Rubella Immunity Status in Pregnancy and Incidence of Congenital Rubella Syndrome: Ten Years of Observation in Trento Province

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Abstract

Introduction: The rubella test in pregnancy it is a recommended practice for all women. This makes it possible to identify situations at risk of congenital rubella and the pregnant women to be offered vaccination in the puerperium.

Materials and methods: The Authors analysed rubella test coverage and the immunity status of pregnant mothers between 2010 and 2019, using birth attendance certificates. The factors associated with a susceptibility state to rubella are also analyzed through a multivariate analysis, according to the logistic model. The incidence of congenital rubella syndrome is also estimated.

Results: Rubella test coverage on 44,473 pregnant mothers was 99.8%. The average proportion of susceptible subjects was 7.42% (6.5 in Italians, 9.9 in foreigners). The trend of susceptible subjects grows over time. Seroconversion was observed in 7 cases, with 1 confirmed case of congenital rubella. Young age, being a foreigner, residing outside the province of Trento, not being married, having a low level of education and being a primiparous are independent risk factors for a state of susceptibility to rubella in pregnant women.

Conclusions: A current information flow such as that guaranteed by the birth attendance certificates allows for monitoring of pregnancy at the population level. In particular, it is also possible to identify women at risk of rubella who should be offered the vaccine before discharge.

Introduction

Rubella is usually a mild self-limiting disease with few complications. If the disease is contracted in pregnancy, especially during the first trimester, it can lead to Congenital Rubella Syndrome (CRS). It is estimated that at least 100,000 children are born with CRS every year worldwide [1,2]. To prevent CRS it is necessary to maintain high levels of vaccination coverage in the general population (herd immunity) and to ensure a high level of immunity in individual women of childbearing age [3,4]. In accordance with the indications of the WHO, Italy approved the national plan for the elimination of measles and congenital rubella in 2003 with the goal of eliminating the endogenous transmission of measles and of reducing the incidence of congenital rubella to less than 1 case/100,000 live births, by 2007. As for women of childbearing age, the aim was to reduce the proportion of susceptible women to under 5%. Checking the immune status against rubella is a recommended practice for all women and as such, in Italy, is exempt from payment [5]. A program to offer anti-rubella vaccination in the puerperium at the maternity units began in the province of Trento (north-eastern Italy, 540,000 inhabitants as of 1.1.2019), in the second half of the 2000s. The recording of data of serological screening for rubella was started during the same period, using the Birth Attendance Certificates (BAC). BAC constitutes the primary source of information on births, antenatal care and childbirth and must be compiled by law throughout Italy by the healthcare professional (usually a midwife) who attend childbirth [6]. This paper reports on the trends for rubella test coverage and for the immunity status of pregnant women receiving care in maternity units of the province of Trento between 2010 and 2019. The temporal trend regarding the proportion of non-immune mothers and the factors associated with a susceptibility to rubella are also analyzed. The incidence of congenital rubella is also estimated.

