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G. Gabutti[a,*], M. Guido[b], M.C. Rota[c], A. De Donno[b], M.L. Ciofi degli Atti[c], P. Crovari[d], the Seroepidemiology Group[1]

[a] Department of Clinical and Experimental Medicine, Section of Hygiene and Occupational Health, University of Ferrara, Via Fossato di Mortara 64, 44100 Ferrara, Italy
[b] Department of Biological and Environmental Sciences and Technologies, Laboratory of Hygiene, University of Salento, Lecce, Italy
[c] National Center of Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanità, Rome, Italy
[d] Department of Health Sciences, Section of Hygiene and Preventive Medicine, University of Genoa, Genoa, Italy

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ABSTRACT

In Italy, although vaccination has been recommended for a number of years, vaccination coverage for mumps is still sub-optimal. The objective of the present study was to evaluate the seroprevalence of mumps antibodies in the Italian population, stratified by age, gender and geographical area. The proportion of individuals positive for mumps antibodies remained stable in the age classes 0–11 months and 1 year (25.4% and 30.8%, respectively) and showed a continuous increase after the second year of life. The percentage of susceptible individuals was higher than 20% in persons 2–14 years of age and exceeded 10% in persons 15–39 years of age. No statistically significant differences were observed by gender or geographical area. Comparison between these results and the data obtained from a 1996 survey showed a statistically significant increase in seroprevalence in the age class 2–4 years. No changes were observed in the other age-groups. The results of this study confirm that the efforts made in recent years to improve vaccination coverage within the second year of life should be strengthened.

1. Introduction

Mumps is an acute contagious disease which is endemic worldwide [1]. Infection typically occurs in childhood, though it can also occur in adults, among whom some complications can be more frequent than among children. Infection, even if asymptomatic, induces a long-lasting immunity [2].

The disease is usually benign, and 30% of paediatric cases are asymptomatic. Severe complications, though rare, include hearing loss in children (5/100,000) and encephalitis (incidence of <2/100,000 cases, of which 1% are fatal). Adults have a greater risk than children of meningo-encephalitis. When acquired after puberty, mumps can be related to orchitis, testicular atrophy and even sterility in males, and to mastitis and oophoritis in females. Mumps infection in the first 12 weeks of pregnancy may result in foetal loss [3]. Other important characteristics of mumps are the occurrence of asymptomatic forms, the infectious period preceding the possible clinical onset, and the lack of a specific therapy.

The epidemiological impact of mumps and its possible sequelae have prompted the development of a vaccine, which currently represents the best option for preventing the disease and its complications.

The mumps vaccine contains live attenuated virus and is available as a single-antigen preparation, as a trivalent combination with measles and rubella vaccines (MMR) [4], or as a quadrivalent combination with measles, rubella and varicella vaccines [5]. More than 10 different live attenuated viral strains are included in mumps vaccines worldwide.

In Italy, for many years the Rubini strain has been widely used. The poor effectiveness in preventing mumps of this strain and its nationwide use has contributed to the failure of control of this disease in the 1990s [6]. In June 2001 the registration of the products containing this specific vaccine strain was revoked [7] and since then widely used live attenuated mumps vaccine strains in Italy have included or include the Jeryl Lynn, Urabe and RIT4385 strains.

The adoption of a single dose schedule has led to a significant decrease in the incidence of mumps, yet outbreaks continue to occur in school settings [8–10]. A two-dose schedule is reportedly even more effective in decreasing mumps incidence and has allowed many countries to achieve near-elimination of the dis-

* Corresponding author. Tel.: +39 0532 455568; fax: +39 0532 205066.
E-mail addresses: giovanni.gabutti@unife.it, gcg@libero.it (G. Gabutti).
[1] D. Bassetti, A. Bechini, S. Boccalini, P. Bonanni, P. Caciagli, A. Camper, A.M. Campa, W. Caraccio, A. Cavallaro, E. Ciamarra, L. Clerico, L. Casentino, E. de Simone, A. Favero, A. Focà, L. Genna, A. Giammanco, A. Giancotti, A. Goglio, S. Grandesso, G.C. Icardi, C. Lolli, D. Marchetti, M. Marsella, P. Martelli, L. Mucignat, D. Palladino, C. Passerini, V. Perani, E. Piscione, F. Rizza, A. Zizza, L. Simula, R. Sforza, D. Tagliatatela, M. Tronci and D. Villalta.

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ease, as defined by WHO (incidence <1 case/100,000 inhabitants) [3,11,12].

