

Rubella immunity status and the active offer of MMR/MMRV vaccination during pregnancy

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Abstract

Introduction. The rubella test during pregnancy makes it possible to identify situations at risk of congenital rubella and those pregnant mothers who should be offered the MMR vaccine.

Materials and methods. The Authors analysed test coverage and the immunity status of pregnant mothers between 2005 and 2017, using birth attendance certificates.

Results. Rubella test coverage on 61,437 pregnant mothers was 99.4%. The average proportion of susceptible subjects was 6.4%. Seroconversion was observed in 7 cases, with 1 confirmed case of congenital rubella. 32% of susceptible subjects were vaccinated, and adherence was seen to be influenced by the characteristics of the pregnant women and of the maternity unit.

Conclusions. A current information flow including a number of healthcare services, is useful both for monitoring the maternity care pathway and for public health purposes.

Key words

- rubella
- rubella test
- pregnancy
- congenital rubella
- MMR/MMRV vaccine

INTRODUCTION

In line with the guidance provided by the WHO's European Region, the Italian National measles and rubella elimination plan that was approved in 2003 set 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 [1].

The consequent review of the national vaccination calendar provided, for all new births, for a first dose of trivalent vaccine (MMR: Measles-Mumps-Rubella) within the first 15 months of life, followed by a second dose at 5-6 years of age. It also envisaged the recovery of vaccination coverage amongst adolescents and women of childbearing potential. Amongst this latter population, the aim was to reduce the proportion of susceptible women to under 5%. As the first edition of the plan did not meet the targets set, the objectives of the second National plan for the elimination of measles and congenital rubella (2010-2015) also included interrupting the endogenous transmission of rubella [2]. The approaches used to provide MMR vaccination were

also confirmed by the most recent review of the Italian National Vaccination Plan [3].

The recent ministerial circulars on recommended vaccination for childbearing and pregnant women, (8.7.2018, 11.12.2018, 11.21.2019) recommend evaluating the immune status of the pregnant women also with respect to chickenpox, actively proposing, where necessary, also the MMRV vaccination [4].

The action taken in response to the WHO's guidance also varied both between European countries [5], and between the individual regions of Italy [6].

In 2005, a study was initiated in the province of Trento (north-eastern Italy, population of 540,000 inhabitants as at 1.1.2018), to monitor the specific immunity status amongst pregnant women, by gathering data on the results of the rubella test performed during pregnancy from birth attendance certificates. Birth attendance certificates constitute 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 was present during childbirth [7]. The birth attendance

certificate used in the province of Trento also records any MMR/MMRV or monovalent rubella vaccination, which is actively offered in all maternity units, after the birth, as part of a programme established with the Provincial Health Service's Department of Prevention, and as such already included in the first provincial prevention plan for 2007-2009 [8].

This paper reports on the trends for rubella test coverage and for the immunity status of pregnant women receiving care in maternity units within the province of Trento between 2005 and 2017, together with the trend regarding the proportion of non-immune mothers who were vaccinated after giving birth and prior to discharge, and the trend regarding the health of babies whose mothers seroconverted during pregnancy.

MATERIALS AND METHODS

The birth attendance certificate 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 during 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 at the Microbiology Unit of S. Chiara Hospital of Trento, which acts as the hub centre for the entire province is Abbott's Rubella IgG/IgM Reagent Kit that uses chemoluminescent immunological technology to capture microparticles. 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. A high IgG avidity (over 20%), indicates a previous infection (more than three months before the date of the test).

The rubella test is part of the screening programme provided to guarantee an adequate monitoring of pregnancy and as such does not involve any co-payment by users. 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 [9].

From 2005, as part of a joint project with the Department of Prevention, the Clinical and Evaluational Epidemiology Service, which also manages all information flows regarding the maternity and paediatric areas, included in birth attendance certificate, which are recorded on electronic storage devices at each maternity unit, not only the result of the rubella test, but also any MMRV/monovalent rubella vaccine administered to the mother. This activity, which is supervised by the same midwives who were present during childbirth, was introduced after an information/ training phase that, at various timepoints, involved all professionals working in the province's maternity wards, which during the study period decreased from 8 in 2005 to 4 in 2018. The flow chart with the time line of all the interventions and the number of pregnant women involved is shown in *Figure 1*.