Materials and Methods

The BAC used in the province of Trento includes a far greater number of variables than the national Ministry of Health template. In addition to other variables, it also collects information regarding infections affecting pregnancy and, in particular, data regarding serological screening tests. These include the results of the rubella test performed to analyse the susceptibility of pregnant women to rubella virus infection. The diagnostic kit used in public health facilities of our province is Abbott's Rubella IgG/IgM Reagent Kit that uses chemo luminescent immunological technology to capture micro particles. The cut-offs used to define positivity for IgG and IgM are respectively 10.0 UI/ml and 1.60 index. Each positive value is subjected to confirmation test. The determination of the avidity of the IgG is expected, for the dating of the infection. An high IgG avidity (over 20%), indicates a previous infection (more than three months before the date of the test). The test is performed in the early weeks of pregnancy and in the case of confirmation of immunity (positive specific IgG with negative specific IgM), prior illness or prior vaccination, it is not repeated. In the presence of a state of susceptibility (IgG and IgM negative), the test is repeated every 4 - 6 weeks, until at least the 5th month [5]. The rubella serological data, as like all other data provided by the BAC, are collected and recorded on electronic storage devices at each maternity unit of our province by the midwives who attend the childbirth. The registration criteria for serological screening are as follows: test not performed, non-immune, immune, in progress, seroconversion in pregnancy. The data regarding the rubella test results that were missing in the BAC database were retrieved retrospectively by the Clinical and Evaluational Epidemiology Service by accessing the Hospital Information System (HIS). It is a repository which contains all the results of user contacts with the provincial health services. For women who seroconverted, it was also necessary to access the HIS to ascertain at what point of the pregnancy the rubella test was found to be positive. We analyzed the coverage of serological screening for rubella between 2010 and 2019 and in relation to the different characteristics of women. We also analysed the time trend of the proportion of non-immune mothers considering the characteristics of the mothers, more specifically, their nationality (Italian vs. other nationalities), age range, residence (in/outside the province), marital status, parity and education level. The factors associated with a susceptibility state to rubella have been analyzed by multiple analysis using the logistic regression model in which the explanatory variables were age range, nationality (Italian vs. other), education level, marital status, parity and residence. The multivariate analysis was performed on all the women tested in pregnancy and separately in the primiparous and in the pluriparous. This is to take into account, on the one hand, the collinearity phenomenon and on the other hand, the effect of a previous vaccination at the birth units. Trend significance was analysed using the Cochran-Armitage criterion and the significance of the differences between the proportions was analysed using the chi squared test or Fisher's exact test. Prevalence estimates and adjusted odds ratios are provided by 95% confidence intervals.

Results

Between 01.01.2010 and 31.12.2019, 44,473 pregnant women received care at hospital maternity units of the province of Trento, with an annual average of 4,450 and a total number of 45,141 live births. The overall average age of the pregnant women rose from 32.0 years in 2010 to 32.5 years in 2019; amongst Italian women the average age was higher than amongst foreign women and rose from 32.9 years in 2010 to 33.2 years in 2019. The modal age range was that between 30 and 34 years, which accounted for 33.9% of all the pregnant women considered in the study period. 25.6% of the total were foreign women, with a proportion that increased over time from 22.9% in 2010 to 25.1% in 2019; 95.5% of the pregnant women were resident in the province of Trento. 99.8% of all pregnant women had a rubella test, considering the entire study period, without variations from one year to the next. No statistically significant differences were observed between Italian and foreign women or with regard to age class, marital status, education level, parity, or residence in or outside Trento province. Lastly, there was no difference in rubella test coverage with regard to the maternity units, with coverage that ranges from 98.7% to 99.9%. The immunity status of the pregnant women undergoing serological testing in the study period (44,393 subjects) is shown in Table 1. The proportion of susceptible women, which was on average equal to 7,42%, increased from 5.9% in 2010 to 12.0% in 2019 (Figure 1), with a statistically significant trend (p-trend <0,01). The proportion of susceptible women remains higher in each year among foreign women than Italians (9,9% vs. 6,5% for the entire period), and this difference is statistically significant (p<0.0001). Women from Asian countries have the highest proportion of susceptibles, with a statistically significant difference (p<0,01) not only compared to Italian women but also compared to all foreign women (Table 2) The socio demographic characteristics of all women and their characteristics in relation to the immune status towards rubella are shown in Table 3. The proportion of women susceptible to rubella is higher in younger women, in foreign women, in residents outside the province of Trento, in unmarried, in women with lower education level and in primiparous. All these characteristics are confirmed as independent risk factors for a condition of susceptibility to rubella on multivariate analysis (Table 4). These results are confirmed in the logistic regression carried out separately in the primiparous. In pluriparous, the trend is very similar even if the differences in the age groups below 24 years and in the upper secondary school category are not statistically significant (Table 5). Of the 11 women, who "seroconverted during pregnancy" as recorded on the birth attendance certificate, just 7 were confirmed as having seroconverted by the data in hospital discharge records, due to recording errors at the maternity ward.