In Italy there are some mandatory vaccinations (diphtheria, tetanus, polio, and hepatitis B), but mumps is not.

In 1982, immunization began to be recommended for pre- and post-pubertal susceptible males [13], and since 1999, a trivalent combined vaccine (MMR) has been available and actively offered free of charge to all children in the second year of life [14]. The 2005–2007 National Vaccination Plan recommends using a two-dose schedule [15]. Although vaccination coverage (VC) has increased as a result of the use of the MMR vaccine, it is still suboptimal. The national mean VC in children 15–23 months of age was estimated to be 56% in 1998 and 77% in 2002 [16,17].

The objective of the present study was to describe the epidemiology of mumps in Italy using a number of data sources and to determine whether or not there have been changes in seroprevalence by comparing the results of two studies conducted 8 years apart.

2. Materials and methods

2.1. Incidence data

In Italy, mumps is subject to mandatory notification [18], and all reported cases are recorded by Italy's National Census Bureau (ISTAT). The clinical case definition is sufficient for a case to be reported; laboratory diagnosis is not required. The clinical case definition is a mono or bi-lateral swelling of salivary glands (parotidis or others glands) lasting at least 2 days and absent/moderate fever, without other concomitant pathologies.

We calculated the incidence for the period 1991–2004 for the entire country and for three main geographical areas (northern Italy, central Italy, and southern Italy and the islands), based on mandatory notifications, using as reference the Italian population included in the national census (for the years 1991 and 2001) or estimates provided by ISTAT (for the remaining years). We also calculated the trend in incidence for the periods 1991–1995, 1996–2000 and 2001–2004, by age class: 0–14, 15–24, 25–64, and ≥65 years. For each of these periods, the trend in incidence by geographical area and the percentage of notifications in different age groups were also determined.

2.2. Analysis of other databases

Given that mandatory notification is affected by underreporting, we analysed data from other databases with information on mumps. In particular, we considered the incidence data for the years 2000–2004 provided by Italy's Paediatric Sentinel Surveillance System of Vaccine-Preventable Diseases (SPES), a network of paediatricians located throughout Italy and co-ordinated by the Istituto Superiore di Sanità (Italy's National Health Institute). We also examined the National Hospital Discharge Database, created in 1994, which collects information on all hospitalisations recorded in Italy [19]. For the analysis of this latter database, we considered the main reason for hospitalization, which is codified using the ICD9-CM code (0072 for mumps). The analysis was performed on data for the period 1999–2004.

2.3. Seroprevalence study

A national cross-sectional population-based seroprevalence study of mumps antibodies was performed on samples collected in the period from January 2003 to October 2004 in each of Italy's 19 Regions and 2 Autonomous Provinces. Assuming an overall mumps prevalence of 70%, a sample size of 2017 sera was required to achieve 95% confidence intervals, with a precision of the estimate of 2%. The samples, taken for diagnostic purposes or routine ascertainment, had been frozen at −20 °C until use and were analysed by the same national reference laboratory (University of Salento, Lecce).

For each individual from whom blood had been collected, the purpose of the study was explained and oral informed consent was obtained. We excluded from the study immuno-compromised patients, patients who had received a blood transfusion in the previous 6 months, and patients with an acute infectious disease.

Each Regional reference laboratory was asked to collect 6 samples for each year of age in the 0–20-year age group, 10 samples for each 5-year range in the 21–40-year age group, and a total of 10 samples for the 41–50-year age group. The samples had to be equally representative of males and females. Mumps antibodies were quantified using an immunoenzyme micro-method (Enzygnost Anti-Parotitis-Virus IgG, Dade Behring, GmbH), which has a high sensitivity and specificity (95.4% and 93.7%, respectively) [20].

The following criteria were applied for the qualitative evaluation:

IgG negative sample	$\Delta E < 0.100$ (cut-off)
IgG positive sample	$\Delta E > 0.200$
Equivocal IgG sample	$0.100 < \Delta E < 0.200$

The equivocal samples were retested: if the result was confirmed, the sample was classified as "equivocal". The IgG positive samples were quantitatively evaluated using the following formula: Log_{10} titer $= \alpha \times \Delta E^{\beta}$, where α and β represent lot-dependent constants. Antibody activity was expressed as titer.

2.4. Statistical analysis

The statistical analysis was performed using STATVIEW 5.1 for Macintosh (Abacus Concepts, Inc., Berkeley, CA, 1992). Seroprevalence data were summarized as percentages, and positive antibody titres were presented as geometric means. Differences between percentages were assessed by the χ^2-test, whereas differences between geometric mean titres were assessed by Student's t-test of logarithmically transformed values. The data were also analysed by gender and geographical area and were then compared with results obtained from a seroprevalence study conducted in 1996 using the same assay and cut-off [21].

