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Seroprevalence of diphtheria and measles antibodies and their association with demographics, self-reported immunity, and immunogenetic factors in healthcare workers in Latvia

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ABSTRACT

Latvia is among European countries with outbreaks of diphtheria and measles. Healthcare workers (HCW) are exposed to infections and can transmit them to unvaccinated patients. We assessed the seroprevalence of antibodies against diphtheria and measles and their association with demographics, self-reported immunity, the presence of the *HLA-B27* allele, and level of interferon regulatory factor 5 (IRF5) in Latvian HCW. Anti-diphtheria and anti-measles IgG antibodies and the level of IRF5 in serum were tested by enzyme immunoassay. The presence of the *HLA-B27* allele was detected by a real-time polymerase chain reaction. The study involved 176 HCW, including 29% doctors and 44% nurses. Among HCW, 95.5% were seropositive for diphtheria. However, only 65.9% had full seroprotection against it. The seronegativity for measles (21.6%) was higher than for diphtheria (4.5%) without differences in gender and medical staff groups. Older age was associated with waning immunity against diphtheria and a higher rate of seropositivity for measles. Considered immunogenetic factors did not affect the level of antibodies, and variability of the level of IRF5 in serum can reflect ageing processes. Self-reported vaccination status had a low informative value regarding full seroprotection against diphtheria and seropositivity for measles indicating the need for pre-vaccination IgG screening in planning the booster vaccination.

Introduction

Despite possibilities for controlling vaccine-preventable diseases (VPDs), they return to Europe and the United States [1]. Latvia is among European countries with diphtheria outbreaks during the last 30 years. From 1994 to 2014, 1,515 diphtheria cases were reported (average annual incidence of 3.2 /100,000), with the highest incidence in age groups 5–19 and 40–49 years. Most cases occurred in unvaccinated adults, and a supplementary immunization campaign for this age group was initiated in 1995 [2]. Although, from 2006 to 2010, 61% of all diphtheria cases in EU countries were registered in Latvia. Measles forms another issue of concern in our country. Three outbakes have been registered in Latvia since 1992, with 21 cases in 1992 (9.3/100,000 population), 36 cases in 2014, and 25 cases in 2018 [3]. Moreover, in the 2014 outbreak, one-third of measles cases were identified in healthcare workers (HCW). HCW contact to the patients, infectious materials, contaminated medical supplies, equipment, surfaces, or air. They may be at higher risk of acquiring and spreading contact-transmissible and respiratory infections due to the nature of their work than community-based working adults [4]. Detecting seronegativity against VPDs can identify HCW with a higher risk for these infections and reduce the risk of nosocomial outbreaks [5].

Previous studies have identified significant problems regarding seroprotection against diphtheria and measles. There is insufficient seroprotection against diphtheria in older age cohorts in most EU countries [6], increasing seronegativity for measles in the younger population [7–10], a poor correlation between self-reported immunity and seropositivity [9,11], and individual variability in response to vaccines [12]. All these tendencies can affect the seroprevalence in HCW. Our study aimed to assess the seroprevalence of diphtheria- and measles-specific IgG antibodies and their association with demographic factors and self-reported immunity in HCW

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in Latvia. An additional issue of our study was the investigation of associations of the levels of specific antibodies with two immunogenetic factors – the presence of the *HLA-B27* allele and the serum level of interferon regulatory factor 5 (IRF5).

Production of sufficient antibody after vaccination depends on a complex of molecular interactions involving the presentation of vaccine epitopes to T-cell receptors through Human Leucocyte Antigens (HLA) molecules on antigen-presenting cells' surfaces, the maturation of naïve $CD4^+$ T-cells to Type 2 T helper cells (Th_2), and the proliferation of B-cells and their differentiation to antibody-secreting plasma cells supported by Th_2 [12–14]. Studies showed the relationship between HLA profile and humoral response to measles vaccines [15,16] and diphtheria vaccine [17]. Some allelic groups, associated with lower humoral response, are also commonly associated with other diseases, which indicate a contribution of genetic factors to the immune responses to diseases, and may have a more general adverse immune effect [15]. For the present study, we have selected the *HLA-B27* allele, which associates with a broad spectrum of inflammatory diseases, including ankylosing spondylitis, reactive arthritis, inflammatory bowel disease, and psoriatic arthritis. The mechanism by which *HLA-B27* causes disease and impair immune response is not fully recognized [18]. Insufficient seroprotection against VPDs in patients with rheumatic diseases is often related to immunosuppressive therapy [19,20]. However, there are studies [21,22] reporting a lower humoral response to some vaccines without any association with the use of prednisolone and methotrexate, age, sex, disease duration, and the level of inflammation [21]. Therefore, it is possible to expect that *HLA-B27* affects the level of specific antibodies.

