A survey of vaccine-induced measles IgG antibody titer and the verification of changes in temporal differences of measles vaccination in young adults

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Abstract

In Japan, sporadic measles cases increased rapidly in 2019 compared to that in past 6 years. To clarify the persistence of immunity against measles in young adult, this study explored the prevalence of IgG antibody titer against measles virus in 18- to 24-year-old young adult participants. Measles-specific IgG antibody titers determined by enzyme immunoassay in serum samples collected from 506 participants between 18 to 24 years were assessed through statistical analyses. Multiple regression analysis revealed that the distribution of measles IgG antibody titers was significantly correlated with medical history ($P < 0.05$), while there was no significant difference among the number of vaccinations related to measles IgG titers. Further, measles IgG titers were significantly different, which was determined by the temporal change that elapsed period after last vaccination ($P < 0.05$). These results indicate that periodic vaccination against measles is required for young and older adults to prevent even sporadic measles infection.

Introduction

In Japan, more than 300 cases of measles were reported, which has increased rapidly compared to that in the past 6 years [1]. Measles cases were reported in 21 of 47 prefectures, and in particular, a third part of measles case were found in Osaka prefecture within 1st to 10th week in 2019 [1]. Taking measles vaccination twice in lifetime induced acquired immunity against measles in more than 95% of people [2, 3]. For the measles vaccination program in Japan, a person born after April 2006 is defined to have received 2 doses of measles vaccine as a periodic inoculation at 1-2 year and 5-7 years of age [4]. Before the Application of these regulations, there used to be only primary vaccination after 12 months of age. Thereafter, there was a change in the regulations of the Ministry of Health, Labor and Welfare recommending 2 doses of measles vaccination for people born before April 2006 with secondary inoculation being received within the duration of 5 years (2008–2012, equivalent to 13 and 18 years of age) as special measures for periodic inoculation [4]. Within the 5 -years, the rate of vaccination ranged from 77.3 to 94.3% [5]; however, recent vaccination rate exhibited more than 90% of people receiving measles vaccines twice in Japan [6]. Except for the

49 people who received secondary vaccination at limited periods, almost all young adults
50 born after April 2006 were vaccinated twice before they were 7 years of age. A large
51 measles outbreak is thought to be physically impossible in later childhood due to the
52 implementation of the measles vaccine program; however, there was insufficient
53 knowledge about the existence of protective antibody titer against measles in young
54 adults who received secondary measles vaccine within the 5 years duration limit.
55 Currently, measles cases are based on age bracket. In brief, more than 50% of measles
56 cases were seen in 15–29-year-old individuals, while less than 10–14-year-old
57 constituted only 12% [1]. Almost all young adults around 20 years of age were
58 subjected to the special measures of periodic inoculation but all of them did not receive
59 the same manner of measles vaccination. In particular, temporal changes in protective
60 serum IgG antibody against measles virus may vary in spite of receiving secondary
61 vaccination lately compared to young adults. However, temporal changes in measles
62 IgG antibody titer in generation of young adults that was subjected to special measures
63 of measles vaccine are obscure. Thus, there is a need to elucidate the factors involved in
64 the risk of the infection as well as the ways of reducing the occurrence of the infection.

65 To clarify the persistence of immunity against measles in young adults, this
66 study explored the prevalence of IgG antibody titer against measles virus in 18–
67 24-year-old young adult participants, and determined the relationships between
68 temporal changes in the antibody.
69

70 Materials and Methods

71 Study design

72 The surveillance was carried out by obtaining samples of sera from 506 young
73 adults between 18 to 24 years of age, who were first-year students in Juntendo
74 University to assess the prevalence of specific IgG antibodies against measles virus. The
75 serum samples were obtained from January 2018 to April 2018. Simultaneously,
76 vaccine history was collected from each individual's maternity passbook. The studied
77 participants also filled out questionnaires aimed at obtaining information about the
78 medical history of vaccination against measles and natural measles infection. The
79 collected information was used for proper interpretation of the obtained results.
80 The study protocol was approved by the Ethics Committee of Faculty of Health

81 and Sports Science, Juntendo University (number 30-2) and informed consent was

82 obtained from all participants and their parents before the study.

83

84 Laboratory methods

85 To determine measles-specific serum IgG antibody titer, the enzyme

86 immunoassay (EIA) was performed in the laboratory of BML, INC. (Tokyo, Japan)

87 using a measles virus immunoglobulin test kit (the Measles IgG-EIA manufactured by

88 Denka Seiken., Co., Ltd, Tokyo, Japan). For the virus antigen, Toyoshima strain was

89 used.