The vaccine is offered to pregnant women with a negative or ambiguous rubella test result, usually on the second day after childbirth or on the day of discharge. The healthcare professionals collect a preliminary pre-vaccination history, using a standard template compiled by the Department of Prevention, and usually offer women the trivalent MMR/MMRV vaccine, which can be replaced with the monovalent rubella vaccine, if requested by the woman.

The maternity units regularly send the MMR/MMRV monovalent rubella vaccination certificates to the

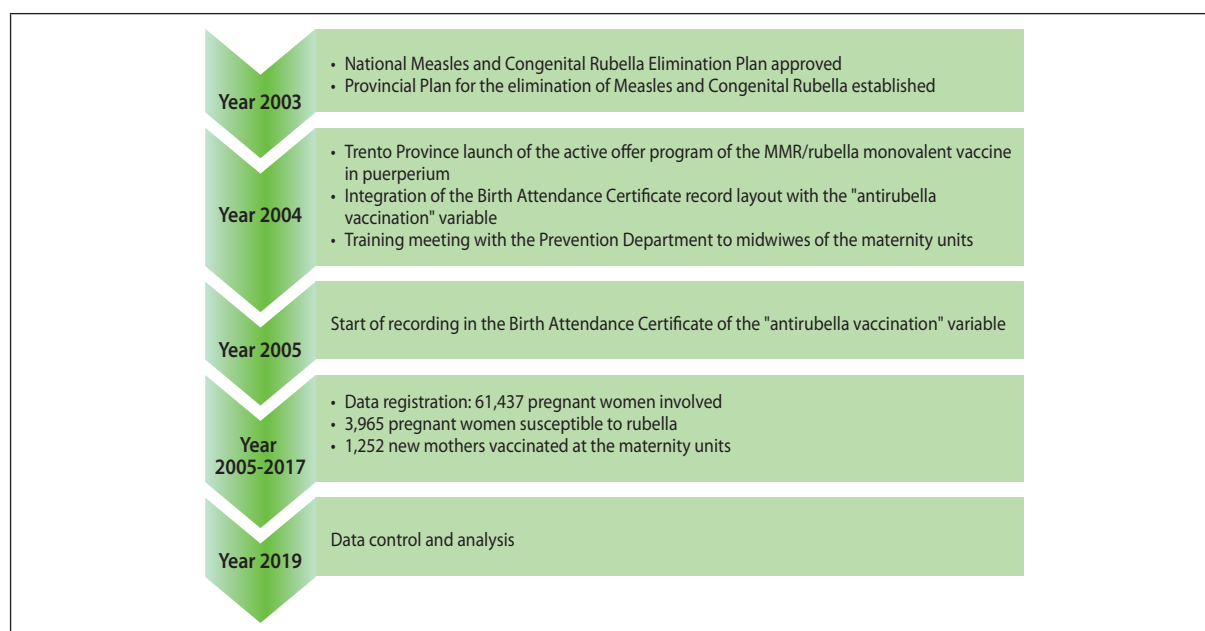


Figure 1
Flow chart of the interventions and women participating.

competent local vaccination services. The certificate includes the name, surname and date of birth of the mother and her child and the vaccine's identification data (batch number, expiry date, etc.). Cases of refusal are also reported, so that vaccination service staff can record it on the baby's electronic vaccination record and offer the mother vaccination when the baby has his/her first vaccination.

In cases of voluntary termination of pregnancy, the healthcare professionals working at the Obstetrics and Gynaecology Unit advise women who are not sure they are protected to have MMR/MMRV or monovalent rubella immunisation at their local vaccination service clinic.

