

Epidemiology of measles, mumps and rubella in Italy

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SUMMARY

A serosurvey for measles, mumps and rubella was conducted in Italy; incidence based on statutory notifications over the last three decades was also calculated. In Italy the diseases followed an endemic–epidemic pattern, with an incidence peak every 2–4 years, and had a limited reduction of incidence attributable to childhood immunization. Lower notification rates were observed in the Southern regions. This is possibly related to greater under notification in the South and is confirmed by our seroprevalence data. Incidence of measles and rubella and proportion of cases among young adults increased significantly in the three decades considered, but not for mumps. Serological data confirmed that these infections are still very frequent in Italy, without significant geographic variation in the country. In the age groups 2–4 and 5–9 years the percentage of individuals still susceptible to each virus was higher than 30%. The proportion of susceptible subjects older than 15 years was similar for the three infections (6·1, 11·7 and 8·8% for measles, mumps and rubella, respectively). The low vaccine coverage for rubella and measles in Italy has so far only partially affected the occurrence of the diseases. No impact of mumps vaccination is visible. The average number of deaths, for each disease, has decreased during the three study periods. Today the priority in Italy is to halt the progressive increase of the mean age of acquisition of the three infections, to eliminate differences in coverage among regions and to conform to European standards. This will be achieved through a combination of increasing MMR vaccine coverage before 2 years of age, implementing vaccination campaigns for low seroprevalence age groups, and/or introducing a second dose of MMR, depending on the level of current MMR coverage.

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INTRODUCTION

Measles, mumps and rubella are acute viral infectious diseases, characterized in the pre-vaccination era by endemic pattern with epidemics occurring every 2–4 years [1].

The burden posed by these diseases is not only due to their ability to spread into the population causing high number of cases, but also to the seriousness of

clinical complications in a not negligible proportion of cases. Moreover, complications during measles infection may be more serious if the infection is acquired in the first year of life or at adult age [2]. Similarly, some serious complications of mumps (i.e. orchitis) are more frequent after puberty [3]. Congenital rubella can occur when the infection is acquired in pregnancy [4].

All these infections and complications can be prevented by vaccination and WHO-EURO has included measles, mumps and rubella as diseases to be eliminated. For measles a target of eradication has been set for the European Region by the year 2007 [5].

Vaccinations against measles, mumps and rubella are not mandatory in Italy and for a long time there has been a great variation among regions in vaccination programmes and in immunization coverage [6]. In 1999 the Ministry of Health set some operative recommendations in order to reduce the regional differences and to reach a national coverage of 95% in the second year of life [7].

To be effective, vaccination programmes must reach high coverage and be organized in order to reduce the proportion of susceptible individuals in the population and, consequently, interrupt transmission [8].

Seroepidemiological studies allow the gathering of information about the proportion of immune and susceptible subjects in the population due to the circulation of infectious agents and allow the evaluation of the impact of vaccination programmes, identifying the need for additional efforts when elimination is feasible [9].

In the present paper results from a national serosurvey are presented and discussed together with disease notification data and vaccine coverage data in order to characterize the epidemiology of these three vaccine preventable viral diseases and estimate the effect of vaccination programmes carried out so far.

MATERIALS AND METHODS

Incidence of diseases

In Italy, clinically diagnosed cases of measles, mumps and rubella must be statutorily notified [10]. Data on each case are recorded on individual forms and eventually entered into a national computerized database at the Italian Institute for Statistics (ISTAT). We analysed notifications of measles, mumps and rubella for the period preceding the collection of sera for the seroprevalence study 1971–96.

Age-specific incidence was calculated for the following age groups: 0–4, 5–9, 10–14, 15–24, 25–44, ≥ 45 years and proportional distribution of cases in the different age groups was computed for the period under study. In the country, the occurrence of the three diseases by geographical area has also been considered for the period 1971–96 (North: Piedmont, Val d'Aosta, Lombardy, Trentino-Alto Adige, Veneto, Friuli-V. Giulia, Liguria, E. Romagna; Centre: Tuscany, Umbria, Marches, Lazio; South: Abruzzi, Molise, Puglia, Calabria, Sicily, Sardinia).

