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Seroprevalence of measles antibodies in the Italian general population in 2019–2020

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ABSTRACT

In Italy, the measles elimination target has not yet been reached despite a significant reduction in cases. A multicenter study was conducted to estimate the prevalence of anti-measles (MV) IgG antibodies in the Italian population by age, sex and geographical area. To determine the level of MV-specific antibodies in sera, the immunoenzymatic assay ELISA was used (Enzygnost Anti-VZV/IgG, Siemens Healthcare Diagnostic Products GmbH, Germany). Overall, 3746 serum samples collected in the years 2019–20 from healthy subjects aged 6–64 years residing in 13 Italian regions. The overall seroprevalence of anti-MV IgG was 91.2 % (90.6 % male, 91.7 % female). Significantly higher seroprevalence values ($p < 0.05$) were recorded for the extreme age groups of the study population (6–9 years: 94.2 %; 40–64 years: 97.6 %). Subjects 20–39 and 40–64 years old had significantly higher antibody titers suggesting a protection against measles mainly derived from natural infection. Seroprevalence was significantly higher in the South (93.2 %) than in the Northern-Central Italy (88.9 %). The results indicate an increase in the overall seroprevalence data compared to previous investigations. However, further efforts must be made to implement and maintain high measles vaccination coverage to avoid the risk of future epidemic outbreaks.

1. Introduction

Measles is an airborne and highly contagious viral infectious disease that can cause serious complications, sequelae, and deaths. The World Health Organization (WHO) estimates that in the period 2000–2021, vaccination against measles prevented about 56 million deaths. However, despite the effectiveness, safety and favorable cost-effectiveness profile of currently available vaccines, approximately 128,000 deaths were estimated globally in 2021, mainly involving unvaccinated or incompletely vaccinated children [1].

Over the period 2000–2021, the estimated vaccination coverage (VC %) with a first dose of measles-containing vaccine (MCV) globally increased from 72 % to a peak of 86 % in 2019, but decreased during the COVID-19 pandemic to 83 % in 2020 and 81 % in 2021. This figure

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represents the lowest value recorded since 2008. Concurrently, the global annual incidence of measles decreased from 145 cases per million population in 2000 to 18 cases in 2016, then rebounded to 120 in 2019, before falling to 21 in 2020 and 17 in 2021 [2].

All six WHO regions have committed to eliminating measles. However, despite 76 countries (39 %) having achieved or maintained measles elimination status by the end of 2021, no WHO region had achieved and maintained elimination, and no African region had eliminated measles. In 2016, the WHO Americas region achieved measles elimination, but endemic transmission was re-established in Venezuela (2016) and Brazil (2018). Since 2016, endemic transmission has been re-established in eight additional countries (Albania, Cambodia, Lithuania, Mongolia, Slovakia, the Czech Republic, the United Kingdom, and Uzbekistan) that had previously achieved verification of measles elimination [2].

At the European level, the number of measles cases reported in recent years has been relatively low compared to the years before 2020 with the majority of cases occurring in five countries (Belgium, France, Germany, Italy, and Poland). However the majority of European countries did not achieve or maintain a VC% $\geq$95 % with two doses of vaccine. Consequently, it is likely that an increase in the number of reported cases will be observed again in the future [3].

In Italy the goal of eliminating measles has been pursued for many years. The National Plan for the Elimination of Measles and Rubella (PNEMORC), which was approved in 2003, has resulted in notable advancements in the implementation of vaccination and the enhancement of the surveillance system [4]. Nevertheless, vaccination coverage remained suboptimal for an extended period and only increased from 2017 as a consequence of Law 119/2017, which defined the urgent provisions for vaccination prevention, establishing, among other vaccinations, the mandatory nature of measles immunization [5].

Data deriving from the surveillance system indicate that in Italy from 2013 (the year in which integrated measles-rubella surveillance was established) to 2022, 14,916 cases were reported (2,270 in 2013, 1,695 in 2014, 256 in 2015, 862 in 2016, 5,397 in 2017, 2,683 in 2018, 1,622 in 2019, 105 in 2020, 8 in 2021 and 18 in 2022) [6].

