






SHORT REPORT

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## Measles in pregnancy: a threat for Italian women?

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### ABSTRACT

Measles in pregnancy may lead to serious sequelae for newborns and mothers. In Italy assessment of immunity against measles is not recommended as pregnancy screening. This study aimed to assess the immunity against measles in pregnant women from Apulia Region in Southern Italy between 2016 and 2017. Overall, 96.9% of pregnant women were positive for anti-measles IgG, younger women aged 19–29 years had a seroprevalence below 90%. No samples were positive for anti-measles IgM. In conclusion, younger pregnant women showed to be at higher risk of contracting measles during pregnancy. These findings have implication for measles vaccination policy and highlight the need for measles antibody testing in pregnancy screening in Italy.

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### KEYWORDS

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Measles is a highly contagious infectious disease that can be prevented by vaccination. Severe central nervous system complications, such as acute post-infection encephalitis and subacute sclerosing panencephalitis (SSPE), can occur with a frequency of 10–20% in industrialized countries.<sup>1</sup> Measles case fatality ratio is estimated to be <0.01% in industrialized countries and depends on the average age of infection, nutritional status, vaccine coverage and access to health care.<sup>1</sup> In Italy, the introduction of Measles, Mumps and Rubella (MMR) vaccine in the national immunization program in 1999 and the institution of the National Plan for Measles and Congenital Rubella Elimination (NPMCRE) in 2003, introducing a two-dose schedule and school catch-up campaigns,<sup>2</sup> led to a substantial decrease in the reported number of measles cases, from 41254 in 1997 to 1435 in 2000.<sup>3</sup> However, although vaccine coverage improved in children, elimination of measles was not achieved and the risk of natural exposure to measles increased in older age groups including women of reproductive age. In fact, during the outbreak occurred in Italy in 2017 the median age of the 4885 reported measles cases was 27 years.<sup>4</sup>

Consistently with the high vaccine coverage reached in Italy for the second dose of measles in 2000 (70%)<sup>5</sup> and subsequent years, although not adequate to interrupt the transmission of the wild virus,<sup>6</sup> a large number of susceptible women born in the 1980s and 1990s, a cohort of women currently in childbearing age, was identified in a survey reported in 2017.<sup>1,7</sup>



When measles occurs during pregnancy, although there is no specific congenital syndrome associated with measles infection, severe co-morbidity and sequelae may occur on both fetus and mother.<sup>8</sup> Adverse perinatal outcomes are characterized by frequent abortions, premature labor and increased risk of fetal

or neonatal mortality associated with placental dysfunction.<sup>9</sup> Pregnant women, who contract measles, have a severe clinical course, with high rates of measles-related miscarriage, severe respiratory distress, pneumonitis, hospital admission and death.<sup>10</sup> Measles occurring in late pregnancy can lead to perinatal infection in the infant, which may be associated with a high mortality and the risk of SSPE.<sup>8</sup> To consider also that infants born from seronegative women are not protected from measles until they will be vaccinated.<sup>1</sup>

Although identification of women at risk of developing measles during pregnancy is not recommended in Italy, serological surveys on pregnant women can respond to the question on whether a measles immunity screening program is necessary in Italy and provide adequate immunization for women of childbearing age. For this purpose, a prevalence study on measles immunity was carried out on serum samples collected in 2016 and 2017 among pregnant women in Apulia, a large region in Southern Italy.

Serum samples of pregnant women were collected from January 2016 to July 2017 in the province of Bari, the most densely populated province of Apulia region in Southern Italy. Samples were anonymously collected in compliance with the Italian ethics law and stored at the internal serum bank of the Laboratory of Molecular Epidemiology, Department of Molecular and Developmental Medicine, University of Siena. Information available for each serum sample were age, gender, pregnancy, place and year of sampling.

Study population is described in Table 1. The mean age was  $34 \pm 5$  years, higher than to the mean age of Italian women at delivery (31.89 years in 2016). Samples were stratified in the following age groups: 19–29, 30–34, 35–39 and 40–44 years old, similar to those used by the Italian National Institute of Statistics.<sup>11</sup>

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**Table 1.** Study population.

Age (Years)	Year of birth (range)	n	%	Mean age (Years $\pm$ SD)
All (19–44)	1972–1998	193	100	34 $\pm$ 5
19–29	1987–1998	39	20.2	27 $\pm$ 2
30–34	1982–1987	76	39.4	32 $\pm$ 1
35–39	1977–1982	54	28.0	37 $\pm$ 1
40–44	1972–1977	24	12.4	41 $\pm$ 1

Serum samples were tested for specific anti-measles IgG and IgM, as a marker of recent infection, using the commercial ELISA Serion Measles Virus IgG (Virion/Serion, Germany) and Enzywell Measles IgM (DIESSE, Italy), respectively. Tests were performed following manufacturer's instructions and results were qualitatively and quantitatively analyzed. Based on the criteria of ELISA for IgG, samples were classified negative if the OD of the sample was below the lower cut off or positive if above the upper cut off. Cut off values were calculated using lot-dependent constants embedded in the barcode of each kit used; all samples were tested with ELISA IgG kit of the same lot. For IgM ELISA, samples were considered positive when the ratio between the OD of the sample and that of the cut off was  $>1.2$ , while negative when the value was  $<0.8$ . In both tests, sera with borderline result were retested in order to assign the positive or negative value.

