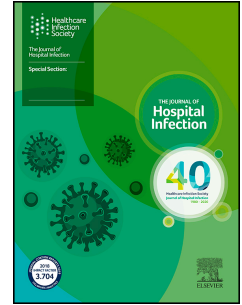


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Summary

Background: Immunity of healthcare workers (HCWs) against measles is a particular concern. They are more likely to contract it than the general population due to their occupational exposure which may cause a nosocomial outbreak.

Aim: To assess the measles immune status of HCWs at five Spanish university hospitals.

Patients and methods: Serologic testing (IgG) for measles by chemiluminescence indirect immunoassay (CLIA) was carried out prospectively and consecutively in HCWs from five university hospitals. All HCWs were classified into four epidemiological groups: vaccinated individuals, those with a history of measles disease, subjects with no history of measles or vaccination, and those who did not know if they had measles or were vaccinated, and into five professional categories: physicians, nurses, nursing assistants, other clinical workers, and non-clinical workers. A logistic regression model was constructed to identify the factors independently associated with immunity to measles.

Results: The study group was composed of 2157 HCWs. 89% had protective antibodies against measles. Of the 238 non-immune HCWs, 199 (83.6%) had been vaccinated as compared to 1084 of the 1919 (56.5%) immune individuals ($p < 0.0001$). The parameters significantly predictive of having protective antibodies against measles were: older age ($p < 0.0001$), epidemiological status ($p = 0.0002$, mainly past measles disease), and professional category ($p = 0.02$, particularly nurses).

Conclusion: This study shows that HCWs, including those previously vaccinated, are currently at risk of measles and suggests that those with a natural history of infection are better protected. Therefore, knowledge and maintenance of immunity to measles are an essential part of infection control among HCWs.

Keywords: measles, seroprevalence, healthcare workers, vaccination, Spain

Introduction

Measles is a highly transmissible and potentially fatal vaccine-preventable disease. In areas with sufficient vaccine coverage (about 96% to achieve herd immunity), new cases and transmission are rarely observed [1]. According to the latest WHO-UNICEF estimate of 2018, Spain is not among the countries with measles vaccination coverage of at least 95% for the first and second doses [2]. Likewise, the second seroprevalence study in Spain 2017-2018 shows measles protection below 95% in the 15-39 year old population [3]. From 1 March 2019 to 29 February 2020, 29 EU/EEA Member States and the UK reported 11,576 cases of measles, 290 (2.5%) of which were in Spain. In addition, this number of measles cases reported may be an underestimation in certain countries [2]. Vaccine refusal, globalization, humanitarian crises and migration, and loss of herd immunity greatly impact current outbreaks.

Regarding current anti-measles vaccination strategies in Spain, measles, mumps, and rubella (MMR) vaccination in children is recommended with two doses, the first at 12 months and the second at 3-4 years old. Adults without a documented history of vaccination should receive two doses of vaccine to those born after 1970. Individuals born before 1970 are considered naturally immune and should not be vaccinated. Moreover, healthcare worker (HCW) vaccination will also be indicated if susceptibility is suspected, either in the absence of previous vaccination (in those born after 1970) or negative serology against measles. However, serology test is not systematically indicated in occupational medicine in Spain.

Immunity of HCWs against vaccine-preventable diseases is a particular concern, as they are more likely to contract them than the general population due to their occupational exposure and may transmit them to their colleagues and patients including those at high risk, with possible consequent nosocomial outbreak [4]. In the case of measles, it has been estimated that HCWs have an 18.6 times higher risk of acquisition compared to adults in the community. Lack of familiarity with measles among young physicians in the post-vaccination era leads to misdiagnosis or delay in diagnosis and delay in contact tracing and control measures, and ultimately to the spread of nosocomial outbreaks [5]. Therefore, knowledge of immunity to measles is an important part of infection control among HCWs, but it is not well known in Spain. Data from several Spanish regions indicate that measles immunity is below what is considered herd immunity [6-10]. The purpose of this study was to assess the measles immune status of HCWs in five hospitals belonging to the HM Hospitals group in Madrid, Spain.

Patients and methods

Between 2017 and 2020, serologic testing for measles was carried out prospectively and consecutively to a group of HCWs by the occupational risk prevention service to HCWs in five university hospitals (HM Madrid University Hospital, HM Montepincipe University Hospital, HM Torrelodones University Hospital, HM Sanchinarro University Hospital and HM Belen University Hospital) belonging to the HM Hospitals Group, a private consortium of general and high complexity hospitals, in Madrid, Spain. Immune status was determined by the detection of measles IgG using chemiluminescence indirect immunoassay (CLIA) (LIAISON[®] Measles IgG), which has excellent sensitivity of 94.7% (95% CI: 91.7-96.9%) and specificity of 97.4% (95% IC: 94.1-99.2%) [11]. Values of 16.5 UA/mL or greater were considered positive. Data related to age, sex, professional category, history of measles infection, and status of vaccination were surveyed. All HCWs were classified into four epidemiological groups: vaccinated individuals, those with a history of measles disease, subjects with no history of measles or vaccination, and those who did not know if they had measles or were vaccinated; and into five professional categories: physicians, nurses, nursing assistants, and other clinical workers. The study was approved by the Ethics Committee of HM Group.