The report of the Eleventh Meeting of the European Regional Verification Commission for Measles and Rubella elimination stated that measles remains endemic in Italy and that further efforts are needed to improve surveillance and increase vaccination coverage [7].

The Immunization Agenda 2021–2030 (IA2030) identifies measles as an indicator of a health system's capacity to provide essential childhood vaccines. IA2030 highlights the importance of implementing a rigorous measles surveillance system to document immunity gaps and achieve 95 % coverage with two doses of MCV in children [8].

In this context, it is important to acquire new data on the prevalence of subjects susceptible to measles and contribute to the evaluation of interventions that have already been implemented. In 2019, the Italian Institute of Health (ISS) promoted a national survey to assess the seroprevalence of antibodies against vaccine-preventable infectious diseases in the Italian general population [9,10]. Here, data on the seroprevalence of antibodies against measles were reported.

2. Materials and methods

2.1. Study design and participants

The study was designed as a not interventional, multicenter study, promoted by the Italian Institute of Health (ISS). A total of thirteen out of twenty-one Italian regions participated in the study, representing a coverage rate of 66.2 % of the Italian population. In particular, seven regions were from Northern-Central Italy (Autonomous Province of Bolzano, Emilia-Romagna, Liguria, Marche, Piedmont, Tuscany and Veneto), and six from Southern Italy and the Islands (Apulia, Basilicata, Calabria, Campania, Sardinia and Sicily).

Anonymous unlinked samples of sera were collected in the period June 2019-May 2020 from healthy subjects aged 6 to 64 years who presented at the collecting Centers for routine laboratory testing. In accordance with the exclusion criteria adopted by each collecting Center, all subjects included in the study were free of any immune-depressive condition or acute infection, and had not recently received a blood transfusion. The samples were stored at a temperature of − 20 °C.

The number of sera required for the study was calculated on the basis of the antibody prevalence estimates in the different age groups obtained from the seroepidemiological studies conducted as part of the European ESEN (European Sero-Epidemiological Network) project [11], whose sampling was carried out for the national seroprevalence studies conducted in 1996, 2003–2004, and 2013–2014 and processed with the same enzyme immunoassay.

2.2. Detection of anti-measles antibodies

All collected sera were analyzed at the Laboratory of Hygiene of the Department of Biological and Environmental Sciences and Technologies, University of Salento, Lecce, Italy. The Enzygnost anti-Measles Virus/IgG enzyme immunoassay (Siemens Healthcare Diagnostic Products GmbH, Germany) was used to determine the levels of measles-specific IgG antibodies in the sera. The intensity of the colorimetric reaction was determined in duplicate using the Labtech Microplate Reader LT4000 (Labtech International LTD, United Kingdom) at 450 nm with a reference wavelength of 620 nm. Absorbance $>$ 0.2 was considered positive and indicated immunity to measles infection; values $<$ 0.1 were considered negative and indicated susceptibility to measles infection. Values between 0.1 and 0.2 obtained twice on the same samples were classified as "equivocal". The absorbance of samples tested as positive was converted to antibody concentration using an algorithm provided by the manufacturer and based on the α-method. Antibody levels were expressed in mIU/mL, based on the WHO international standard for measles immunoglobulin in serum. According to the manufacturer, the sensitivity and specificity of the test were equal to 99.6 % and 100 %, respectively.

2.3. Statistical analysis

Available participants data (age, sex, and region) and immunoenzymatic results were entered into a Microsoft Excel database. The evaluation of the prevalence of anti-measles IgG in the study population by age group was performed using the chi-squared test. The same test was used to compare data stratified by geographical area. Anti-MV IgG concentration values were compared among age groups using the non-parametric Kruskal-Wallis test, as their distribution was not normal. In all cases, the significance level was set at 0.05.