Mortality

Mortality data were also obtained for the period 1980–96, 1996 being the most recent year for which data were available.

Vaccination coverage

Data on vaccination coverage were available from two wide cluster sampling surveys carried out in 1993 and in 1998 on children aged 12–24 months.

Serosurvey

Anonymous unlinked samples of residual sera from routine laboratory testing were provided by a reference laboratory in each region. Sera from individuals known to be affected by immunosuppressive conditions or by an acute infection or to have recently undergone blood transfusion were excluded. All individuals who provided serum samples gave verbal informed consent. Consent for minors was provided by parents.

According to the seroprevalence study protocol [11], the sample size was set at 3400 sera. Specifically, 100 samples for each 1-year interval in the age-range 0–19 years (a total of 2000 samples) were taken and 200 samples for each 5-year or 10-year interval for ages 20 years and over (i.e. 20–24, 25–29, 30–34, 35–39, 40–49, 50–59, and 60 and over, to a total of 1400 samples). Eighteen out of 20 Italian regions provided serum samples, which were divided by age-group (for samples from individuals under 1 year of age, the age in months was specified).

A total of 3538 samples were collected from September 1996 to October 1997 and were stored at -20°C until tested for measles, mumps and rubella antibodies.

Detection of antibodies

Serological testing was performed at the University of Genoa (Department of Health Sciences, Hygiene and Preventive Medicine Section). The serological assays were standardized within the European Sero-Epidemiology Network project [12].

Commercial Enzyme Linked Immuno Sorbent Assays (ELISA), (Enzygnost anti-Measles-virus/IgG, Enzygnost anti-Rubella-virus/IgG, Enzygnost anti-Mumps-virus/IgG, Behring) were used to detect and quantify human IgG antibodies to measles, rubella and mumps viruses in serum.

Sensitivity and specificity of the methods used are, according to the manufacturer, respectively 99.6% and 100% for measles, 100% and 98.5% for rubella and 95.4% and 93.7% for mumps.

The results are expressed in mIU/ml for measles, IU/ml for rubella and U/ml (titre) for mumps.

Statistical analysis

The crude annual incidence rates were computed using national population as reported in censuses conducted in 1961, 1971, 1981 and 1991. Rates, standardized by age, were computed using the 1991 census population as the reference population.

Data were analysed by means of the χ^2 test and Student's *t* test; the χ^2 test was used to compare percentages and Student's *t* test was performed to assess differences among means. Geometric mean titres (GMTs) were computed on all positive antibody titres as arithmetic means of logarithmically transformed values.

RESULTS

Incidence

The annual standardized incidence rates in the period 1971–96 for measles, mumps and rubella showed an endemic–epidemic pattern (Fig. 1) with the characteristic incidence peak every 2–4 years, particularly evident for measles and rubella.

For measles the average standardized annual incidence was 75.1, 83.0 and 66.6 cases per 100 000 inhabitants respectively in the period 1971–80, 1981–90 and 1991–6.

For mumps, overall incidence increased over the last two decades; the average standardized annual incidence was 59.4 cases per 100 000 inhabitants in the

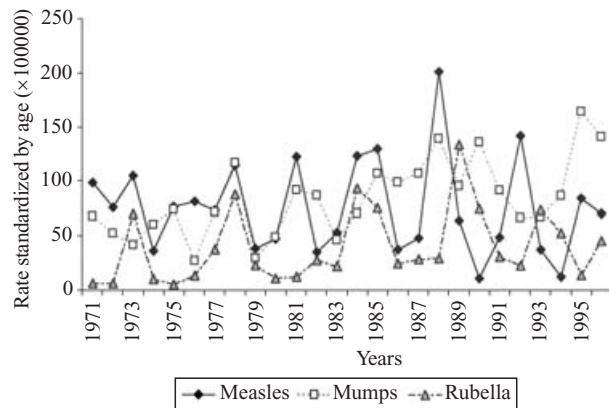


Fig. 1. Measles, mumps and rubella incidence ($\times 100\,000$) according to official notifications; Italy, 1971–96.

period 1971–80, 98.6 in the 1980s and 103.5 in the period 1991–6.

