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Serological Evaluation for Measles, Rubella, Mumps among Albanian and Italian Medical Students Enrolled in a University in Tirana

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Introduction

Transmission of vaccine-preventable diseases (VPDs) and epidemics continue to occur in various healthcare settings even in countries with long-standing vaccination programs, placing patients and healthcare workers (HCWs) at risk of morbidity or even mortality.[1] Numerous epidemics of rubella, chickenpox and pertussis[2,3] have been traced to HCWs. The onset and evolution of such epidemics is facilitated by the fact that many VPDs spread rapidly within closed contexts and can manifest themselves with atypical symptoms, so they are often not suspected early. Compared to children, adults tend to have a more severe clinical course and more complications more often when affected by different VPDs (for example, measles, chickenpox). Vaccination of healthcare workers is justified to directly protect themselves and indirectly protect patients[4] however, inadequate coverage of healthcare workers against VPDs is a global problem.[5,6] According to the ECDC, hospital workers are 13 times more at risk than the general population.[7]

Measles is an acute, highly infectious disease that is transmitted through airborne respiratory droplets or by direct contact with the nasal secretions of infected individuals. Two doses of the vaccine achieve 97% efficacy in preventing measles, while one dose is 93% effective. Therefore, the World Health Organization (WHO) recommends two doses and coverage of at least 95% to ensure herd immunity to prevent epidemics and to provide indirect protection to unvaccinated individuals.[8] In recent years, there has been a drastic decline in measles vaccination coverage in Europe, probably responsible for several epidemic peaks.[9] The average coverage of measles vaccinations in Europe reaches just 91% and only six countries (Croatia, Hungary, Iceland, Portugal, Slovakia, and Sweden) report coverage of the two doses of measles vaccine at or above 95%.[10] In Italy, in 2013, vaccination coverage in children at 24 months exceeded 90%, while in 2016 it was significantly reduced, reaching 87%. In 2017, Italy recorded one of the highest measles infection rates.[10] According to WHO, measles cases in Europe increased fourfold in 2017, affecting more than 21,000 people and causing 35 victims. They were mainly detected in Romania (5608 cases), Italy (5098 cases), Greece (967 cases) and Germany (929 cases).[11]

This worrying situation led to the entry into force of the legislative decree on mandatory vaccination in June 2017. In 2018, vaccination coverage was achieved with the first dose, recommended at 24 months through the tetravalent MPRV vaccine (measles, mumps, rubella, chickenpox), by 93.22% and for the second dose, recommended after 5 years, by 89.20%. The trend is worsening: coverage for the first dose of measles vaccine in 2020 was 91, 79%, highlighting a decrease of 2.7% compared to the previous year.

In the first two months of 2019, 34,300 measles cases were reported in 42 countries in the WHO European Region, including 13 measles-related deaths, in three countries (Albania, Romania and Ukraine). Most cases have been reported in Ukraine, with over 25,000 cases (>70%). As of 28 March 2019, the WHO European Region reported a total of 83,540 measles cases and 74 related deaths for 2018. This compares to 25,869 cases and 42 deaths in 2017 and 5,273 cases and 13 deaths in 2016.[12] During 2020, measles cases decreased in all EU countries (6252 cases) thanks to social distancing, isolation and other preventive measures taken for COVID-19, but in 2021 cases have increased again and over 21,000 cases were reported.[13] Between March 2022 and February 2023, WHO updated measles cases (1861). Among these, 1728 (93%) were found mainly in ten countries: Tajikistan (610 cases), Turkey (466 cases), Russian Federation (414 cases), United Kingdom (67 cases), Serbia (40 cases), Austria (33 cases), Kyrgyzstan (29 cases), Poland (28 cases), France (22 cases) and Belgium (19 cases).[14] During the 2017-2018 measles epidemic in Europe, healthcare-associated transmission accounted for a significant portion of the measles-associated burden. Healthcare workers have also been disproportionately affected, accounting for up to 7 and 4.2 percent of notified cases in Italy and Greece, respectively. In this context, increasing attention has been paid to HCWs: compared to the general population, HCWs are estimated to be at greater risk of contracting VPDs such as measles, exposing both colleagues and patients.[15]

In particular, this study has two purposes: first, we wanted to investigate the serological coverage among future healthcare workers and quantify the problem based on nationality. Second, we wanted to identify the vaccination rate epidemiologically.

