

MEASLES AND MUMPS IMMUNITY IN NORTHERN GREECE, 2004-2007

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A cross-sectional study was conducted in order to determine the prevalence of mumps and measles antibodies in a representative sample of the general population in Northern Greece between January 2004 and May 2007. Overall, 900 healthy individuals participated in the study. The great majority were found to be protected against measles. The total protection rate against mumps was significantly less (87% versus 72%, respectively; $p < 0.01$). Compared to all other age groups, statistically significantly lower protection rates were found in children younger than 1.5 years ($p < 0.01$). The lowest rates of all adult groups were found in the age group of 21 to 30 years (86% and 68% for measles and mumps, accordingly). In conclusion, protection rates against both measles and mumps seem to be lower than expected in certain age groups, such as infants and young adults.

Introduction

Outbreaks of communicable diseases may occur many years after a period of low incidence following the introduction of vaccination, if a significant number of susceptible individuals has gradually accumulated. Serological surveillance studies can monitor changes in the prevalence of antibodies and possibly predict disease transmission by mathematical models [1].

Measles and mumps occur worldwide, but their incidence has decreased since the introduction of the measles, mumps, rubella (MMR) vaccine. Serious clinical complications such as encephalitis or orchitis are not rare [2-3]. Despite immunisation, mumps and, especially, measles outbreaks are still reported in Europe, even in highly vaccinated populations [4-8].

In Greece, measles vaccination was introduced in the early 1970s, when vaccines became commercially available. Vaccination at the age of 15 months was introduced in the national immunisation schedule in 1981; the MMR vaccine was introduced in 1989. Previous immunisation rates with the monovalent vaccines were significantly lower and the vaccine was given on a voluntary basis. Vaccination with a second dose of MMR at the age of 11-12 years was introduced in the national immunisation schedule in 1991, and since 1999 this second dose has been administered between the ages of four and six years. The national immunisation policy currently includes two doses of the combined MMR vaccine, one at 12-15 months, and a second at 4-6 years.

Since the introduction of vaccination, the reported incidence of measles and mumps has declined. According to the Greek Child

Health Institute, mumps and measles outbreaks have become very rare [9,10]. However, periodic outbreaks of both diseases continue to occur, and the last outbreak of measles was reported in 2005 [11-13], with 171 cases recorded between September 2005 and March 2006. Of the 171 patients, 159 (93%) were from Northern Greece [12]. The aim of the present cross-sectional study was to determine the prevalence of mumps and measles antibodies in a representative sample of the general population in Northern Greece.

Methods

Study population

The study population was recruited from the outpatient clinics of Papageorgiou General Hospital, Thessaloniki, Northern Greece. The sample included healthy individuals who underwent blood tests as part of a routine check-up between January 2004 and May 2007. Informed consent was obtained from all participants or their parents or guardians. Information including name, sex and date of birth was extracted. Data on vaccination history were not obtained as they were not available in the original data set. Subjects were excluded from the study if they presented with acute infections or had received blood transfusions in the three months prior to the study. The study did not require ethical approval by the Ethical Review Board of the Papageorgiou General Hospital.

Ten age groups were composed as follows; infants younger than six months and 0.5-1.5 years old, children 1.5-5, 5-11, and 11-20 years-old, adults 21-30, 31-40, 41-50, and 51-60 years-old, and elderly individuals over 60. Sample size was set to be proportional to the age-specific population size of Northern Greece, an estimated 2.77 million people, representing approximately 25% of the total population in Greece [14].

Sample analysis

Blood samples were obtained by venous puncture and centrifuged. The sera were stored at -20°C and used only once after thawing. Serological analysis was carried out at the microbiology/virology/biochemistry laboratory of the Papageorgiou General Hospital, Thessaloniki, Northern Greece. Blood serum levels of measles and mumps immunoglobulin G (IgG) antibodies were determined by commercial IgG-specific enzyme-linked immunosorbent assays (Genzyme Virotech GmbH, Rüsselsheim, Germany) according to the manufacturer's instructions. The coefficient of variation of the method used was $< 9\%$. IgG levels of > 12.0 Virotech Units (VE) were considered as the minimum protective level. Each serum titre was determined in duplicate.

Statistical analysis

The antibody prevalence was calculated for both sex and age groups. The chi square test was used to compare proportions. The Fisher's exact test was applied when the expected frequencies were below five. All calculations were carried out using SPSS version 14.00 (SPSS, Chicago, IL, USA).