3. Results

3.1. Incidence data

Based on data provided by ISTAT, mumps was confirmed to affect a large portion of the population and to be characterized by an endemo-epidemic course, with outbreaks every 4–5 years. The overall annual incidence ranged from 125.1 to 4.5 cases per 100,000 population in the years 1991–2004 (Fig. 1).

For all three periods (1991–1995, 1996–2000 and 2001–2004) and the different age groups (0–14, 15–24, 25–64 and >65 years), it was clear that mumps mainly affects children (0–14 years). However, in this age group, the incidence progressively and significantly decreased ($p < 0.01$), from 409.2 cases per 100,000 population in 1991–1995, to 365.9 in 1996–2000 to 97.6 in 2001–2004. A similar trend, with a significantly decreasing incidence, was found in the other age groups when comparing different periods ($p < 0.01$, except for persons older than 65 years of age when comparing 1996–2000 to 2001–2004, $p < 0.05$).

When comparing persons 0–14 years of age to all older individuals, the differences in the percentage of cases did not significantly change over the three periods. The analysis by geographical area showed that the trend in incidence was similar when comparing

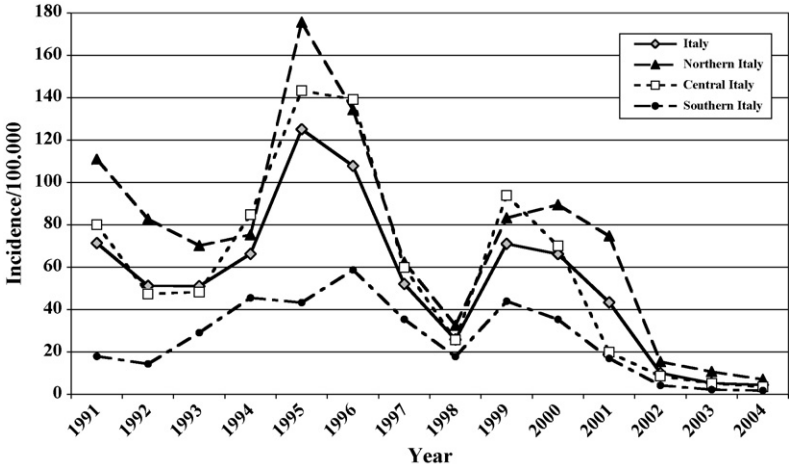

Figure 1. Annual mumps incidence per 100,000 population in Italy between 1991 and 2004 (total and by geographic areas) (Italy's National Census Bureau, ISTAT).

Table 1
Incidence of mumps per 100,000 children 0–14 years, Italy, 2000–2004

Year	Northern (Italy)	Central (Italy)	Southern (Italy)	Italy
2000	1917	2274	1830	1939
2001	1518	665	761	1039
2002	302	206	150	220
2003	215	81	116	149
2004	109	65	54	79

Data from paediatric sentinel surveillance (SPES).

the three areas and that there was a clear north–south gradient, with the highest incidence consistently found for northern Italy, followed by central and southern Italy (Fig. 1).

3.2. Analysis of other databases

In the period 2000–2004, 11,697 cases of mumps were reported to SPES, with the annual incidence progressively decreasing from 1939 per 100,000 children (0–14 years) (2000) to 79 per 100,000 children (2004). In general, incidence rates were higher in northern and central Italy than in southern Italy (Table 1).

According to the National Hospital Discharge Database, in the period 1999–2004 there was an annual mean of 363 hospitalizations and 247-day-hospital admissions for mumps, with a peak in 2000 (619 and 325 hospitalizations and day-hospital admissions, respectively). The mean duration of stay was 2.54 days.

3.3. Seroprevalence study

Overall, 3094 blood samples were analysed; 2276 were positive, 621 were negative, and 197 were equivocal. The seroprevalence showed a typical pattern. In the first year of life (when children are passively protected by the mother), 25.4% of individuals 0–11 months old were seropositive; among 12–23-month olds, the seroprevalence was 30.8% (difference not significant). For 2–4-year olds, the seroprevalence significantly increased (64.4%, $p < 0.01$ compared to 12–23-month olds); it continued to increase with age, though not always significantly: 65.0%, 78.9%, 83.5%, 89.2% and 92.8%, respectively, for the age classes 5–9, 10–14, 15–19, 20–39 and >40 years (Fig. 2). Of note was the finding that the percentage of seronegative individuals was greater than 20% in the age groups 2–4, 5–9 and 10–14 years and greater than 10% in the age classes 15–19 and 20–39 years.

