



Rubella serosurvey and factors related to vaccine hesitancy in childbearing women in Italy

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ABSTRACT

Voluntary termination of pregnancy (VTP), pre-conception and post-partum phases, as well as Occupational Medicine consultation for healthcare workers are opportunities for screening and vaccinating rubella seronegative childbearing women. However, data about vaccination acceptance following these phases is rarely reported.

A retrospective study over a 2-year period (2016–2017) was performed, evaluating the prevalence of rubella seronegative women which underwent VTP (wVTP), mothers in early puerperal phase (mEPP) and childbearing healthcare workers (CbHW) aged 15–49 years. Anti-rubella vaccination rates and factors associated with vaccine hesitancy (VH) were investigated.

Anti-rubella IgG titres were assessed in 8623 women. Seroprevalence of rubella susceptibility was 7.9% (wVTP 6.4%; mEPP 17.4%; CbHW 9.3%). Anti-rubella vaccination rates were found to be different in the three groups (wVTP 37.1%; mEPP 10.9%; CbHW 25.4%), specifically in 2016 and among women born in Italy. VH rate was higher in 2017, especially among wVTP and CbHW. Anti-rubella vaccination rates in wVTP vs. mEPP was higher in women born in Italy but not in those born abroad. Multivariable analyses demonstrated significantly higher risk of VH for mEPP (OR 8.2; 95% CI: 3.9–16.9) and women reporting history of allergy to drugs, food or environmental agents (OR 2.7; 95% CI: 1.4–5.1).

During the analyzed period childbearing women included in this study were not adequately protected against rubella. Anti-rubella vaccination rates were widely unsatisfactory. Being mEPP and reporting allergy were significantly associated to higher rates of VH. Tailored strategies targeting on vaccine safety are needed for retention of these women in immunisation programmes.

1. Introduction

Rubella is a viral infection, which is spread through the respiratory route. It is presently considered a re-emerging vaccine-preventable disease together with measles and mumps. It mostly results in self-limiting upper respiratory symptoms, fever, lymphadenopathy and cranial/cervical-distal maculopapular rash. Among adults, complications such as encephalitis, haemorrhagic syndromes and orchitis have been largely described. During pregnancy, rubella virus can infect both placenta and foetus increasing morbidity, disability and mortality load (Lambert et al., 2015). During the first trimester, rubella infection can lead to miscarriage, death of foetus, stillbirth, or congenital rubella

syndrome. After week 31 of gestation vertical transmission risk increases progressively, climbing up to 100% at week 36. Moreover, an increased risk of endocrinopathies such as thyroiditis and diabetes mellitus has been found to be associated with congenital rubella infection (Schwarz, 2017).

Eliminating rubella in five World Health Organization regions in order to prevent rubella infection complications is an international community aim for 2020 (*The Global Vaccine Action Plan 2015–2020*, 2012; *European Vaccine Action Plan 2015–2020*, 2014). Providing free of charge, measles, mumps and rubella (MMR) vaccines to all adolescents and adults has been established to be the right strategy in order to reduce rubella susceptibility below 5%.

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Vaccine hesitancy (VH) has been defined as a delay in acceptance or refusal of vaccine despite availability of vaccination services. Causes of VH are multiple, various and context-related, usually linked to complacency, convenience and confidence (MacDonald, 2015). Low health professional education about evidence of vaccination effectiveness, benefits and safety and patient beliefs have been considered the main obstacles to satisfactory vaccination coverage (Giambi et al., 2018; Stark et al., 2016; La Torre et al., 2017; Little et al., 2015).