In the same periods the average standardized annual incidence per 100 000 inhabitants for rubella was 27.4, 52.9 and 40.7 (Fig. 1).

Comparing trends in different age groups in the three periods 1971/80, 1981/90 and 1991/6, some important features were evident.

For measles, incidence progressively decreased ($P < 0.01$) in the age groups 0–4 and 5–9 years while it significantly increased in the age groups 10–14, 15–24 and 25–44 years ($P < 0.01$) (Fig. 2a).

Incidence of mumps significantly ($P < 0.01$) increased in the period under consideration in the age groups 0–4, 5–9 and 10–14 years; in the age groups 15–24, 25–44 and ≥ 45 years, incidence remained almost stable in the period 1981/90 and then slightly decreased in the period 1991/6 ($P < 0.01$) (Fig. 2b).

Incidence of rubella in the age groups 0–4 and 5–9 years significantly ($P < 0.01$) increased in the decade 1981/90 and subsequently decreased; on the contrary, in the age groups 10–14 and 15–24 years incidence significantly ($P < 0.01$) increased in the period 1981/90 and remained high in the following years (Fig. 2c).

Analysing data notified in the three periods considered, it is noteworthy that, for measles and rubella, the proportion of cases among young adults increased significantly ($P < 0.01$ in the age groups 10–14, 15–24, 25–44 and ≥ 45 for measles and $P < 0.01$ in the age groups 10–14 and 15–24 for rubella). For mumps, the percentage of cases did not show any trend.

Comparing the incidence by different geographical areas (Northern, Central and Southern Italy) a great disparity in the number of notified cases was evident, with significantly lower rates in the Southern regions,

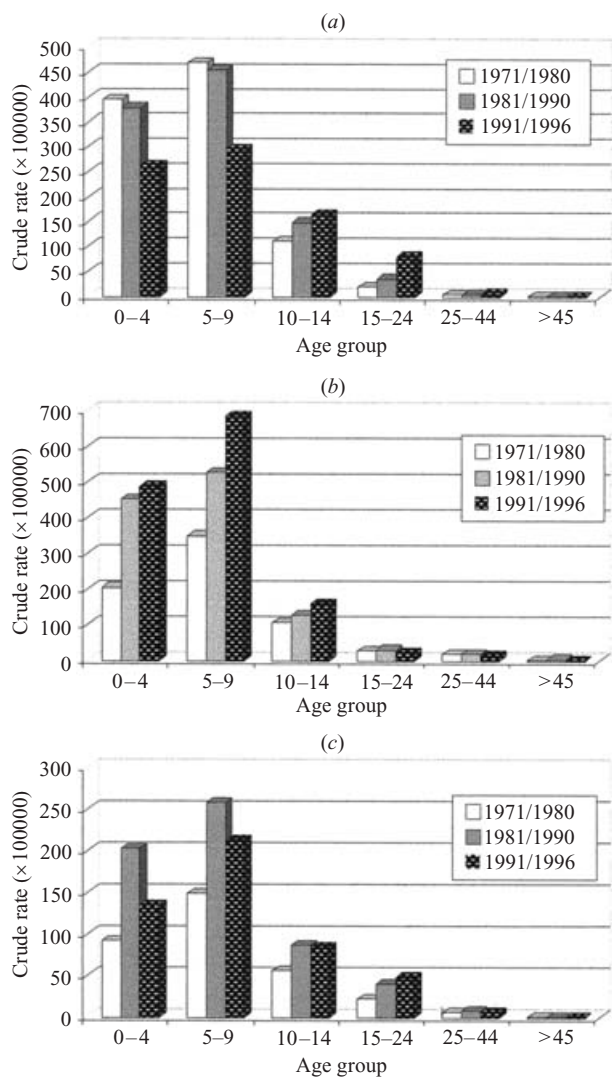


Fig. 2. Measles (a), mumps (b) and rubella (c) incidence by age group according to official notifications; Italy, 1971–96.

even if trends were overlapping. For measles, in the North, incidence reported in the decades 1971–80 and 1981–90 is three times the incidence reported in the South, while in the period 1991–6 this difference decreases by 1.5 times. For mumps, the incidence is constantly three times higher in the North of the country, whereas for rubella, the ratio between notification rates in Northern and Southern Italy decreases from 5.5 in the period 1981–90 to 2.9 in the period 1990–6 (Fig. 3).