No statistically significant difference was found in seroprevalence when comparing males and females (Fig. 2). The trend in seroprevalence was basically uniform when comparing the three geographic areas, with no significant differences (Fig. 3).

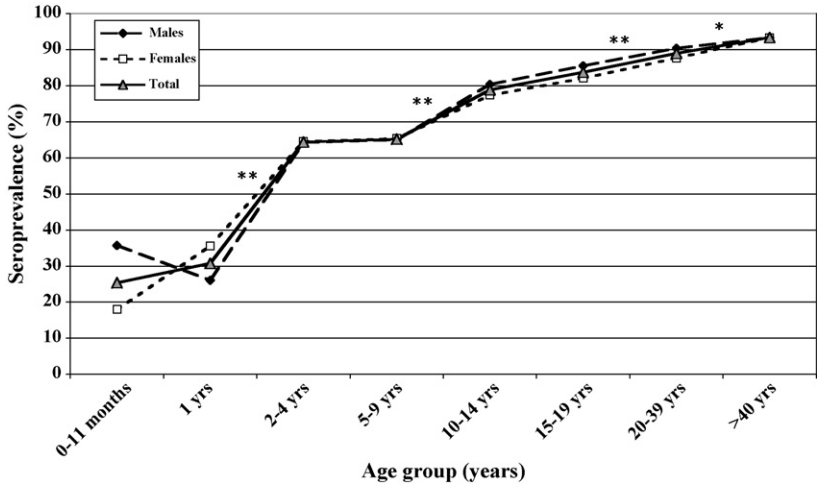

Figure 2. Mumps seroprevalence by age group and gender in Italy (2004). χ^2-test: $^*p < 0.05$; $^{**}p < 0.01$.

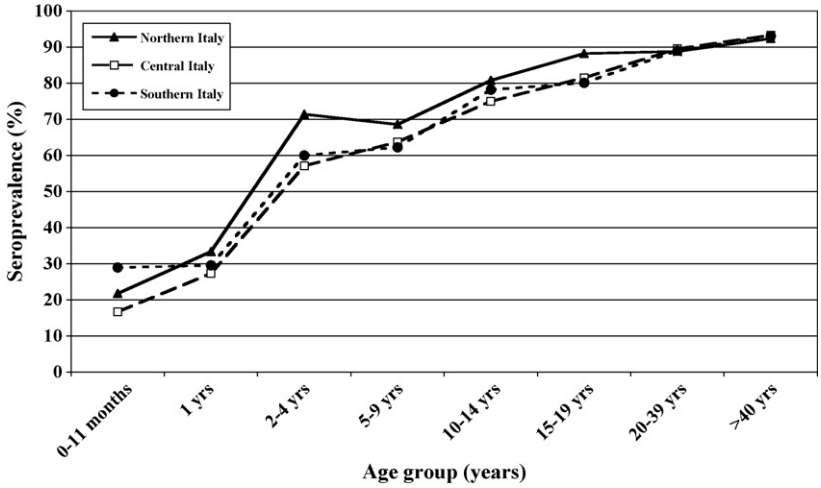

Figure 3. Mumps seroprevalence by geographical area in Italy (2004).

Figure 4. Comparison between mumps seroprevalence by age-group, Italy 1996 and 2004. χ^2-test: $^{**}p < 0.01$.

The GMT progressively increased up to 10–14 years and then significantly ($p < 0.01$) decreased in the age class 15–19 years. There were no significant differences when comparing males and females, except for the age group 15–19 years ($p < 0.01$).

3.4. Comparison of seroprevalence data from 1996 and 2004

Only in the age group 2–4 years was the seroprevalence in the survey conducted in 2004 statistically higher than that in 1996 ($p < 0.01$). No significant differences were detected in other age classes (Fig. 4).

4. Discussion

Before vaccination was introduced, mumps was a common infectious disease in all parts of the world, with the highest annual incidence among 5–9-year olds. In many countries, the availability of safe and efficacious vaccines has led to a rapid decrease in morbidity. According to WHO, in 2004, mumps vaccination was included in the vaccine schedules of 109 countries, which constitutes a marked increase with respect to the 74 countries in 1999. In 2004, a two-dose vaccination schedule, mainly with the MMR vaccine, was extensively adopted (in 82% of the 109 countries) [22].

