Research

Pattern of susceptibility to measles in Italy

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On the basis of seroprevalence and incidence data we describe the distribution of individuals susceptible and immune to measles in Italy in 1996–97. In regions where vaccination coverage was at least 70%, approximately 10% of 3-year-old children were susceptible to measles, whereas 40% were in this category in regions with lower vaccination coverage. Seroprevalence among children older than 4 years was similar for the two groups of regions; in the age group 20–39 years it was approximately 95%. During 1990–96 in the regions with lower vaccination coverage the incidence was highest among children aged 4–6 years, and the median age of cases was 7 years; in the regions with higher vaccination coverage, however, the incidence remained at around 5% for the age group 4–16 years, and the overall median age was 10 years. These data confirm the partial reduction in measles incidence in Italy, although transmission has still not been interrupted. The size and geographical distribution of the current pool of susceptible individuals can be expected to present an obstacle to measles elimination if appropriate vaccination strategies, such as catch-up campaigns, are not adopted.

Keywords: measles, epidemiology; measles vaccine; disease susceptibility; seroepidemiologic studies; cluster analysis; statistical distributions; Italy.

Voir page 954 le résumé en français. En la página 955 figura un resumen en español.

Introduction

In Italy the annual reported incidence of measles was approximately 150 per 100 000 inhabitants in the pre-vaccine era, and epidemics occurred almost every two years. The measles vaccine, first made available in 1976, has been recommended for children aged 13–15 months since 1979 (*1*), although vaccination is still not mandatory. A cluster survey in 7 of the country's 20 regions in 1993 showed that regional coverage ranged from 9% to 53% (*2*). This variability was confirmed by a similar survey of the 1996 birth cohort in 19 regions: coverage ranged from 25.5% to 87.7%, and the average was estimated to be 56% (*3*).

The objective of the present study was to evaluate the distribution of individuals susceptible and immune to measles by comparing the seroprevalence for measles with the incidence of the disease in regions with different levels of vaccination coverage. This information has the potential to provide indications on the epidemiology of the disease, which is especially important in view of the plan to eliminate measles in Europe.

Methods

Using sources of data described below, we evaluated and compared the seroprevalence, disease incidence and vaccination coverage for measles in almost all of Italy's regions.

Serosurvey

We collected anonymous unlinked samples of residual sera used in routine testing from a reference laboratory in each region. We excluded samples from individuals known to have an immune depressive disease or an acute infectious disease, or who had recently received a blood transfusion. Verbal informed consent was given by all adults from whom

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serum samples were obtained; consent for minors was provided by parents or legal guardians.

On the basis of a previous document (*4*) we calculated that a minimum of 3400 serum samples would be needed for the seroprevalence analysis: 100 for each year in the age range 0–19 years (i.e. 2000 samples), and 200 for each of the age ranges 20–24, 25–29, 30–34, 35–39, 40–49, 50–59 and 60 and over (i.e. 1400 samples). More samples were collected for the age range 0–19 years because these cohorts had been affected by vaccination. Eighteen regions provided samples, and these were allocated to the different age groups; for samples from individuals under 1 year old the ages in months were specified.

The 3569 samples collected between September 1996 and October 1997 were stored at –20 °C until tested for measles antibody

Detection of antibodies

Serological testing was performed at the University of Genoa's Department of Health Science. The serological assay was standardized within the European Sero-Epidemiology Network project (*4*). A commercial enzyme-linked immunosorbent assay, which according to the manufacturer had a sensitivity of 99.6% and a specificity of 100%, was used to detect and quantify human IgG antibodies to measles virus in serum (Enzygnost anti-measles virus/IgG, Behring, Germany). The results were read as optical density at 450 nm, and antibody concentrations were determined in mIU/ml, using dilution curves of an in-house standard serum calibrated against the international standard for measles (SSI, Copenhagen preparation).