Results

Overall, 900 healthy individuals participated in the study. The age-stratified population consisted of 428 males and 472 females (48% and 52%, respectively). The demographic distribution of each study group was similar to that of the entire northern Greek population. In particular, 6% of the tested individuals were younger than six months old, 6% were 0.5 to 1.5 years-old, 6% were 1.5 to 5, 6% were 5 to 11, 12% were 11 to 20, 14% were 21 to 30,

14% were 31 to 40, 14% were 41 to 50, 12% were 51 to 60, and 10% were 60 years-old (>1/10,000 representation in all age groups, except for the age group over 60 years). A total of 900 serum samples, collected during the study period, were analysed. The population distribution, according to age and sex, and the seroprevalence results are presented in Table 1.

The majority of our study population was found to be protected against measles (87%). Although most individuals were protected against mumps, too, the total protection rate against mumps was significantly lower (72%) ($p < 0.01$). The levels of protective antibodies against both diseases were higher in those older than 1.5 years. The protection rates found in children younger than 1.5 years (i.e. in the first two age groups) were statistically significantly lower than in all other age groups ($p < 0.01$).

TABLE 1

Mumps and measles seroprevalence, Northern Greece, January 2004 - May 2007

Age Groups	No. Tested			Measles [No (%) IgG positive]			Mumps [No (%) IgG positive]		
	F	M	Total	F	M	Total	F	M	Total
<6months	24	30	54 (6%)*	18 (75%)	18 (60%)	36 (67%)	10 (42%)	6 (20%)	16 (29%)
0.5-1.5 years	24	30	54 (6%)*	6 (25%)	8 (27%)	14 (26%)	2 (8%)	6 (20%)	8 (15%)
1.5-5 years	24	30	54 (6%)*	20 (83%)	26 (87%)	46 (85%)	18 (75%)	22 (73%)	40 (74%)
5-11 years	32	22	54 (6%)*	30 (94%)	20 (91%)	50 (93%)	26 (81%)	18 (82%)	44 (81%)
11-20 years	44	64	108 (12%)*	40 (91%)	58 (91%)	98 (91%)	32 (73%)	52 (81%)	84 (78%)
21-30 years	82	44	126 (14%)*	70 (85%)	40 (91%)	110 (87%)	54 (66%)	32 (73%)	86 (68%)
31-40 years	76	50	126 (14%)*	74 (97%)	48 (96%)	122 (97%)	64 (84%)	38 (76%)	102 (81%)
41-50 years	60	66	126 (14%)*	56 (93%)	62 (94%)	118 (94%)	54 (90%)	50 (76%)	104 (83%)
51-60 years	60	48	108 (12%)*	54 (90%)	48 (100%)	102 (94%)	50 (83%)	44 (92%)	94 (87%)
>60 years	46	44	90 (10%)**	44 (96%)	42 (95%)	86 (96%)	34 (74%)	34 (77%)	68 (76%)
Total	472	428	900 (100%)	412 (87%)	370 (86%)	782 (87%)	344 (73%)	302 (71%)	646 (72%)

F: Females; M: Males.

* representing >1:10,000 age-stratified individuals in the general population.

** representing <1:10,000 age-stratified individuals in the general population.

FIGURE 1

Measles IgG antibody-positives by age group and sex, Northern Greece, January 2004 - May 2007