2.4. Ethical aspects

The study was approved by the Ethical Committee of the Istituto Superiore di Sanità (ISS) and was conducted according to the protocol previously adopted in other seroepidemiological studies conducted in Italy and in Europe (European Sero-Epidemiological Network: ESEN). The collection of samples was carried out in compliance with the current legislation on the protection of personal data.

The samples were coded with a specific code identifying the collecting Center, followed by a number in progressive order, without any reference that could be traced back to the patient's name or initials. The residual sera were anonymized and the only demographic data available were age, gender, and geographical area of residence. Blood samples, after the separation of the serum component, were destroyed in accordance with current safety regulations.

3. Results

3.1. Study population

Overall, 3746 serum samples were collected in 2019–2020 from subjects aged 6 to 64 years residing in 13 Italian regions: 1807 (48.2 %) from the regions of Northern-Central Italy (Autonomous Province of Bolzano, Emilia Romagna, Liguria, Piedmont, Veneto, Marche, Tuscany), 1939 (51.8 %) from Southern and Insular Italy (Basilicata, Calabria, Campania, Apulia, Sardinia, Sicily).

The subjects were divided into 5 age groups: 376 (10.0 %) were aged between 6 and 9 years, 571 (15.3 %) between 10 and 14 years, 556 (14.8 %) between 15 and 19 years, 1698 (45.3 %) between 20 and 39 years, 545 (14.6 %) between 40 and 64 years. The subjects were equally divided between the two sexes (Table 1).

3.2. Seroprevalence

The results showed that 3247 samples were positive and 315 negative. The remaining 184 samples, confirmed as "equivocal", were excluded from the analysis. The overall seroprevalence was 91.2 % (95 % CI = 90.2–92.1 %), without significant difference ($p > 0.05$) between males (90.6 %, 95 % CI = 89.1–92.0 %) and females (91.7 %, 95 % CI = 90.4–93.0 %) (Table 2).

The seroprevalence decreased significantly ($p < 0.05$) from the 6–9 age group (94.2 %) compared to the following age groups (10–14 years: 89.5 %; 15–19 years: 89.7 %; 20–39 years: 89.3 %) and then increased significantly in the older age group (97.6 %) (Fig. 1).

Fig. 2 shows the distribution of anti-MV IgG concentration values in each age group. On average, the subjects aged 20–39 and 40–64 years old had significantly higher ($p < 0.05$) antibody titers (5,297 ± 6,967 mIU/ml; 12,186 ± 8,113 mIU/ml, respectively) than the younger age groups (6–9 years: 3,425 ± 4,391 mIU/ml; 10–14 years: 2,340 ± 3,403 mIU/ml; 15–19 years: 2,698 ± 4,311 mIU/ml).

Geographical distribution showed an overall significantly higher seroprevalence ($p < 0.05$) in Southern and Insular Italy (93.2 %; 95 % CI = 92.0–94.4 %) compared to Northern-Central Italy (88.9 %; 95 % CI = 87.3–90.5 %) (Fig. 3).

When analyzing the seroprevalence in the different age groups stratified by geographical area (Northern-Central Italy vs Southern-Insular Italy), significant differences ($p < 0.05$) were observed in the age groups 6–9 years (90.9 % vs. 97.0 %), 15–19 years (85.4 % vs. 94.2 %) and 20–39 years (87.4 % vs. 90.9 %). In contrast, seroprevalence in the age groups 10–14 years (87.9 % vs. 91.3 %) and 40–64 years (96.7 % vs. 98.3 %) was not significantly different ($p > 0.05$) between the two geographical areas (Fig. 4).

Considering the individual regions participating in the study (Fig. 5), only Sicily (95.5 %) showed a seroprevalence above the 95 % threshold, set to achieve herd immunity. The other Southern-Insular regions recorded values above the Italian average (91.2 %) seroprevalence (Basilicata: 94.1 %; Apulia: 93.4 %; Campania: 92.9 %; Sardinia: 92.1 %; Calabria: 91.2 %). On the other hand, the Northern-Central regions showed a lower seroprevalence than the Italian average (91.2) (Emilia Romagna: 91.1 %; Veneto: 89.5 %; Liguria: 89.4 %; Marche: 89.2 %; Tuscany: 88.8 %; Piedmont: 88.6 %; Autonomous Province of Bolzano: 85.9 %).

