Ann Ig. 2024 Nov-Dec; 36(6): 660-667 doi: 10.7416/ai.2024.2632. Epuib 2024 May 2.

Anti-rubella seroprevalence assessment in an adult sample population in Italy

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Keywords: Rubella; seroprevalence; vaccination coverage; congenital rubella syndrome (CRS); ELISA; Italy
Parole chiave in italiano: Rosolia; sieroprevalenza; copertura vaccinale; sindrome da rosolia congenita; ELISA; Italia

Abstract

Introduction. *Despite global immunization efforts, rubella remains a public health concern, particularly in high- and middle-income countries. This study focused on rubella seroprevalence in the province of Florence, Italy, aiming to identify susceptibility clusters, especially among women in their childbearing age.*
Methods. *A cross-sectional study was conducted between April 2018 and December 2019, enrolling 430 adult subjects (age over 18 years). Serum samples were collected, and anti-rubella antibodies were quantified using the ELISA test. Data were analyzed descriptively and compared by sex, nationality, and age groups using statistical tests.*
Results. *The overall rubella seroprevalence was high (92.3%), with no significant differences between genders or nationalities. Among childbearing-age females (18-49 years), the highest seroprevalence was observed in the 30-39 age group (94.1%). However, susceptibility clusters exceeding the 5% threshold set by WHO were identified, especially in females aged 40-49 years (7.0%).*
Conclusions. *Despite high overall seroprevalence, the study identified pockets of susceptibility, even in childbearing age women. Continuous monitoring, targeted immunization strategies, and public health interventions are recommended to maintain rubella elimination, emphasizing the importance of sustained vaccination efforts to protect vulnerable populations.*

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Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

Introduction

Rubella is an acute infectious disease caused by the *Rubella virus* and clinically characterized by fever and rash. Although it has generally a mild outcome, when contracted by a pregnant woman, it can have severe consequences on the developing fetus, leading to miscarriage, stillbirth, or a range of congenital anomalies collectively known as congenital rubella syndrome (CRS) (1). Rubella is transmitted through respiratory secretions, and it has a short incubation period of 12 to 23 days (2). Its highly infectious nature makes it an important public health concern, particularly among pregnant women (1). Given the potential harm to the fetus, vaccination against rubella has become a routine part of childhood immunization schedules worldwide in association with "catch-up" vaccination campaigns for older age groups (3). Epidemiological data show that rubella, rubella in pregnancy and CRS are still a serious public health problem in high- and middle-income countries, despite the existence of established immunization programs and surveillance systems (4). Regarding the European Region, 376 rubella cases were reported in nine EU/EEA Member States and the UK in the period March 2019 - February 2020 (5), the highest number of cases being reported by Poland (277 cases), Germany (55 cases), Italy (30 cases). However, data from Poland should be interpreted with caution, as only 3/277 cases (1%) were laboratory confirmed (5). In Italy, since 2013 a total of 252 rubella cases were reported, describing a reducing trend from 65 cases in 2013 to 7 reported cases in 2022 (6). In Tuscany, a decreasing trend of cases was reported since the early 2000 and only one case of rubella was reported in 2020 (7). Our study aimed to investigate the rubella seroprevalence in adult (18-99 years) subjects in the province of Florence (Italy), to find out possible pockets of susceptibility, especially among women of childbearing age, and therefore to address target immunization strategies.

Methods

This study was conducted as part of a broader project that involved analyzing the prevalence of vaccine-preventable infectious diseases (measles, rubella, varicella, hepatitis A and B, and tetanus) in different age groups in the province of Florence (8-12). The specific focus of this study was to investigate the prevalence of rubella immunity in the adult population. The main objective was to identify potentially vulnerable groups, particularly among young women (18-49 years).

Sample recruitment and sera collection

Sample collection was performed between April 2018 and December 2019 at one of the Central Tuscany Local Health Unit (LHU) facility center located in Florence. The research was carried out in compliance with the principles outlined in the Declaration of Helsinki, and the protocol received authorization from the ethics committees at the local level (Project identification code: DSS UNIFI, n. 98/2017). A sample of 430 individuals, which accounts for 0.05% of the adult population in the province of Florence (totaling 836,324 in 2018), was selected using convenience sampling. To reflect the demographic composition of the general adult population more accurately, this sample was stratified by sex and age: this stratification ensured that the proportions of participants in each subgroup mirrored those in the wider adult population. During the enrollment phase, individuals who did not have residency in the Florence province, immunocompromised patients, individuals currently receiving immunosuppressive treatment, those who had contracted an acute infectious disease (including measles, rubella, varicella, hepatitis A, and hepatitis B) within the preceding two weeks, and those who had received a blood transfusion within the six months leading up to the study were excluded from participation. All blood samples collected underwent centrifugation at 1600 rpm at a temperature of 4°C. The resulting sera were then preserved at -20°C until they were analyzed for detection of anti-rubella antibodies.