Statistical analysis

Continuous variables are reported as median and interquartile range (IQR) and categorical variables as n (%). Categorical variables were compared with the Chi-square test or Fisher's exact test, as appropriate, and the Mann-Whitney and Kruskal-Wallis tests were used for the comparison of continuous variables in two or more groups, respectively. A logistic regression model was constructed using the variables with a p-value <0.1 in the comparative analyses to identify the factors independently associated with immunity to measles. SPSS v. 25.0 software (IBM Corp., Armonk, New York, USA) was used for statistical calculations. A p-value <0.05 for a two-sided test was considered statistically significant.

Results

The study group was composed of 2157 consecutive HCWs (176 physicians, 851 nurses, 602 nursing assistants, 384 other clinical workers, and 144 non-clinical workers). The median age was 35.0 years (IQR 30.0-42.0) and 1744 of them (80.9%) were women. Table I shows the demographic data according to the different professional categories. All HCWs were classified into four epidemiological groups: vaccinated individuals (n=1283, 59.5%), those with a history of measles disease (n=281, 13.0%), subjects with

no history of measles or vaccination ($n=51$, 2.4%), and those who did not know if they had measles or were vaccinated ($n=542$, 25.1%). The age differed among these four epidemiological groups considered altogether ($p<0.0001$). Vaccinated individuals constituted the youngest group (median 31.0, IQR 28.0-34.0), whereas those with a history of measles disease were the oldest (45.0, 41.0-53.0). Individuals unaware of their measles status and those with no prior measles or vaccination had intermediate and similar ages (42.0, 38.0-48.0 and 42.0, 38.0-45.0, respectively, $p=0.5$). Except for the latter, all other intergroup comparisons yielded statistically significant age differences ($p<0.001$).

Regarding the measles immune status, the vast majority of the HCWs (1919, 89.0%) had protective antibodies against measles, whereas the remainder 238 individuals (11.0%) were not immune to the infection. There were no differences in the immune status according to sex (89.3% immune women vs. 87.4% men, $p=0.3$). Of the 238 non-immune HCWs, 199 (83.6%) had been vaccinated, 23 (9.7%) did not know their measles status, 9 (3.8%) had no history of measles nor were vaccinated and 7 (2.9%) had a history of measles ($p<0.0001$). Regarding the professional categories, 91 (38.2%) were nurses, 69 (29%) nursing assistants, 50 (21.0%) other clinical workers, 16 (6.7%) non-clinical workers, and 12 (5.0%) physicians ($p=0.3$). Figure 1 depicts the proportion of individuals who did not have protective immunity against measles according to the measles/vaccination status, as well as the statistical comparisons among the diverse groups. The highest rates of immunity were observed in the HCWs who had had measles disease in the past, and the lowest in those who did not receive vaccine nor had had measles infection.

Table II shows the measles and vaccination status according to the diverse professional categories. A history of measles disease was somewhat more common among physicians and nursing assistants (about 19%) than in the remainder groups (about 10%), whereas the nurses' group had substantially higher rates of vaccination (about 75%) than the other professional categories. The differences among the diverse categories considered altogether were statistically significant ($p<0.0001$). In the logistic regression model, which adequately fitted the data according to the Hosmer-Lemeshow goodness-of-fit test, the parameters significantly predictive of having protective antibodies against measles were older age ($p<0.0001$), epidemiological status ($p=0.0002$, mainly past measles disease), and professional category ($p=0.02$, particularly nurses) (Table III). Sex ($p=0.5$) and other epidemiological and professional intergroup comparisons were not significantly associated with immunity.