Vaccine coverage

The results obtained from a EPI cluster sampling survey carried out in seven regions in 1993 on the 1991 birth cohort showed an immunization coverage

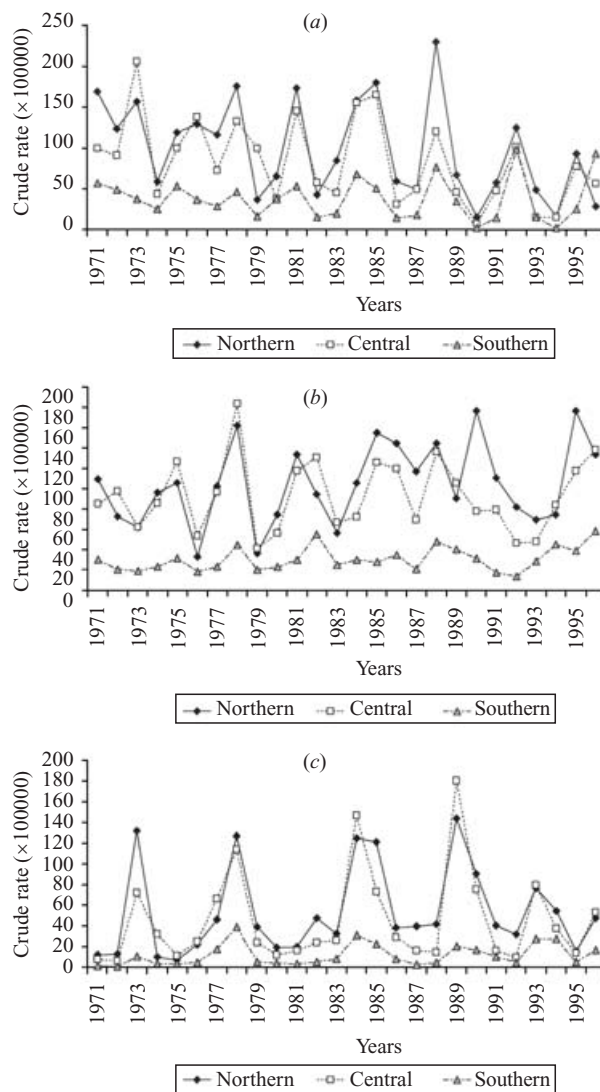


Fig. 3. Measles (a), mumps (b) and rubella (c) incidence by geographical area according to official notifications; Italy, 1971–96.

for measles ranging from 9 to 53% [13]. A similar survey carried out nationwide in 1998 on the 1996 birth cohort showed higher coverage (56%) [6], even though still insufficient for controlling the disease. Since measles vaccine is administered in 94% of cases as MMR vaccine, vaccination coverage for mumps and rubella is estimated to be around 53% in the second year of life.

Deaths

A yearly average of 13.3 deaths caused by measles were reported in 1980–9 while in the 1990–6 period the average number was 7.2. Analysing death data by

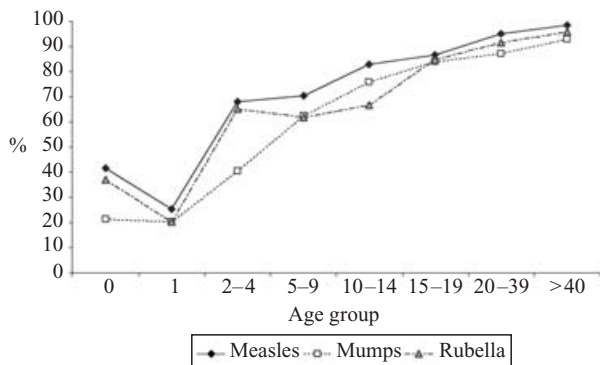


Fig. 4. Measles, mumps and rubella seroprevalence by age group; Italy, 1996–7.

age group, a similar shift in the age of deaths as there have been for acquisition of disease has been highlighted in the two periods. The percentage of deaths in the age group older than 14 years is increased from 30% in the period 1980–9 to 60% in the period 1990–6.

