Prevalence and management of rubella susceptibility in healthcare workers in Italy: A systematic review and meta-analysis

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Abstract

Introduction: In the pre-vaccination era, all adults acquired immunity status due to natural infections during childhood and adolescence, whereas universal mass vaccination has changed the seroepidemiology of rubella among adults, showing lack of immunity in some subgroups. National and international guidelines recommend evaluating all healthcare workers (HCWs) for their immune status to rubella and possibly vaccinating those who are seronegative. We conducted a systematic review and meta-analysis to estimate the susceptibility rate to rubella among HCWs in Italy and to explore possible options for the management of those found to be susceptible.

Methods: Eight studies were included in the meta-analysis, selected from scientific papers available in the MEDLINE/PubMed and Google Scholar (till page 10) databases between January 1, 2015 and November 30, 2021. The following terms were used for the search strategy: (sero* OR seroprevalence OR prevalence OR susceptibilit* OR immunit* OR immunogenict*) AND (healthcare worker* OR health personnel OR physician* OR nurse OR student*) AND (rubella OR german measles OR TORCH) AND (Italy)

Results: The prevalence of rubella-susceptible HCWs was 9.0 % (95 %CI: 6.4–12.1 %). In a comparison of female vs. male serosusceptible HCWs, the RR was 0.67 (95 %CI = 0.51–0.88). Occupational medicine examinations for rubella screening with possible subsequent vaccination of seronegatives and exclusion of susceptible HCWs from high-risk settings were common management strategies.

Conclusions: HCWs susceptible to rubella are an important epidemiological concern in Italy, and efforts to identify and actively offer the vaccine to this population should be increased.

Conclusion

In the pre-vaccination era, rubella was endemic in all the countries in the world and all adults acquired immunity status due to natural infections during the infancy and adolescence. Universal mass vaccination carried out in the last 20 years in developed countries changed the seroepidemiology of rubella among adults, showing lack of immunity in some subgroups, such as healthcare workers (HCWs)[1].

According to recommendations from the U.S. Centers for Diseases Control and Prevention, healthcare workers (HCWs) should have presumptive evidence of immunity to rubella. Rubella immunity in HCW is defined by the following:

- written documentation of vaccination with two doses of rubella-containing vaccine administered at a minimum interval of 28 days
- laboratory evidence of immunity
- laboratory confirmation of a history of the disease
- birth before 1957 [2].

This recommendation is crucial for certain subgroups of HCWs, such as those working in Obstetric Departments, who are in direct contact with pregnant women. Despite these recommendations, there is good evidence of significant susceptibility to rubella among HCWs. A 2014 study [3] described a significant proportion of susceptible Spanish HCWs to rubella (3 %), linked to a missed vaccination or waning IgG levels after immunization.

Susceptible HCWs represent a risk both to themselves and to patients in their hospitals and clinics and are therefore an important public health concern. A 2014 review reported known cases
of HCW-to-patient transmission of the most common vaccine-preventable infections in healthcare settings. It concluded that vaccination is the primary method of protection from the risk of work-related infection for both HCWs and the patients in contact with them [4].

In Italy, a single-antigen measles vaccine was introduced in the 1970s. Since 2003, the national vaccination schedule has recommended universal mass vaccination consisting of two doses of measles, mumps and rubella (MMR) vaccine (the first dose at 12–15 months and the second at 5–6 years of age) [5]. In 2017, the Italian government made rubella vaccination compulsory for infants and teenagers [5]. Although this vaccination strategy was very effective, rubella has yet to be eliminated. Indeed, from 2013 to 2018, despite a slight increase in 2017, the incidence of rubella cases remained relatively low over the period considered; concerning rubella congenital syndrome, no more than one case has been reported in Italy since 2014 [6]. The Italian Ministry of Health [7], in accordance with international guidelines [2], recommends the control of the rubella immunity status of all HCWs and the vaccination of those without immunity, especially those in close contact with patients at risk of severe rubella complications (pregnant women, newborns, immunocompromised, etc.). Nonetheless, there are no Italian national data on rubella vaccination coverage and immunization status of HCWs.

To estimate the prevalence of HCWs in Italy susceptible to rubella, we conducted a systematic review of the relevant literature and a meta-analysis. Options suggested by these studies for the management of susceptible HCWs were also analyzed.