The data that were missing from the birth attendance certificate database regarding the rubella test results or vaccination were retrieved retrospectively by the Clinical and Evaluational Epidemiology Service by accessing the Hospital Information System, which contains all the results of user contacts with the provincial health services. For women who seroconverted, it was also necessary to access the Hospital Information System to ascertain at what point of the pregnancy the rubella test was found to be positive.

Between 2005 and 2017, the birth attendance certificate database was used to analyse the proportion of pregnant women who had the rubella test of those receiving care at the maternity units in the province and, therefore, the trend for immunity to the rubella virus. We also analysed the time trend of the proportion of non-immune mothers who were administered MMR/MMRV/monovalent rubella vaccine after giving birth. The data regarding the rubella test and immunisation were analysed considering, on the one hand, the characteristics of the maternity unit and, on the other, the characteristics of the mothers, more specifically, their nationality (Italian vs. other nationalities), age range, parity and academic qualifications. The factors associated with adherence with the offer of post-natal immunisation were analysed by multiple analysis using the logistic regression model in which the explanatory variables were age range, nationality (Italian vs other), academic qualifications, marital status, parity and the maternity unit. Babies whose mothers seroconverted during pregnancy were evaluated to establish their state of health, using the information present in both the Hospital Information System and Hospital Discharge Records, by extracting records with a "7710" code for both the first diagnosis and subsequent co-diagnoses. Trend significance was analysed using the Cochran-Armitage test for trend and the significance of the differences between the proportions was analysed using the chi squared test or Fisher's exact test. The statistical analyses were performed using Epi-Info software.

RESULTS

Between 01.01.2005 and 31.12.2017, 61,437 pregnant women received care at hospital maternity units in the province of Trento, with an annual average of 4,720 and a total number of 62,275 live births during the observation period. The overall average age of the pregnant women rose from 31.2 years in 2005 to 32 years

in 2017; amongst Italian women the average age was higher than amongst foreign women and rose from 32.6 years in 2005 to 33 years in 2017. The modal age range was that between 30 and 34 years, which accounted for 34.7% of all the pregnant women considered during the study period. 23.7% of the total were foreign women, with a proportion that increased over time from 18.7% in 2005 to 26.2% in 2017; 95% of the pregnant women considered during the study period were resident in the province of Trento.

Considering the entire study period, 99.4% of all pregnant women had a rubella test, with a coverage that ranged from 98.8% in 2005 to 99.9% in 2017. Practically all of the pregnant women had a serological rubella test, with a slightly (not statistically significant) lower coverage rate in mothers aged 15-18 years (97.5%) and in those residing outside the province (97.8%). No statistically significant differences were observed in the serological results between Italian women (99.7%) and women of other nationalities (99.2%), or with regard to parity or academic qualifications. Lastly, there was no difference in rubella test coverage with regard to the maternity ward, with coverage that ranges from 98.7% to 99.9%.

The immunity status of the pregnant women undergoing serological testing during the study period (61,103 subjects) is shown in *Table 1*. A certain non-homogeneity can be observed regarding age range (*Table 2*), where the proportion of susceptible subjects is higher than expected, in a statistically significant manner ($p < 0.001$), in the <25 years age ranges and decreases with an increase in age, with a statistically significant trend ($p < 0.01$).