Voluntary termination of pregnancy (VTP), pre-conception and post-partum phases (Hisano et al., 2016), as well as Occupational Medicine assessments for healthcare workers were deemed to be opportunities for screening and vaccinating rubella seronegative women of childbearing potential. However, data about vaccination acceptance following these phases is rarely reported or considered suboptimal (Little et al., 2015; Pettinicchio et al., 2018; Santoro et al., 2016). In spite of implementation of several immunisation strategies, as in-hospital vaccination before discharge or active calls by public health services, anti-rubella vaccination rates following VTP in Italy have been considered worrying and widely unsatisfactory (Pettinicchio et al., 2018). Italian surveillance data from 2005 to 2013 reported 75 cases of congenital rubella infection and 160 cases of rubella infection in pregnancy, highlighting a probable underestimation due to unclassified newborns and women lost to follow-up (Giambi et al., 2015). Identifying rubella susceptibility and factors related to VH in childbearing women is necessary to develop and implement tailored strategies (Jarrett et al., 2015) which can prevent rubella infection complications, above all during pregnancy.

The aims of this study were to assess rubella susceptibility and anti-rubella vaccination rates of seronegative women which underwent VTP (wVTP), mothers in early puerperal phase (mEPP) and childbearing healthcare workers (CbHW). Where available, factors associated to VH in wVTP and mEPP were also evaluated in order to help clinicians identify women at higher risk of VH that should be included in targeted strategies aiming at higher retention in vaccination programmes.

2. Materials and methods

A monocentric retrospective study over a 2-year period (2016–2017) was performed at a tertiary hospital, primarily evaluating prevalence of rubella susceptibility in wVTP, mEPP and CbHW aged 15–49 years. Demographic characteristics and first dose anti-rubella vaccination rates before discharge for wVTP and mEPP and at the time of Occupational Medicine consultation for CbHW were analyzed and compared among groups. All the anti-rubella seronegative women which refused anti-rubella vaccination were considered hesitant.

wVTP and mEPP were compared and factors related to VH assessed. Age, country of birth (born in Italy vs. born abroad), parity (≥ 1 child vs. nulliparous), previous VTP, reported comorbidities, allergy to drug/food/environmental agents, week of gestation at the time of termination in wVTP and performance of caesarean delivery in mEPP were the variables available in the medical records that have been analyzed in these two groups only, as they were not available for CbHW. Patient records were anonymized and de-identified prior to analysis. The study was not submitted to the Ethics Committee's approval because it was carried out within the local transposition of what the Italian National Plan for the Elimination of Measles and Congenital Rubella advised.

Anti-rubella immunoglobulin G (IgG) titres were assessed using chemiluminescent immunoassay technology (Liaison XL – DiaSorin, Saluggia, Italy), according to the manufacturer's instructions. Serum samples with anti-rubella IgG ≥ 10 IU/ml were considered positive and serum samples with anti-rubella IgG ≤ 6 IU/ml were considered negative. Intermediate serologic results (6.1–9.9 IU/ml) were reassessed with enzyme linked fluorescent assay (VIDAS – bioMérieux, Marcy l'Étoile, France), which were then considered negative when second appraisal of anti-rubella IgG titres were ≤ 10 IU/ml.

Descriptive data are shown as absolute (n) and relative (%)

frequencies for categorical data and as mean \pm standard deviation (SD) for continuous variables. At univariate analysis, Chi-square test was carried out for categorical variables, and analysis of variance (ANOVA) with Bonferroni correction for continuous variables in order to assess whether significant differences could be detected among the 3 groups. Chi-square test or Fisher's exact test, as appropriate, were also performed to compare wVTP and mEPP and to detect possible predictors of VH stratifying by year of serology testing.

Multivariable analysis models were then fitted to evaluate the independent effect of clinically relevant variables and those that turned out to be significantly associated to VH at univariate analysis: VH was set as the dependent variable of a logistic regression model whereas group (wVTP vs. mEPP), age, country of birth (born in Italy vs. born abroad), parity (≥ 1 child vs. nulliparous) and allergy were taken as independent variables. For all tests, a p-value ≤ 0.05 was considered significant. All analyses were performed with Stata 14.