Table 1
Distribution of collected samples stratified by gender and age group.

Age groups (years)	Males (n)	Females (n)	Total (n)
6–9	186	190	376
10–14	290	281	571
15–19	285	271	556
20–39	791	907	1698
40–64	260	285	545
TOTAL	1812	1934	3746

Table 2
Results of ELISA tests conducted on valid samples divided by gender.

	Valid samples(n)	Positive samples		Negative samples	
		n	%	n	%
Mals	1717	1555	90.6	162	9.4
Females	1845	1692	91.7	153	8.3
TOTAL	3562	3247	91.2	315	8.8

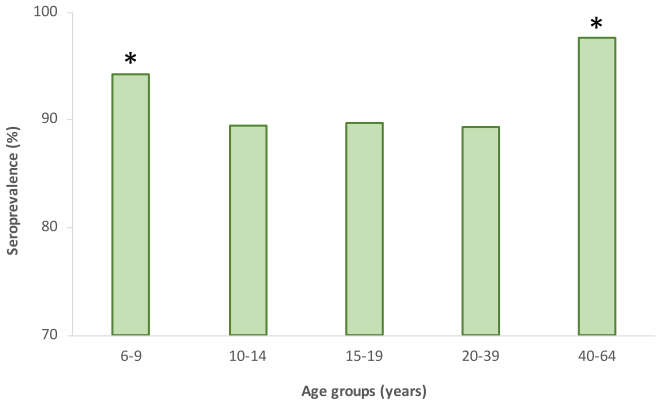

Fig. 1. Seroprevalence of anti-MV antibodies by age group in the Italian population. * different ($p < 0.05$) from 10 to 14, 15–19, 20–39 age groups. Significance was calculated by chi-square test.

4. Discussion

According to WHO, measles remains a leading cause of childhood mortality worldwide, despite the availability of a safe and effective vaccine [7]. In 2020, WHO published the Measles and Rubella Strategic Framework with the goal of achieving the elimination of these diseases [12]. Identifying and addressing measles and rubella immunity gaps as well as maintaining and improving surveillance are among of the identified seven strategic priorities included in this document. The same priorities have been included in other documents published by WHO [13,14]. In 2019, global efforts to improve immunization coverage resulted in a peak coverage rate of 86 % with the first dose of vaccine [8]. However, the COVID-19 pandemic has had a negative impact on the achievement of the elimination target. In addition, over the past decade there was a concerning resurgence of vaccine-preventable disease outbreaks in developed countries worldwide. In Europe, ECDC reported 14,732 cases of measles between February 2017 and January 2018, with Romania and Italy accounting for the largest number of cases (35 % and 34 %, respectively). In 2019, 13,199 cases were reported, with France, Romania and Italy recording the highest number of cases (2,636, 1,706, and 1,619, respectively). Suboptimal vaccination coverage was identified as the main cause of this high incidence, with the majority of those affected resulting unvaccinated [15].

The most recent ECDC epidemiological report indicates a 99 % decrease in cases of measles across Europe in 2022 compared to 2018, with 127 cases recorded and no deaths. The observed epidemiology of measles is likely to have been influenced by the COVID-19 pandemic as well as the control and prevention measures implemented during that period, together with the possible underreporting of measles cases [3].