Serological Analysis

A quantitative measurement of anti-rubella antibodies was obtained using the commercial ELISA kit Anti-rubella virus (IgG) by EUROIMMUN®. All collected sera were tested for anti-rubella IgG antibodies, and each sample was classified as follows:

- Positive: anti-rubella antibodies ≥11 IU (International Unit)/ml;
- Negative: anti-rubella antibodies <8 IU/ml;
- Borderline: anti-rubella antibodies ≥8 IU/ml and <11 IU/ml.

Statistical Analysis

The serological IgG rubella test results were gathered and organized into a dedicated spreadsheet. A descriptive analysis was performed and seroprevalence

data were reported by sex and nationality: we designated individuals as "Italians" if they possessed Italian citizenship or foreign individuals who were either born in Italy or adopted Italian citizenship. Those who were born outside of Italy but held dual citizenship (Italian and foreign) or only possessed foreign nationality were categorized as "non-Italian". Subsequently, we focused on rubella seroprevalence among females in their childbearing age, aged between 18 and 49 years, stratified by age groups. Rubella seroprevalence rates were calculated along with their corresponding 95% Confidence Interval (CI).

To compare different groups, statistical tests such as Fisher's exact test and the Chi-square test were employed when appropriate. The analyses were performed with RStudio (Version: 2023.06.1+524. Posit team (2023). Rstudio: Integrated Development Environment for R. Posit Software, PBC, Boston, MA (URL http://www.posit.co/). A significance level of $p < 0.05$ was considered statistically significant.

Results

This study recruited 430 subjects aged 18-99 years old and divided into seven age groups, as shown in Table 1. Males and females were evenly distributed, representing the 46.3% and the 53.7% of the sample population, respectively.

Table 2 shows the proportion of positive, negative, and borderline subjects by sex (male/female) and nationality (Italian/non-Italian).

A vast majority of the enrolled subjects were positive (397/430, 92.3%, 95% CI: 89.8-94.8). Overall, 6.3% (95% CI: 4.0-8.6) of the participants had negative results, and 1.4% (95% CI: 0.3-2.5) were borderline. Among the participants, 92.2% (95% CI: 88.6-95.8) of females tested positive for anti-rubella, while 6.5% (95% CI: 3.19-9.81) were negative and 1.3% (95% CI: 0-2.82) had borderline results. Italians showed a positivity rate of 92.5% (95% CI: 89.7-95.3), with 6.4% (95% CI: 3.8-9.0) negative and 1.1% (95% CI: 0-2.20) borderline results, while non-Italians had a positivity rate of 90.7% (95% CI: 82.6-98.9), 5.6% (95%CI: 0.8-12.0) negativity, and 3.7% (95% CI: 0-9.0) borderline.

Figure 1 shows the distribution of positive, negative, and borderline subjects in the different age groups analyzed and by sex distribution.

The main results indicate high rates of rubella positivity in different age groups. In the first age group (18–49 years, n=205, 107 females and 98 males), 91.6% (95% CI: 86.3-96.9) of females tested positive for rubella. In the second age group (50-64 years, n=95, 49 females and 46 males), a high percentage of both males (93.9%, 95% CI: 87.0-100.0) and females (95.7%, 95% CI: 90.0-100.0) were positive. In the last age group (≥ 65 years, n=130, 75 females and 55 males), 92% of females (95% CI: 85.9-98.1) and 92.8% of males (95% CI: 86.0-99.6) were rubella positive. There were also some negative and borderline results observed across the age groups, but - overall

Table 1 - Enrolled subjects divided by age group and sex.

Age group (years)	Male (n)	Female (n)	Total (n)
18-29	29	30	59
30-39	32	34	66
40-49	37	43	80
50-59	35	37	72
60-69	30	34	64
70-79	25	30	55
80-99	11	23	34
Total	199	231	430

Table 2 - Anti-rubella seroprevalence in the enrolled population. Percentages are related to each row.