Sera were classified as negative if the optical density was less than 0.100, (150 mIU/ml). If it was higher than 0.200 (350 mIU/ml) they were classified as positive. Sera with optical densities between 0.100 and 0.200 (150–350 mIU/ml) were retested, and if this result was obtained again they were classified as equivocal.

Statistical analysis

The data were analysed by means of Epi Info version 6.04 (Centers for Disease Control and Prevention, Atlanta, USA; and WHO). The percentages of positive, negative and equivocal sera were calculated. The χ^2 test was used to assess differences in seroprevalence. Geometric mean titres (GMTs) were computed on all positive antibody titres as arithmetic means of logarithmically transformed values, along with their respective 95% confidence intervals.

Incidence of measles

The notification of measles has been mandatory in Italy since 1934. Cases are recorded on individual forms and the information is entered into a computerized database at the Italian National Institute for Statistics (ISTAT). We conducted a linear regression analysis on the data for 1960–96. The annual national rates were computed and directly standardized by using the age distribution of the national population as reported in censuses conducted in 1961, 1971, 1981 and 1991.

The lifetime cumulative incidence rate per 10^5 population in 1996 ($i_{k,1996}$) for each age (k) was computed by totalling all notified cases of measles by birth cohort in the period 1980–96, using the 1991 census population as denominator:

$$i_{k,1996} = [(n_{k,\,1996} + n_{k\text{-}1,\,1996\text{-}1} + \ldots + n_{k\text{-}k,\,1996\text{-}k}) / pop_{k,\,1991}]100\,000,$$

where n is the number of notified cases at each specific age in each specific calendar year. Mortality data were also obtained from ISTAT for the period from 1980 to 1994, the latter being the most recent year for which data were available (*5*).

Vaccination coverage

Vaccination against measles has been recommended for children aged 13–15 months in Italy since 1979, yet no reliable estimates of coverage based on routine data collection are available at the national level. However, ad hoc surveys were conducted in different regions in 1984 (*6*), 1993 (*2*) and 1998 (*3*). Coverage in 1984 was very low, ranging from an average of 12.6% in the north to 4.1% in the south.

Data on vaccination coverage in 1993 for children born in 1991 were available for only seven regions, where it ranged between 11% and 52.6%. The 1998 survey showed that coverage exceeded 70% in only one region. This survey allowed both regional and national measles vaccination coverage to be estimated for children aged 12–24 months, i.e. born in 1996, in 19 regions (births in these regions represent 90% of all births in the country). The results of the 1998 survey have been used in the present analysis. The regions were divided into two groups based on coverage (up to and including 69%; 70% and above).

Coverage was less than 70% in 14 regions with a total population of 37 622 151, where it ranged from 25.5% to 64.8%. The five regions with at least 70% coverage had a total population of 19 155 880, and here coverage ranged from 72.3% to 87.7%.

Results

Seroprevalence

The numbers and proportions of serum samples classified as positive or equivocal are reported by age group in Table 1. In the age group 0–6 months, seroprevalence was 58.8%, probably because of the presence of maternal antibodies; in the age group 7–11 months it was 19.4%. At 1 year of age the seroprevalence was 24.8%, and in the age group 2–4 years it was 68.1%. Seropositivity was slightly higher (70.7%) in the age group 5–9 years and continued to increase in the older groups: in the age groups 15–19, 20–39 and 40 and more years it was 86.5%, 95.1% and 98.5% respectively. No significant differences in antibody levels between males and females were observed.

The proportions of equivocal sera were highest in the age groups 0–6 months (9.8%) and 5–9 years

Table 1. **Measles seroprevalence in the examined population, stratified by age group**