Discussion

HCWs are at greater risk of measles than the general population and can lead to nosocomial outbreaks, which spread rapidly in enclosed spaces, particularly in populations under 40 years of age with poor vaccine coverage [4,5,12-19]. A delay in diagnosis due to the inexperience of physicians or atypical presentation in adults may facilitate the spread of infection [5-10,12-18]. Measles is usually mild in previously healthy children. However, it can be more severe and complicated in adults and immunosuppressed patients [5,20]. Susceptibility to measles in HCWs has changed over time and differs by geographical area [6-10,21-29]. The most recent systematic review and meta-analysis conducted in EU/EEA countries and the UK involving nineteen studies has shown that the prevalence of measles-susceptible HCWs was 13.3% [29]. Our findings and previously published studies suggest that measles immunity of HCWs in Spain is below that of the general population [3,6-10,30] and does not meet the herd immunity criteria [2,3]. The prevalence of HCWs susceptible to measles may vary according to the method of assessment and is usually higher by survey than by direct determination in blood specimens [27], as performed in our study. Sex, age, HCWs born in the post-vaccination era, and professional categories can be determinants in the measles immune status of HCWs [6,7,9,24-29,31]. In our study, the highest rates of immunity were observed in the HCWs who had measles disease in the past and were the oldest (even considering that this group is under-represented in the sample analysed), and 83.6% of non-immune HCWs had been vaccinated, who were the youngest, as already described above [27,29]. In addition, measles in HCWs previously vaccinated with two doses has been reported in several nosocomial outbreaks [12-15]. This reflects a longer duration of immunity in naturally immunized HCWs than in vaccinated HCWs [3,29,32]. In an Italian retrospective cohort of medical students and residents of the University of Bari, an important proportion of subjects immunized for measles do not show a protective IgG titre in the 10 years after vaccination [32]. In parallel to the development of neutralizing antibodies, CD4+ T helper-cell stimulation and activation of cytotoxic CD8+ T-cell are also induced by measles infection or vaccination, which achieves viral elimination and long-term anti-measles specific immunity [33]. However, it has been observed that in vaccinated individuals and those with a history of measles disease, there are waning antibody titres over time which might indicate a waning protection. Therefore, a booster immunization with an anti-measles vaccine could induce strong cell-mediated memory immune responses against measles. Data evaluating the effectiveness of booster immunization should be analysed in long-term future studies.

Regarding predictive factors related to the measles immune status of HCWs, age, and male sex have been previously associated with immunity [7,9,34-36]. Our study has shown that age ($p<0.0001$), epidemiological status ($p=0.0002$, mainly past measles disease), and professional category ($p=0.02$, particularly nurses) are the parameters significantly predictive of having protective antibodies against measles.

Knowledge of immune status to measles and vaccination of HCWs are the only reliable protective measures to prevent nosocomial measles outbreaks. The development and promotion of adequate policies in both areas should be considered a priority [19]. Only 17 out of 30 European countries had specific recommendations for measles vaccination in HCWs and it is only mandatory in Finland [37]. In Spain, HCWs born before 1970 are considered immune to measles because they have had the disease [38]. However, some studies conducted in our country do not confirm this [30,34]. HCWs are in the best position to understand the benefits of vaccination, but they have a certain scepticism towards it. Considering all the above [19,32,34,37,38], it seems reasonable to establish protocols for action based on the measles immunization status of the HCWs to prevent nosocomial outbreaks. We have proposed one for the HM Hospitals Group. HCWs born before 1970 are considered immune assuming that the margin of error is minimal. In HCWs born after 1970 with no history of measles or vaccination and those who did not know if they had measles or were vaccinated, vaccination is advised. In HCWs vaccinated more than 10 years ago and born after 1970 a quantitative measles IgG antibodies determination is performed. If the HCW is unprotected, vaccination with a booster dose is advised. HCWs vaccinated less than 10 years ago are considered immune to measles.

Concerning the cost-effectiveness of vaccination against measles in HCWs, in our study, each serological test costs 24.14 €, and one dose of MMR vaccine 17.83 €. However, as it would have been necessary to administer two doses of MRM vaccine to 85% of the HCWs, the total cost would amount to 34,233 €, higher than the 27,241 € spent on antibody determination. Therefore, we recommend extending the pre-vaccination screening to identify the real susceptible workers [39].

In conclusion, this study shows that HCWs are currently at risk of measles, including those who have been vaccinated, and suggests that those with a natural history of infection are better protected. Therefore, knowledge and maintenance of immunity to measles are an essential part of infection control among HCWs. Vaccination should be individualized, even in previously vaccinated HCWs with booster doses, and can be cost-effective.

Conclusions

This study shows that HCWs, including those previously vaccinated, are currently at risk of measles and suggests that those with a natural history of infection are better protected. Therefore, knowledge and maintenance of immunity to measles are an essential part of infection control among HCWs.

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Conflict of interest statement

All the authors declare that they have no conflicts of interest.