Group	Positive samples n (%)	Negative samples n (%)	Borderline samples n (%)	Total samples n
Male	184 (92.5)	12 (6.0)	3 (1.5)	199
Female	213 (92.2)	15 (6.5)	3 (1.3)	231
Italian	348 (92.5)	24 (6.4)	4 (1.1)	376
Non-Italian	49 (90.7)	3 (5.6)	2 (3.7)	54
Overall	397 (92.3)	27 (6.3)	6 (1.4)	430

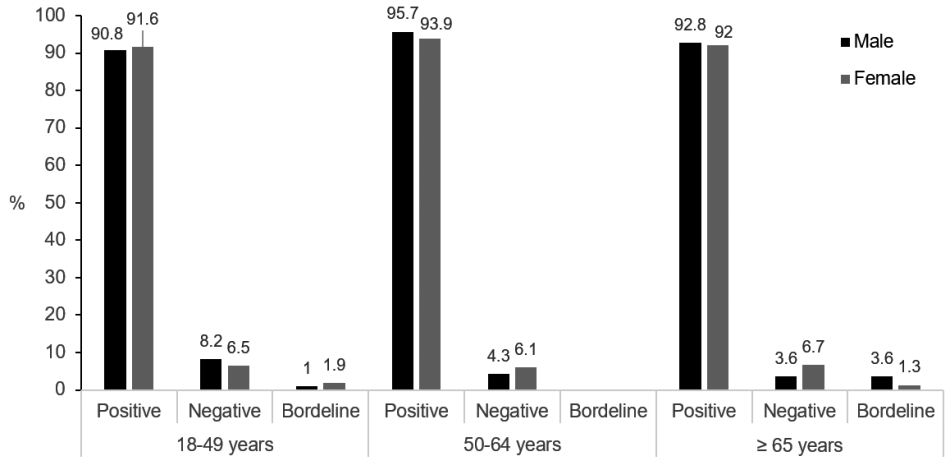

Figure 1 - Rubella seroprevalence distribution by sex and age group in our sample.

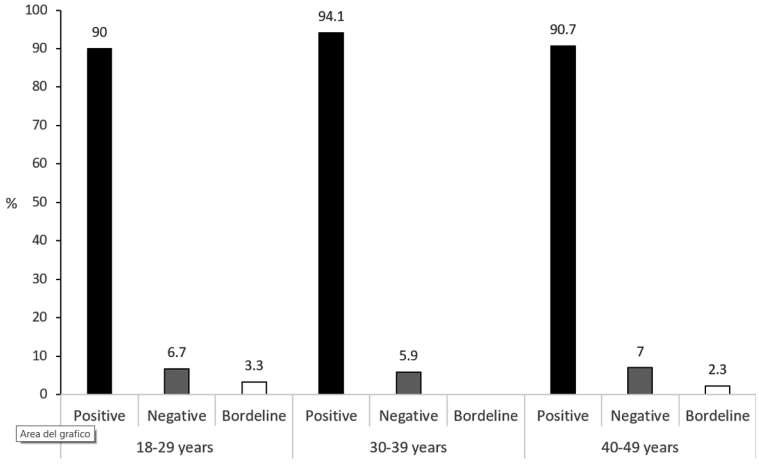

Figure 2 - Rubella seroprevalence in childbearing age women (18-49 years), by age group.

- they accounted for less than 10%. Figure 2 shows the results of the analysis of the 107 sera collected from women of childbearing age (18-49 years old), it was observed that those aged 30-39 years old were the most positive among all age groups, with a positivity rate of 94.1% (95% CI: 86.2-100.0).

This was followed by the age group of 40-49 years, which showed a positivity rate of 90.7% (95% CI: 82.0-99.4). Finally, women aged between 18-29 years old had a positivity rate of 90.0% (95% CI: 79.3-100.0). It is important to note that, in our sample, women of childbearing age who are susceptible (negative) exceed the WHO threshold of 5% for the elimination of congenital rubella (13). No borderline subjects were found in the 30-39 age group. Additionally, no statistical differences between groups (e.g., rubella seroprevalence in female vs male, Italians vs non-Italians, or between different age groups in childbearing age women) were found.

Discussion

In this study, we investigated the rubella seroprevalence in adult subjects in the province of Florence (Italy), with a specific focus on identifying vulnerable groups, particularly among women of childbearing age. The findings of our work hold several implications for public health and provide valuable insights to rubella control efforts in Italy and specifically in the Tuscany region.