The overall epidemiological profile of measles cases outlined by the ECDC confirms that the disease continues to affect all age groups, with children under one year of age exhibiting the highest incidence. In fact, newborns are generally too young to be vaccinated and should be protected by herd immunity. In addition, 80 % of reported cases between 1–4 years were unvaccinated. This is the age group in which most EU

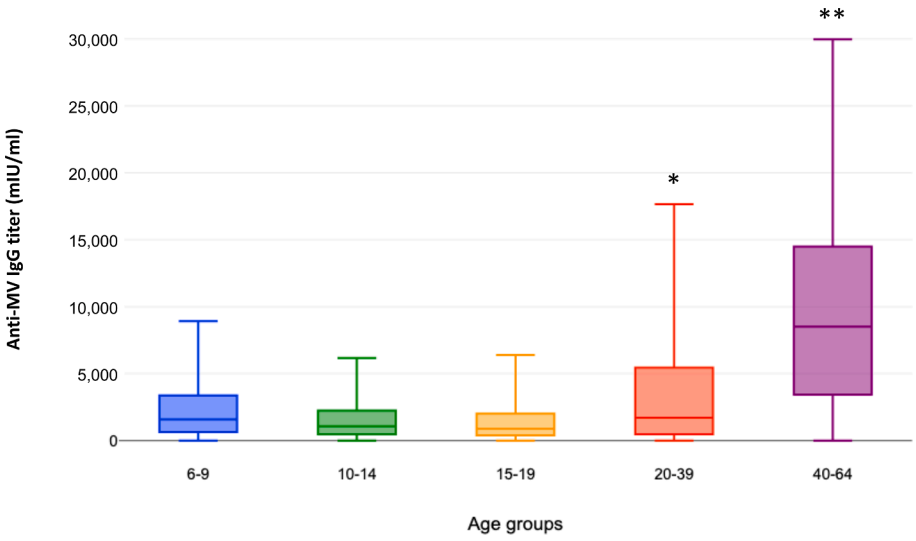

Fig. 2. Quartile distribution and median value of anti-MV IgG concentration values in each age group. * different ($p < 0.05$) from 6 to 9, 10–14, 15–19, 40–64 age groups; ** different ($p < 0.05$) from 6 to 9, 10–14, 15–19, 20–39 age groups. Significance was calculated by Kruskal-Wallis test.

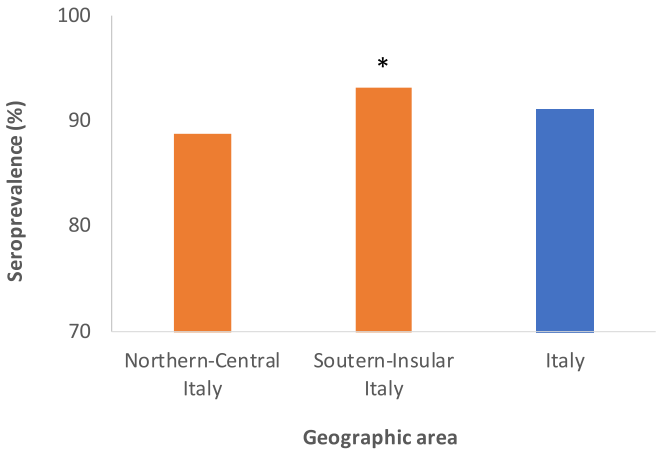

Fig. 3. General seroprevalence of anti-measles antibodies stratified by geographical areas. * different ($p < 0.05$) from Northern-Central Italy. Significance was calculated by chi-square test.

countries administer the first dose of measles vaccine through national vaccination programs. The data reported for 2022, similar to previous years, indicate that, although current vaccination programs in the EU specifically target this age group, a substantial number of children remain unvaccinated.

However, it is important to note that measles is no longer exclusively a childhood disease. In fact, adults continue to be affected as well. In 2022, the ECDC reported that individuals aged 20 years and older accounted for 26 % of reported cases. Of these individuals, 72 % were unvaccinated, while 28 % had received at least one dose of the vaccine, with an unknown number of doses [3].

The critical coverage threshold for achieving effective herd immunity against measles is 95 % [16]. Nevertheless, even in countries where the average vaccination coverage of the population is above the herd immunity threshold, it is not uncommon for small population groups to have significantly lower coverage, thus acting as a "hot spot" for the onset of outbreaks [17].

