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Varicella seroepidemiology and immunization in a cohort of future healthcare workers in the pre-vaccination era

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ABSTRACT

Objectives: The goal of this study was to establish the seroprevalence of positive antibodies against varicella and compliance with varicella vaccination in the pre-vaccination era.
Methods: A cohort of 10 683 Italian students from Padua University Medical School (from 2004 to 2019) were enrolled and classified as unvaccinated, vaccinated once, or vaccinated twice against varicella, according to their vaccination certificate. The antibody titre was measured and the seroprevalence of positive subjects was determined. Subjects with negative or equivocal antibodies were invited for vaccination, and then the antibody titre was retested.
Results: Unvaccinated students were mostly seropositive (95.6%), compared with vaccinated students who were less seropositive (68.0% after one dose and 78.6% after two doses) and had significantly lower antibody titres ($p < 0.0001$). The post-test vaccination had a positive response rate of 85.4%: 67.4% after one dose and 91.4% after two doses.
Conclusions: In the pre-vaccination era, only 3.3% of future healthcare workers were vaccinated against varicella (1.1% once and 2.2% twice). Vaccination or revaccination of negative and equivocal individuals could reduce the number of susceptible people. Implementation of varicella vaccine (two doses) in healthcare workers is of primary importance to reduce the risk of transmission.

Introduction

It is estimated that varicella disease causes a global annual of 4.2 million cases of severe complications (with hospitalization) and 4200 deaths (varicella disease burden, 2014). On the other hand, the case fatality rate is largely lower (0.1 per 100 000 cases) than that for measles (1.7) and pertussis (1.1). In the pre-vaccination era, the epidemiology of varicella in European countries was over 90% (Bollaerts et al., 2017).

The varicella vaccine was introduced in 1995 in the United States and has been available since 2001 in Italy, the first European country to include it in the vaccination programme. The vaccination has been implemented in the Veneto region in a two-dose schedule since 2005, and the universal vaccination programme has been implemented since 2003 in eight Italian regions. In 2013, the Interregional Group on Varicella Vaccination (IGVV) stated that vaccination coverage after the first dose at 24 months of age was high in all regions (84–95%), and adverse effects of the vaccine were rare (Bechini et al., 2015). Seropositivity in Europe is higher than 90% (Helmuth et al., 2015).

Universal mass vaccination for varicella reduces the rate of disease incidence (Henry et al., 2018; Zhu et al., 2018), hospitalization (Pozza et al., 2011; Lopez et al., 2011), and death (Marin et al., 2011) by more than 80% (Varela et al., 2019). Three years after the IGVV was established, the immunization coverage was approximately 70%, and the rate of adherence to vaccination in the Veneto region increased to 86.5% in the 2006 cohort (Baldo et al., 2009).

After Law Decree n. 73 June 7, 2017, varicella vaccination became mandatory in Italy for new-borns and for adolescents up to 16 years of age, and the vaccination schedule is two doses of vaccine (first dose at 13–15 months, second dose at 6 years of age) alone or in combination with measles, mumps, and rubella, with a live-attenuated varicella virus (Oka strain). However, a shorter interval between the doses is preferable to reduce breakthrough of the disease (Bonanni et al., 2013).

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The two doses of vaccine recommended since 2006 by the Advisory Committee on Immunization Practices and implemented in the United States since 2007 (Leung and Harpaz, 2016) reduced varicella cases by half in Connecticut (Kattan et al., 2011) and protects against all forms of varicella disease (Prymula et al., 2014).

The aim of this study was to investigate (1) the seroepidemiology of varicella in medical school students attending Padua University, (2) the frequency of varicella vaccination in the pre-vaccination era, and (3) seroconversion following vaccination of the subjects found to be negative or equivocal during the screening.

Materials and methods

Setting

Students at the Medical School of Padua University were enrolled to evaluate coverage against varicella infection and compliance with varicella vaccination.

A total of 10 683 students attending the medical school between 2004 and 2019 were enrolled: 3731 were male and 6952 were female. Most of the students (10 327; 3606 male and 6721 female) were unvaccinated, and only 356 (3.3%) were vaccinated (125 male and 231 female). Among them, 122 had been vaccinated once (44 male and 78 female) and 234 had been vaccinated twice (81 male and 153 female). All enrolled students were born in Italy and provided a vaccination certificate released by the Public Health Office. Furthermore, the students were subdivided into three age groups as follows: born before 1980, born between 1980 and 1990, and born after 1990. This subdivision allowed the differences in vaccination compliance for students born before and after 1990 to be highlighted. As demonstrated previously, 1990 was a watershed date for a significant increase in compliance with vaccinations (Trevisan et al., 2020).