3. Results

3.1. Seroprevalence of rubella susceptibility and anti-rubella vaccination rates

Anti-rubella IgG titres were assessed in 8623 women (wVTP n = 6319; mEPP n = 780; CbHW n = 135). Most of them (66.7%; n = 5748) were born in Italy: 61% (n = 3852), 60.4% (n = 471) and 93.5% (n = 1425) of wVTP, mEPP and CbHW, respectively. The overall prevalence of rubella susceptibility was 7.9% (n = 680): 6.4% (n = 402), 17.4% (n = 136), 9.3% (n = 142) in wVTP, mEPP and CbHW, respectively. The prevalence of rubella susceptibility in women born in Italy (8.5%; n = 490) was generally found to be higher than in women born abroad (6.6%; n = 190). Among women born in Italy the prevalence of rubella susceptibility was 6.8% (n = 262), 19.3% (n = 91) and 9.6% (n = 137) in wVTP, mEPP and CbHW, respectively. Showing a similar trend, prevalence of rubella susceptibility among women born abroad was 5.7% (n = 140), 14.6% (n = 45), 5.1% (n = 5) in wVTP, mEPP and CbHW, respectively.

Demographic characteristics and anti-rubella vaccination rates of rubella seronegative women according to group are shown in Table 1. Comparing the three groups, a statistically significant different distribution of age (p = 0.003) and country of birth (born in Italy vs. born abroad; p < 0.001) were observed. mEPP were found to be older than women of the other two groups; CbHW were almost all born in Italy. Considering the whole sample of women born abroad, 31.2% were born in Eastern Europe, 19.9% in Asia, 18.3% in Sub-Saharan Africa, 17.2% in Central and South America, 11.8% in North African countries and 1.6% in Europe or North America (data not shown).

Data about anti-rubella vaccination rates of seronegative women showed statistically significant differences among the three groups (p < 0.001) with lower vaccination rate in mEPP. However, stratifying by year and country of birth, this finding turned out to be significant only in 2016 among women born in Italy (p < 0.001) but not in 2017, neither among women born in Italy (p = 0.054) nor among those born abroad (p = 0.436).

No significant differences were found for anti-rubella vaccination rates when women born in Italy and those born abroad were compared (p = 0.089), even after year stratification. VH turned out to be significantly higher in 2017 than in 2016 (p < 0.001) among women of both groups. Among women born abroad, no association between macro-region of birth and VH was observed (p = 0.882), both in 2016 and 2017 (data not shown).

3.2. Focus on wVTP and mEPP and factors related to vaccine hesitancy

Data and comparisons about anti-rubella vaccination rates and VH in wVTP and mEPP groups, stratified by year, are shown in Table 2. wVTP and mEPP were found to be similar for country of birth (born

Table 1
Demographic characteristics and anti-rubella vaccination rates of rubella seronegative women according to group.

	Total n = 680	Voluntary termination of pregnancy n = 402	Puerperal phase n = 136	Childbearing healthcare workers n = 142	p value
Mean age ± SD (years)	29.2 ± 7.7	28.5 ± 7.6	30.8 ± 6.2	28.5 ± 8.7	0.003
Born in Italy % (n)	72.1 (490)	65.2 (262)	66.9 (91)	96.5 (137)	< 0.001
Anti-rubella vaccination rate (n) %	30.4 (207)	37.1 (149)	16.2 (22)	25.4 (36)	< 0.001
Anti-rubella vaccination rate in 2016% (n)	47.9 (158)	60.6 (129)	16.7 (11)	35.3 (18)	< 0.001
Anti-rubella vaccination rate in 2017% (n)	14 (49)	10.6 (20)	15.7 (11)	19.8 (18)	0.104
Anti-rubella vaccination rate in patients born in Italy % (n)	28.6 (140)	36.6 (96)	9.9 (9)	25.6 (35)	< 0.001
Anti-rubella vaccination rate in 2016 in patients born in Italy % (n)	46.5 (106)	61.4 (86)	4.8 (2)	36.7 (18)	< 0.001
Anti-rubella vaccination rate in 2017 in patients born in Italy % (n)	13 (34)	8.1 (10)	14 (7)	19.3 (17)	0.054
Anti-rubella vaccination rate in patients born abroad % (n)	35.3 (67)	37.9 (53)	28.9 (13)	20 (1)	0.458
Anti-rubella vaccination rate in 2016 in patients born abroad % (n)	51 (52)	58.9 (43)	37.5 (9)	0 (0)	0.052
Anti-rubella vaccination rate in 2017 in patients born abroad % (n)	17.1 (15)	18.2 (10)	20 (4)	33.3 (1)	0.436

