

Assessment of varicella underreporting in Italy

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SUMMARY

We conducted a study to assess the degree of varicella underreporting in Italy, and its distribution by age group and geographical area. Underreporting in individuals from 6 months to 20 years of age was computed as the ratio between the varicella seroprevalence in 1996 and the 1996 lifetime cumulative incidence based on statutory notifications. The degree of underreporting at the national level was 7·7 (95% CI 7·4–7·9); underreporting was greater in older age groups and in southern Italy. Quantification of underreporting can contribute to better understanding of the burden of varicella and to evaluating the potential impact of mass vaccination.

INTRODUCTION

Varicella is an acute, highly infectious disease caused by varicella zoster virus (VZV); children are the most affected age group and the lifetime risk of acquiring varicella exceeds 95% [1]. Safe and efficacious live-attenuated vaccines against VZV infection have been available since the 1970s. Mass vaccination has been shown to be cost-effective from the societal perspective in the short term [2], and up to now has been introduced in the United States and Japan [3, 4].

In Italy, although the currently licenced VZV vaccine is recommended for high-risk groups [5], it is still being debated whether or not to introduce immunization against varicella in the national childhood vaccination programme [6, 7]. Modelling studies have stressed the long-term potential risks (e.g. the shift of the mean age of infection to higher age groups) of vaccination strategies which fail to reach

high vaccination coverage [8]. The sub-optimal vaccination coverage achieved in Italy for other diseases, particularly measles [9], represents a serious concern to recommending varicella vaccination in infancy.

To evaluate the cost-benefit of vaccination programmes, and their effect on the epidemiology of the disease, knowledge of pre-vaccination incidence is important [10]. The most common source of incidence data is routinely collected case notifications, but failure to report is common and must be taken into account. In addition, undernotification can vary by time and geographical area, giving false trends.

In Italy, the reporting of cases of varicella has been statutory since 1934; cases are reported on an individual form which is sent to the Italian National Institute for Statistics (ISTAT) [11]. Based on these reports, a recent study has shown that there has been a trend of increase in the reported varicella incidence from 50 cases per 100 000 population in the 1960s to more than 200 cases per 100 000 population in the 1990s [12]. Nonetheless, the incidence in the 1990s is 2·5–7·5 times lower than the incidence observed in

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other western countries prior to mass childhood vaccination [13, 14], suggesting the presence of underreporting. The objective of the present study was to assess the underreporting of varicella in Italy, including the degree of underreporting by age group and geographical area.

METHODS

We assessed the degree of underreporting of varicella by comparing age-specific seroprevalence with lifetime cumulative incidence of varicella for individuals ranging in age from 6 months to 20 years.

Seroprevalence

The seroprevalence data were obtained from a national survey conducted in 1996–7, during which 3179 samples were collected from residual sera of routine laboratory testing, in 18/20 Italian regions. In the age-group 0–20 years, each region provided 100–110 serum samples for each year of life [12]. Samples from individuals known to have an immunosuppressive or acute infectious disease and those from individuals who had recently undergone a blood transfusion were excluded from the study. For the present study, we only analysed the 2164 samples obtained from individuals between the ages of 6 months and 20 years. Individuals less than 6 months of age were excluded because of the presence of maternal antibodies, and individuals older than 20 years because the VZV antibody prevalence after this age in Italy is greater than 90% [12]. The number of samples collected in each age-group was: 485 in the age-group 6 months–4 years, 543 in the age-group 5–9 years, 519 in the age-group 10–14 years, and 617 in the age-group 15–20 years. Anti-VZV specific IgG was detected using a commercially available ELISA (Enzygnost anti-VZV/IgG, Dade Behring GmbH). Sera were classified as positive if the optical density (OD) was higher than 0.2, as borderline if the OD was between 0.1 and 0.2, and as negative if the OD was lower than 0.1. Borderline sera were excluded from further analysis. For each age group, we calculated the VZV seroprevalence per 100 individuals and the relative 95% confidence intervals (95% CI), both nationally and by geographical area (i.e. northern, central and southern Italy). The statistical significance of differences in VZV seroprevalence by geographical area was assessed by the χ^2 test.

Lifetime cumulative incidence

We calculated the age-specific lifetime cumulative incidence of varicella using the individual notifications of cases which occurred in the period 1976–96 (source: ISTAT). The lifetime cumulative incidence rate per 100 population (i_k), for each birth cohort k , was computed by cumulating the age-specific incidence of varicella by year in the period 1976–96, according to the following:

$$i_{k,1996} = \left(\frac{n_{k,1996}}{POP_{k,1996}} + \frac{n_{k-1,1995}}{POP_{k-1,1995}} \dots \right. \\ \left. + \frac{n_{k-k,1996-k}}{POP_{k-k,1996-k}} \right)$$

where n is the number of notified cases at each specific age in each specific calendar year, and the denominator is the population of the same age in the same calendar year. The lifetime cumulative incidence by age-group (i.e. 6 months–4 years, 5–9 years, 10–14 years and 15–20 years) was then computed as the average of the lifetime cumulative incidences of each year of age.