Subjects with negative or equivocal antibodies were invited for vaccination (or for revaccination if they had already been vaccinated), and those who complied had their antibody titre retested.

Data were obtained during health surveillance according to the law; as such, the approval of the ethics committee was not required. However, students signed an informed consent form for the processing of personal and sensitive data, in which they also expressed consent to the possibility that the data collected would be processed anonymously for epidemiological investigations and/or for scientific research purposes. Almost all unvaccinated subjects reported a varicella history (a specific questionnaire was administered to the students); if not, the vaccination certificate among their notes explained if they were immune to varicella.

Measurement of antibodies

Varicella IgG antibodies were measured using a commercial enzyme immunoassay (EIA) Enzygnost (Dade Behring, Marburg, Germany). The antibody levels were reported as positive (higher than 100 IU/ml), negative (lower than 50 IU/ml), or equivocal (50–100 IU/ml). As the significance of equivocal results is unclear, these were statistically processed as negative, in accordance with the US Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, 1999). To enable statistical evaluation of the antibody titre, when not available, negative results and equivocal results were assigned an arbitrary value of 50 IU/ml and 87 IU/ml, respectively, according to the median derived from known values.

Statistical analysis

The statistical analyses were performed with a 2×2 Chi-square test (Yates correction) to compare the seroprevalence of varicella antibodies. The mean values and median values were compared with parametric (unpaired *t*-test) and non-parametric (Mann–Whitney *U*-test) tests, respectively. Spearman's rank correlation was used to correlate the antibody titre and intervals from vaccination, if applicable. Other statistical analyses were descriptive. Statistical significance was set at $p < 0.05$. Statsdirect version 2.7.7 (Statsdirect Ltd, UK) was employed for the analyses.

Results

Unvaccinated students were largely seropositive (95.6%), with few cases (0.6%) of equivocal results. The cohort born between 1980 and 1990 had significantly lower seropositivity (92.2%) than the cohort born between 1990 and 2000 (96.4%) ($p < 0.0001$). Vaccinated subjects showed significantly lower seropositivity (68.0% for one dose and 78.6% for two doses) than unvaccinated students ($p < 0.0001$), with an increase in equivocal results (one and two doses overall, 6.2%; 7.4% after one dose; 5.6% after two doses; and only 0.6% if unvaccinated). These results are summarized in Table 1. A graph representation of varicella seroprevalence in the unvaccinated and in the unvaccinated plus vaccinated (once and twice) groups over the years is presented in Figure 1; the two graphs are similar and the differences are not statistically significant.

Furthermore, the antibody titre was evaluated in vaccinated and unvaccinated students (Table 2). Unvaccinated subjects had a significantly higher antibody titre than vaccinated students (both one dose and two doses) ($p < 0.0001$), while there was no significant difference in the antibody titre between those with one dose and those with two doses of the vaccine; however, after two doses the titre was approximately 20% higher.

Finally, the interval between the antibody titre analysis and the vaccine dose when vaccinated once was 8.8 ± 3.1 years, and between the antibody titre analysis and the second dose was 5.4 ± 1.9 years. No correlation was observed between antibody titre and the interval since vaccination (data not shown).

A fair number of individuals who were unprotected (negative or equivocal) against varicella presented for post-test vaccination

Table 1
Seroprevalence of varicella antibodies in unvaccinated and vaccinated students.

	Number	Positive	%	Equivocal	%
Unvaccinated	10 327	9869	95.6	65	0.6
Cohort born before 1980	495	468	94.5	3	0.6
Cohort born 1980–1990	4204	3878	92.2	26	0.6
Cohort born 1990–2000	5627	5422	96.4[a]	36	0.6
Vaccinated once	122	83	68.0[b]	9	7.4[c]
Cohort born before 1980	0				
Cohort born 1980–1990	7	2	28.6	1	14.3
Cohort born 1990–2000	115	81	70.4	8	7.0
Vaccinated twice	234	184	78.6[b,d]	13	5.6[b]
Cohort born before 1980	0				
Cohort born 1980–1990	33	23	69.7	6	18.2
Cohort born 1990–2000	201	161	80.1	7	3.5
All vaccinated (once or twice)	356	267	75.0	22	6.2[b]
Cohort born before 1980	0				
Cohort born 1980–1990	40	25	62.5	7	17.5
Cohort born 1990–2000	316	242	76.6	15	4.7

[a] Positive results were significantly higher ($p < 0.0001$) in this cohort compared with the 1980–1990 cohort.
[b] $p < 0.0001$ for positive results in those vaccinated once or twice versus the non-vaccinated.
[c] Equivocal results were significantly higher ($p < 0.0001$) in the vaccinated subjects than in the non-vaccinated subjects.
[d] $p = 0.0391$ for vaccinated twice versus vaccinated once.