In Italy, between 2017 and 2018, there was a notable increase in the number of measles cases compared to previous years. The epidemic initially affected the regions of Northern and Central Italy and then spread to the Southern regions. The primary contributing factor to this epidemic was the low vaccination coverage, which, over the years, led to an accumulation of individuals susceptible to infection. The proportion of vaccinated subjects has increased over time, particularly since 2017 after the introduction of mandatory vaccination. However, it has consistently remained below the 95 % threshold required to interrupt the virus transmission [18].

The present study shows an overall seroprevalence of 91.2 %. Despite this high proportion of subjects with a protective level of anti-measles antibodies, the present study highlights an insufficient protective immunity of the general population against measles which could explain the continued circulation of the virus and the failure to achieve the elimination goal.

Subjects aged 6–9 years and 40–64 years had higher seroprevalence compared with other age groups. In the younger age group, the high seropositive rate is likely attributable to the measles vaccination administered in accordance with the National Immunization Plan. In the older age group, it is plausible that immunity derives mainly from natural infection and only partly from vaccine administration, as voluntary vaccination with one dose has been recommended by the Ministry of Health since 1979 [19]. The higher IgG levels in the older age groups provide evidence that protection against measles was mainly due to natural infection, which resulted in a greater and longer-lasting antibody response [20,21].

A study conducted between 1996 and 1997 compared the seroprevalence of measles antibodies in different European countries. Italy was the only country with a high susceptibility to measles due to its low seroprevalence compared to other countries (Finland, Germany, Denmark, France, Norway, Great Britain and the Netherlands). The proportion of seronegative subjects aged 2–19 years was considerably higher than in the same age groups in other countries (2–4 years: 29.8 %; 5–9 years: 25.0 %; 10–19 years: 13.9 %). In contrast, in the older age groups (20–30 years: 4.3 %; >40 years: 1.3 %) the data on seronegative rates were comparable between different countries [22]. Furthermore, data showed a significant difference in seroprevalence between children aged 2–4 years from high and low vaccination coverage regions (81 % vs. 62 %) [19].

A study conducted in Italy in 2003–2004 reported a seroprevalence of 77.2 % (95 % CI 75.7–78.7). In the 0–1-year age group, 34.9 % of children were seropositive. Seroprevalence rates increased significantly in children aged 2–4 years (74.5 %), remained almost stable until 19 years (5–9 years: 67.4 %; 10–14 years: 60.3 %; 15–19 years: 71.8 %) and increased further to 91.4 % and 97.7 %, in the 20–39 and ≥ 40 years age groups, respectively [23]. The overall seroprevalence rate recorded in