Estimate of underreporting

The degree of underreporting was computed as the ratio between the 1996 VZV antibody prevalence and the 1996 lifetime cumulative incidence. The degree of underreporting was estimated as national average, by age group (i.e. 6 months–4 years; 5–9 years; 10–14 years; and 15–20 years), and geographical area. The 95% confidence intervals of the degree of underreporting were computed by dividing the lower and upper 95% CIs of seroprevalence estimates by the life-time cumulative incidence. Differences among age-groups and geographical areas were assessed by the χ^2 test.

RESULTS

The 1996 VZV antibody prevalence and lifetime cumulative incidence of varicella per 100 individuals are shown in Figure 1 by age group and geographical area. The VZV antibody prevalence for the entire study population was 64%. VZV antibody prevalence increased from 22.2% in children from 6 months to 4 years of age, to 61.6% in the 5–9-year age group, 82.3% in the 10–14-year age-group and 83.3% in the 15–20-year age group. The highest increase in VZV antibody prevalence was observed between 5 and 6 years of age (from 37.9% to 61.5%, equal to an

Table 1. *Varicella underreporting ratio by age group and geographical area; Italy 1996*

| Age group | Underreporting ratio (95% CI) | | | |
|------------------|-------------------------------|---------------|---------------|------------------|
| | Italy | North | Centre | South |
| 6 months–4 years | 7.5 (6.3–8.8) | 3.5 (2.5–4.4) | 5.1 (2.9–7.2) | 37.7 (28.6–46.8) |
| 5–9 years | 5.9 (5.5–6.3) | 3.2 (2.9–3.5) | 5.2 (4.4–6.0) | 20.1 (17.7–22.5) |
| 10–14 years | 7.6 (7.3–7.9) | 4.1 (3.9–4.3) | 6.5 (6.0–7.1) | 27.3 (25.2–29.4) |
| 15–20 years | 9.3 (9.0–9.7) | 5.3 (5.0–5.5) | 7.9 (7.4–8.5) | 32.5 (30.4–34.6) |
| Total | 7.7 (7.4–7.9) | 4.2 (4.0–4.4) | 6.5 (6.1–7.0) | 27.8 (26.2–29.3) |