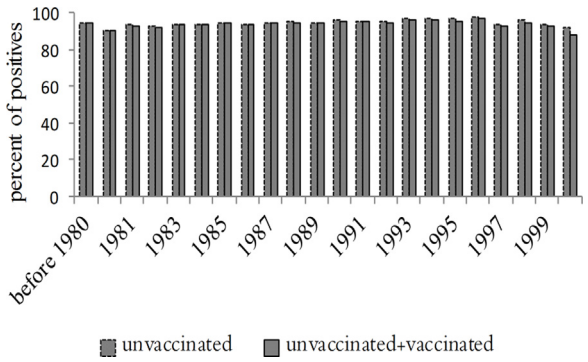

Figure 1. Seropositivity rate by date of birth in unvaccinated and vaccinated plus unvaccinated subjects.

Table 2
Varicella antibody titre in unvaccinated and vaccinated students.

	Varicella antibody titre, IU/ml			
	Number	Mean ± SD	Median	Range
Unvaccinated	10 327	1287 ± 898	1100	10–7600
Cohort born before 1980	495	1361 ± 1045	1110	50–6100
Cohort born 1980–1990	4204	1358 ± 973	1200	14–7300
Cohort born 1990–2000	5627	1227 ± 818[a,b]	1100	10–7600
Vaccinated once	122	608 ± 655[c]	343	50–2906
Cohort born before 1980	0			
Cohort born 1980–1990	7	370 ± 534	50	50–1200
Cohort born 1990–2000	115	623 ± 661	360	50–2906
Vaccinated twice	234	731 ± 832[c]	390	14–4100
Cohort born before 1980	0			
Cohort born 1980–1990	33	565 ± 671	220	50–2800
Cohort born 1990–2000	201	758 ± 854	400	14–100
All vaccinated (once or twice)	356	689 ± 777[c]	365	14–4100
Cohort born before 1980	0			
Cohort born 1980–1990	40	531 ± 647	180	50–2800
Cohort born 1990–2000	316	709 ± 791	390	14–4100

SD, standard deviation.
[a] Significantly different ($p = 0.0006$) compared with the cohort born before 1980.
[b] Significantly different ($p < 0.0001$) compared with the cohort born 1980–1990.
[c] Significantly different ($p < 0.0001$) compared with unvaccinated subjects.

(67.1%); however, only 46.6% of these were retested for the antibody titre. Overall, 85.4% seroconverted, predominantly if vaccinated twice (91.4%) when compared with a single dose (67.4%). These results are summarized in Table 3. It is important to note that no vaccinated student reported any major symptoms as a result of vaccination.

No significant differences in antibody seroprevalence according to sex or age were detected in either the unvaccinated or vaccinated (once or twice) subjects.

Discussion

Students attending courses at the Medical School of Padua University, future healthcare workers (HCWs), were evaluated for the seroprevalence of varicella antibodies. All students were born before the year 2001, i.e., before the implementation of varicella vaccination in Italy (2001). Probably for this reason, only 3.3% overall had been vaccinated (1.14% once and 2.19% twice). Most of the unvaccinated students (95.6%) showed positive antibodies, whereas vaccination did not appear as effective in inducing an antibody response (68.0% after one dose and 75.0% after two doses). In addition, the antibody levels after vaccination were found to be about a half of the levels after varicella disease.

The results are congruent with those reported in the literature, with

several studies reporting an immune coverage in different populations of between 93% and 98% (Vandersmissen et al., 2000; Trevisan et al., 2006; Trevisan et al., 2007; Tafuri et al., 2015), signifying that wild-type virus circulating in the community is sufficient to maintain a high level of herd immunity.

Approximately 70% of the negative or equivocal subjects adhered to post-test vaccination, and less than 50% of them were rechecked for their varicella antibody titre. Two doses of vaccine increased the seropositivity to over 90%. These results partially agree with previous evidence: varicella vaccine efficacy in a 10-year follow-up study was estimated to be 94.4% after one dose and 98.3% after two doses (Kuter et al., 1991). On the other hand, vaccination significantly increased the rate of equivocal results, as has been observed for measles (Trevisan et al., 2015).