90

91 Statistical analysis

92 To identify the factors that influence measles-specific IgG antibody titer, multiple

93 regression analysis was performed. To avoid multicollinearity, factors were preliminary

94 determined with bivariate analysis and were confirmed to have no correlation.

95 Differences in the IgG antibody titers between the participants that had a medical

96 history of measles and those without history were evaluated with the unpaired *t*-tests.

97 To compare differences in IgG antibody titers among the numbers of vaccination and
98 temporal characteristics, a one-way analysis of variance (one-way ANOVA) was
99 employed. When there were significant statistical differences, the data were further
100 analyzed using the Bonferroni *post hoc* test to determine the significance between the
101 groups. Differences were considered significant for P values of less than 0.05.
102

103 Results

104 Outline of survey participants

105 During the blood collection for determining antibody titers in this surveillance,
106 participants who were 18 years of age were 80% of total survey participants while the
107 remaining 20% of participants were ≥ 19 years old. All the subjects who were 19 years
108 old did not receive secondary inoculations. Approximately 80% of the participants
109 received secondary vaccination, and 10% received only primary vaccination (Table 1).
110 Approximately 4% of participants had a medical history of measles based on
111 self-assessment information.
112

113 Table 1 Outline of measles-vaccine induced antibody survey participants

114

Characteristic	Number	Percentage
115 Total	506	100
Age,Y		
116 Mean	18	-
117 Range	17-24	-
Sex		
118 Female	160	32
119 Male	346	68
Vaccination		
120 1	56	11
121 2	399	79
3	21	4
122 Unvaccinated	30	6
123 Medical history	22	4

124

125 Measles-IgG titer and temporal characterization

126 The mean value of measles-specific IgG antibody titer determined by EIA

127 exhibited 13.4 ±12.0 (Mean ± standard deviation) ranging from 0.8 to 128 (Table 2).

128 The period of the month when primary and secondary vaccines were received exhibited

23.6±32.5 and 152.2 ±25.4 month, respectively. The recommended age for primary measles vaccination was to be from 12 to 90 months during 1995 to 2000, and therefore, the duration for primary vaccination was extended. Almost all participants corresponded to the special measure that was recommended for secondary vaccination at 13 years of age during 2008 to 2013, indicating that more than 80% of participants received secondary vaccination at the assigned period. Regarding all the vaccinated participants, an average of 7 years passed from last vaccination.

Table 2 Measles-specific IgG antibody titer and temporal characteristics of participants.

Item	Mean	Range	Number
Measles-specificIgG titer	13.4	0.8 - 128	506
1st vaccination months	23.6	11- 263	476
2nd vaccination months	152.2	16 - 265	420
3rd vaccination months	156.0	53 - 238	21
Elapsed months after last vaccination	83.3	0 - 237	476

145 ## Divergence of measles-IgG antibody titers by medical history

146 To discern mode of measles IgG antibody titer's distribution, multiple regression
147 analysis was performed for the IgG antibody titers and temporal characteristics. It was
148 observed that almost all parameters related to temporal characteristics had
149 multicollinearity. Thus, multiple regression analysis was performed based on Table 1
150 listed items devoid of temporal information. Of these, the distribution of measles IgG
151 antibody titers was significantly correlated with medical history of measles ($P < 0.05$).
152 Then, the differences in measles IgG antibody titers between presence and absence of
153 medical history were compared by the unpaired *t*-tests (Figure 1). The IgG antibody
154 titers collected from participants who had medical history of measles (27.0 ± 31.8) were
155 significantly higher than titers from participants who had no history (12.8 ± 9.9, $P <$
156 0.05).

157 Figure 2 shows measles IgG antibody titers that were divided into each numbers
158 of measles vaccinated and unvaccinated participants. The measles IgG antibody titers
159 from the participants who had a medical history of measles were excluded from Figure
160 2 and statistical analysis since almost all participants who had a medical history had

been unvaccinated and exhibited higher IgG antibody titer than participants who had no history. The results of one-way ANOVA showed that there was no significant difference among the number of vaccinations.

