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The epidemiology of mumps in Italy

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

Original Citation:

The epidemiology of mumps in Italy / Gabutti G; Guido M; Rota MC; De Donno A; Ciofi Degli Atti ML; Crovari P; Seroepidemiology Group; Bassetti D; Bechini A; Boccalini S; Bonanni P; Caciagli P; Camper A; Campa AM; Caraccio W; Cavallaro A; Ciamarra E; Clerico L; Casentino L; de Simone E; Favero A; Focà A; Genna L; Giammanco A; Giancotti A; Goglio A; Grandesso S; Icardi GC; Lolli C; Marchetti D; Marsella M; Martelli P; Mucignat L; Palladino D; Passerini C; Perani V; Piscione E; Rizza F; Zizza A; Simula L; Sforza R;

Availability:

This version is available at: 2158/968388 since:

Published version:

DOI: 10.1016/j.vaccine.2008.03.040

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Publisher copyright claim:

(Article begins on next page)

ARTICLE INFO

Article history:

Received 17 January 2008

Received in revised form 13 March 2008

Accepted 19 March 2008

Available online 8 April 2008

Keywords:

Mumps

Seroprevalence

Vaccination

ABSTRACT

In Italy, although vaccination has been recommended for a number of years, mumps is still sub-optimal. The objective of the present study was to evaluate mumps antibodies in the Italian population, stratified by age, gender and geographical area. The prevalence of mumps antibodies remained stable in the age class 2–4 years (25.4% and 30.8%, respectively) and showed a continuous increase after the age of 5 years. The percentage of susceptible individuals was higher than 20% in persons 2–14 years of age, 10% in persons 15–39 years of age. No statistically significant differences were found between geographical area. Comparison between these results and the data obtained from a statistically significant increase in seroprevalence in the age class 2–4 years. No statistically significant differences were found in the other age-groups. The results of this study confirm that the efforts made in increasing vaccination coverage within the second year of life should be strengthened.

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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, preceding the possible clinical onset, and the need for specific therapy.

The epidemiological impact of mumps and the need for vaccination have prompted the development of a vaccine, which represents the best option for preventing the complications.

The mumps vaccine contains live attenuated virus, available as a single-antigen preparation, as a trivalent vaccine with measles and rubella vaccines (MMR) [4], or as a combination with measles, rubella and varicella vaccines (MMRV). Ten different live attenuated viral strains are currently used in mumps vaccines worldwide.

In Italy, for many years the Rubini strain has been used. The poor effectiveness in preventing mumps and the lack of nationwide use has contributed to the failure to reduce the disease in the 1990s [6]. In June 2001 the register of mumps vaccines containing this specific vaccine strain was updated. Since then widely used live attenuated mumps vaccines have included or include the Jeryl Lynn, Urbani and

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

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biology 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 1017 sera was required to

equally representative of males and females. Samples were quantified using an immunoenzyme assay (Eitest Anti-Parotitis-Virus IgG, Dade Behring) with high sensitivity and specificity (95.4% and 99.4%, respectively).

The following criteria were applied for classification:

IgG negative sample
IgG positive sample
Equivocal IgG sample

The equivocal samples were retested. If confirmed, the sample was classified as "equivocal". If not confirmed, samples were quantitatively evaluated using the formula: $\text{Log}_{10} \text{titer} = \alpha \times \Delta E^\beta$, where α and β represent constants. Antibody activity was expressed as

2.4. Statistical analysis

The statistical analysis was performed using SPSS 16.0 for Macintosh (Abacus Concepts, Inc., Berkeley, CA). Incidence data were summarized as percentages. Titres were presented as geometric mean titres. Differences between percentages were assessed by the χ^2 -test. Differences between logarithmically transformed values. The data were stratified by gender and geographical area and were then compared. Data obtained from a seroprevalence study conducted using the same assay and cut-off [21].

3. Results

3.1. Incidence data

Based on data provided by ISTAT, mumps affected a large portion of the population and followed an endemo-epidemic course, with outbreaks. The overall annual incidence ranged from 125.1/100,000 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. However, in this age group, the incidence progressively decreased ($p < 0.01$), from 409.2 cases per 100,000 in 1991–1995, to 365.9 in 1996–2000 to 97.6 in 2001–2004, trend, with a significantly decreasing incidence in the other age groups when comparing different periods (for persons older than 65 years of age when comparing 1991–1995 to 2001–2004, $p < 0.05$).

When comparing persons 0–14 years of age, the differences in the percentage of cases were not significant over the three periods. The analysis showed that the trend in incidence was s

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

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 hospitaliza-

tions and 247-day-hospital admissions for mumps in 2000 (619 and 325 hospitalizations and day admissions, respectively). The mean duration of stay was 1.5 days.

3.3. Seroprevalence study

Overall, 3094 blood samples were analysed. Of these, 621 were negative, and 197 were equivocal. The remaining 2276 showed a typical pattern. In the first year of life (0–11 months), 25.4% of children are passively protected by the mother), 25.4% of children 12–23 months old were seropositive; among 12–23-month olds, the seroprevalence was 30.8% (difference not significant compared to 12–23-month olds); it continued to increase significantly (compared to 12–23-month olds): 65.0%, 78.0%, 92.8%, respectively, for the age classes 5–9, 10–14, and >40 years (Fig. 2). Of note was the finding that the proportion of seronegative individuals was greater than 10% in the 2–4, 5–9 and 10–14 years and greater than 5% in the 15–19 and 20–39 years.

No statistically significant difference was found in seroprevalence when comparing males and females in any age group. Seroprevalence was basically uniform when comparing geographic areas, with no significant differences

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

0-11 months 1 y 2-4 y 5-9 y 10-14 y 15-19 y 20-39 y >40 y

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 immunize rapidly to achieve and maintain high VC, there was a rapid decrease in morbidity [3].

In Italy, mumps vaccination was introduced in the early 1980s and in 1982 the Ministry of Health introduced the vaccination of susceptible males, both in the presence and absence of combined MMR vaccines. In 1990, the immunization of both males and females was introduced and MMR vaccination has been included in the national schedule since the beginning of 1990s. A vaccine commercially available contained at least two of the following mumps strains: Jeryl L and Edmonston. The impact of vaccination on mumps was significant: notifications changed from 62,000 per year in 1980 to 45,000 in the period 1990–1997. Epidemics occurred every 3–4 years and over 80% of cases were up to 15 years of age. During 1990s the incidence of cases in already vaccinated subjects prompted several studies on the efficacy of commercially available vaccines. The result was that the Rubini strain had a lower efficacy (23–31%) and that its wide use could be a risk for the control of mumps at national level [23]. In July 2001 products containing Rubini were withdrawn [7].

(from 85.7% in 2004 to 87.5% 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

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