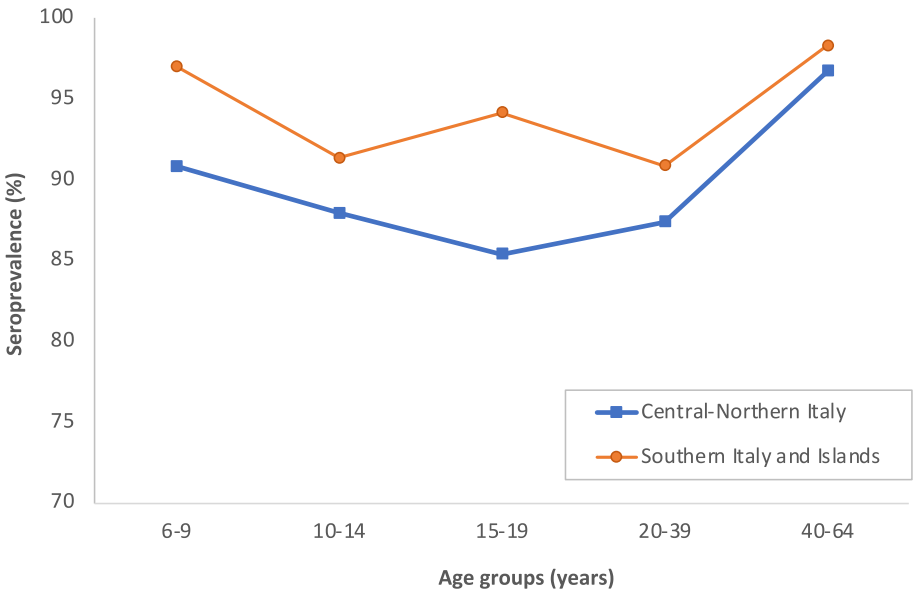

Fig. 4. Seroprevalence of anti-measles antibodies in the two geographical areas stratified by age group.

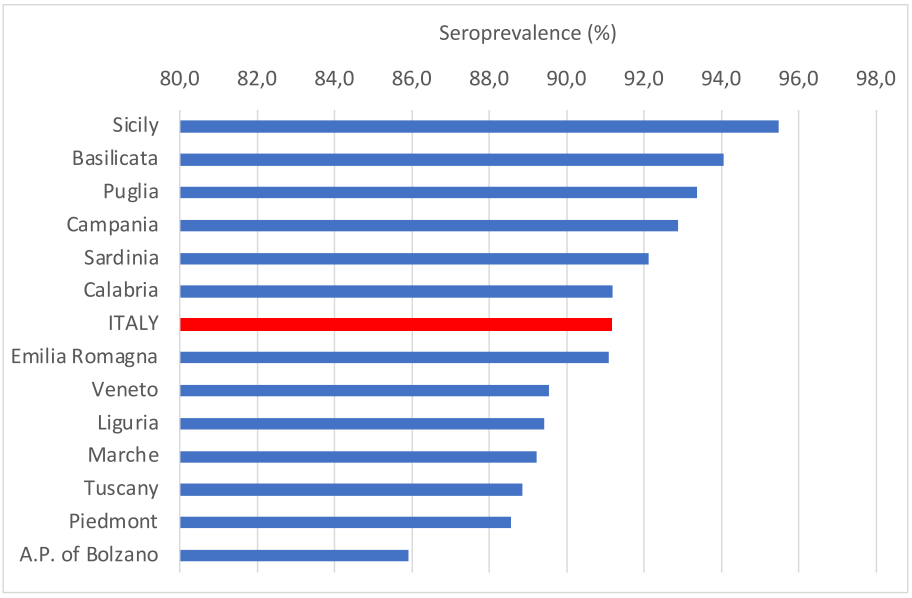

Fig. 5. Seroprevalence of anti-measles antibodies stratified by the regions participating in the study.

2003–2004 (77.2 %) was significantly lower than that observed in 1996–1997 (83.1 %). Seroprevalence rates observed in children up to 9 years of age were quite similar in both the 1996–1997 and 2003–2004 surveys. In contrast, the seroprevalence rates in subjects aged 10–39 years were significantly lower in 2003–2004 than in 1996–1997.

The overall seroprevalence reported in the present study is significantly higher than that reported in previous surveys performed in 1996–97 and 2003–04 using the same sampling methodology and laboratory tests. In particular, a comparison of the results obtained in this study with those reported in Rota et al. [23] and an analysis of the seroprevalence by birth cohorts in the two observation periods demonstrate an increase within the same cohort. Specifically, the seroprevalence of the 2000–2002 birth cohort (which can be identified in the 15–19 age group in this study) increased from 74.5 % in 2003–2004 to 89.7 % in 2019–2020 while the seroprevalence of the 1965–1984 birth cohort (included in the 40–64 age group of the present study) was 91.4 % in 2003–2004 and 97.6 % in 2019–2020.