For mumps a total of 21 deaths were reported in the period 1980–9 (yearly average of 2.1) and a total of 4 deaths in the period 1990–6 (yearly average 0.6), while a total of 17 deaths for rubella were reported in the period 1980–9 (yearly average of 1.7) and a total of 3 deaths in the period 1990–6 (yearly average of 0.4).

Seroprevalence

A total of 3538 samples collected in the period September 1996–October 1997 from 18 regions were analysed. Seroprevalence showed a decrease in the first months of life due to loss of maternal antibodies, and a continuous increase after the first year of life. In the age groups 2–4 and 5–9 years the percentage of individuals still seronegative for each virus was higher than 30%; in the case of rubella this percentage remained stable even in the older age group 10–14 years (33.3% of seronegative subjects). In the age group 2–4 years the proportion of subjects positive for measles and rubella antibodies was 59%, probably attributable to vaccination, while the proportion of children immune to all three infections at the same age was only 32% indicating a different immunogenicity of the three vaccines. At 14 years of age only 46% of subjects had antibodies against all the three diseases.

Seroprevalence for measles exceeded 80% from the age of 14 years, while for mumps and rubella the same level of seroprevalence was reached later at 19 years (Fig. 4). Although measles, mumps and rubella are

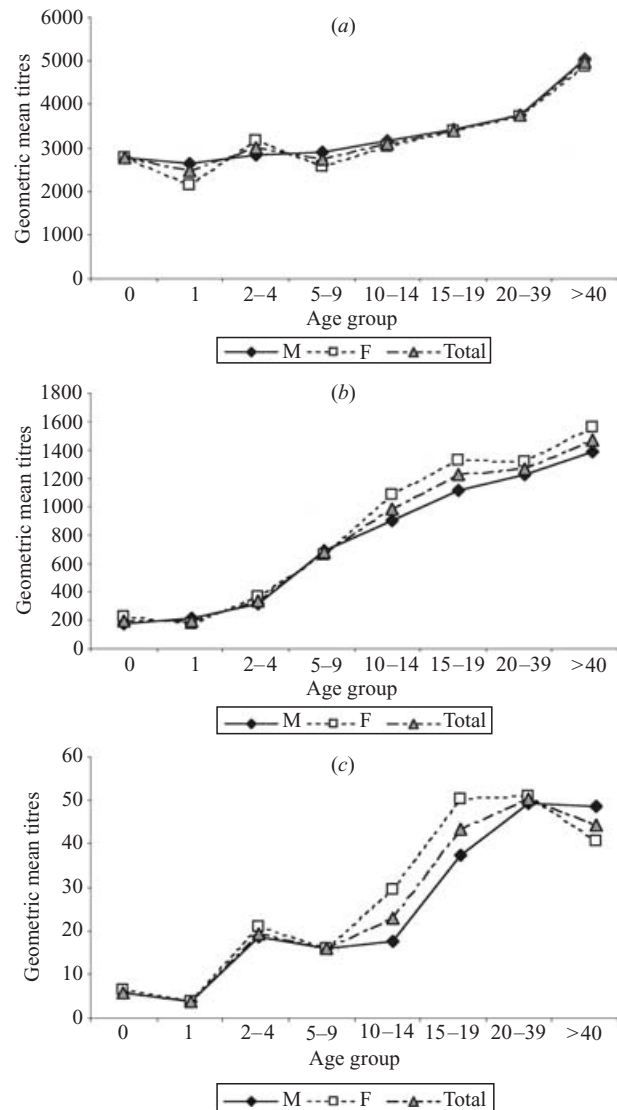


Fig. 5. Geometric mean titres for measles (a), mumps (b) and rubella (c) antibodies by age group and gender; Italy, 1996–7.

very frequent infectious diseases among children, a proportion of susceptible individuals over 20 years of age was present in 1996/7 (respectively 6.1% for measles, 11.7% for mumps and 8.8% for rubella in individuals ≥ 15 years).