Materials and Methods

In March 2023, we conducted a cross-sectional study to evaluate the vaccination coverage and immunological status of medical students of the Catholic University "Our Lady of Good Counsel" of Tirana (Albania) who were carrying out their internship at the

Polyclinic of the University of Rome Tor Vergata (Italy). Medical students were either from Albania or Italy. Socio-demographic characteristics (gender, age, country of origin) were collected.

Serological data was obtained from blood tests: study participants underwent venepuncture of the cephalic vein, median cubital vein, or basilic vein to obtain blood for routine blood tests. A 10 ml blood sample was collected and delivered to the laboratory to detect measles-specific IgG antibodies. A semi-quantitative evaluation of specific IgG antibodies was obtained with the Alifax VIRCLIA® KIT VIR VCM054 Measles IgG test, which uses chemiluminescence immunoassay technology (CLIA) with sensitivity and specificity values of 98% and 100% respectively. Serum IgG values were expressed as a signal-to-cut-off ratio (S/CO); values above 1.0 S/CO were considered protective based on actual testing. Antibody titers were tested for three contagious diseases to understand the immune status of the students: Rubella, Measles, and Mumps.

The ethical committee for research in Human Subjects of the Hospital approved the study (approval n.133/21).

All results were entered in a Microsoft Excel worksheet, and then analysed using SPSS version 25.0. Pearson's correlation test was used to measure the association between continuous variables. A p-value < 0.01 was considered statistically significant. Subsequently, the variables under study were evaluated with regression analysis, using the immune status (measles, mumps, rubella and chickenpox) for each disease as the independent variable and socio-demographic information (gender, age, nationality) as the dependent variables. The odds ratio was calculated between the serology results for measles and nationality (Italians/Albanians).

Results

In total, 137 medical students enrolled in the 2017/2018 and 2018/2019 academic years took part in the survey (27 males and 110 females). Among them, 27 (19%) were Italians and 110 were Albanians (81%). The mean age was 24.5 years ± 2 SD. (range: 22-37 years).

Table 1. Socio-demographic variables

Variables		Totals
Age	Mean age	24.5 ±2 SD
Gender	Male	27 (19%)
	Female	110 (81%)
Nationality	Italians	27 (19%)
	Albanians	110 (81%)

When testing antibody titers for Rubella, Measles, Mumps, missing data for a total of 3 students were excluded from the database. Specifically, the detected antibody titers were:

- For rubella 81% (n.110)
- For mumps 77% (n.105)
- For measles 37% (n. 51).

Among the diseases with the lowest protection, measles was identified as the most problematic, with only the 37% of the total (n.51 students) being protected.

The sample was stratified by nationality to understand the differences between the two nationality groups, based on a different vaccination policy between Italy and Albania. The analysis showed that in the Italian group 24 students out of a total of 27 (89%) were protected against Rubella, while in Albanian group 87 students out of a total of 111 (78%). Therefore, the number of Albanian individuals unprotected for rubella among Albanians was quite high (21%; n.23 individuals). For mumps, the data indicates that the percentage of students with a protective antibody level was almost the same in both the two groups, 74% and 77% respectively. Protection against measles was not satisfactory among the two groups: the protective antibody titer among Albanians was only 29%, which means that the 71% was not immunized. As for Italian students, immunization reached 67%, while 33% resulted unprotected: a significant difference emerged between the two nationality groups (p<0.01).

The relationship between nationality and immune status against measles was confirmed by the odd ratio: the risk of being unprotected at the start of the internship for medical students was almost five times higher in Albanian individuals (OR: 4.6; IC: 1.9-11.4).

Discussion

Recent reviews of EU immunization policies for HCWs have highlighted significant differences between countries in terms of recommended schedules, mode of implementation (mandatory or recommended), target groups and healthcare context.[16] These heterogeneous policies significantly influence the immunization rate in all countries and could imply different risks of spreading the disease from HCWs. In previously published studies, low immunization rates for some important VPDs have been reported among European healthcare workers, including those employed in high-risk settings.[17-21] Albanian students showed a lower rate of serological protection for measles than their Italian colleagues. This low level of protection among Albanian students was also confirmed in another study, where the immunization rate was only 44%.[22] In Albania, although a large number of vaccinations are compulsory in childhood and must be carried out in health facilities, recent studies have revealed a strong concern for the