IRF5 is an intracellular protein and a transcription factor that regulates the expression of different pro-inflammatory cytokines, such as Type I interferons, interleukin-6 (IL-6), IL-17, IL-23, tumor necrosis factor-α (TNF-α), and chemokines [23] and drives proliferation and differentiation of B-cells to specialized antibody-secreting cells [24]. In addition, the interaction between *IRF5* and other genes could enhance the antibody responses to microbial vaccines [25]. Similar to *HLA-B27*, *IRF5* also contributes to many inflammatory and autoimmune diseases [26,27]. Based on a recently confirmed extracellular presence of IRF5 [28], we tested the hypothesis that the level of IRF5 in serum can affect the level of specific antibodies against VPDs.

Methods

Study sample

The cross-sectional study was performed in 2020. A convenient sample included HCW from different hospitals in Latvia. HCW were defined as a totality of individuals working in health care settings [5]. We divided HCW into three main categories as doctors, nurses, who have direct contact with patients, and other HCW, who have direct or indirect contact with patients, including technical, cleaning, and administrative staff. All participants were without documented *HLA-B27* associated inflammatory diseases.

The study was approved by the Ethics Committee of Rīga Stradiņš University (No. 6–3/42). The study was performed in accordance with the Declaration of Helsinki. All participants signed the informed consent form.

Data collection

Data were collected with a structured interview on demographics, vaccination status against measles and diphtheria, history of both infections, and *HLA-B27* associated inflammatory diseases. Self-reported information was based on interviews and vaccination cards, if available. Blood samples were obtained from all participants and stored at −80 °C until analysis.

Laboratory tests

IgG antibodies against diphtheria toxin were detected in serum by enzyme-linked immunosorbent assay (ELISA, Euroimmun, Germany). The protective level of antibodies against diphtheria was defined as antibody level ≥ 0.01 international units per ml (IU/ml) [29]. Additionally, the levels of antibodies formed three categories based on international cut-off standards [30]. The full seroprotection for diphtheria was defined as antibody levels ≥ 0.1 IU/ml, and levels of 0.01–0.09 IU/ml were considered as basic clinical protection against diphtheria. Antibody levels < 0.01 IU/ml were classified as seronegativity.

Measles IgG antibodies were detected by indirect sandwich chemiluminescence immunoassay (CLIA, LIAISON, DiaSorin S.p.A., Italy, test specificity: 97.4%, 95% confidence interval: 94.1–99.2%, and sensitivity: 94.7%, 95% confidence interval: 91.7–96.9%) using an automated analyzer. Accordantly the manufacturer, the cut-off value of LIAISON Measles IgG immunoassay equates to 175 mIU/mL WHO Third International Standard for Anti-Measles, NIBSC code: 97/648. We have applied the cut-off value for anti-measles IgG, defined in assay instruction, which concurs with the cut-off used in recent studies on seroprevalence [9,31,32]. Therefore, the seropositivity for measles was defined as antibody level ≥ 16.5 arbitrary units (AU/ml). The seronegativity for measles was < 13.5 AU/ml. The antibodies level 13.5–16.4 AU/ml was defined as equivocal.

HLA-B27 allele was detected by real-time polymerase chain reaction (RT-PCR) using a commercially available kit (DNA-technology, Russia).

IRF5 was measured in serum using sandwich ELISA (Nordic BioSite, Sweden) according to manufactured instruction. The sensitivity of test was 0.094 ng/ml, and detection range 0.156–10.0 ng/ml.

Statistical analysis

The relationships of the seroprotection status against diphtheria and seropositivity for measles with categorical variables were assessed with a chi-square test. The positive predictive value (PPV) and the negative predictive value (NPV) for the self-reported vaccination were calculated after the exclusion of cases with undefined status, using serological tests as a gold standard. Spearman's rank correlation coefficient was applied for assessing the relationships among the level of antibodies, IRF5, and age. These statistical analyses were performed using the IBM SPSS Statistics 22.0 for Windows. Path analysis assessed a complex effect of demographic and immunogenetic factors on the level of antibodies against diphtheria and measles. It was conducted using 'lavaan' (0.6–8) statistical package for R [33].