Age group	N° of sera tested	N° of positive sera (%)	N° of equivocal sera (%)	GMT[1] (positive)	95% confidence interval
0–6 months	51	30 (58.8)	5 (9.8)	1868.5	1346.8–2592.4
7–11 months	36	7 (19.4)	1 (2.8)	2765.7	1302.5–5872.5
1 year	101	25 (24.8)	2 (2.0)	2718.2	1820.1–4059.3
2–4 years	339	231 (68.1)	7 (2.1)	2464.1	2177.2–2788.9
5–9 years	542	383 (70.7)	25 (4.6)	2388.9	2160.9–2641.0
10–14 years	520	432 (83.1)	8 (1.5)	2786.9	2546.3–3050.1
15–19 years	525	454 (86.5)	6 (1.1)	4315.4	3980.4–4678.7
20–39 years	835	794 (95.1)	5 (0.6)	5213.4	4956.3–5483.8
⩾ 40 years	620	611 (98.5)	1 (0.2)	4404.0	4156.0–4666.7
Total	**3569**	**2967 (83.1)**	**60 (1.7)**	**3049.9**	**2444.1–3805.8**

[1] GMT = geometric mean titre expressed in ELISA mIU/ml.

(4.6%); the proportions of such sera in the other age groups were negligible.

The GMTs for positive sera tended to increase with increasing age (Table 1).

There was a significant difference between the regions with high vaccination coverage (⩾70%) and those with low coverage (<70%) in respect of seroprevalence in children aged 2–4 years (81% and 62% respectively, $P = 0.001$) (Fig. 1); the greatest difference occurred at 3 years of age. For older individuals, seroprevalence was very similar in high-coverage and low-coverage regions.

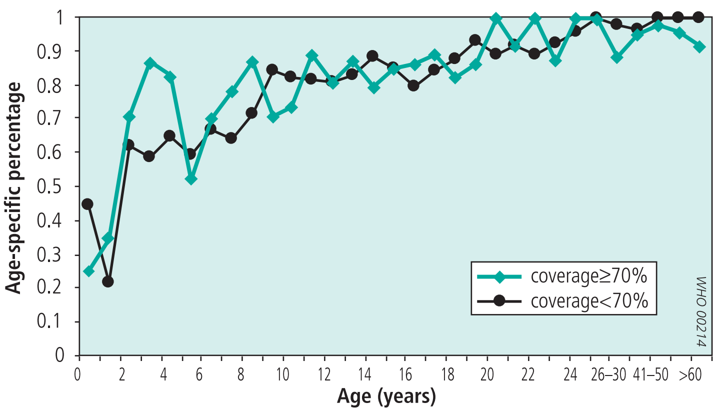
Incidence

The annual standardized incidence of measles for 1960–96 is shown in Fig. 2. Before 1976, the year in which the measles vaccine was made available in Italy, the average annual incidence was 150 cases per 100 000 inhabitants; in the 1980s it was 81 per 100 000, and in the period 1990–96 it was 46 per 100 000 (*7*). The decrease in the standardized rates over the 36-year period is statistically significant ($P<0.01$), with a yearly mean decrease of approximately 1000 cases (1–10% of total notifications).

Since the introduction of the vaccine in 1976 there have been some epidemic years; no clear modifications in the epidemiological pattern have been evident. The median age at which the infection is acquired has increased from 6 years (1980–89) to 9 years (1990–96).

The pattern of measles mortality has been similar to that of incidence, decreasing from an average of 13.3 deaths per year in 1980–89 to one of 7 per year in 1990–94 (*5*).

Fig. 1. **Age-specific seroprevalence in regions with high vaccination coverage and regions with low vaccination coverage**



Seroprevalence and incidence

The observed seroprevalence was compared with the lifetime cumulative incidence of measles by one-year age group up to 17 years of age (Fig. 3). The increase in seroprevalence at 2–4 years of age is not matched by the age-specific cumulative incidence (probably because of underreporting and vaccination), whereas for older persons the trends follow a parallel pattern.

A comparison of regions by level of vaccination coverage revealed no differences in the proportional distribution of notified measles cases by age (Fig. 4) for 1980–89, and the median age of notified cases was 6 years for both groups. For 1990–96 the proportion of notified measles cases peaked at around 8% in the age range 4–6 years (Fig. 5) in regions with low coverage, whereas in those with high coverage the proportion remained at around 5% in the age range 4–16 years. In the period 1990–96 the median age of notified cases was 7 years in regions with low vaccination coverage and 10 years in those with high coverage. In both groups of regions there was a slight peak at 18–19 years of age (3% for low-coverage regions and 5% for high-coverage regions). The average annual incidence of measles in 1990–96 for the population aged 0–40 years was higher in regions with high coverage (112 cases per 100 000 inhabitants) than in those with low coverage (77 cases per 100 000), and age-specific rates diverged after 4 years of age, higher incidences occurring in regions with higher coverage.