According to the World Health Organization (WHO) Position Paper (2014) (WHO, 2014), one dose of vaccine reduces severe morbidity and mortality, but it is not sufficient to prevent virus circulation and outbreaks, whereas two doses are more effective in reducing the number of infected subjects and outbreaks. Furthermore, the WHO (2014) suggests that susceptible HCWs should be vaccinated with two doses of vaccine. The same opinion was expressed in the Italian National Vaccination Prevention Plan 2017–2019, which strongly suggested that HCWs be vaccinated against seven transmissible diseases including varicella. In 2017, the so-called 'Pisa card', drafted by several scientific societies during the national conference "*Medice cura te ipsum*" (Pisa, March 27–28, 2017), also suggested varicella vaccination among other recommendations.

Table 3
Post-test varicella vaccination compliance, percentage of seroconversion, and antibody titre according to one or two doses of vaccine.

Negative or equivocal		Post-test vaccinated		Re-tested after vaccine		
547 of 10 683	5.1%	367 of 547 Re-tested	67.1%	171 of 367	46.6%	
Vaccinated one dose		Vaccinated two doses				
43 of 171	25.1%	128 of 171 Re-tested	74.9%			
Positive after vaccination						Significance one vs two doses
After both		After one dose		After two doses		
146 of 171	85.4%	29 of 43 Re-tested	67.4%	117 of 128	91.4%	$p = 0.0003$
Antibody titre after vaccination						
Both doses		One dose		Two doses		Significance one vs two doses
Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	
868 ± 1031	470	849 ± 1238	200	875 ± 957	605	t = NS MW: $p = 0.134$

MW, Mann–Whitney test; NS, not significant; SD, standard deviation.

It is unclear whether vaccination can induce long-term persistence of antibodies and the significance of waning antibodies, but antibody waning has been documented not to be related to an increased risk of breakthrough disease (Kuter et al., 2004). In countries where the wild-type varicella virus is still circulating, the persistence of the antibody titre is probably related to boosting by exposure to the virus (WHO, 2014).

The critical vaccination coverage is estimated to be 90–92% and the basic reproduction rate (R_0) is estimated to be 12–13 (Anderson and May, 1990); however, R_0 was recently reduced to 4.64 in Italy (Melegaro et al., 2011), similar to that in the United Kingdom and lower than those in Belgium, Finland, and Poland.

There are further questions regarding the following findings: (1) 20% of subjects vaccinated with one dose develop varicella (Chaves et al., 2008), because the effectiveness is approximately 72–81% (Bayer et al., 2007; Seward et al., 2008). Universal routine vaccination against varicella does not appear to increase susceptibility in adults (Tafuri et al., 2014; Baxter et al., 2014), with a decrease in morbidity from 150.7 cases per 100 000 (2001–2010) to 102.6 cases per 100 000 (2010) (Trucchi et al., 2015). (2) The one-dose schedule is effective at reducing disease incidence, but it does not prevent varicella outbreaks (Fu et al., 2015), whereas the two-dose schedule appears to reduce the number, size, and duration of outbreaks (Leung et al., 2015).

One dose of vaccine is not sufficient to maintain herd immunity. Thus HCWs should all receive the two-dose vaccination (Lopez et al., 2006), and screening should be performed on this group. If the antibody titre is equivocal or negative, then vaccination is recommended when there is no documentation of vaccination or a lack evidence of past infection (CDC, 1999), and a new specimen should be submitted within 4 weeks to demonstrate seroconversion.

Negative or equivocal results after the two-dose schedule should be retested before a new booster dose, and HCWs should be advised of the signs and symptoms of infection and how to manage them appropriately according to local protocols if they develop varicella, in which case they should be temporarily removed from their charge (Russi et al., 2009). In any case, varicella breakthrough among vaccine recipients without seroconversion is typically mild, suggesting that cell-mediated immunity allows protection for vaccine recipients even in the absence of a detectable antibody response (Ampofo et al., 2002).

In conclusion, the strength of this research is in the number of subjects investigated (over 10 000), but the weakness is that the vast majority (96.7%) were unvaccinated. A correct evaluation of the vaccination efficacy is therefore entrusted to numbers that are too small to draw adequate conclusions. Further studies are necessary and will be performed once we are able to analyse medical students born after the implementation of varicella vaccination in Italy. Furthermore we suggest (1) varicella screening in all HCWs, especially if they have been vaccinated, and (2) the necessity to check the possibility of waning of antibodies in vaccinated subjects at least 10 years after vaccination.

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Conflict of interest

The authors declare no conflict of interest.

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