The GMTs for measles showed that after a slight decrease in the first year of life, there is a progressive and continuous increase in the older age groups, (Fig. 5a); significant differences among gender were not evident except for the age group 1 year of age ($P < 0.05$) and > 40 years ($P < 0.05$). For mumps, the GMT increased continuously with age and there was a significant difference between genders with higher

values in females of 15–19 years ($P < 0.05$) age group and > 40 years ($P < 0.05$) age group (Fig. 5b), while for rubella there was a significant difference in GMTs between male and female in the age group 10–14 years ($P < 0.05$) (Fig. 5c).

From the analysis of data by geographical areas (Northern, Central and Southern Italy) the seroprevalence for the three diseases was substantially homogeneous. The only relevant differences were in the age group 10–14 years for measles ($P < 0.05$) with a higher seroprevalence in the Southern regions; in the age group 5–9 years ($P < 0.01$) for mumps, with a higher seroprevalence in the Northern regions; in the age group 10–14 ($P < 0.01$) and 20–39 years ($P < 0.01$) for rubella, with a higher seroprevalence respectively in the Southern regions and in the Northern regions.

DISCUSSION

Monitoring the circulation of vaccine-preventable infection in the general population is the priority when assessing the impact of immunization programmes and setting the targets for further actions. Data from various sources contribute to the monitoring: incidence, seroprevalence and vaccination coverage. In Italy incidence data are largely underestimated and in the case of measles, mumps and rubella this is mainly due to undernotification. Even though overall undernotification is decreasing, the different incidence rates for these diseases in the North and in the South of the country, underline that there is still a greater degree of undernotification in the South of the country. This assumption is well supported by our seroprevalence data.

Seroprevalence studies are important because they allow an estimate of the amount of susceptible and immune subjects in the population, and, when integrated with available incidence data, to assess the impact of immunization programmes [14].

In designing this seroprevalence study, we attempted to ensure that the sample be representative, following guidelines provided by the European Project for the Sero-epidemiological Surveillance of Vaccine-Preventable Diseases [11].

Vaccination against measles, mumps and rubella is not mandatory in Italy and vaccine coverage is sub-optimal as shown by the last nation wide vaccination survey carried out in 1998 on the 1996 birth cohort which indicated that the national vaccination coverage against measles in the age group 12–23 months

was approximately 56%, with wide regional differences in the proportions of immunized children, ranging from 26 to 87% [6]. The estimated vaccination coverage for mumps and rubella in the second year of life is about 53%.

In line with the Italian immunization policy, recommended by the Ministry of Health in the 1980s, in some regions selective vaccination of pre-pubescent females for rubella has been performed but no systematic coverage data are available.

Measles

In Italy, measles is a very frequent disease in infancy. Vaccination against measles was introduced in Italy at the end of 1970s. Single antigen measles vaccine was offered at 13–15 months of age and it was replaced by MMR vaccine (at the same age), when it became available. However, the different implementation of the vaccination strategy all over the country led to a very heterogeneous regional situation with a national estimated coverage around 56% [6, 15]. This is coherent with the results of the present study. In fact, the epidemiological trend was different in the various regions and the low, unsatisfactory vaccination coverage led to a reduction of incidence and to an increase of the mean age of acquisition of the disease.

According to measles notifications, before the 1990s the great majority of children acquired the disease before the age of 10, while after the 1990s an increase of notifications in subjects older than 10 years was observed, pointing out a shift in the age distribution of cases compatible with the partial reduction of incidence attributable to vaccination.

The serosurvey results showed that the proportion of immune subjects rapidly increases in childhood from 25.5% in the age group 1 year to 68.1% in the age group 2–4 years, probably due to immunization, reaching 70.7% in the age group 5–9 years. The subsequent increase of seroprevalence attributable to natural infection is smaller: from 83.1 to 98.6% in the age groups from 10–14 to > 40 years.

