first measles vaccination was postponed to 12 months from 9 months old. A further study aiming at the cohort after 2006 will be needed to monitor the change of seroprevalence in the new generation. Thirdly, the residual samples from subjects aged 11—30 years were not randomly selected in the 2010 cohort, and the sample size was relatively small in the serosurveys in the hospital outbreak. The antibody data within one month and on month 4 postimmunization were from different groups. The longitudinal titer changes after one month may not be precisely estimated. Finally, the immunization history against measles in childhood was unavailable for a substantial proportion of participants. The impact of the age when 2nd vaccination was administered cannot be evaluated in this study.

Conclusion

Population susceptibility to measles disease is preferably estimated by measurement of antibodies with neutralizing activity. By this functional assay, approximately 10% of the young Taiwanese population aged 11—30 years might remain vulnerable to classic measles diseases. The lack of protective immunity was associated with a trend toward the early age of the very first measles vaccination and was more common in adults than in teenagers. The waning immunity can be boosted within 5 days of reimmunization, but the long-term durability remains unknown and further study to address this issue is warranted.

Transparency declaration

All authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.01.012.