Discussion

Vaccination against poliomyelitis, diphtheria, tetanus and hepatitis B is mandatory in Italy and is provided free to all infants through the National Health Service at a coverage rate of around 95%. Vaccination against measles, however, is not mandatory. Few data are available at the national level on coverage for non-mandatory vaccinations, and no reliable routinely collected national data are available for vaccinations provided at the recommended age of 13–15 months. The proportion of vaccinated children in each region is determined by local vaccination programmes, some of which have existed since measles vaccination was first recommended in 1979 (*1*). Local vaccination campaigns were often conducted to promote vaccination but many of them were not continued routinely, even though vaccination in infancy is the most cost-effective means of controlling measles (*8*). Consequently, both vaccination coverage and the incidence of measles vary widely between birth cohorts and geographical regions, and only a partial reduction in incidence has been achieved, without modifying the typical cyclical pattern of the disease.

Before the introduction of the measles vaccine the age distribution of individuals immune to measles was a marker of disease incidence, and high seroprevalence rates in early childhood were associated with relatively poor socioeconomic circumstances and conditions of hygiene. In 1984 it was reported that 50% of children in the age range 2.9–5.5 years were naturally immune to measles in Italy (*9*). In southern areas of the country, naturally acquired immunity was reached at an earlier age, and at 10–11 years of age the prevalence of immune individuals was close to 92%. There were very few susceptible individuals above these ages.

A recent vaccination survey (*3*) indicated that the national vaccination coverage was approximately 56% among the target population. There were wide regional differences in the proportions of immunized children, ranging from 26% to 87% of the 1996 birth cohort.

The results of the present serosurvey show that the proportion of immune individuals differs between geographical areas only in children below 6 years of age. Even in the regions with the highest coverage the proportion of the population vaccinated has improved only recently.

The representativeness of the residual serum samples could be a shortcoming for children up to 3 years of age, who could overrepresent children with health problems potentially associated with a lack of vaccination at the expected age. In this case, our results could underestimate the true antibody prevalence. On the other hand, the consistency between seroprevalence and observed vaccine coverage suggests that if a bias is present it is not large enough to invalidate our results.

Our serological study has shown that approximately 70% of children in their third year of life have acquired immunity against measles and that the regional differences in seroprevalence are attributable to variability in vaccination coverage. However, the uncoordinated use of the available vaccine has led to the accumulation of a different pool of susceptible individuals spread over a wider age range than in the pre-vaccine era, when only 8% of the population

Fig. 2. **Measles annual standardized incidence rates per 100 000 from official notifications in the period 1960–96**

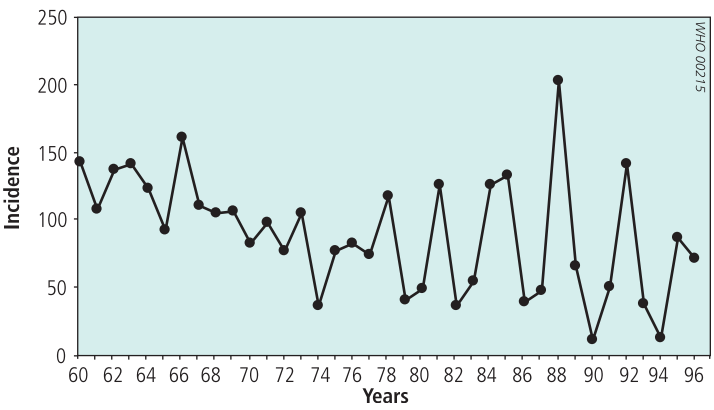


Fig. 3. **Measles seroprevalence in 1996–97 and lifetime cumulative incidence of measles by one-year age-group, up to 17 years of age (rates per 100 000 population)**