Table 2. Immunological status

Infectious disease	Immunological status	Italians	Albanians	Totals
Rubella	Protected	24 (89%)	86 (79%)	110 (81%)
	Not Protected	3 (11%)	24 (21%)	27 (19%)
Measles	Protected	18 (67%)	33 (30%)	51 (37%)
	Not Protected	9 (33%)	77 (70%)	86 (63%)
Mumps	Protected	20 (74%)	85 (77%)	105 (77%)
	Not Protected	7 (26%)	25 (23%)	32 (23%)

safety and effectiveness of vaccines.[23] Vaccines must be stored within a specific temperature range from production until vaccination. This time-lapse can take up to a year or longer. This is because temperatures that are too high or too low can cause the vaccine to lose its potency. Once a vaccine loses its potency, it cannot be recovered or regained. In some inland areas in Albania, there has been some concern regarding the vaccine cooling system in the past, problems have been reported with the cooling equipment and temperatures of vaccines that had not been stored properly. The investment in the cold chain equipment, used for vaccine storage, recently benefited due to the latest COVID pandemic, presumably showing a threat in the cold chain before the last recent years. With funding from UNICEF, WHO has recently installed three new cold storage facilities to strengthen cold chain capacity in some areas of Albania.[24] In 2018-2019, a large measles epidemic occurred, with nearly 1,700 cases reported, highlighting the difficulty of maintaining optimal vaccination coverage all over the country.[25,26]

In the present study, the immunization rate of subjects was less than 70%, raising concerns regarding the risk of nosocomial measles infection for these workers.[27-29] The effectiveness of the MMR (measles, mumps, and rubella) vaccine may vary depending on the specific strain of circulating viruses. Variations in strains can affect the vaccine's ability to offer complete protection against these diseases. For example, the effectiveness of the MMR vaccine, containing the Jeryl Lynn strain, for the prevention of mumps is 72% with a single dose and 86% with two doses. Therefore, it is important that vaccines are formulated to cover the most common viral strains circulating in a given geographic region in order to maximize the effectiveness of vaccination. In Italy, there is no mandatory national measles vaccination policy for medical students and healthcare workers, except in two Italian regions, and non-immune people are sometimes offered vaccination in the workplace, but more often they are referred to a public service immunization program, resulting in a delay or failure to administer the vaccine. In Albania there is no vaccination policy for medical students as well. In a previous study, direct vaccine administration was shown to be more effective and cheaper than other strategies.[30] Maintaining routine coverage of at least 95% will stop transmission of the virus, so raising awareness among stakeholders and HCWs of the risk of the disease is crucial. The elimination of this pathology is possible thanks to the presence of vaccines which, however, must be administered adequately. It is estimated that 95% of the population needs to be vaccinated with two doses of measles vaccine to achieve protection of the entire population and prevent outbreaks. Given the inadequate vaccination coverage in Italy and Albania and the circulation of the measles virus, we recommend vaccination in childhood according to the vaccination calendar, serological evaluation and possible vaccination for HCWs who do not declare this type of vaccination or do not have protective antibody titers.[31] This strategy has been found in previous studies to be highly effective from a cost and savings point of view.[32] Our study shows that 18 women are not protected from rubella. This information is concerning and indicates a potential risk of disease for these female students in case of future pregnancy.

This work has many possible limitations. First, the circumstances of vaccination (type of vaccine administered, storage conditions, etc.) may have varied between study countries, resulting in different immunogenicity of the vaccine. Secondly, the epidemiology of measles in various regions of the world is heterogeneous and the effect of a natural booster can consequently vary, depending on the probability of coming into contact with the virus. Third, the students involved may not be fully representative of the population of origin, as they probably belong to the upper social class.

Conclusions

The results of our study, although carried out on a small sample, highlight a concerning proportion of medical students who are serologically non-immune to measles. Measles immunity rates were heterogeneous depending on the country of origin, raising concerns about the high risk of measles transmission among students from areas with the lowest immunization rates. Although the sample size is limited, these initial findings can provide a foundation for future studies that aim to assess the immune status of students in the medical area. Based on the reported data, there is a strong indication to implement a mandatory immunization schedule for HCWs at the time of their hiring. Considering the limited protection period for these vaccines, it could be recommended that students receive a mandatory booster for these vaccines during the university course, particularly when working in high-risk areas.

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