Our study reveals a high overall seroprevalence of rubella (92.3%) among adults. This suggests that a significant proportion of the population has acquired

immunity already in young adults by the age of 18 years, possibly through vaccination or exposure to the virus. Our results also indicate that rubella antibodies seroprevalence is still high, in comparison with the earlier study conducted in Tuscany in 2005-2006, which showed an overall seropositivity of 90.6% (14). The rates are similar (although a bit lower in older groups and higher in younger groups) if we compare the childbearing age women groups: our study reported 90% of rubella antibody prevalence in women aged 18-29 years (87-89% in 2005-2006), 94.1% in women aged 30-39 years (93.6% in 2005-2006), 90.7% in women aged 40-49 years (95.5% in 2005-2006). The high rubella antibody seroprevalence found in our present study is also consistent with the low number of cases of rubella notification reported in the past years. Indeed, three cases were reported in 2013, two of which were in pediatric age and 1 in the 15-34 age group, one case in 2020 involving a woman between 35 and 64 years old and 0 cases in 2021-2022) (7). This evidence emphasizes the importance of continued efforts to maintain high immunization coverage to prevent outbreaks and protect potentially susceptible individuals, especially after rubella elimination was declared in Italy (15).

The fight to eliminate rubella has indeed begun in Italy decades ago: the rubella vaccine has been available since 1972. Initially, vaccination was only recommended for pre-adolescent girls, but rubella vaccination was universally recommended from the 1990s, with the introduction of the Measles-Mumps-Rubella (MMR) combined vaccine (16). Currently, the national vaccination schedule mandates two doses of the MMR vaccine: the first dose at 12-15 months of age and the second dose at 5-6 years, and for women of childbearing age (17,18). The Italian National Plan for the Elimination of Measles and Congenital Rubella (PNEUMoRc) was implemented since 2003, with the aim to reach the objectives by 2020 and to prevent CRS by achieving high vaccine coverage (VC) rates: this plan contributed to a significant increase in vaccine coverage rates, helped by the introduction of mandatory vaccination in 2017 (16, 19-23). All these combined efforts led, in July 2023, to the announcement of rubella "elimination" in Italy, that is the interruption of the endemic transmission of a disease for a period of at least 12 months or more according to the surveillance system in place, as announced by WHO's Regional Verification Commission for the Elimination of Measles and Rubella in the European Region (15). Moreover, CRS has been subject to notification in Italy since 2005; since then, there has been a significant reduction in the notification trend, accounting for a total number of 88 cases in 2005, two cases in 2017 and one imported case in 2018 (24). In 2018, the national vaccination coverage for rubella in the 2016 birth cohort was indeed high, reaching 93.2%, and Tuscany had the highest coverage (95%) among all regions (25). Despite the overall increasing trend, the target goal of 95% vaccination coverage against MMR, in Italy, was only achieved in the 2015 cohort (at the age of 36 months) (26, 27). However, there remains a concern regarding the proportion of individuals susceptible to rubella, which is still alarmingly high at nearly 10% in adults, including women of childbearing age. This is particularly significant considering WHO recommendations, which set a 5% threshold of susceptibility for young women as a criterion for rubella elimination in European countries (13).

When considering the adult female population in childbearing age, few seroprevalence studies related to the Italian context are available. A recent national surveillance study conducted in Italy between 2017 and 2020 reported that only 44.9% of women remember having been vaccinated against rubella while 37.3% report not knowing their status, and 1.8% report being susceptible (28). The lack of awareness is a problem and indicates a low-risk perception and attention to reproductive health, both on the part of the women directly concerned and presumably by the healthcare providers who should inform them. This involves encouraging them to check their immune status and, if necessary, get vaccinated (29). It is likely that many of the women not knowing their vaccination status are not susceptible to rubella due to a previous exposure to the virus or a previous vaccination that they do not recall. Finally, it must be acknowledged that rubella outbreaks commonly impact individuals who have not developed immunity in areas or populations where overall immunity levels are not sufficient, largely attributed to inadequate vaccination rates, and international migrants are often regarded as a vulnerable population with an elevated susceptibility to infectious diseases, including rubella (30). An encouraging finding in our results is the equitable distribution of rubella immunity across both sexes and different nationalities.

As a limitation of our study, the cross-sectional design limits our ability to establish causal relationships, and the data are referring only to the Tuscany region. Additionally, our study did not explore potential factors contributing to the observed seroprevalence in different groups (e.g. assess vaccination status),

which warrants further investigation in future research. Low differences in seroprevalence by age groups, even not statistically significative, could be attributed to the number of samples by subgroups. However, our study's strengths lie in the fact that sample size is proportional by age and sex, to the population residing in the province of Florence and represents a comprehensive assessment of rubella antibodies seroprevalence in that area. Although the seroprevalence found in our study is high, there is a proportion of susceptible individuals among young people and women of childbearing age that requires attention for future prevention strategies. The threshold of less than 5% susceptibility among women of childbearing age has not been reached. Despite the current interruption of endemic transmission in Italy, the risk for susceptible women in their childbearing age remains because they could travel to areas where rubella transmission is still endemic. It is necessary for the data on the elimination of endemic circulation to be confirmed over time, and the risk of infection has not been completely eliminated.