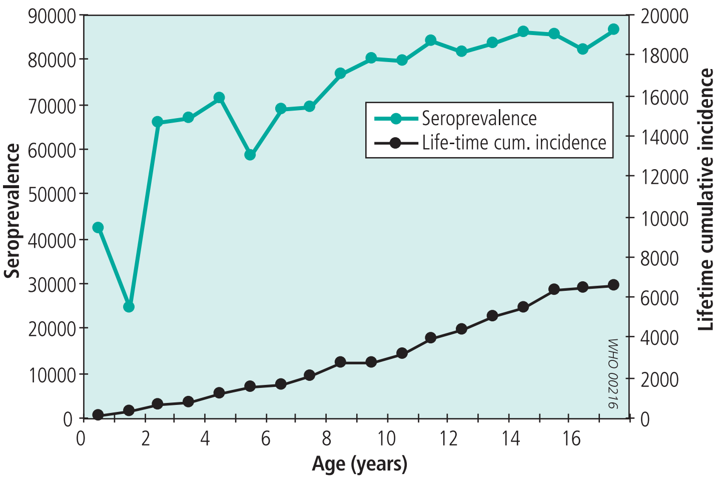
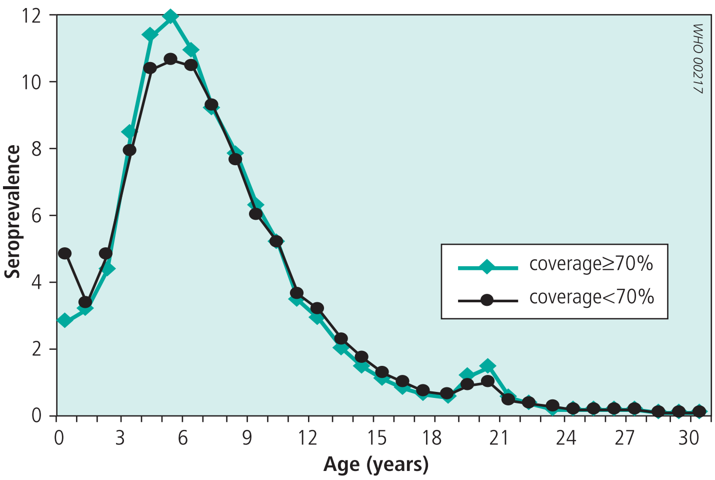
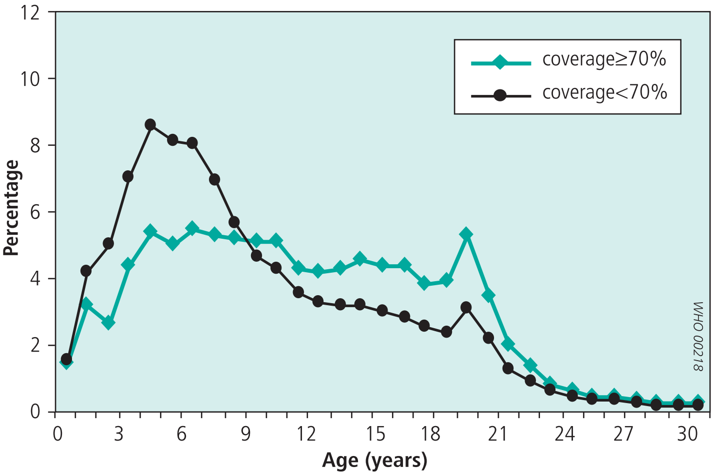


Fig. 4. **Proportional distribution of notified measles cases by age in the period 1980–89, by regions grouped by current vaccination coverage**



above 10 years of age was susceptible to measles. Vaccination can provide individual protection under such circumstances but no additional benefit to the community (*9*). The interruption of measles transmission in Italy can only be achieved by increasing the

Fig. 5. **Proportional distribution of notified measles cases by age in the period 1990–96, by regions grouped by current vaccination coverage**



rates of routine childhood immunization and organizing catch-up campaigns aimed at reducing the size of the susceptible population.