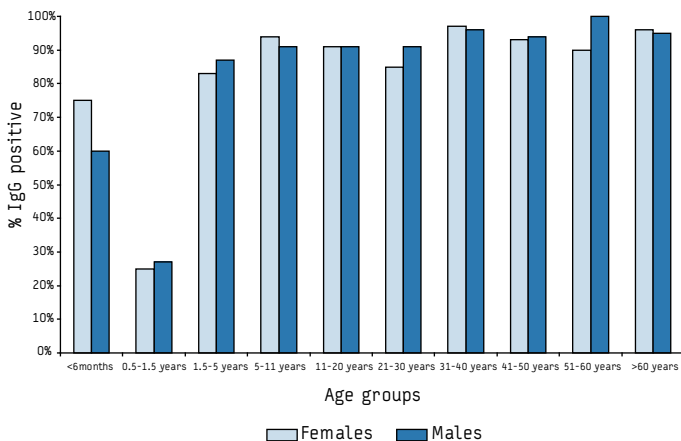
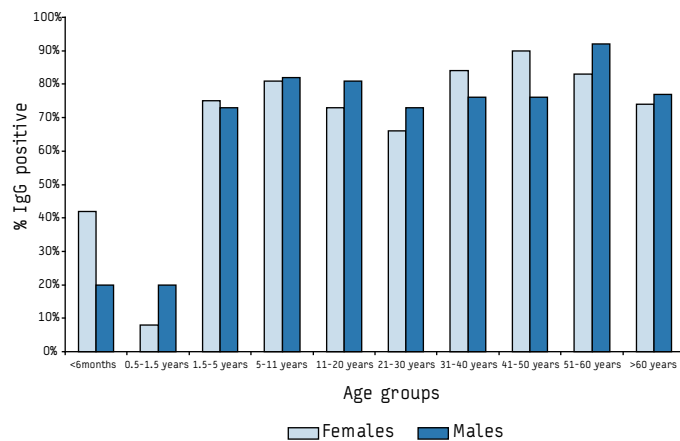


FIGURE 2

Mumps IgG antibody-positives by age group and sex, Northern Greece, January 2004 - May 2007



Those younger than six months old had higher seroprevalence rates against both diseases compared to the 0.5-1.5-year-olds (Table 1 and Figures 1 and 2). The average prevalence of mumps IgG in this group (29%) was lower than that of measles IgG (67%) and also lower than the average prevalence in all adults groups (e.g. 81% and 97%, respectively, for the 31-40 year-olds).

Another interesting finding was the low proportion of protected individuals in the group of 21- to 30-year-olds (87% and 68% for measles and mumps, respectively). This age group had the lowest seroprevalence rates of all adult groups (Figure 1), although overall, the measles and mumps IgG seroprevalence showed a continuous increase from pre-school age to adulthood. This difference was statistically significant ($p < 0.05$).

There was no significant difference in the levels of anti-measles IgG between males and females in all age groups ($p > 0.05$): 86% of the tested males and 87% of the tested females had protective antibody levels against measles. In addition, 71% of the tested males and 73% of the tested females had IgG-positive antibody titres against mumps. However, in the case of mumps, a statistically significant difference in the protection rate between males and females was found in those younger than six months old (42% versus 20%, respectively; $p < 0.01$) and the 41- to 50-year-olds (90% versus 76%, respectively; $p < 0.05$).

Discussion

During the past 25 years, measles and mumps incidence in Greece has been steadily declining, due to the MMR active vaccination programme. Vaccination coverage of pre-school children, school children and adolescents with one dose of MMR vaccine is $>95\%$ [9]. The second dose covers approximately 60–80% of the indigenous child population – a significant increase compared to the coverage 10 years ago which was only 36.5% [9]. However, two-dose vaccine coverage has been found to be very low, only 2–12%, in certain minority populations [15]. According to a recently published study, the vaccination coverage in adolescents is not satisfactory, mainly due to non-compliance with the second vaccine dose [10].

The most interesting finding of the present study was that 13% and 28% of the Northern Greek population are not protected against measles and mumps, respectively. This is probably due to the relatively low coverage with the MMR vaccine, which is reflected in an insufficient proportion of individuals in the general population who are positive for MMR-specific antibodies. The total protection rate for mumps was significantly lower than for measles. These findings are consistent with other European studies, which showed that different patterns are observed between measles and mumps seroprofiles [16,17]. In particular, as recent outbreaks have proved, the low vaccine coverage has reduced, but not completely stopped viral circulation amongst infants, resulting in the accumulation of a pool of susceptibles amongst older children and adults compared to the prevaccination era [16].

In addition, we noticed a difference in the seroprevalence of antibodies against measles and mumps, although both vaccines are administered simultaneously. This may be attributed either to primary or secondary MMR vaccine failure or to problems regarding the standardisation procedure of the laboratory assay used to determine the antibody levels [17]. On the contrary, the mumps and measles virus antibodies prevalence reported in European countries with a low incidence of the diseases, such as Finland [16] or Luxembourg [18], is significantly higher. These countries seem to

be near the elimination of both diseases. However, importation and circulation of wild virus strains in clusters of religious or minority groups can not be excluded even there.