Methods

Search strategy and selection criteria

The Scopus, MEDLINE/PubMed and Google Scholar databases (up to page 10, as already after the first 5 pages the search results were far from the search string, ten records per page) were systematically searched; records were ordered by best match. Research articles, letters to the editor, reviews and meta-analyses published between January 1, 2015 and November 30, 2021 were included in our search. The following terms were used for the search strategy, according to PICO framework: (sero* OR seroprevalence OR prevalence OR susceptibility OR immunity OR immunogenicity) AND (healthcare worker* OR health personnel OR physician* OR nurse OR student*) AND (rubella OR german measles OR TORCH) AND (Italy). Studies in English or Italian and without full text were included. Abstracts without full-text, letters to the editor not reporting original data, papers not reporting epidemiological data (editorials, commentaries, etc.), studies in which susceptibility was evaluated by surveys or those in which only vaccination coverage was reported, and all studies focusing on questions unrelated to the purpose of this review (vaccine hesitancy, vaccine knowledge, attitudes, etc.) were excluded. When necessary, study authors were contacted for additional information. References of all articles were reviewed for further study. The list of papers was screened by title and/or abstract independently by two reviewers who applied the predefined inclusion/exclusion criteria. Discrepancies were recorded and resolved by consensus.

Extracted data included year, sample size, sampling approach, number of susceptible HCWs, professional category, Italian region and options for managing susceptible HCWs.

Quality assessment

The quality of selected studies was assessed according to the STROBE checklist, which includes 22 methodological questions [8]. Quality assessment was not performed for studies without full text. Studies assessed according to STROBE had minimum and maximum possible scores of 0 and 44, respectively, and were classified as low quality (<15.5), moderate quality (15.5–29.5) or high quality (30–44).

The risk of bias for each study was independently assessed by two researchers. Discrepancies were recorded and resolved by consensus. The quality of papers not published in English was not assessed.

Pooled analysis

Two different meta-analysis groups were performed: the first included all HCWs, the second compared susceptibility by sex (female vs. male). For comparisons by sex, the risk ratio (RR) and 95 % confidence interval (95 %CI) were calculated. In addition, for the first meta-analysis, a separate analysis was carried out using only high-quality papers (it was not possible to perform this sub-analysis for the sex comparison analysis, because of the small number of included studies).

The pooled proportion in the meta-analysis was calculated using the Freeman-Tukey double arc sine transformation to stabilize variances, and the DerSimonian-Laird weights for random effects models, with the estimate of heterogeneity obtained from the inverse-variance fixed-effects model. The pooled prevalence and the associated 95 % Wald confidence interval were plotted, and a forest plot was drawn. The $I^2$ statistic was calculated as a measure of the proportion of the overall variance attributable to heterogeneity between-studies rather than to chance. Heterogeneity between studies in different groups was also assessed. A p-value < 0.05 was considered to indicate statistical significance of heterogeneity.

Funnel plots were used to assess publication bias. A study distribution with a symmetric funnel shape indicated no significant bias, whereas an asymmetric funnel indicated publication bias. Egger’s test for small-study effects was also performed.

A sensitivity analysis was conducted to evaluate stability, in which among the studies included in this systematic review, one study at a time was excluded, and the conclusion based on the others was then re-evaluated for severe distortion.

Statistical analysis was conducted using STATA MP17 and Review Manager 5.4.1 software.

Strategies to promote vaccination among susceptible HCWs and characteristics of serosusceptible HCWs were collected from all available studies and the respective findings were compared, with particular attention to the evidence presented in several of the included papers.

Results

Identification of relevant studies

The flow-chart, constructed following PRISMA guidance [9] (Fig. 1), shows the process of article selection. According to the aforementioned inclusion criteria, three articles were identified in Google Scholar, four in Scopus and eight in MEDLINE/PubMed. After exclusion of duplicate articles in the two databases, there were nine eligible studies [8–16] (Table 1), of which eight were quantitative [10–17] and one was qualitative [18]. The remaining 88 studies did not match the inclusion criteria [19-107].
Quality assessment

The STROBE checklist was applied appropriately to the included studies and 63 % were determined to be of high quality (Table 1). The impact of study quality was assessed in a sub-analysis.

Pooled analysis

According to our meta-analysis of HCWs, the prevalence of susceptibility to rubella was 9.0 % (95 %CI: 6.4–12.1 %), in accordance with an $I^2$ of 96.7 % and a p-value for the heterogeneity test of $< 0.0001$ (Fig. 2). Based on high-quality articles only, the pooled prevalence among all HCWs was 8.3 % (95 %CI = 5.2–12.2 %; $I^2 = 97.3; \ p < 0.0001$).

When comparing rubella serosusceptibility between female and male HCWs, the RR was 0.67 (95 %CI = 0.51–0.88; $I^2 = 68.0 %; \ p = 0.03$; Fig. 3).