The partially limited viral circulation resulted in a lower seroprevalence in the age group 10–19 years than had occurred in the pre-vaccine era. The concentration of susceptible individuals by age is revealed by the notified cases of measles, whose median age has increased from 6 years to 9 years. In particular, a peak in incidence has been observed for males at 18 years of age, i.e. at the time of compulsory military service. Because the frequency of complications is higher when measles infection is acquired during youth or adulthood, a dose of measles-mumps-rubella vaccine at enrolment in the military has been included since April 1998 in the routine vaccinations given to all recruits. Although this practice can be expected to reduce the risk of severe cases and fatalities in a select at-risk group (i.e. young males living in a closed community), it cannot interrupt the circulation of the infection and leaves unprotected the still susceptible female population of the same age.

The incidence of measles can be used to monitor progress in the control of the disease. However, the actual incidence has been estimated to be 10 times greater than the incidence suggested by notifications (*9*). Surprisingly, the number of notifications is lower in regions with low vaccination coverage than in regions with higher coverage, whereas, on the basis of the observed age-specific seroprevalence for the population over 4 years of age, the circulation of the infection is expected to be the same. The lower observed incidence in regions with lower coverage could be attributable to greater underreporting in these regions. A nationwide programme for eliminating measles, endorsed by all regions, would probably result in an increase in the observed incidence because of an increase in the sensitivity of the notification system.

In Italy, reducing the regional differences in vaccination coverage and reaching a national coverage of 95% in the second year of life should be a priority for meeting the target set by WHO (*10*) and by the Italian National Health Plan (*11*) for the year 2000. Catch-up activities targeting adolescents (12–14 years of age) would help to avoid the occurrence of complicated cases in older persons and the need for administering vaccines to adults. In order to increase coverage it is necessary not only to promote vaccination and educate parents and health staff but also to overcome the differences in local strategies which have influenced vaccination coverage. ■

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Résumé

Caractéristiques de la sensibilité à la rougeole en Italie

En Italie, la couverture vaccinale antirougeoleuse est très variable d'une région et d'une cohorte de naissance à l'autre. Les estimations nationales les plus récentes indiquent que 56 % des enfants sont vaccinés contre cette maladie au cours de leur deuxième année. L'épidémiologie de la rougeole est par conséquent caractérisée par une forte circulation de l'infection. L'absence de stratégie de prévention coordonnée a fait que l'on retrouve des sujets sensibles dans différentes classes d'âge et différentes régions du pays.

L'objectif de la présente étude était de décrire pour la rougeole la répartition des sujets sensibles et des sujets immunisés en comparant la séroprévalence et l'incidence de la maladie dans des régions ayant différents taux de couverture vaccinale.

On a estimé la séroprévalence par âge à partir de 3569 prélèvements de sérum anonymes, non reliés, recueillis en 1996-1997 dans la population générale de 18 des 20 régions du pays. Dans les régions où la couverture vaccinale était d'au moins 70 %, environ 10 % des enfants de 3 ans étaient sensibles à la rougeole ; dans les régions où la couverture était inférieure, 40 % des enfants de cet âge étaient sensibles. Pour les enfants de plus de 4 ans, le taux de séroprévalence a été le même pour les deux groupes de régions, ce qui indique des antécédents d'exposition au vaccin ou à la maladie identiques. La séroprévalence augmentait avec la classe d'âge : chez les 20-39 ans, 95 % de la population étaient séropositifs pour la rougeole, alors que chez les gens plus âgés, la population presque tout entière était séropositive, sans qu'il y ait eu de différence marquée entre les régions.

