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Original article

Seroepidemiology of measles, mumps, and rubella infections in Apulia, Italy

Séroépidémiology des infections de Rougeole, d'Oreillons et de Rubéole dans les Pouilles, l'Italie

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Abstract

Background. **–** The seroepidemiological study of measles, mumps and rubella infections was conducted in 1‰ of the population comprising groups aged 1–15 years in Apulia, according to the 1991 census.

Methods. **–** The concentration of human IgG antibodies for the three viruses was determined with an ELISA immunoenzymatic test (Dade-Behring); the geometric mean titer (GMT) specific for each disease and adjusted to the age groups (1, 2–4, 5–9, and 10–15 years) was also calculated.

Results. **–** Seroprevalence showed a typical trend. Following the physiological fall in maternal antibodies, an increased prevalence was recorded after 1 year. The trend recorded and, in particular, the marked increase in the seroprevalence data between the 1-year and the 2–4 year age groups are indicative, at least partially, of the impact of vaccination; this aspect is less evident in the case of mumps, where seroprevalence increases progressively with age. It should be noted that the number of individuals susceptible to the three viruses remains high (> 35%) in the 2–4, 5–9, and 10–15 age groups.

Conclusion. **–** This seroprevalence study seems to confirm an insufficient impact of vaccination and a continuous circulation of the wild-type viruses; for these reasons an implementation of vaccination programs is mandatory.

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Résumé

Objectif. **–** L'étude séroépidémiologique des infections de rougeole, d'oreillons et de rubéole a été menée dans les Pouilles sur l'1‰ de la population âgée de1 à 15 ans, selon le recensement 1991.

Méthodes. **–** La concentration des anticorps humains d'IgG pour les trois virus a été déterminée avec un test immunoenzymatique d'Elisa (Dade-Behring) ; on a calculé le détail du titre de moyen géométrique (GMT) pour chaque maladie proportionné aux catégories d'âge (1, 2–4, 5–9, et 10–15 ans).

Résultats. **–** La séroprévalence a montré une tendance typique. Après la chute physiologique des anticorps maternels, on a enregistré une prédominance croissante après la première année de vie. La tendance enregistré et, en particulier, l'augmentation marquée des données de séroprévalence dans les catégories d'âge 2–4 ans est indicative, du moins en partie, de l'impact de la vaccination. Cet aspect est moins évident dans le cas des oreillons, où la séroprévalence augmente progressivement avec l'âge. Il convient de remarquer que le nombre d'individus sujets aux trois virus augmente (> 35%) dans les catégories d'âge 2–4, 5–9, et 10–15 ans.

Conclusion. **–** Cette étude de séroprévalence semble confirmer un impact insuffisant de la vaccination et d'une circulation continue du sauvage-type virus ; c'est pour cela qu'une application des programmes de vaccination est obligatoire.

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Mots clés : Pouilles ; Rougeole ; Oreillons ; Rubéole ; Séroépidémiologie

1. Introduction

Measles, mumps and rubella (MMR) are highly contagious, airborne infections with a peak incidence occurring in children during their first 10 years of life. These infections cause a major public health problem when one considers the total number of patients needing medical attention, the frequency of some "minor" complications (otitis, arthralgia, myalgia, arthritis, meningism, etc.), as well as the risks related to serious complications (orchitis, postinfectious encephalitis, subacute sclerosing panencephalitis, pneumonia, meningitis, and, in the case of rubella, the congenital syndrome) [1].

For these reasons, the World Health Organization (WHO), while establishing the objectives with regard to vaccine-preventable diseases, has underlined the importance of a definite and continuous action towards measles, mumps and rubella infections.

In particular, the WHO has pointed out that eradicating/eliminating these three diseases requires the achievement of high vaccination coverage (CV) (>90%) [2].

Only with high vaccination levels the resulting herd immunity would provide an indirect protection to unvaccinated susceptible individuals also, as in the presence of high CV (>90%) wild-type viruses would be less likely to circulate and infect susceptible individuals [3]. It should be noted that the vaccination levels not sufficiently high to eliminate/eradicate an infectious disease induce substantial changes in the disease epidemiology in the long run. In fact, while the absolute number of cases is reduced, the mean age of acquisition shifts upwards [4]. This effect, designated as "perverse", is particularly dangerous in the case of MMR, as the frequency and severity of their complications are directly proportional to the age of acquisition; moreover, the greater the age of acquisition, the larger the number of infections in women of childbearing age. This event is generally unfavorable, more so in the case of rubella [5].