In countries where it was possible to implement vaccination and to rapidly achieve and maintain high VC, there has been a consistent decrease in morbidity [3].

In Italy, mumps vaccination was introduced in the beginning of 1980s and in 1982 the Ministry of Health recommended vaccination of susceptible males, both in pre- and post-puberty. The availability of combined MMR vaccines permitted to start the immunization of both males and females in the second year of life and MMR vaccination has been included in the national vaccine schedule since the beginning of 1990s. At that time the vaccines commercially available contained at least 5000 TCID50 of one of the following mumps strains: Jeryl Lynn, Urabe and Rubini. The impact of vaccination on mumps was inadequate; notifications changed from 62,000 per year in the period 1980–1989 to 45,000 in the period 1990–1997. Epidemic peaks were registered every 3–4 years and over 80% of cases involved children up to 15 years of age. During 1990s the observation of mumps cases in already vaccinated subjects prompted even in Italy some studies on the efficacy of commercially available vaccines; the result was that the Rubini strain had a very low efficacy level (23–31%) and that its wide use could be related to the unsatisfactory control of mumps at national level [23–25]. For these reasons, in July 2001 products containing Rubini strain were withdrawn [7].

In 2002, MMR vaccination, previously included in the national vaccination schedule in 1999 [14] with the recommendation of administering the first dose to children between 12 and 15 months of age, and a second dose at 5–6 or 11–12 years of age, was included among the vaccinations that each region must provide free-of-charge to all children [26]. This decision has played an important role in improving MMR vaccination coverage, especially in the south where, according to 1998 EPI survey, one of the main reasons reported by parents for not vaccinating their children was related to the fact that the vaccine was not provided free of charge [27].

A second cluster sampling survey conducted in 2003, by using the same method of the previous survey, revealed a vaccination coverage rate of 77%, in the same age group [27].

This increase was confirmed by routinely collected data on VC (from 85.7% in 2004 to 87.3% in 2005), as a result of the activities required by the national plan for the elimination of measles and congenital rubella through vaccination with the combined MMR vaccine [28].

However, VC is still not sufficient because the control and/or elimination/eradication of an infectious disease can only be achieved by reaching and maintaining a 95% VC [4], so as to avoid undesired effects, such as new cohorts of susceptible individuals, an increase in the mean age of acquisition of the infection, and the broadening of the inter-epidemic period. The commitment made by Italy to eliminate measles and congenital rubella (<1 case/100,000 newborns) by 2010 [29] will also allow Italy to reach the targets established for mumps for the WHO European Region, which have been endorsed in the 2003–2005 National Health Plan and the 2005–2007 National Vaccine Plan [15,30,31].

In Italy, mumps incidence remained almost unchanged until 2001 (range: 25.9–125.1/100,000 inhabitants) and outbreaks were reported every 2–4 years. Since 2002, notifications have rapidly decreased, and in 2004 the lowest number of cases (2,604) was reported (incidence of 4.5/100,000 inhabitants). In the same period, data collected by the Istituto Superiore di Sanità through the SPES sentinel network confirmed this trend yet highlighted that the routine notification system suffers from remarkable underreporting. Concerning this last point, it should be stressed the need for a better case definition for surveillance as mumps symptoms can be easily misinterpreted if not associated to an outbreak. Noteworthy, when the incidence of mumps decreases, laboratory confirmation should be necessary. Nonetheless, recent epidemiological data show a decrease in mumps cases yet not an increase in the mean age of acquisition of infection, as already reported in other countries [32–35].

Comparison of seroprevalence data from 1996 and 2004 showed a statistically significant increase in seroprevalence only in the age class 2–4 years (41.2% vs. 64.4% in 1996 and 2004, respectively) [21]. This seems to be the result of the latest immunization campaigns; the efforts recently sustained in order to address the national plan for the elimination of measles and congenital rubella through vaccination have had a significant impact on seroprevalence data.

Of note is the finding that in this age class, as well as in the 5–9- and 10–14-year age classes, more than 20% of children were seronegative, and more than 10% of individuals 15–39 years of age were susceptible.

These results demonstrate that VC in Italy is still sub-optimal and that there exists a risk of outbreaks. The lack of adequate vaccine data processing management in some Regions and the high rate of parents (18%) who intend to vaccinate their children at an older age [17] could explain these observations and represent a critical point in planning further priority activities.

In conclusion, this research highlights that vaccination strategies and programmes should be further strengthened if the targets against mumps are to be attained. Surveillance systems and seroprevalence studies can be very important for the prevention and control of infectious diseases, enabling the evaluation of the impact of the interventions adopted.

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