Temporal changes in measles-IgG antibody titers

To verify the temporal changes in measles IgG antibody titers after the last vaccination, the elapsed periods were divided into 5 periods including 3 month or less (n = 9), 4–12 months (n = 8), 13–60 months (n = 31), 61–72 months (n = 279), and 73 months or more (n = 73). In measles vaccine program, almost all participants received secondary vaccination at 13 years of age, and thus, approximately 70% of participants were observed in the period 61–72 months. Excluding measles IgG antibody titers from the participants who had a medical history and those who were unvaccinated, one-way ANOVA showed that there were significant differences among the 5-periods (Figure 3, $P < 0.05$). Although secondary period (4-12 month) contained a few dispersed measles IgG antibody titer values, the mean values of measles IgG antibody titer decreased with the prolonged period. The Bonferroni *post hoc* test showed that there were 4 significant

177 differences between each period ($P < 0.05$), indicating that measles IgG antibody titer

178 retains high value if elapsed period is short after last vaccination.

179

180 Discussion

181 To protect from measles virus infection, measles-specific serum IgG antibody

182 titer determined by the EIA method was required 12 or more, and in case of unsatisfied

183 titer, additional vaccination was recommended [7]. Although average measles IgG

184 antibody titer of total participants slightly exceeded 12, 56% of measles IgG antibody

185 titers from 284 participants showed less than 12. These results indicate that more than

186 half of the studied participants required additional dose to protect against measles.

187 According to WHO announcement, Japan was verified as having achieved measles

188 elimination that was defined as interruption of endemic measles virus transmission for

189 at least 36 months [8]. Nevertheless, measles cases from foreigners in Japan have

190 occurred sporadically [1, 9-12]. Based on our surveillance, one of the causes may be

191 non-persistent protection by measles IgG antibody titer in young adults. When measles

192 was endemic in Japan, approximately 200,000 people, mainly children, were infected

193 with measles virus in the year 2000 [13, 14]. Thereafter, an attempt to raise coverage of
194 measles vaccination and to enforce 2 doses vaccination rigorously was successfully
195 achieved, which led to the elimination-period [8]. Currently, protection against measles
196 infection has been achieved; "however, the generation with insufficient immunization
197 against measles virus is mainly the young adults suggesting that periodic monitoring of
198 measles epidemic and acquired immunity against measles virus in young adult is
199 required.

200 Further, this surveillance focused on the temporal status of measles IgG antibody
201 from last vaccination, although there was no significant difference in measles IgG
202 antibody titers after primary and secondary vaccination. In the United States,
203 vaccination schedule and patterns are similar to those in Japan, and measles was
204 declared eliminated with the absence of continuous measles transmission for a period
205 greater than 12 months in the United States in the year 2000 [15]. However, endemic
206 outbreaks of measles were reported to be yet to occur [16-18], and in rarity, a part of
207 those outbreaks was caused by unvaccinated population [19]. For primary vaccine
208 failure, CD46 and TLR8 variants were considered involved in the occurrence of measles

209 vaccine failure [20]. Although it will be possible to have such cases, epidemiological
210 studies have demonstrated the efficacy of measles vaccine. In brief, 95% of children
211 who received measles vaccine acquired immunity against measles virus, and further,
212 additional secondary vaccine led to more than 99% immunization in children [21-23].
213 These results revealed that epidemic outbreaks might be caused by the unvaccinated
214 population or large number of international travelers [3]. Further, according to the large
215 surveillance by healthcare workers, serum measles IgG antibody titers from adults less
216 than 29 years of age showed susceptibility to measles [24]. Single dose of measles
217 vaccine in adults was reported to have significantly increased serum IgG titers even in
218 the initial insufficient IgG titers [25]. Sporadic infection may occur in young and older
219 adults under unprotected conditions and with reduced vaccine-induced IgG antibody
220 titer due to the temporal changes after last vaccination and consequent susceptibility to
221 infection. These results also suggest that preventive vaccination against measles is
222 required for young and older adults to prevent even sporadic measles cases.
223

224 # Acknowledgements

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302

303 # Figure legends

304 Figure 1. Comparison of measles-specific IgG antibody titers based on the medical

305 history of participants.

306 The plots of IgG antibody titer that were more than 60 were omitted from Figure 1. The

307 whiskers extended to data points that were less than 1.5 x IQR away from 1st/3rd

308 quartile.

309

310 Figure 2. Comparison of measles-specific IgG antibody titers between the number of

311 vaccinated and unvaccinated participants.