There were therefore effectively 7 women who seroconverted during pregnancy, of whom 5 were foreign and 2 were Italian, for an overall seroconversion rate of 0.15/1000 and a seroconversion rate of 0.43/1000 amongst foreign women and 0.060/1000 amongst Italian women. The seroconversion rate was seen to be 7 times higher amongst foreign women than amongst Italian women. In the cohort of pregnant women included in this study, there was just one case of congenital rubella, following infection of the mother (of Romanian origin) confirmed around the 15th week of gestation. The child was found to have a significant psychomotor retardation and hearing loss. The estimated incidence of congenital rubella is equal to 0.22/100.000/year.

Immunity status	Frequency	%
Susceptible	3,294	7.4
Immune	41,092	92.5
Seroconversion in pregnancy	7	0.01
Total	**44,393**	**100.0**

Table 1: Province of Trento. Immunity status of women undergoing the rubella test in pregnancy at the province's Maternity units. Period 2010-2019.
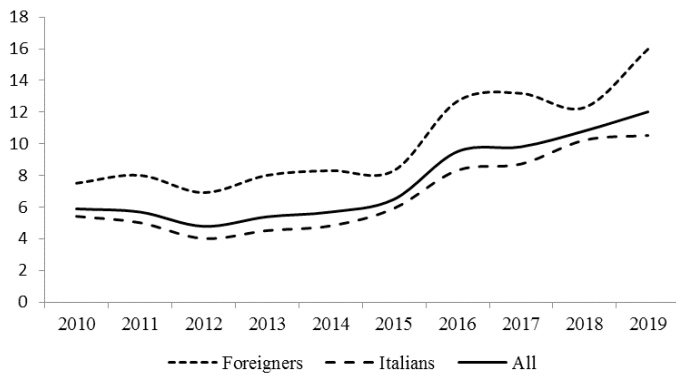

Figure 1: Province of Trento. Annual proportion of women susceptible to rubella infection amongst women Receiving care in the province's maternity units. All pregnants and pregnants grouped by nationality. Trend for 2010-2019.

Geographical Area	% Susceptible to rubella Infection
East European countries	9.1
North western European countries	9.3
America	9.9
Africa	10.5
Asia	12.3

Table 2: Province of Trento. Proportion of foreign women susceptible to rubella infection. By geographical area of origin. Period 2010-2019.

Parameters	Total cases	% Susceptible
Age class		
15-18	147	15.6
19-24	3,639	10.9
25-29	9,874	9.5
30-34	15,062	6.7
35-39	11,683	5.6
40 +	3,988	6.5
Citizenship		
Italians	33,044	6.5
Foreigners	11,349	9.9
Residence		
In Trento province	42,392	7.3
Outside Trento province	2,001	10.2
Marital status		
Married	29,551	6.8
Maiden	13,428	8.6
Others	1,414	8.1
Education level		
University degree	14,968	6.2
Upper secondary school	22,281	7.4
Lower secondary school	6,183	10.4
Primary school/no qualification	961	10.5
Parity		
Primiparous	21,291	8.4
Pluriparous	23,103	6.5

Table 3: Province of Trento. Socio-demographic characteristics of all pregnant women who have been tested For rubella serology and the percentage of susceptible to rubella. Period 2010-2019.

Parameter	Odds Ratio	95%	C.I.
25-29 years vs. 30 +	1,36	(1,25	1,48)
18-24 years vs. 30 +	1,31	(1,16	1,48)
Foreigners vs. Italians	1,40	(1,29	1,53)
Not Residents vs. Residents	1,22	(1,05	1,42)
Not Married vs. Married	1,28	(1,19	1,39)
Secondary School vs. University degree	1,16	(1,06	1,26)
Junior high school or less vs. University degree	1,51	(1,35	1,69)
Pluriparous vs. Primaporous	1,22	(1,13	1,32)

Table 4: Determinants of rubella susceptibility in pregnancy. All pregnant women tested. Adjusted Odds ratios (95%CI).