In Italy, MMR vaccinations are not mandatory. Based on the data available, the estimated CV is unsatisfactory [6].

As a matter of fact, a great variation among regions in terms of vaccination programs and immunization coverage has been observed [7]. In southern Italy, and particularly in Apulia, the CV is still below 80%.

The Ministry of Health, with the circular no. 12, on 13th July 1999 [8], has provided some operative instructions for the implementation of vaccination programs against MMR to reach high CV rates in all regions. For this reason, it was planned as a two-dose strategy. The main point of this program was the recommendation of the use of the second dose, only in areas where the CV rate of the first one was more than 80%.

According to the interventions set by the Ministry of Health in 1999 [8], the regions with low CV% (<80%) have to increase coverage up to 95% for all children within 2 years of age, to plane catch up of susceptible subjects at every contact with the health service after 2 years, and to continue with selective rubella vaccination for adolescent girls till the achievement of CV >95% with two doses of MMR vaccine. As an alternative, mass campaigns can be planned to rapidly decrease the number of susceptible individuals older than 2 years.

In regions, where MMR CV% is more than 80% for all children within 2 years and the rate of susceptible subjects older than 2 years is less than 10% it has been planned to increase the CV% of age and to 95% within 2 years and to introduce a second dose of MMR vaccine at 5–6 or 11–12 years of age.

An additional problem is the incompleteness of morbidity data. Despite their being notifiable [9], these three diseases are still greatly underreported, particularly in southern Italy. This fact affects all information systems based on a passive reporting system and prevents a correct epidemiological analysis.

Availability of precise epidemiological and vaccination data is essential, as an adequate surveillance system allows to evaluate the trend of the diseases in space and time, identify possible outbreaks early, define health interventions, and verify the achievement of goals [10].

Within this context, we identified the importance of a seroepidemiological study in the population aged 1–15 years in Apulia, southern Italy, where the CV% against MMR in subjects between 12 and 24 months of age is estimated to be 50.6% [11].

2. Materials and methods

The seroepidemiological study was conducted in a number equivalent to 1‰ of the population comprising groups aged 1–15 years in Apulia, according to the 1991 census (888,881 inhabitants).

Sera were collected according to the European Project for the Seroepidemiological Surveillance of vaccine-preventable diseases [12]. Anonymous unlinked samples of residual sera from routine laboratory testing were collected, excluding samples from subjects with immunosuppressive or acute infectious disease and from individuals recently transfused. Informed consent was provided by parents or legal guardians.

Sera were aliquotated and stored at –20 °C until they were tested for the detection of antibodies specific for MMR viruses.

The concentration of human IgG antibodies for the three viruses was determined with an ELISA immunoenzymatic

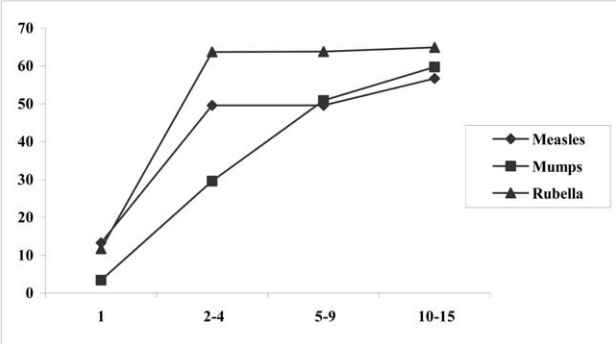

Fig. 1. MMR seroprevalence in Apulia.
Fig. 1. Séroprévalence de la rougeole, des oreillons et de la rubéole dans les Pouilles.

test (Dade-Behring) by following the manufacturer's instructions, which indicated that the sensitivity and specificity of the methods were 99.6% and 100% for measles, 95.4% and 93.7% for mumps, and 100% and 98.5% for rubella, respectively.

The analytical sensitivity (cut-off value) of the different tests is 4 IU/ml for rubella, 150 mIU/ml for measles, and 231 U/ml for mumps.

The geometric mean titer (GMT) specific for each disease and adjusted to the age groups (1, 2–4, 5–9, and 10–15 years) was compared using Student's *t*-test; one half the cut-off value was assigned to the negative samples. The percentages were compared with χ^2 test and Fisher's exact test.