Table 1

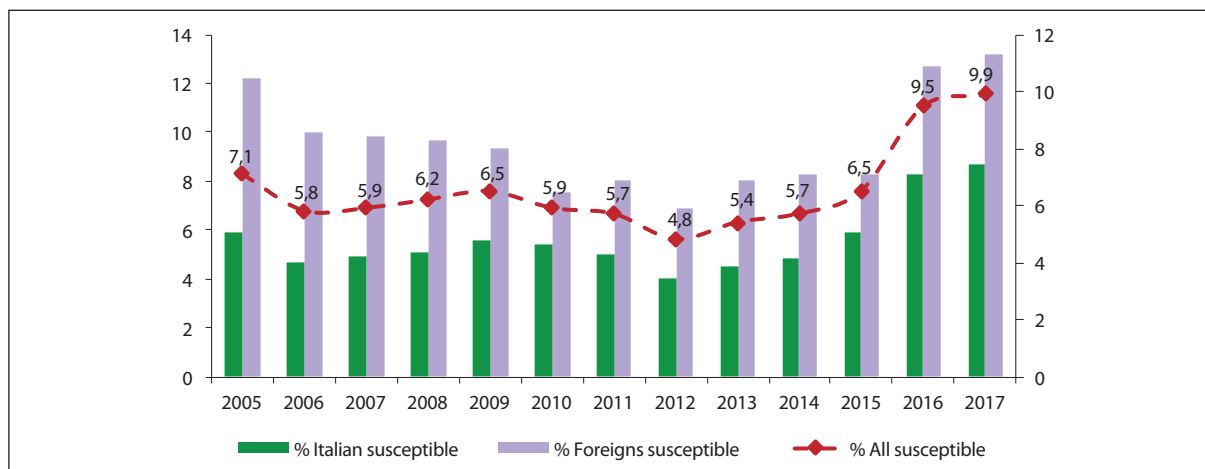
Province of Trento. Immunity status of women undergoing the rubella test during pregnancy receiving care in the province's maternity units. Period: 2005-2017

Immunity status	Frequency	%
Susceptible	3,965	6.49
Immune	57,131	93.50
Seroconversion during pregnancy	7	0.01
Total	61,103	100.00

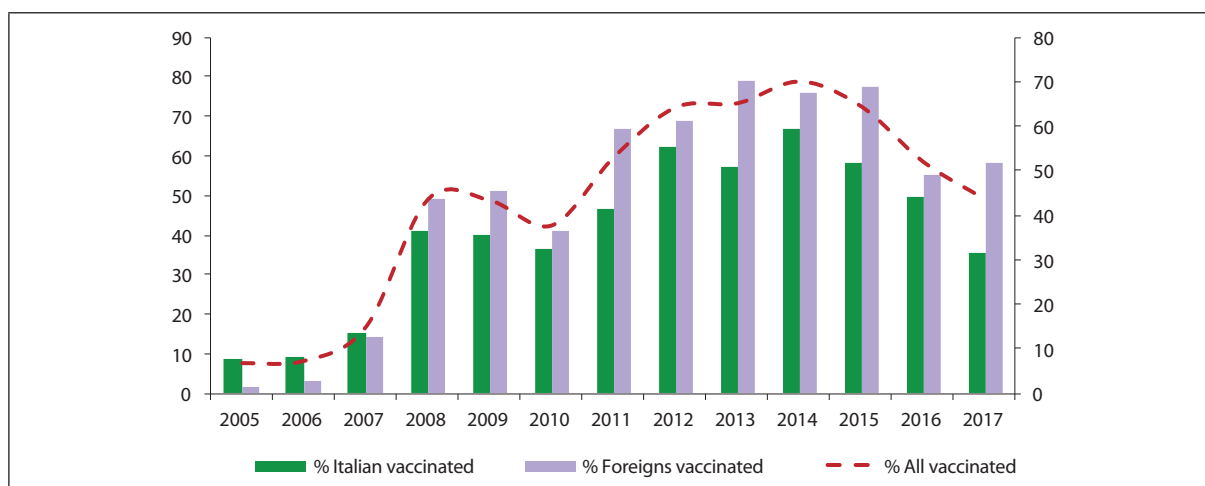
Table 2

Province of Trento. Proportion of subjects susceptible to rubella by age range in women undergoing the rubella test during pregnancy receiving care in the province's maternity units. Period: 2005-2017

Age range	% susceptible to rubella
15-18	14.5
19-24	9.4
25-29	7.8
30-34	5.7
35-39	5.2
40+	5.1

**Figure 2**

Province of Trento. Annual proportion of women susceptible to rubella infection amongst women receiving care in the province's maternity units. All pregnant and pregnant grouped by nationality. Trend for 2005-2017