Dans l'ensemble, les notifications de cas de rougeole ont montré une tendance à la baisse au cours des dernières décennies, avec des cycles épidémiques certaines années, confirmant la réduction partielle du nombre de cas ; toutefois, le cycle de transmission de la rougeole n'a toujours pas été interrompu. Entre 1990 et

1996, dans les régions où la couverture vaccinale était faible, la répartition proportionnelle des notifications par âge montrait un pic vers 4-5 ans ; en revanche, dans les régions où la couverture était d'au moins 70 %, les cas étaient répartis de façon à peu près égale entre 4 et 16 ans, indiquant que ces sousgroupes étaient ceux dans lesquels les sujets sensibles étaient concentrés. Dans les régions à faible couverture, l'âge médian des cas notifiés était de 7 ans, tandis que dans les régions à forte couverture il était de 10 ans. En moyenne, 7 décès dus à la rougeole ont été notifiés chaque année entre 1990 et 1994. Aucune des cibles opérationnelles fixées par l'OMS pour l'élimination de la rougeole n'a été atteinte en Italie.

Il faudrait que l'Italie adopte des stratégies appropriées pour interrompre la transmission de la rougeole dans l'important réservoir de sujets sensibles qu'elle possède et pour accroître la couverture vaccinale chez l'enfant.

Resumen

Distribución de la susceptibilidad al sarampión en Italia

La cobertura de vacunación en Italia varía mucho entre regiones y cohortes de nacimiento. Las estimaciones nacionales más recientes indican que el 56% de los niños de 1 a 2 años de edad están inmunizados contra la enfermedad. La epidemiología del sarampión se caracteriza, por consiguiente, por una elevada circulación de la infección. Dada la falta de una estrategia de prevención coordinada, se encuentran personas susceptibles en distintos grupos de edad y en distintas partes del país.

El objetivo del presente estudio fue describir la distribución en Italia de las personas susceptibles y las personas inmunes al sarampión comparando la seroprevalencia y la incidencia de la enfermedad entre regiones con distintos niveles de cobertura de vacunación.

Se estimó la seroprevalencia específica por edades en 3569 muestras de suero anónimas e independientes obtenidas durante 1996-1997 en la población general de 18 de las 20 regiones del país. Se estimó que en las regiones con una cobertura de vacunación de al menos el 70%, aproximadamente el 10% de los niños de tres años de edad eran susceptibles al sarampión; en las regiones con una cobertura de vacunación más baja, el 40% de los niños de esa edad se encuadraban en esa misma categoría. Los niños mayores de cuatro años presentaban una tasa de seroprevalencia similar en los dos grupos de regiones, indicio de que habían tenido una historia similar de exposición a la vacuna o a la enfermedad. La seroprevalencia aumentaba en los grupos de más edad: en el grupo de 20 a 39 años, el 95% de la población era seropositiva para el sarampión, mientras que en el de personas de más edad era seropositiva casi toda la población, sin que hubiera diferencias notables entre las regiones.

En conjunto, la cifra de casos de sarampión notificados ha mostrado una tendencia descendente en los últimos decenios, con ciclos de años epidémicos, confirmándose la reducción parcial del número de casos; sin embargo, no se ha interrumpido aún el ciclo de transmisión del sarampión. En 1990-1996, en las regiones con baja cobertura de vacunación la distribución proporcional de casos notificados por edades presentaba un pico a los 4-5 años, mientras que en las regiones con una cobertura de vacunación de al menos el 70% los casos de 4 a 16 años estaban representados por igual; se evidenciaban así los subgrupos en los que se concentraban las personas susceptibles. En las regiones de cobertura baja, la edad mediana de los casos notificados era de siete años, mientras que en las regiones de cobertura alta era de 10 años. En el periodo 1990-1994 se notificó un promedio anual de siete defunciones por sarampión. No se ha alcanzado en el país ninguna de las metas operacionales fijadas por la OMS para la eliminación del sarampión.

En Italia deberían adoptarse estrategias apropiadas para interrumpir la transmisión del sarampión entre el gran conjunto de personas susceptibles y para aumentar la cobertura de vacunación sistemática en la infancia.

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