3. Results

Altogether, 870 sera were tested for MMR, which corresponded to 1‰ of the population comprising groups aged 1–15 years in Apulia.

Seroprevalence showed a typical trend. Following the physiological fall in maternal antibodies, an increased prevalence was recorded after 1 year.

Specifically, the seroprevalence of measles increased significantly from the 1-year to the 2–4 year age groups (13.3% vs. 49.6%; $P < 0.01$); subsequently, no significant variations in seroprevalence were reported (49.6% and 56.7% in the 5–9 and the 10–15 age groups, respectively) (Fig. 1).

Similarly, the seroprevalence of mumps was significantly different between the 1-year and the 2–4 year age groups (3.4% vs. 29.6%; $P < 0.01$) and between the 2–4 and the 5–9 age groups (29.6% vs. 50.9%; $P < 0.01$). Seroprevalence in the 10–15 age group (59.8%) was not statistically different from that in the 5–9 age group (50.9%) (Fig. 1).

With regard to rubella virus infection, it should be noted that, as in the case of measles, after a significant increase was recorded between the 1-year and the 2–4 year age groups (11.7% vs. 63.7%; $P < 0.01$), seroprevalence remained virtually unvaried between the 5–9 and the 10–15 age groups (63.8% and 64.9%, respectively) (Fig. 1).

The trend recorded and, in particular, the marked increase in the seroprevalence data between the 1-year and the 2–4 year age groups are indicative, at least partially, of the impact of vaccination; this aspect is less evident in the case of mumps, as seroprevalence increases progressively with age. It should be noted that the number of individuals susceptible to the three viruses remains high (>35%) in the 2–4, 5–9, and 10–15 age groups.

The number of individuals simultaneously positive for antibodies specific for measles and rubella was 40.0%, 27.6% and 36.1% in the 2–4, 5–9, and 10–15 age groups, respectively, while the subjects positive for the three viruses were 20%, 18.5% and 16.4% in the 2–4, 5–9, and 10–15 age groups, respectively.

With regard to measles, the GMT in the samples tested showed a significant increase between the 1-year and the 2–4 year age groups (from 120.7 to 502.4 mIU/ml; $P < 0.01$), a stable level between the 2–4 and 5–9 age groups, and a subsequent marked rise between the 5–9 and 10–15 age groups (456.8 and 753.2 mIU/ml, respectively; $P < 0.01$) (Fig. 2).

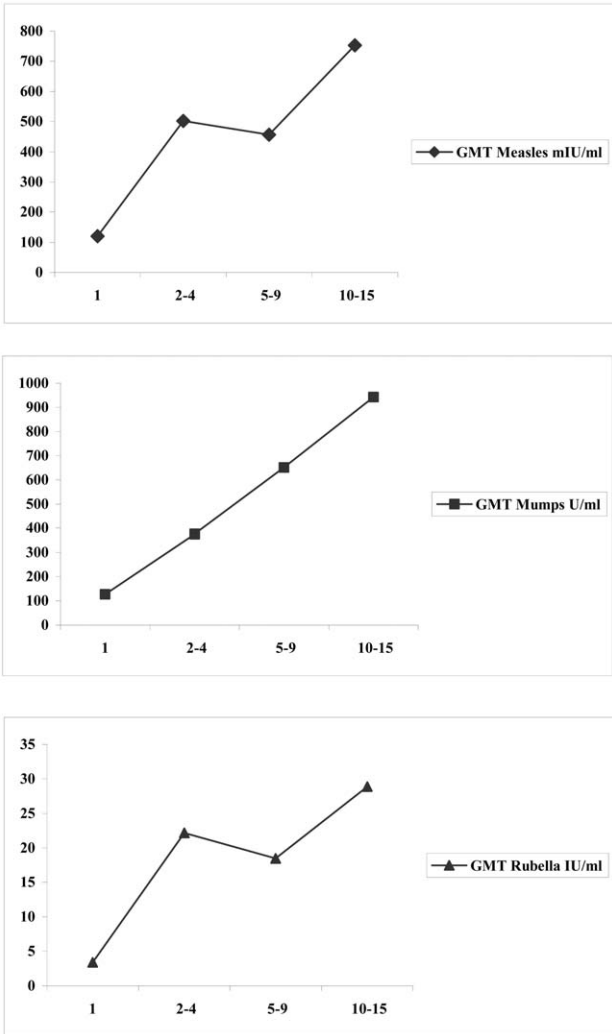

Fig. 2. MMR GMTs in Apulia.
Fig. 2. Les TMG de la rougeole, des oreillons et de la rubéole dans les Pouilles.