**Figure 3**

Province of Trento. Annual proportion of women susceptible to rubella infection vaccinated against rubella in the province's maternity units. All pregnant and pregnant grouped by nationality. Trend for 2005-2017

The proportion of susceptible women, which was on average equal to 6.4%, increased from 7.1% in 2005 to 9.9% in 2017 (Figure 2), with an increase that, overall, was not statistically significant. This increase is only statistically significant amongst pregnant women under 24 years of age, in whom it rose from 18% in 2005 to 30% in 2017. The proportion of susceptible women remains higher in each year among foreign women than Italians (9.4% vs 5.5% for the entire period), and this difference was statistically significant ($p < 0.001$). No other difference was observed with regard to parity or academic qualifications.

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 0.11/1000 and a sero-

conversion rate of 0.34/1000 amongst women of other nationalities and 0.042/1000 amongst Italian women. The seroconversion rate was seen to be 8 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.

In all, 1,252 women were administered MMR/MMRV or monovalent rubella vaccine in the province's maternity units, equal to 31.6% of susceptible subjects. The proportion of vaccinated subjects followed an increasing trend over time (Figure 3), and this trend would appear to be statistically significant ($p < 0.01$) despite undergoing a certain drop in the last three years of the study. Vaccines were administered to 27.2% of susceptible Italian women and 38.3% of susceptible women of other nationalities, with a statistically significant differ-

ence in favour of foreign women ($p < 0.001$). The characteristics of susceptible women according to the adherence to the vaccination offer and the factors associated with adhering to the vaccination offer are reported in Table 3. Young age at childbirth (< 24 years), a primiparous condition, and foreign nationality were the independent personal characteristics that were most statistically significantly associated with adherence with the offer of rubella immunisation. Childbirth at a maternity unit with approximately 500 births a year or less was another factor seen to be associated with vaccination adherence. When all other conditions were equal, marital status and academic qualifications did not appear to affect vaccination adherence.

DISCUSSION

Serological determination of the specific IgG antibody titre during the first antenatal consultation in order to evaluate immunity to the rubella virus and the consequent need for immunisation in the post-partum period is the most common screening strategy in developed countries, with coverage levels of approximately 90-95% [10].

The use of a current information flow such as the birth attendance certificate database in order to monitor the presence of infections during pregnancy can prove convenient, despite being demanding for the ma-

ternity unit professionals who, amongst other things, have to retrieve, check and record the pertinent data. Use of 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 [6].

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 [11-15]. The data extrapolated from birth attendance certificates 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 birth attendance certificates alone. Birth attendance certificates can nevertheless prove to be useful for monitoring a specific public health initiative, such as offering rubella immunisation to susceptible pregnant women, which is one of the cornerstones of the prevention of congenital rubella syndrome and as such is recommended by the WHO [16].

The rubella test is performed in practically all of the pregnant women receiving care at the maternity units

Table 3

Province of Trento. Characteristics of pregnant women susceptible to rubella infection and their adherence to the immunization offer (absolute numbers, percentage, multivariate adjusted odds ratio and 95% confidence intervals). Period: 2005-2017

Characteristics	Susceptible		Vaccinated		Multivariate Analysis	
	N	%	N	%	Odds Ratio	95% C.I.
	3965		1.252	31.6		
Maternity units (MU) by number of births per year						
MU with <500 births	1594	39.6	396	24.8	1.80	1.53-2.12
MU with 500-1000 births	894	22.5	327	36.5	0.92	0.77-1.10
MU with >1000 births	1477	37.1	529	35.8	1	
Age class						
<=24 y	566	14.3	244	43.2	1.29	1.01-1.66
25-29 y	1053	26.6	358	34.8	1.18	0.95-1.46
30+ y	2346	59.1	650	27.7	1	
Citizenship						
Foreigners	1390	35.1	551	39.6	1.82	1.55-2.12
Italian	2575	64.9	701	27.2	1	
Marital status						
Married	2659	67.1	820	30.8	1.08	0.92-1.28
Unmarried	1149	29.0	392	34.1	1	
Other	157	3.9	40	25.5	1.14	0.76-1.70
Education						
Primary school/no education	140	3.5	58	41.4	0.78	0.52-1.15
Lower secondary school	987	24.9	283	28.7	1.14	0.92-1.42
Upper secondary school	1980	50.0	645	32.6	0.89	0.74-1.07
University degree	858	21.6	266	31.0	1	
Parity						
Primiparous	2006	50.6	755	37.6	1.72	1.47-2.01
Pluriparous	1959	49.4	497	25.4	1	