312 The plots of IgG titer that were more than 60 were omitted from Figure 2. The measles

313 IgG antibody titers from the participants who had a medical history were excluded from

314 Figure 2 and statistical analysis. The whiskers extended to data points that were less

315 than 1.5 x IQR away from 1st/3rd quartile. There were no significant differences

316 between number of vaccinated and unvaccinated participants based on one-way

317 ANOVA ($P \geq 0.05$).

318

319 Figure 3. Comparison of measles-specific IgG antibody titer among 5-periods of

320 elapsed months after last vaccination

321 The plots of IgG titer that were more than 60 were omitted from Figure 3. The measles

322 IgG antibody titers of both the participants who had a medical history and the

323 unvaccinated participants were excluded from Figure 3 and statistical analysis. The

324 whiskers extended to data points that were less than 1.5 x IQR away from 1st/3rd

325 quartile. One-way ANOVA showed that there were significant differences among the

326 5-periods ($P < 0.05$). An asterisk denotes a significant difference between periods with

327 connected line ($P < 0.05$).

328

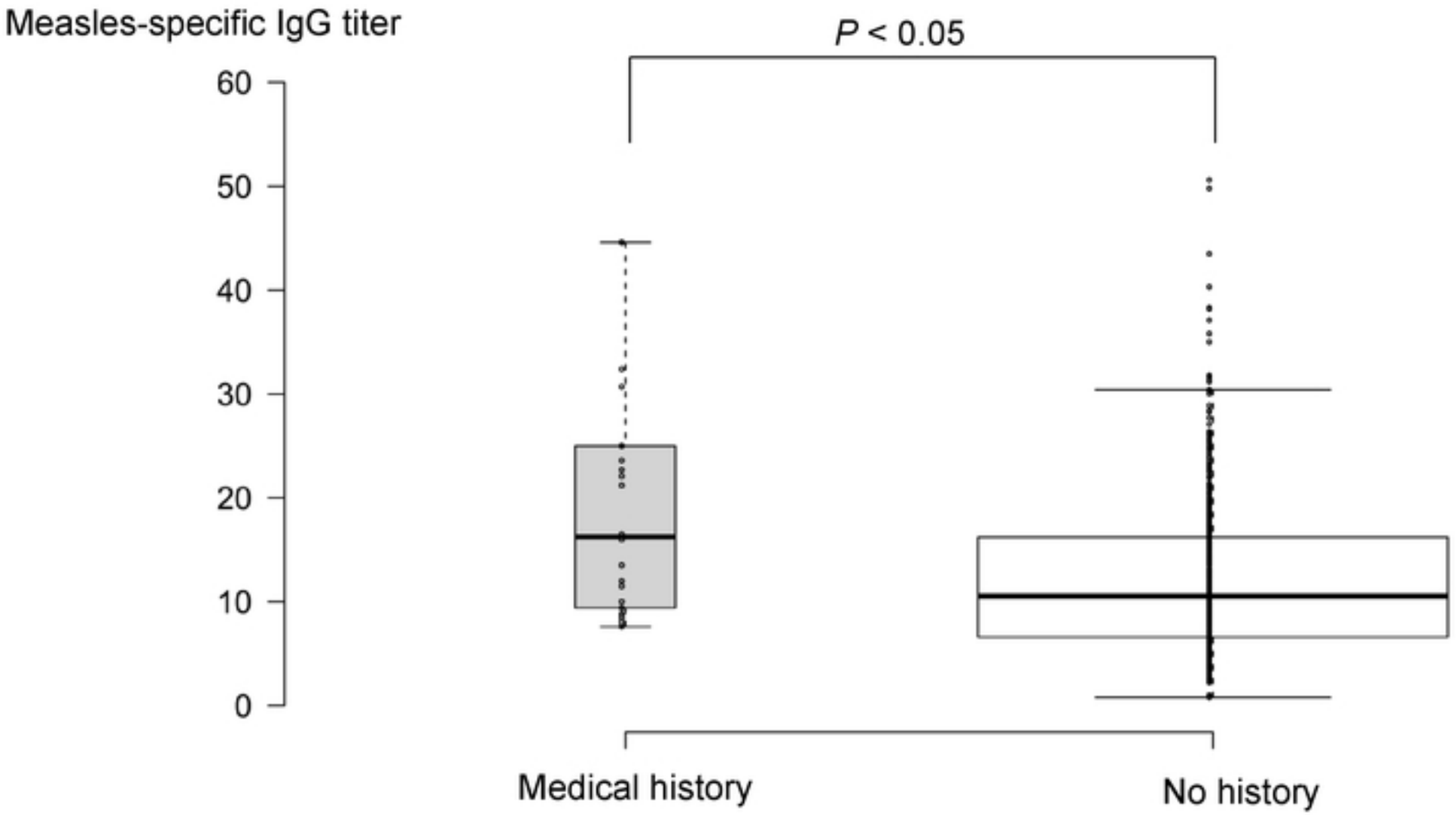
Measles-specific IgG titer
P < 0.05
60
50
40
30
20
10
0
Medical history
No history