Upon analysis of the data by geographical area, we found a significantly lower seroprevalence in Northern-Central Italy than in Southern Italy, particularly in the 6–9, 15–19 and 20–39 age groups. This is in line with the results of a 2003–2004 survey [23]. The differences between geographical areas could be partially attributed to the fact that the incidence of measles in 2018 was 41.8 cases/1,000,000 inhabitants, with higher average values observed in the Southern and Island regions than in the Northern-Central regions [24], although in 2019 the observed incidence decreased (27.0 cases/1,000,000 inhabitants), with higher average values in the Northern and Central Italy and lower in the South [25]. Nonetheless, the higher seroprevalence recorded in Southern Italy is in contrast with data on vaccination coverage, which was generally higher in the Northern-Central regions than in the Southern ones [26]. In fact, until 2016, vaccination coverage was lower than the national average in most Southern regions, particularly for the second dose. In 2017 and 2018, greater regional homogeneity was achieved with regard to the first dose, with most regions having a vaccination

coverage > 90 %. In contrast, heterogeneity remained high for the second dose in both years. In 2018, only two regions reached the target of 95 %, Tuscany for the first dose and Basilicata for the second dose [27].

The higher incidence of measles recorded in the Northern Italian regions, in contrast to higher vaccination coverage, may be attributed to several factors. These include the oscillatory pattern that measles epidemiology usually follows, as well as the prevalence of individuals susceptible to the infection. The latter may be influenced by the presence of migrants, who are more concentrated in Northern Italian regions [28] and usually have a higher susceptibility to measles infection than in the destination countries [29].

National guidelines and recommendations on immunization strategies are provided by the Ministry of Health. However, the Italian healthcare system is highly decentralized, with immunization activities coordinated at the regional level. Consequently, different regions may have implemented different strategies to promote vaccination over the years. Recent epidemics have demonstrated the importance of maintaining high vaccination coverage through effective vaccination and awareness campaigns targeting the entire population and risk groups. In this context, the introduction of compulsory vaccination has represented an important step forward in increasing coverage in new birth cohorts; however, susceptible adults still need to be vaccinated (catch-up strategy) to achieve elimination. In order to interrupt the transmission chain quickly, it is also necessary to strengthen the system for detecting and managing epidemic outbreaks.

This study has some limitations. The survey did not include children under the age of six, thus precluding the assessment of the rate of protection in this age group and the possibility of comparisons with other age groups or with previous studies. In addition, the sampling was carried out before the COVID-19 pandemic, therefore it is not possible to assess any decline in the vaccination coverage attributable to the pandemic.

5. Conclusions

The present study shows an increase in the overall seroprevalence (91.2 %) compared with previous investigations, with differences among geographical areas and age groups. However, measles remains a public health issue and represents a challenge for Italy and all European countries. Given the suboptimal vaccination coverage (< 95 %) in a number of countries, an increase in measles cases is likely to be observed in the future [3]. Further efforts are needed to implement and maintain high measles vaccination coverage and to avoid the risk of future epidemic outbreaks.

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Institutional Review Board Statement.

The study was approved by the Ethical Committee of the Istituto Superiore di Sanità (ISS) and performed accordingly to the protocol previously adopted in other sero-epidemiological studies performed in Italy and in Europe (European Sero-Epidemiological Network: ESEN). The collection of samples was conducted in compliance with current Italian legislation on the protection of personal data.

Informed Consent Statement.

Not applicable. Anonymous unlinked residual sera were used and the only available demographic data included age, gender and geographical area of residence.

CRediT authorship contribution statement

Tiziana Grassi: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Francesco Bagordo:** Writing – review & editing, Data curation. **Maria Cristina Rota:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Marco Dettori:** Writing – review & editing, Data curation. **Tatjana Baldovin:** Writing – review & editing, Data curation. **Francesco Napolitano:** Writing – review & editing, Data curation. **Alessandra Panico:** Writing – original draft, Investigation. **Elvira Massaro:** Writing – review & editing, Data curation. **Serena Marchi:** Writing – review & editing, Data curation. **Gabriella Furfaro:** Writing – review & editing, Data curation. **Palmira Immordino:** Writing – review & editing, Data curation. **Marta Savio:** Writing – review & editing, Investigation. **Giovanni Gabutti:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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