Sensitivity analysis did not show severe distortion by any specific study. In the publication bias analysis, there was no obvious asymmetry in the funnel plots and no strong evidence of publica-
tion bias (Fig. 4). The p-value in the Egger’s test was 0.062 for the sex-based sub-analysis.

Suggestions and procedures for managing rubella susceptibility in HCWs

All studies concluded that screening for HCWs is essential to prevent nosocomial clusters and that promotion of an adequate immunization program should be a priority of Occupational Medicine services. Two studies [12,18] focused on the cost-effectiveness of such strategies, consistently finding that an immunization strategy with pre-vaccination screening was more cost-effective than a hypothetical vaccination strategy without screening. Leone Roberti Maggiore U et al. [18] reported that multicomponent, dialogue-based interventions were found to be the most effective interventions for achieving better immunization coverage among HCWs.

In most studies, the immunization status of the person prior to serologic testing is known and includes several non-seroprotected individuals who remained unvaccinated; however, in many cases, among the twice-vaccinated there are those who are still serosusceptible [10,12–14]. Bianchi FP et al. [14] conducted a serosurvey of 2,000 fully vaccinated individuals and determined that 9% were still susceptible to rubella. In the study by Trevisan A et al. [10], 190 (3%) of 6,382 participants who had received two doses of vaccine remained seronegative. Coppetta L et al. [12] found a seronegativity rate of 6.8% in cohorts of fully immunized female nurses.

Several of the included studies [10,12–14] reported a higher proportion of serosusceptible HCWs among those born in the post-vaccination era than in the pre-vaccination era and thus naturally immunized. Serosusceptibility among the former can be traced to
the fact that measles-mumps-rubella (MMR) vaccine-induced IgG antibody titers decrease by 5–7 % per year even after a second dose of the vaccine. In this context, three studies [12–14] determined that the interval since the last dose of MMR vaccine seemed to influence the persistence of circulating antibodies, assessing that vaccine-induced humoral immunity seemed to persist for 10–15 years. Trevisan A et al. [10] reported that antibody titer is significantly greater when the vaccine is administered in adolescence than in childhood. On the contrary, Coppetta L et al. [11] observed that antibody titer was not correlated with the age at which the vaccine was administered, in fact the rate of serological protection was the same both in those who had received the vaccination in early childhood (1–3 years old) and in adolescence.

The need for one or more doses of MMR vaccine in serosusceptible HCWs has been discussed in many of the studies. Three studies [10–12] concluded that additional doses of vaccine and retesting should be considered for serologically unprotected HCWs, especially if they are females of childbearing age. Bianchi FP et al. [13,14] described the management of serosusceptible HCWs, medical students and medical residents at Bari Policlinico General University Hospital (Italy), regardless of vaccination status (none or two doses of vaccine) and recollection of having had the disease.

For the never immunized group, the rubella vaccination protocol consisted of two doses of MMR vaccine administered 28 days apart and followed by a blood test. For the fully vaccinated group, a booster dose of MMR vaccine was provided, followed 20 to 25 days later by a second blood test to retest IgG titers. If the value determined in the re-evaluation exceeded the cut-off used for the laboratory test performed, the HCW was classified as seroconverted; if the titer was still negative, another dose of vaccine was administrated (28 days after the first booster) and again after 20–25 days IgG levels were measured. For medical students and residents who remained seronegative after vaccinations, re-evaluation for rubella infection was recommended in all cases of exposure, with possible administration of immunoglobulin. Screening was voluntary and vaccination was not mandatory, with its refusal having no consequences in terms of suitability for work [14]. Thus, at the end of screening, the Occupational Health physician listed the placement options for each potential HCW according to his/her susceptibility/immunity status and a risk assessment. For susceptible HCWs who refused one or more vaccines, exclusion from occupational settings that included patients at high infectious risk (e.g., pregnant women, immunocompromised patients) was recommended [13]. The authors reported high vaccination compliance among susceptible HCWs and medical students/residents and a seroconversion rate > 90 % after a booster dose(s). These were not followed by any serious adverse events.

Finally, several recent papers advocated mandatory vaccination, especially for HCWs working in departments where high-risk patients are treated [13,14,16].

Discussion

Our meta-analysis estimated a susceptibility rate for rubella among HCWs in Italy of 9 % (95 %CI = 6–12 %), higher than the value reported in a 2014 study (3 %) [3] and similar to the rate reported in a 2019 meta-analysis that investigated the susceptibility of Italian HCWs to measles (9 %; 95 %CI = 6–13 %) [108].