Figure 1

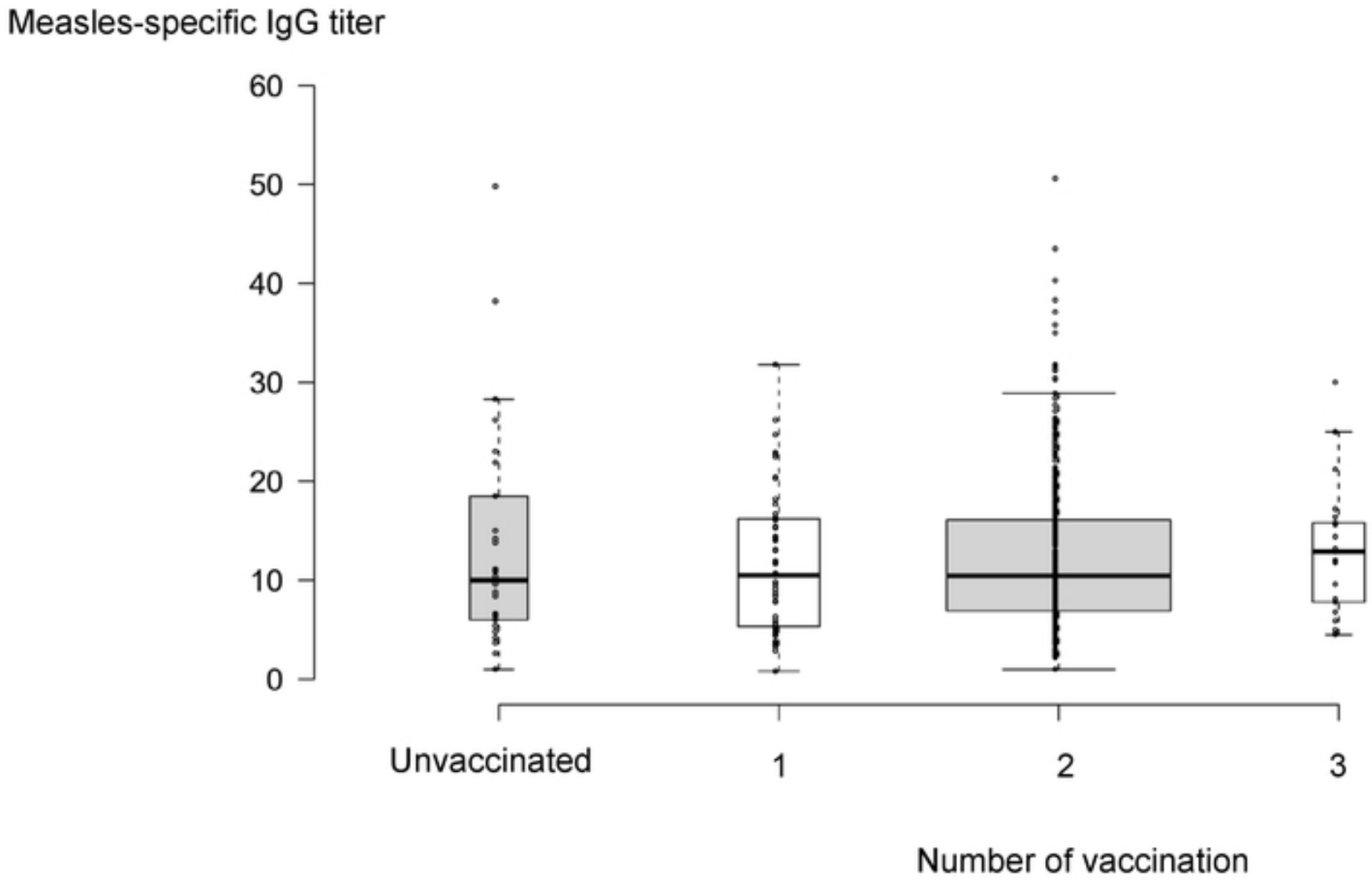
Measles-specific IgG titer
60
50
40
30
20
10
0
Unvaccinated
1
2
3
Number of vaccination