The GraphPad Prism 7 software was used for statistical analysis of the results. Seroprevalence rates were calculated along with the corresponding confidence intervals (95% CI). Geometrical mean titer (GMT) was calculated for different age groups and One-Way ANOVA test was used to compare GMT  $\pm$  SD among different age groups. Statistical significance was set at  $p < .05$ .

Anti-measles IgG prevalence in overall population was 96.9% (95% CI, 93.3–98.8). All subjects in the age groups 30–34 and 40–44 years were positive (100–95% CI, 95.2–100), while 96.3% (95% CI, 87.2–99.5) of the 35–39 years group were seropositive. In the youngest age group of 19–29 years 89.7% (95% CI, 75.8–97.1) had IgG against measles (Table 2).

Anti-measles IgG GMT was 1409 mIU/ml (95% CI, 1243–1597) in positive samples. GMTs were similar among age groups, except for the 40–44 years old age group that had the highest value of anti-measles IgG GMT with 1975 mIU/ml (95% CI, 1514–2577) (Table 2).

All samples were negative to ELISA IgM.

In this study we found that a high proportion of pregnant women had antibodies against measles, with a seroprevalence  $>95\%$  in all age groups considered (100% in 30–34 and 40–44 age

groups, 96.3% in 35–39 age group), except for younger women of 19–29 of whose seroprevalence is just  $<90\%$  (89.7%).

This age group of 19–29 years old corresponds to women born between 1987 and 1998 prior the introduction of the second dose of MMR vaccine in Italy.<sup>2</sup> In 1993, the vaccine coverage at 24 months for the first measles dose in the Italian Southern regions ranged between 8.6% in Naples urban area and 18.7% in Abruzzi region, while in 1998, reached 50.6% in Apulia region.<sup>12,13</sup> Since this age group corresponds to the target population of the catch-up campaign in schools planned by NPMCRE since 2003, it is possible that these women received at least one dose of MMR vaccine. A reasonable assumption is that the 19–29 years old age group had a low vaccination coverage for both first and catch-up dose, in addition to the reduced possibility to contract natural infection in a period of a decreased circulation of the virus.<sup>14</sup> On the other hand, older women, born between 1972 and 1977 during a period of intense wild virus circulation and prior the introduction of measles vaccine (recommended in Italy since 1979),<sup>12</sup> had higher antibody levels than the younger age groups.<sup>1</sup> The lack of information about vaccination status does not allow us to speculate if low IgG titers in women under 40 years (especially for 30–34 years old age group) depends on the waning of vaccine-induced protection or on the absence of natural exposure to wild measles virus.

This study has some limitations. The relatively small number of samples tested and the fact that were collected only in Apulia region may limit the extrapolation of our findings to all Italy. The lack of information regarding the vaccination status of subjects makes difficult to interpret whether the presence and level of anti-measles antibody are due to vaccination or to natural exposure to wild virus. The findings of this study confirm those reported from other European countries,<sup>15,16</sup> where younger women are more susceptible to measles and had a lower IgG titer than women born before 1980.

To our knowledge, this is the first study to evaluate the immune status of pregnant women to measles in Italy.

Considering that in Italy measles elimination goal is far to be achieved and the virus still circulates widely in the population,<sup>6</sup> analysis of immunity status against measles infection should be introduced as screening tests before pregnancy, especially for younger women, together with an adequate catch-up vaccination campaign targeting non-immune women of childbearing age or adolescents. In the context of the 2010–2015 Italian NPMCRE, recommendations were included

**Table 2.** Prevalence and titers of anti-measles IgG.

IgG	Positive			Negative		Total n
	n	% (95% CI)	GMT (95% CI)	n	% (95% CI)	
Age at enrollment (Years)						
Overall (19–44)	187	96.9 (93.3–98.8)	1409 (1243–1597)***	6	3.1 (1.1–3.6)	193
19–29	35	89.7 (75.8–97.1)	1369 (985–1904)***	4	10.3 (2.9–24.2)	39
30–34	76	100 (95.2–100)	1272 (1069–1515)***	0	0 (0–4.7)	76
35–39	52	96.3 (87.2–99.5)	1436 (1080–1910)***	2	3.7 (0.4–12.7)	54
40–44	24	100 (85.7–100)	1975 (1514–2577)	0	0 (0–14.2)	24

Data reported in the table represent the prevalence (reported as number and %) of positive and negative samples by age groups. IgG titers of positive samples are indicated as GMT expressed in mIU/ml. 95% CI is reported for percentage and GMT values. \*\*\* $p < .0001$  vs. 40–44 years old age group.

to increase the outreach for MMR vaccine (containing both measles and rubella vaccines) among women of childbearing age with actions on increasing awareness on the risk of contracting measles during pregnancy, and administration of MMR vaccine to susceptible women in all opportunities of encounter with the Health System (i.e., administration of other vaccines, the first pap-test screening, after delivery or after abortion) <sup>17</sup>.

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