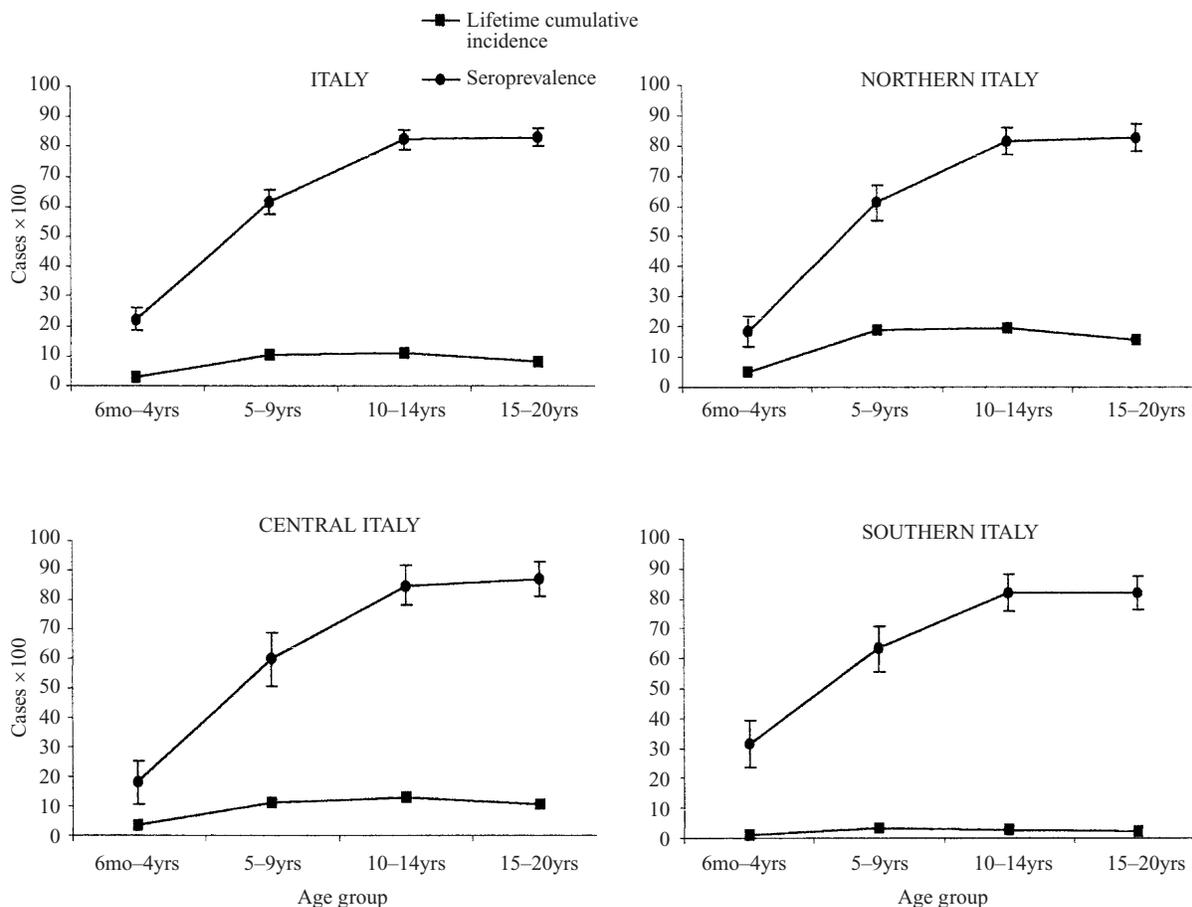


Fig. 1. Seroprevalence (with 95% CI) and lifetime cumulative incidence of VZV infection by age group and geographical area; Italy, 1996.

increase of 38.4%). A second smaller increase was observed between 8 and 10 years of age (from 67.9% to 81.3%, equal to an increase of 16.5%).

The VZV antibody prevalence by age group did not significantly vary by geographical area, except when considering children in the 6 months–4 year age group, among whom the VZV antibody prevalence was significantly higher in southern Italy compared to the other parts of the country (31.5% in southern

Italy; 18.0% in central Italy and 18.3% in northern Italy; $P = 0.007$).

The lifetime cumulative incidence increased from 2.9 in children from 6-months to 4 years of age, to 10.5 in the 5–9-year age group, and 10.8 in the 10–14-year age group; in the 15–20-year age group, the lifetime cumulative incidence decreased to 8.9%.

The degree of underreporting by age group and geographical area is reported in Table 1. Overall, at

the national level, the ratio between VZV antibody prevalence and lifetime cumulative incidence was 7.7. The lowest degree of underreporting was observed in children in the 5–9 year age group, corresponding to the 1987–91 birth cohort. From 10 to 20 years of age, the degree of underreporting increased steadily, reaching 9.3 in individuals aged 15–20 years, born in the years 1976–81. All of the differences by age group were statistically significant ($P < 0.01$), except when comparing the 6 months–4 year age group with the 10–14-year age-group.

The degree of underreporting was markedly higher in southern Italy, compared to the rest of the country. In northern Italy, the degree of underreporting for all ages was 4.2, ranging from 3.2 in children aged 5–9 years to 5.3 in individuals aged 15–20 years. In central Italy, it was 6.5 for all ages, ranging from 5.1 in children aged 6 months–4 years to 7.9 in the 15–20 age group. In southern Italy, the overall degree of underreporting was 27.8, ranging from 20.1 in children aged 5–9 years to 37.7 in children aged 6 months–4 years. When comparing age-specific underreporting within the same geographical area, all of the differences were statistically significant ($P < 0.01$), except when comparing children in the 6 months–4 year age group to those in the 5–9-year age group, both in northern and central Italy.

DISCUSSION

In Italy, since routine vaccination against varicella is not currently recommended and performed, the seroepidemiology exclusively reflects the immunity induced by VZV infection. We analysed data derived from residual sera from routine laboratory testing; since laboratory testing is unusual in children, residual sera could refer to children with health problems that would lead to a higher risk of acquiring varicella (e.g. congenital or acquired immunosuppression), or even to being vaccinated against the disease. Nevertheless, the exclusion criteria used in the seroepidemiology study should have resulted in these children being excluded, thus avoiding an overestimation of seroprevalence.

Asymptomatic varicella infections are rare and clinical diagnosis is highly specific; furthermore, a recent study has shown that in Italy almost all cases occurring in children and adolescents have been diagnosed by a physician [7]. In fact, differences in access to care by age and social class are minimal, since primary health care is provided to all individuals

free-of-charge by paediatricians and general practitioners contracted by the National Health System. Therefore, cases reported by physicians should ideally reflect the actual number of infections. For this reason, varicella is particularly suitable for comparing seroepidemiology data to those obtained from notifications, and for the purpose of this study, underreporting is meant as the gap between cases occurring in the community and those notified.