The origin of antibodies – whether due to infection or to vaccination – could not be defined as data on vaccination status or past history of measles or mumps infection were not obtained. Children younger than 1.5 years (the two first age groups), had significantly lower protection rates against both diseases, compared to all other groups. The sub-cohort of those younger than six months old, however, had higher seroprevalence rates against measles than the 0.5-1.5-year-olds (67% versus 26%, respectively). This was to be expected due to the rapid decline of the maternal antibody levels within the first six months of life. For measles, loss of detectable maternal antibodies seemed to follow a slower pattern in time. These findings confirm previous studies showing that a window of susceptibility to both infections exists between the decay of passively acquired maternal antibodies and the start of the immune response elicited by vaccination [19]. To propose a change regarding the right timing for the administration of the first dose of the MMR vaccine and the vaccination of women of reproductive age, a balance between the need to minimise the length of the window period and the development of an optimal immune response to the vaccine should be determined.

The proportion of protected individuals was considerably lower in the age group of 21-30-year-olds (87% and 68% for measles and mumps, respectively). Lower immunity among young adults, especially males of reproductive age, has been frequently reported [4-6, 8, 20-22]. Older adults seem to be better protected, probably due to the fact that they have developed natural immunity the era before MMR vaccination was adapted in a nationwide scale. For young Greek adults born between the years 1975-1986, low MMR vaccine coverage during the first vaccination decade and the lack of booster vaccinations, as well as the coverage by the general community immunity, are possible additional explanations of low seroconversion rates, especially because the extent of natural booster is not well known.

To reach disease elimination, all susceptible individuals need to be immunised. Several alternative strategies could be launched to achieve this goal, such as offering measles vaccination to all age groups without a history of natural disease, or providing all age groups who have only received one dose of MMR vaccine a second dose in order to avoid breakthrough infections. Such strategies would include compulsory vaccination of children entering day-care facilities and/or primary school and of adolescents before entering middle school [23]. In addition, such supplemental immunisation activities targeting the population younger than 25 years (undergraduate and postgraduate students) should be expanded to those older than 25 years, provided that they belong to a “high risk” group (teaching staff, army, police, border troops, staff members of hospital units). Factors that impede children from hard-to-reach populations, such as the Roma and immigrant communities, from being immunised must be adequately addressed and special strategies should be developed to reach these populations on a regular basis.

We did not find a statistically significant difference in the seroprevalence rates against measles between males and females against measles in any of the age groups. However, it would be interesting to investigate the difference in protection rate against mumps that we noticed between males and females younger than

six months old and the group of 25-50-year-olds, a fact that could possibly be attributed to the small sample size.

The present study has certain drawbacks. Firstly, the cross-sectional type, while useful for generating hypotheses, does not permit hypothesis testing and is prone to late-look bias. Secondly, we tried to ensure that our sample was representative of the general population. The individuals included in the survey were selected randomly after stratification into age groups. The size of each age group was supposed to be proportional to the size of the same age group in the general population. However, this was not possible for all age groups. In particular, serum samples for the over 60 year-old group were extremely difficult to obtain. Moreover, our samples came from hospitals and not from municipalities (e.g. schools). As only people coming to the clinic voluntarily were included in the study, people from hard to reach communities – with probably lower vaccination rates – were not investigated, making our study vulnerable to selection bias. Nevertheless, the study population consisted of healthy individuals, undergoing blood tests as a part of a routine check-up or to obtain health certificates. Finally, the lack of clear international standards for laboratory seroprevalence testing [24] made it extremely difficult to compare our serology results with those from other countries, in which the extent of vaccination coverage and booster vaccinations varies greatly.

Conclusion

In conclusion, Northern Greece seems to remain an intermediate susceptibility country for both mumps and measles. Although the prevalence of measles antibodies is clearly higher than that of mumps, the measles outbreak in 2005-2006 revealed that indigenous disease is still present. In certain age groups such as infants and young adults born in the 1970s and 1980s, protection rates against both diseases are low. As non-compliance with the second MMR dose seems to be one of the main causes of inadequate adolescent vaccination coverage and, consequently, of the low seroprevalence rates observed in this and other studies, special attention must be paid to strengthen the two-dose MMR vaccination programmes and to improve surveillance schemes. Concrete measures to be taken in order to improve the current situation and to make progress towards elimination targets include: sustaining routine immunisation services, providing supplementary immunisation activities for susceptible population subgroups, strengthening surveillance by rigorous case investigations and laboratory confirmation, and improving the availability of high-quality information for both health professionals and the general public on the benefits and risks associated with immunisation.

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