Conclusions

Our study contributes valuable insights to the ongoing efforts aimed at rubella control and prevention of congenital rubella syndrome in the province of Florence. The high overall seroprevalence, equitable distribution of immunity and sustained protection across age groups are positive indicators of the low risk of rubella infection. Based on our findings, we confirm the importance of continuous monitoring of rubella antibodies seroprevalence rates, and the maintenance and strengthening of current rubella vaccination programs to sustain the achieved high levels of immunity in the adult population and to confirm the interruption of endemic rubella transmission in Italy (15). However, the fight against rubella is still ongoing, due to clusters of susceptibility found throughout the population: therefore, these findings have important implications for public health policies and preventive interventions to ensure the maintenance of rubella elimination status and to promote the well-being of vulnerable populations in the region.

Author Contributions: conceptualization, P.B., A.B., S.B., B.B., B.Z., M.DR., C.S.; methodology, P.B., A.B., S.B., B.B, B.Z., M.DR., C.S.; validation, P.B., A.B., B.B., B.Z.; formal analysis, M.DR., M.B., E.S.; investigation, P.B., A.B., S.B., B.Z., M.DR., J.B., I.B., M.C., M.I., F.M., D.P., G.S., L.B., S.B., M.DF., G.G., G.M., M.GS.; resources, P.B., A.B., S.B.; data curation, B.Z., B.B., M.DR., M.B., E.S., L.B., M.DF., G.G., G.M., M.GDS.; writing—original draft preparation, M.DR., C.S.; writing—review and editing, P.B., A.B, S.B., B.B., M.B., E.S., B.Z., J.B., I.B., M.C., M.I., F.M., D.P., G.S., L.B., S.B., M.DF., G.G., G.M., M.GS ; visualization, M.DR., C.S.; supervision, P.B., A.B., S.B.; project administration, P.B., L.B., M.DF., G.G., G.M., M.GS. All authors have read and agreed to the published version of the manuscript.
Funding: This research received no external funding.
Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local Ethics Committee (project identification code: DSS-UNIFI, number of Ethics Committee approval registry 98/2017).
Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.
Data Availability Statement: Data supporting the reported results are available from the corresponding author upon reasonable request.
Conflicts of Interest: The authors declare no conflict of interest.

Riassunto

Valutazione della sieroprevalenza della rosolia in un campione di adulti in Italia

Introduzione. Nonostante gli sforzi globali di immunizzazione, la rosolia continua a rappresentare una sfida per la salute pubblica, in particolar modo nei paesi con economie avanzate e intermedie. Il presente studio ha come obiettivo quello di stimare la sieroprevalenza della rosolia nella provincia di Firenze, in Italia, al fine di identificare particolari cluster di suscettibilità, specialmente tra le donne in età riproduttiva.

Metodi. È stato condotto uno studio trasversale nel periodo compreso tra aprile 2018 e dicembre 2019 su un campione di 430 adulti (età superiore ai 18 anni). Sono stati raccolti campioni sierici e quantificati gli anticorpi anti-rosolia mediante il test ELISA. L'analisi dei dati è stata di tipo descrittivo e ha previsto confronti basati su sesso, nazionalità e fasce d'età, impiegando test statistici.

Risultati. La sieroprevalenza della rosolia nel campione esaminato si è dimostrata elevata (92.3%), senza significative differenze in base al genere o alla nazionalità. Tra le donne in età fertile (18-49 anni), la più alta sieroprevalenza è stata rilevata nel gruppo di età 30-39 anni (94.1%). Tuttavia, sono stati identificati cluster di suscettibilità che superano la soglia del 5% stabilita dall'OMS, in particolar modo nelle donne di età compresa tra 40 e 49 anni (7.0%).

Conclusione. Nonostante l'elevata sieroprevalenza generale, lo studio ha individuato focolai di suscettibilità, inclusi nelle donne in età fertile. Saranno necessari un monitoraggio continuo, strategie di immunizzazione mirate e interventi di sanità pubblica per mantenere l'eliminazione della rosolia, enfatizzando l'importanza di un impegno vaccinale sostenuto per proteggere le popolazioni vulnerabili.

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