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Table I. Demographic data of the different professional categories.

	n (%)	n (% of women)	Age median (IQR)
Physicians	176 (8.2%)	119 (67.6%)	40.0 (35.0-47.0)
Nurses	851 (39.5%)	738 (86.7%)	33.0 (29.0-37.0)
Nursing assistants	602 (27.9%)	534 (88.7%)	38.0 (31.0-46.0)
Other clinical workers	384 (17.8%)	239 (62.2%)	37.0 (31.3-44.0)
Non-clinical workers	144 (6.7%)	114 (79.2%)	35.0 (32.0-40.0)
All categories	2157 (100%)	1744 (80.9%)	35.0 (30.0-42.0)

Table II. Measles and vaccination status of the diverse professional categories.

	Measles and vaccination status				Total
	Vaccinated	Past measles	nM-nV	Unknown status	
Physicians	81 (46.0%)	33 (18.8%)	6 (3.4%)	56 (31.8%)	176 (100%)
Nurses	637 (74.9%)	82 (9.6%)	10 (1.2%)	122 (14.3%)	851 (100%)
Nursing assistants	311 (51.7%)	117 (19.4%)	10 (1.7%)	164 (27.2%)	602 (100%)
Other clinical workers	166 (43.2%)	35 (9.1%)	21 (5.5%)	162 (42.2%)	384 (100%)
Non-clinical workers	88 (61.1%)	14 (9.7%)	4 (2.8%)	38 (26.4%)	144 (100%)

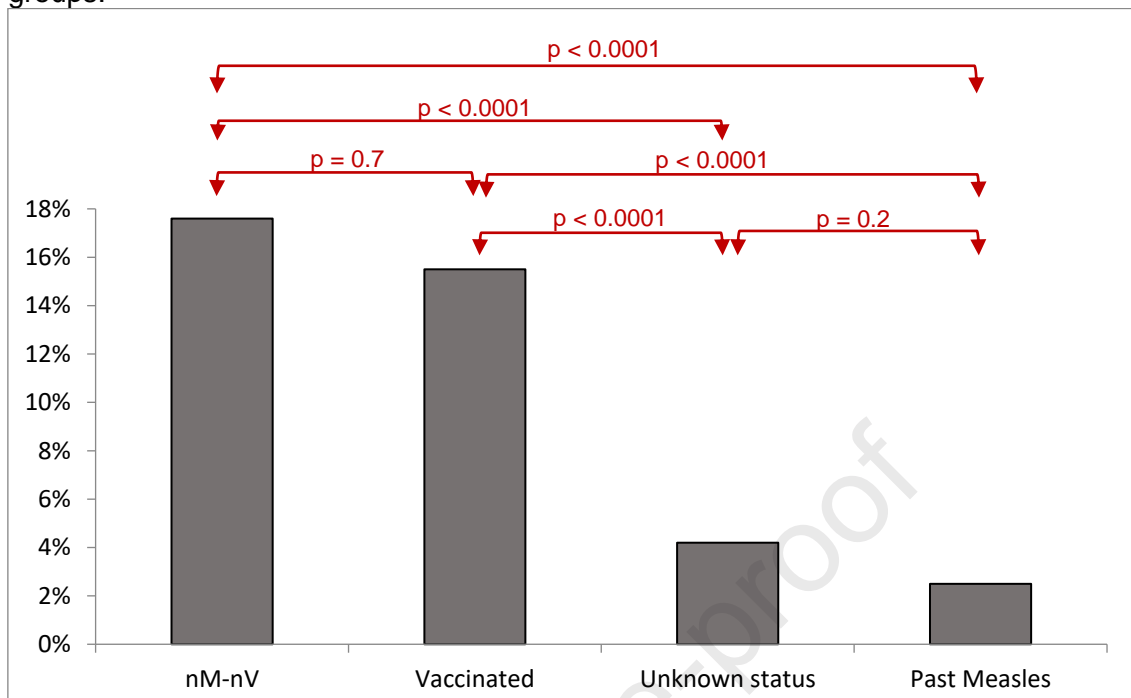
nM-nV denotes no measles and no vaccination.

Table III. Variables independently associated with immunity to measles.

	OR (95% CI)	p
Age	1.069 (1.039-1.100)	<0.0001
Prior measles/vaccination status	-	0.0002
Past measles vs. nM-nV	6.164 (2.135-17.795)	0.0008
Past measles vs. vaccinated	3.020 (1.290-7.069)	0.01
Unknown vs. vaccinated	2.242 (1.310-3.838)	0.003
Unknown vs. nM-nV	4.576 (1.962-10.673)	0.0004
Professional categories	-	0.02
Nurses vs. nursing assistants	1.582 (1.121-2.232)	0.009
Nurses vs. other clinical workers	1.794 (1.214-2.650)	0.003

nM-nV: denotes no antecedent of measles disease and not vaccinated.

Figure 1. Lack of protective immunity against measles in the diverse epidemiological groups.



nM-nV: denotes no antecedent of measles disease and not vaccinated.