Seroprevalence data showed that Italy is a country at high susceptibility for measles since almost 30% of individuals in the age groups 2–4 and 5–9 were still seronegative. In addition, even though the seronegativity decreased with increasing age, it remained $> 10\%$ until 15–19 years.

So far, the impact of vaccination has been limited to younger individuals and after a decline in the overall incidence, a large amount of cases can be expected

because of the accumulation of susceptible individuals in absence of an optimal vaccination coverage.

Rubella

Vaccination against rubella with live attenuated vaccines started in Italy in the early 1970s, targeted at pre-pubescent females. Even though many regions adopted this strategy and routinely offered the vaccine, there were great differences among geographic areas even within the same region. Nowadays, most of the rubella vaccinations are performed using the combined measles–mumps–rubella (MMR) vaccine in childhood, but the estimated vaccine coverage rate remains unsatisfactory [6].

The incidence of rubella did not change in the last decades meaning that even if a part of the population has been immunized, the overall risk of acquiring the infection in the population has not been lowered. On the contrary, the attainment of a vaccine coverage not sufficient to eradicate the disease, has entailed, as in the case of measles, only a partial reduction of incidence related to an increase of the median age of acquisition of the disease, which in the case of rubella is much more dangerous considering the possible consequences of infection acquired in pregnancy [16].

The increase of the seroprevalence among individuals from 10 to 30 years reflects the continuous circulation of the wild virus due to the inadequacy of the vaccination strategy.

Data stratified by region confirm a different use of the vaccine in the various geographic areas.

Mumps

The incidence of mumps remained substantially unchanged in the last two decades showing no impact from MMR vaccine use. As a matter of fact, immunization against mumps has been recommended in Italy to special target groups of the population such as young adult males particularly at risk of infection or complications (military recruits, etc.) [17].

Although vaccination coverage with the combined MMR vaccine is largely unsatisfactory the epidemiology of mumps seems to be unaltered, with an increase in incidence during the last years even in the age groups targeted for the vaccination. The explanation for such observation, to some extent, could be the use of less efficacious vaccines including the Rubini strain [18].

Conclusion

For many years, the WHO (European region) has targeted measles, mumps and rubella as diseases for which it is possible to plan eradication [5]. Unfortunately, up to now elimination has not yet been achieved; in particular, in Italy the low vaccine coverage has reduced, but not stopped, viral circulation for measles and rubella, resulting in a pool of susceptible individuals among older children and among adults, while no control was achieved for mumps.

For these reasons the National Health Plan has set as a target the achievement of a vaccination coverage for measles, mumps and rubella of 95% within the second year of age for all newborns [19]. Considering that the eradication of the three diseases without negative effects (mainly represented by the increase of the mean age of acquisition of the disease) is possible only with a very high vaccination coverage, in 1999 the Ministry of Health provided Regions and Local Health Units with some operative instructions [7] for the implementation of vaccination programmes against these diseases. Moreover, the use of mumps vaccine containing Rubini strain was discontinued in July 2001.

Considering the epidemiological situation and taking into account the serosurvey results, the priority objectives in Italy are to halt the progressive increase of the mean age of acquisition of the infections, to eliminate differences in coverage among regions and to conform to European standards.

To achieve these objectives, the strengthening of health education activities, targeted to parents and to health workers, is essential in order to increase the compliance to recommended vaccinations.

Considering substantial regional variation in vaccination coverage, two types of intervention have been decided. The first, to be adopted by regions where vaccine coverage is less than 80%, anticipates: increasing coverage up to 95% within 2 years of age; a catch up of susceptible individuals at every contact with the health service after 2 years of age; and continuing with selective rubella vaccination for adolescent girls until the achievement of coverage >95% with two doses of vaccine MMR. As an alternative, mass campaigns can be organized in order to rapidly decrease the number of susceptible individuals older than 2 years of age.

In areas where vaccine coverage for MMR is more than 80% by the age of 2 years and the percentage of susceptible individuals older than 2 years of age is

less than 10%, it was planned to increase the vaccine coverage by 2 years of age up to 95% and to introduce a second dose of MMR vaccine at 6 or 12 year of age.

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