Figure 2

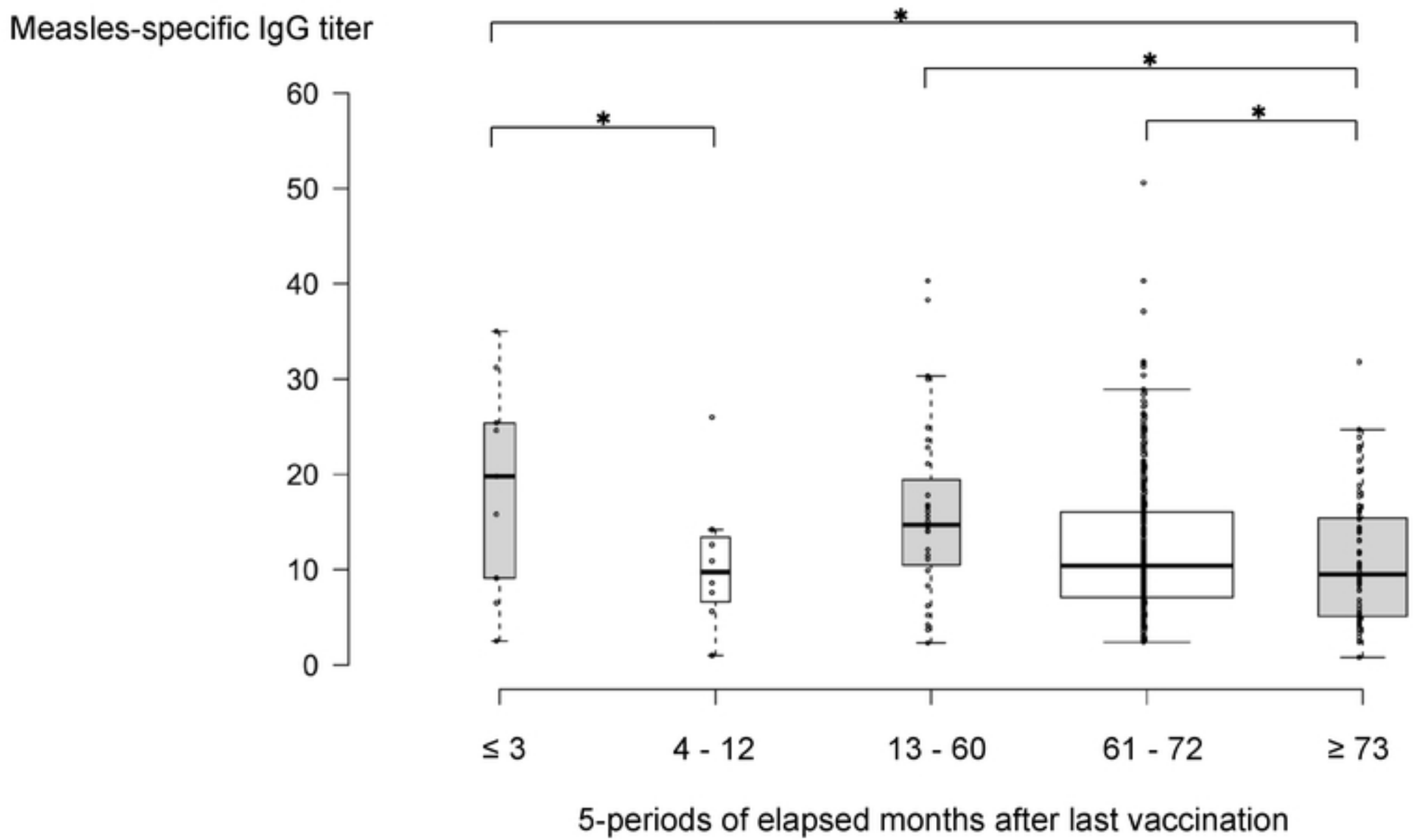
Measles-specific IgG titer
60
50
40
30
20
10
0
*
*
*
*
≤ 3
4 - 12
13 - 60
61 - 72
≥ 73
5-periods of elapsed months after last vaccination

Figure 3