To our knowledge, this is the first study to find that male HCWs were less likely than females to have circulating anti-rubella IgG, via estimation of a Risk Ratio (RR = 0.67; 95 %CI = 0.51–0.88). Sex differences in response to vaccination or infection have been examined in several studies [109–113], but our analysis is the first that demonstrate sex-based differences for rubella infection/vaccination. Females generally have more effective immune responses after immunization and against infection, with immunological, hormonal, genetic, microbiotic, and environmental factors likely contributing to the difference between males and females with respect to rubella. Furthermore, anti-rubella immunization campaigns were historically focused on females to avoid the risk of congenital rubella, and this may explain our results. Indeed, Bertoccello C et al. [114] reported that in a sample of Italian medical students the completion of rubella vaccination was significantly higher in females than males (93.8 % and 84.8 %, p < 0.0001, respectively).

The systematic review also showed a higher risk of loss of seroprotection in HCWs born in the post-vaccination era and thus unlikely to be exposed to the wild virus, whose circulation has decreased since the introduction of vaccination.

Few studies have described the management of susceptible HCWs, but the protocol developed by Bianchi FP et al. [13,14] has been shown to have high efficacy and safety. However, the management of HCWs vaccinated with two doses but still without circulating antibodies remains problematic. Should they receive one or more MMR booster doses? Picone et al. [115] have shown that even those who are determined to be rubella antibody negative can be antibody positive by other methods or show a secondary immune response to revaccination. On the other hand, the literature includes reports of measles in fully vaccinated HCWs [116–119], so theoretically it may also be possible considering rubella. In addition, this systematic review and meta-analysis determined a substantial proportion of non-seroprotected HCWs among those vaccinated with two doses.

The main limitation of this meta-analysis was the high heterogeneity across studies, as indicated by I² values; but the use of a random-effect analysis minimized this bias. Differences in the techniques used to analyze blood samples also complicated comparisons between studies. This is a major limitation of our study because, as reported by Vauloup-Fellous C [120], the standardization of rubella IgG assays is not effective, with different levels of International Units per milliliter reported for a same sample, and consequently different interpretations of the result; it leads to misinterpretation of results, sometimes causing adverse clinical outcomes. Nevertheless, the chemiluminescence-based method of the LIAISON® Rubella IgG II system [121] was used in five studies; other techniques with different cut-offs to define immunity were also employed in the other three studies, but this did not appear to be a critical issue for the generalization of our results. It was also not possible to stratify susceptible HCWs on the basis of their vaccination status or previous illness. However, a strength of our
review and meta-analysis was the large sample size resulting from the collation of selected papers, which improved the statistical analysis and provided a better view of rubella immunity among Italian HCWs. In addition, since several studies investigated a younger cohort of HCWs, this view is up-to-date and reliable. Finally, sub analysis by sex provided information, including RR value, not previously reported in the literature. Future meta-analysis in the following years should focus should include more studies to perform sub-analysis per age, occupation, reagents and geographical area; indeed, as evidenced by an our previous study [108], we found that there are regional differences in measles antibody prevalence and it may possible for rubella as well.

The elimination of rubella is a 20-year objective of national and international public health institutions [122], but the many elements that emerged from this study and reported in the recent scientific literature highlight the challenges in achieving this goal. It is therefore incumbent on national and international public health institutions to support the development of innovative strategies to address rubella risk, especially in the high-risk nosocomial setting. Attempts to educate HCWs and medical students need to be strengthened [43], as efforts thus far have proved insufficient to bridge the immunization gap. The solution proposed in most of the recent scientific literature is to make vaccination of HCWs mandatory [13,14,16] in order to reduce the risk of nosocomial transmission by patients and HCWs themselves. In Italy, three regions approved a specific law that made vaccinations mandatory for HCWs, based on fitness for work assessed by occupational health physicians [123], similar to the protocol described by Bianchi FP et al. [13]. The impact of this law on the immunization status of HCWs has yet to be reported, but is expected to be encouraging.

Conclusion

In conclusion, even in the era of the COVID-19 pandemic, diseases such as rubella still pose a threat in hospital and community settings that cannot and must not be forgotten by policy makers. In the state of emergency the world currently finds itself in, quick and firm decisions must be made. Reducing the susceptible HCWs would reduce the risk of nosocomial transmission of rubella and thus protect high-risk patients (pregnant women, newborns, immunosuppressed, etc.). Other issues, perhaps more difficult for public health institutions to resolve, are the management of HCWs who have been vaccinated with at least two doses of MMR vaccine but remain sero-susceptible and the decrease in circulating antibodies over time among those vaccinated. Nevertheless, our results highlight that healthcare professionals susceptible to rubella are a genuine public health concern in Italy and that more targeted efforts are needed to identify these individuals and actively offer them the vaccine. Finally, it should be considered that rubella immunization policies are also useful to achieve the goal of measles elimination.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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