With regard to mumps, the GMT showed a significant rise from one age group to the next ($P < 0.01$), reaching 943.3 U/ml in the 10–15 year age group (Fig. 2).

With regard to rubella, GMT increased significantly between the 1-year and 2–4 year age groups (3.4 and 22.2 IU/ml, respectively; $P < 0.01$) and between the 5–9 and 10–15 age groups (18.5 and 28.9 IU/ml, respectively; $P < 0.01$) (Fig. 2).

4. Discussion

Seroprevalence studies allow for evaluating the impact of a certain infectious disease and/or its vaccination in a population [13], by integrating the data derived from notifications. These data are highly underestimated and, in the case of MMR, this depends not only on underreporting, but also on under diagnosing, as these infections, in particular rubella and mumps, can occur with few or no symptoms.

In Apulia, as in the rest of the country, measles is regarded as an extremely frequent, endemic, children's infection, with epidemics recurring every 3–4 years [14].

The seroprevalence study shows that, from the age of 1 year onwards, the number of individuals with antibodies specific for the measles virus rises from 13.3% in children aged 1 year to 49.6% in the 2–4 and 5–9 age groups. Seroprevalence further increases to 56.7% in the 10–15 age group.

Based on the data collected, it emerged that, also in Apulia, the measles seroepidemiological pattern corresponds to high susceptibility, with a percentage of seronegative subjects greater than 35% in the 2–4, 5–9, and 10–15 age groups. The impact of vaccination can, therefore, be only partially observed.

Similarly, the rubella seroprevalence study seems to confirm an insufficient impact of vaccination [15] and a continuous circulation of the wild-type virus.

With regard to mumps, the results are similar to those for measles and rubella. Specifically, it should be noted that, also in Apulia, for a long time, the mumps vaccination was conducted with a product not optimal in terms of immunogenicity, which may account for the different seroepidemiological trend compared with the other two infections considered. This remark is confirmed by the fact that in the 2–4 age group, the number of individuals with antibodies for all three infections corresponded to 20.0% vs. 40.0% of individuals with antibodies specific for measles and rubella.

The WHO Regional Office for Europe has long established objectives with regard to some children's vaccine-preventable infections, including MMR [16].

Unfortunately, to date these goals have not been achieved as yet.

Italy, in particular, is still far from meeting this goal, compared with other European countries. The National Health Plan 1998–2000 has established, as a priority, the achievement of MMR CV of 95% by the second year of age for all newborns [17]. In fact, sustaining the eradication of these three infections and avoiding "perverse effects" (mainly, the rise in the mean age of acquisition) require high CV. More recently, "specific operational directions" have been provided "in order for the Regions, Local Health Agencies, and all other agencies specifically mentioned in the National Vaccine Plan, to implement the MMR vaccination, aimed at the control and elimination of the target infections" [14].

Once the objective of a high MMR CV% is achieved (>95% by the second year of age for all newborns and <10% of susceptible subjects older than 2 years), the two-dose strategy will be fully implemented (first dose at 12–15 months of age and second dose at 5–6 or 11–12 years of age) [8].

In Apulia, the CV rate against MMR in children aged 12–24 months is 50.6% [11]. This CV% is quite similar to the one shown by the last national vaccination survey carried out in 1998 in which a national CV in the 12–24 months age class equal to 56% was reported [7]. According to our data, the health education campaign should be maintained and aimed to create cooperation between parents and healthcare personnel (Public Health, Pediatricians, etc.) in order to increase the non-mandatory vaccination programs.

Considering the inadequate CV in Apulia, it is necessary to define interventions in all those areas, where measles CV by the second year of age is below 80%, such as:

- raising CV to 95% by the second year of age for all newborns;
- recovering susceptible subjects at each contact with the vaccination service after the second year of age for all newborns;
- maintaining selective rubella vaccination programs for pre-pubertal girls until coverage over 95% is achieved by two doses of MMR vaccine. Alternatively, special campaigns may be organized to reduce dramatically and rapidly the number of susceptible subjects older than 2 years.

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