Bold values denote statistical significance at the $p < 0.05$ level.

in Italy vs. born abroad; $p = 0.755$ in 2016, $p = 0.376$ in 2017), parity ($p = 0.178$ in 2016; $p = 0.926$ in 2017), allergy to drug/food/environmental agents ($p = 0.277$ in 2016; $p = 0.258$ in 2017), but significantly different for age ($p = 0.037$ in 2016, $p = 0.010$ in 2017), previous VTP in 2016 ($p = 0.027$) and comorbidities ($p < 0.001$) both in 2016 and 2017. Generally, wVTP were younger and had already undergone VTP in the past more than mEPP while mEPP reported more comorbidities.

About 23% of wVTP and 30% of women in mEPP group reported history of allergy to either drugs, food or environmental agents.

Anti-rubella vaccination rate was found to be significantly higher in wVTP than in mEPP in 2016 ($p < 0.001$), whereas no significant differences were detected in 2017 ($p = 0.258$). The same happened when groups were compared stratifying for country of birth (born in Italy vs. born abroad), as we found significant differences between the 2 groups in 2016 among women born in Italy ($p < 0.001$), but not in 2017 ($p = 0.233$). No differences were detected when the same comparisons

involved women born abroad.

mEPP and wVTP groups turned out to be significantly different when compared for VH using 2016 data, also stratifying for parity (nulliparous $p < 0.001$; ≥ 1 child $p < 0.001$), previous VTP ($p = 0.021$) and history of allergy to drug/food/environmental agents ($p = 0.002$). The same analyses on 2017 data did not detect significant differences between the two groups.

Analyzing the two groups separately, no statistically significant association was found between VH and week of gestation at time of VTP in wVTP group ($p = 0.477$) and between VH and caesarean delivery in mEPP group ($p = 0.561$), even when stratifying by year (data not shown).

Likewise, no statistically significant associations, neither at univariate nor at multivariable analysis, were found when 2017 data were analyzed to detect possible predictors of VH. Table 3 shows the results of univariate and multivariable analyses on 2016 data only. The significant associations between VH and both mEPP and allergy history,

Table 2
Data and comparisons about anti-rubella vaccination rates and vaccine hesitancy in wVTP and mEPP groups stratified by year.

	2016			2017		
	Voluntary termination of pregnancy n = 213	Puerperal phase n = 66	p value	Voluntary termination of pregnancy n = 189	Puerperal phase n = 70	p value
Mean age ± SD (years)	28.7 ± 7.8	30.9 ± 5.7	0.037	28.1 ± 7.4	30.8 ± 6.7	0.010
Born in Italy % (n)	65.7 (140)	63.6 (42)	0.755	65.6 (124)	71.4 (50)	0.376
Anti-rubella vaccination rate % (n)	60.6 (129)	16.7 (11)	< 0.001	10.6 (20)	15.7 (11)	0.258
Anti-rubella vaccination rate in patients born in Italy % (n)	61.4 (86)	4.8 (2)	< 0.001	8.1 (10)	14 (7)	0.233
Anti-rubella vaccination rate % in patients born abroad % (n)	58.9 (43)	37.5 (9)	0.064	18.2 (10)	20 (4)	0.428
Vaccine hesitancy % (n)	39.4 (84)	83.3 (55)	< 0.001	89.4 (169)	84.3 (59)	0.258
Nulliparous % (n) ^a	56.5 (108)	47 (31)	0.178	55.9 (100)	56.5 (39)	0.926
Vaccine hesitancy % (n)	40.7 (44)	87.1 (27)	< 0.001	88 (88)	82.1 (32)	0.359
≥ 1 child % (n) ^a	43.5 (83)	53 (35)	0.178	44.1 (79)	43.5 (30)	0.926
Vaccine hesitancy % (n)	37.4 (31)	80 (28)	< 0.001	89.9 (71)	86.7 (26)	0.633
Previous voluntary interruption of pregnancy % (n) ^a	32.5 (62)	18.2 (12)	0.027	20.7 (37)	11.6 (8)	0.097
Vaccine hesitancy % (n)	38.7 (24)	75 (9)	0.021	78.4 (29)	75 (6)	0.835
Comorbidity % (n) ^a	12.6 (24)	31.8 (21)	< 0.001	14 (25)	46.4 (32)	< 0.001
Vaccine hesitancy % (n)	50 (12)	66.7 (14)	0.259	80 (20)	87.5 (28)	0.441
Reported allergy to drug/food/environmental agents % (n) ^a	23.6 (45)	30.3 (20)	0.277	23.5 (42)	30.4 (21)	0.258
Vaccine hesitancy % (n)	55.6 (25)	95 (19)	0.002	92.9 (39)	90.5 (19)	0.742