Note: in the multivariate analysis, the reference category is the one with the odds ratio=1 and the bold character indicates a p value less than 0.05.

in the province of Trento, without any relevant variations from one year to another, with values that would appear to be higher than those reported in other regions of Italy [6]. The level of rubella test coverage does not vary with maternal characteristics such as academic qualifications and parity and only appears to be slightly lower amongst the younger age ranges and those living outside the province. No inequalities were observed in the access to or use of the test with regard to nationality, neither was there any non-homogeneity with regard to the maternity units or health districts attended by women living in the province. This demonstrates the homogeneity and equality of the management of maternity care throughout the area. The average proportion of susceptible women for the whole study period was 6.5%, which is lower than reported in prior Italian studies [6], but substantially in line with studies conducted in other European [17] and Asiatic [18, 19] countries.

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 [19-24] 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. Our results confirmed that the proportion of susceptible subjects is higher amongst foreign women [12, 13; 20-22], 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. Overall, the proportion of susceptible pregnant women is still above both national and international targets [2, 3].

Although the seroconversion rate was very low, it was nevertheless 8 times higher in foreign women than amongst Italian women [10]. 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 1.5/100,000 live births, a value that exceeds the national value provided by the surveillance system for congenital rubella and rubella during pregnancy [25].

Almost 1,250 women were immunised after giving birth, equal to an average of 31.6% of susceptible subjects, over the entire study period, with an increasing trend up to 2014 that was followed by a decrease, possibly due to the expansion of the anti-vaccination movements that had a certain impact, even locally. Offering MMR/MMRV/monovalent rubella immunisation in the postnatal period is a good opportunity for increasing vaccine coverage, if we consider that each user contact with the health services could provide an opportunity to offer an effective prevention practice [26, 27]. This

specific action, which must be combined with the vaccination campaign address the general population, would appear to be both feasible and sustainable, within the context of a strong interaction between the various provincial healthcare services. Nevertheless, it is necessary to question the validity of the level of vaccination adherence achieved, considering that the level of adherence presents a dual stratification in accordance with maternal characteristics and maternity ward characteristics. As far as maternal characteristics are concerned, foreign mothers, primiparous mothers and younger mothers show better adherence with the offer of immunisation. With regard to the characteristics of the maternity unit, vaccination adherence is higher in maternity wards with a lower number of births. This may be due not only to greater staff sensitivity, but also to the fact that healthcare professionals in smaller maternity units have fewer time restraints. This may facilitate communication between healthcare professional and user/patient, as postulated in previous Italian studies [28, 29]. It could be useful to analyse the barriers to vaccination perceived by mothers, in order to adjust the criteria and approach used to propose MMR/ monovalent rubella vaccination in the post-partum period [30].

CONCLUSIONS

It is essential to continue monitoring access to the rubella test and seroconversion during pregnancy in the context of better interaction between maternity unit, the department of prevention and the epidemiology service, as we are still far from the targets set. 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 routinely collected data nevertheless require a certain degree of quality control, especially for a precise definition of seroconversion and the analysis of the neonate outcomes. In this perspective, the possibility of accessing hospital information systems would appear to be very useful, without being particularly time-consuming, at least on a local level. It will be necessary to analyse the long-term outcomes of offering MMR/MMRV monovalent rubella immunisation in the postnatal period, in order to establish to what extent it improves vaccination coverage in women of childbearing potential.

Conflict of interest statement

The Authors report no conflicts of interest.

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