Parameters	Odds Ratio	95%	C.I.
25-29 years vs. 30 +	1,16	(1,02	1,33)
18-24 years vs. 30 +	1,05	(0,83	1,34)
Foreigners vs. Italians	1,71	(1,52	1,93)
Not Residents vs. Residents	1,29	(1,02	1,64)
Not Married vs. Married	1,29	(1,14	1,46)
Secondary School vs. University degree	1,13	(0,99	1,29)
Junior high school or less vs. University degree	1,49	(1,28	1,75)

Table 5: Determinants of rubella susceptibility in pregnancy. Pluriparous. Adjusted Odds ratios (95%CI).

Discussion

The use of a current information flow such as the BAC database in order to monitor the occurrence of infections in pregnancy can prove convenient. The information obtained using this approach makes it possible to obtain an overview of the whole population considered, rather than of a specific facility. This undoubtedly brings advantages in terms of data bias over studies based on samples from a single facility [7-11]. This approach also appears to be limited in Italy, where experiences have only been recorded, at least to the authors' knowledge, in the province of Trento and the Emilia-Romagna region [12]. The data extrapolated from BAC nevertheless require a certain amount of cross-checking with other sources, such as hospital information systems, especially when data are missing or inaccurate, or in the case of prospective data, such as those regarding babies whose mothers seroconverted, whose subsequent health status cannot be defined by BAC alone. The serological rubella test is performed in practically all of the pregnant women receiving care at the maternity units of the province of Trento, without any relevant variations from one year to another. Our values appear to be higher than those reported in other regions of Italy [12]. The level of rubella test coverage does not vary with maternal characteristics nor with the characteristics of the maternity units. This demonstrates the homogeneity and equality of the management of maternity care throughout the whole province. The average proportion of susceptible women for the whole study period was 7.42%, which is lower than reported in prior Italian studies [12], but substantially in line with studies conducted in other European [13] and Asiatic [14,15] countries. There is a growth over time in the proportion of susceptible women, as reported in previous studies [16-18]. This may be attributable to several factors. One of these factors may be the reduction in vaccination coverage in the general population as an effect of the anti-vaccine movements. This may also have contributed to reduce the efficiency of the vaccination program for susceptible mothers in the puerperium. Another factor can be represented by the increase in the foreign population in the province of Trento, especially by the female population of childbearing age whose rubella susceptibility rates are higher than Italians. Our results confirmed that the proportion of susceptible subjects is higher amongst foreign women [8,9,19-21] a fact that must be taken into due consideration in view of the increase in various areas of the country in the number of foreign women of childbearing potential associated with migratory processes. Besides being a foreigner, there are other factors that are associated with a state of susceptibility to rubella in pregnant women. One of the most important seems to be the young age. The proportion of susceptible subjects would appear to be higher amongst younger women of up to 24 years of age, as reported in previous studies [15-23] and this sub-population underwent an increase in susceptible women over time, most likely due to a reduction in immunisation adherence during childhood and adolescence. The educational qualification is also an important variable as previously reported [16-18]. Overall, the proportion of susceptible pregnant women is still above both national and international targets [3,4]. It is possible and also desirable to implement targeted recovery interventions starting from the characteristics of susceptible women. Finally the seroconversion rate was very low, it was nevertheless 7 times higher in foreign women than amongst Italian women [24]. The retrospective assessment of babies born to mothers who seroconverted revealed, over a long period of time, just one case of congenital rubella, equal to 0.22/100,000 live births per year, a value less than the national value provided by the surveillance system for congenital rubella [25].

Conclusions

It is essential to continue monitoring access to the rubella test and seroconversion during pregnancy in the context of better interaction between all health services operating in the community. Current information flows that are suitably combined with other data sources to meet the user's needs are extremely useful not only for monitoring maternity care, but also for analysing the process and outcome data of a public health initiative. The study provides information on the subpopulations on which to act with priority to ensure protection against rubella by improving the vaccination offer in the puerperium.

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