Bold values denote statistical significance at the $p < 0.05$ level.

^a Data not available for: 22 women belonging to voluntary termination of pregnancy group in 2016; 10 and 1 woman belonging to voluntary termination of pregnancy and puerperal phase groups respectively in 2017.

Table 3

Uni- and multivariable analyses for vaccine hesitancy predictors. Data are shown as percentages (absolute frequencies) if not otherwise stated.

	VH yes n = 139	VH no n = 140	Univariate analysis		Multivariable analysis	
			OR (CI 95%)	p-Value	OR (CI 95%)	p-Value
mEPP (vs. wVTP group)	39.6 (55)	7.9 (11)	7.68 (3.59–16.4)	< 0.001	8.18 (3.95–16.9)	< 0.001
Born in Italy (vs. born abroad)	65.5 (91)	62.9 (88)	1.12 (0.68–1.83)	0.649	1.05 (0.58–1.89)	0.879
Parity, ≥1 child (vs. nulliparous)	45.4 (59)	46.5 (59)	0.96 (0.58–1.57)	0.863	0.91 (0.49–1.68)	0.765
Comorbidity, yes (vs. no)	20.0 (26)	15.0 (19)	1.42 (0.74–2.73)	0.288	–	–
Reported allergy, yes (vs. no)	33.8 (44)	16.5 (21)	2.58 (1.41–4.73)	0.001	2.68 (1.40–5.15)	0.003
Mean age ± SD	28.9 ± 7.4	29.3 ± 7.3	–	0.586	0.98 (0.94–1.02)	0.438

Bold values denote statistical significance at the $p < 0.05$ level.

which were found at univariate analysis were confirmed when the logistic regression model was carried out, showing a higher risk of VH among mEPP (OR 8.2; 95% CI: 3.9–16.9) and for women reporting allergy (OR 2.7; 95% CI: 1.4–5.1).

4. Discussion

The prevalence of rubella susceptibility was found to be higher than 5% over the analyzed period. Childbearing women included in this study, especially if mEPP, turned out not to be adequately protected against rubella. Our study also highlighted that women born in Italy were more susceptible to rubella than women born abroad. Furthermore, mEPP had a lower acceptance of anti-rubella vaccination than women of the other two groups, especially in 2016 and if born in Italy. Being mEPP and reporting allergy to drug/food/environmental agents were shown as predictors of VH in 2016. This finding was observed in the context of a reduction in anti-rubella vaccination rate between 2016 and 2017, especially among wVTP and CbHW, and in spite of a low anti-rubella vaccination rate in mEPP hampering an accurate identification of factors related to VH. Being CbHW did not seem to particularly improve attitude and behaviours toward vaccination.