The results of this study show that in the years 1976–96, the degree of underreporting was 7.7, meaning that approximately only 1 case of varicella out of 8 was reported in individuals between the ages of 6 months and 20 years. Since we calculated underreporting as the ratio of VZV antibody prevalence to lifetime cumulative incidence by age-group, this ratio only reflects the overall underreporting over a 20-year-period. Thus, this study does not allow the degree of annual underreporting of varicella to be estimated and thus we cannot calculate the adjusted annual incidence rates. Nevertheless, the degree of underreporting estimated in this study is consistent with the difference observed in the varicella incidence in Italy in the 1990s estimated using statutory notifications and the incidence observed in other western countries before the introduction of mass vaccination [13, 14]. Moreover, the degree of underreporting in children is consistent with results of varicella surveillance conducted by sentinel networks of primary care paediatricians in Italy, which show that the estimated incidence in children up to 14 years of age is 5 times greater than that estimated by statutory notifications [7, 15]. Also, the degree of underreporting in children is consistent with the estimate of varicella underreporting obtained under the assumption that for highly infectious diseases nearly all individuals would be infected well before reaching adulthood; thus, assuming a stable population, the number of births should correspond to the number of cases [16]. In the years 1990–6, in fact, the mean annual number of notified cases of varicella was 102155, whereas the mean annual number of births was 546521, accounting for an underreporting ratio of 5.3.

Our findings that the degree of underreporting was lowest in children aged 5–9 years could be explained by two factors: the time-period in which these cases occurred (i.e. the early 1990s), and the age of these children, who are attending primary school. With regard to the time-period effect, from the 1970s to the 1990s the incidence of varicella in Italy based on

statutory notifications showed an increasing trend [12]. The first increase was observed in the mid 1980s, with a further increase in the early 1990s, coinciding with the revision of the national statutory notification system [17]. This revision reduced the number of statutory notifiable diseases from 71 to 47, and divided these diseases into five classes, according to their public health relevance. The revision probably increased the level of compliance with disease notification; for this reason, it is likely that the increasing trend in varicella incidence observed over time can be attributed to an increase in case reporting.

Fewer cases were probably reported in the older birth-cohorts, who contracted the disease in the late 1970s and in the 1980s, compared to the younger birth-cohorts, who acquired varicella in the 1990s. This was confirmed by the finding that the lifetime cumulative incidence estimated by statutory notifications is lower in the 15–20-year age group than in the 10–14-year age group. Since lifetime cumulative incidence cannot decrease with increasing age, this is probably due to different degrees of underreporting by birth-cohort. Furthermore, the underreporting estimated in the 15–20-year age-group (i.e. 9.3) is very close to that estimated for measles in the 1970s and 1980s [18].

Nevertheless, the time-period effect cannot completely explain the pattern of underreporting by age, since we observed a higher underreporting of cases in children aged 6 months–4 years than in the 5–9-year age group. In Italy, children acquiring varicella are excluded from school and are required to present a medical certificate for readmission. These certificates are usually provided by public health officials who are probably more aware than general practitioners of the relevance of infectious disease notifications, and this can contribute to increased case reporting. Since the 6 months–4 years age group includes a high percentage of children who do not attend school, this could explain the lower rate of reporting.

The much greater degree of underreporting in southern Italy has also been observed for other infectious diseases, such as pertussis and measles [18, 19]. However, the reason for this phenomenon has never been thoroughly investigated, although it could be related to differences in the performance of health care facilities. Other indicators, such as a higher infant mortality rate and a lower vaccine coverage [9, 20], support this hypothesis. To improve the reporting of cases, an in-depth study of the reasons for underreporting should be conducted.

Knowledge of underreporting by geographical area could also contribute to interpreting incidence data for similar infectious disease. For example, a study on measles epidemiology in Italy showed that the incidence estimated by statutory notifications was lower in the south, where vaccination coverage was lower, than in the north, where coverage was higher [21]. This paradoxical incidence pattern can be explained by the higher degree of underreporting in the south.

Statutory notification of infectious diseases is a longstanding tradition in Italy, insofar as some diseases, such as measles and diphtheria, have been notifiable for more than a century. The statutory notification system offers the potential advantages of being exhaustive and of allowing historical trends to be evaluated. Nevertheless, this study confirms that the degree of underreporting can be very high; its modifications over time and by geographical area can greatly bias incidence estimates.

Knowledge of varicella underreporting can contribute to estimating the burden of disease in Italy and to evaluating the suitability of introducing large scale vaccination programmes. In addition, if mass vaccination is introduced, the incidence estimates adjusted for underreporting will constitute the baseline for estimating the effectiveness of vaccination programme. Nevertheless, since case notification could vary after the introduction of vaccination, further evaluation of underreporting will be needed, and additional serological surveillance can be conducted, as this avoids the problem of both underreporting and selective-reporting.

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