The achieved prevalence of rubella susceptibility in this study confirmed data of a recent meta-analysis (Pandolfi et al., 2017) showing that, at a global level, the proportion of rubella-susceptible childbearing women is still high. The higher susceptibility to rubella among women born in Italy confirmed previous Italian reports focused on wVTP (Pettinichio et al., 2018) and continues to show a dramatically higher susceptibility rates when compared to women born in other European countries, especially if mEPP (Vilajeliu et al., 2015).

In this study, women born abroad seem to be well represented due to their frequent access to hospital care for VTP and delivery procedures, but our data showed differences to that extracted from the last surveys on serological status among childbearing immigrants in Italy (Fabiani et al., 2017; Lo Giudice et al., 2014; De Paschale et al., 2012). We may speculate that it was probably due to their epidemiological characteristics, possibly related to both origin from not-high migratory pressure countries and sufficient length-of-stay in Italy contributing to higher responsiveness to public health agenda targets.

Differences in anti-rubella vaccination rates especially in 2016 and in women born in Italy were due to a higher VH in mEPP. This finding was not confirmed in 2017 probably due to the increase in VH, especially among wVTP. No significant differences in anti-rubella vaccination rates were achieved in women born abroad along the study period probably due to the same reason.

The higher rate of VH in 2017 than in 2016 both in women born in Italy and abroad was probably the main finding of this study, but further studies are needed to confirm this data and to follow possible epidemiological and immunisation trends. Despite not being designed to identify causes of VH, we may argue that one possible related cause could be the divisive political electoral campaign, focusing on the recently approved law on mandatory vaccinations in 2017 (*Disposizioni urgenti in materia di prevenzione vaccinale*, n.d.), which increased

confusion on public perception about vaccines. Similarly, significant anti-rubella vaccination rate differences between 2016 and 2017 prompted a separate analysis of factors related to VH after stratifying by year. Despite MMR vaccine safety and its lack of untoward effects (Finale et al., 2017), anti-rubella vaccination rate in mEPP, especially if born in Italy, was lower than in the other groups, showing that VH-related factors in the postpartum phase are probably context specific and vaccination following delivery was probably considered more stressful or harmful than after VTP. Moreover, we can also speculate that a considerable percentage of mEPP, above all if multiparous and with previous VTP, had already hesitated to be vaccinated in the past and should be considered refractory. Reporting allergy to drug/food/environmental agents as a factor associated with VH should work as a flashing light alerting physicians at anamnesis for probable VH, but this needs to be confirmed by other studies, maybe more specifically designed to study this relationship. Low rates in anti-rubella vaccination in CbHW showed that knowledge and confidence in recommended immunisation practice are still far to be achieved (Genovese et al., 2019).

The study has some limitations. Despite of being the first study assessing and comparing rubella susceptibility and vaccination rates in wVTP, mEPP and CbHW, childbearing women not screened for rubella in our laboratory and vaccinated in our hospital centre were not included in this study. This could have caused an underestimation of anti-rubella immunisation rate. Another limitation includes having considered only the first dose of anti-rubella vaccination rates, blanking adherence to the second one and vaccination possibly administered in other health facilities.

5. Conclusions

This study shows that an important percentage of childbearing women accessing a tertiary hospital care of one of the most populated Italian cities are still susceptible to rubella infection, and that, most of them, above all mEPP and those reporting allergy, hesitate to vaccinate. Clinicians should be aware of these findings in order to develop dialogue-based strategies targeting vaccine safety for retention of these women in immunisation programmes. Further qualitative and quantitative studies are needed in order to confirm the achieved data and help overcome sociocultural beliefs related to VH not examined in this survey.

Contributors

Boattini M, Sacchi A, Pittaluga F and Cavallo C designed the study; Boattini M, Bianco G, Iannaccone M, Masuelli G and Coggiola M acquired data; Boattini M and Charrier L analyzed and interpreted data; Boattini M and Bianco wrote the paper; all authors revised the article critically and approved the final version.

Ethics

The study was conducted in accordance with the Declaration of Helsinki, all appropriate permissions were obtained.

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Declaration of Competing Interest

None.

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