Results

The participants were 176 HCW aged 21 to 78 (M = 44.4, SD = 13.3 years), and 160 (91%) of them were females. Among the participants, 19 (10.8%) were 21–26 years, 32 (18.2%) were 26–35 years, 33 (18.8%) were 36–45 years, 53 (30.1%) were 46–55 years, 34 (19.3%) were 56–65 years, and 5 (2.8%) were older than 65 years. Participants were 51 doctors (29%), 77 nurses (44%), and 48 other workers (27%), including technical and administrative personnel.

HLA-B27 positive were 23 (13%) of HCW while negative was 151 (86%), and two cases were missed. The mean level of IRF5 in serum was 1.15 ± 0.70 ng/ml.

Among HCW, 168 (95.5%) participants had anti-diphtheria IgG antibodies at the level above 0.01 IU/ml, and 116 (65.9%) had the full seroprotection against diphtheria (IgG ≥ 0.1 IU/ml). For measles, 136 (77.3%) HCW had the positive level of antibodies (≥16.5 AU/ml), and 2 HCW (1.1%) had the equivocal level. Altogether, 84 (47.7%) of HCW had full seroprotection against diphtheria and seropositivity for measles, but 8 (4.5%), 38 (21.6%), and 8 (4.5%) were seronegative for diphtheria, measles, or both infections, respectively. Table 1 presents data reflecting the objective level of antibodies against diphtheria and measles and self-reported information about vaccination status or disease history.

Surveying HCW showed that 165 (93.8%) reported vaccination against diphtheria and 102 (58.0%) vaccination against measles. The history of diphtheria or measles was reported by 2 (1.1%) and 30 (17.0%) HCW, respectively. Unclear vaccination or disease history status was reported by 5 (2.8%) for diphtheria and 53 (30.1%) for measles. Among HCW with unclear diphtheria vaccination or disease history, there were no HCW with seronegativity for diphtheria. Contrary, among HCW with unclear measles vaccination or disease history, 9 (23.7%) had seronegativity for measles.

For diphtheria, the comparison of self-reported and seroprotection statuses demonstrated that PPV and NPV were 95.8% and 16.7% for basic clinical protection and 66.7% and 66.7% for full seroprotection, respectively. For measles, the comparison of statuses demonstrated that the PPV and NPV were 72.5% and 4.8% for positive and equivocal levels and 71.6% and 4.8% for positive only.

Considering the significance of full protection for HCW, further analyses were conducted for full seroprotection for diphtheria (≥0.10 IU/ml) and seropositivity for measles (≥16.5 AU/ml). The full seroprotection status against diphtheria (Table 2) did not show significant relationships with staff group, gender, self-reported immunity, or the presence of *HLA-B27*. Seropositivity for measles was associated with the self-reported vaccination status and did not associate with other factors. The HCW reporting no vaccination demonstrated the highest proportion of full seropositivity. It reflects findings on NPV, indicating that self-reported unvaccinated status has a low informative value regarding measles.

Following correlation analysis (Table 3) revealed a negative correlation of age with the level of antibodies against diphtheria and a positive correlation with the level of antibodies against measles. Age also positively correlated with the level of IRF5.

Fig. 1 reflects the distribution of the full seroprotection against diphtheria and seropositivity for measles in different age groups of health care workers.

More than two-thirds of HCW with full seroprotection against diphtheria were in age groups under 46 years. In age groups over 55, full seroprotection against diphtheria was detected in one-third of HCW. In contrast, the seropositivity for measles was the highest in HCW older than 55. Some immunity gap (only 53% of HCW with seropositivity for measles) was observed in 26–35 years.

A more complex statistical model of path-analysis assessed the effects of a set of independent variables – age, sex, and presence of *HLA-B27* – on two dependent variables – anti-diphtheria IgG and anti-measles IgG – simultaneously (Fig. 2). In addition, the observed correlation with age allowed us to consider IRF5 as a possible immunological mediator of the effects of genetic and demographic factors.

The results confirmed that age negatively predicted the level of antibodies against diphtheria and positively predicted those against measles. The positive effect of age on the level of IRF5 was only marginal. The effects of other variables, the covariance between antibodies, and the mediating role of IRF5 were not significant. The explained variance was relatively higher for anti-measles IgG (26%) than for anti-diphtheria IgG (16%).

Discussion

Seroprevalence of diphtheria and measles in HCW

Despite a high percent of HCW (95.5%) with protective antibodies against diphtheria [29] in our group, only 65.9% of them had the full seroprotection against it (antibodies ≥ 0.10 IU/ml). This level of antibodies can provide a more successful reduction of the rate of diphtheria [29], as it is also considered in recent studies [9,11,34,35]. The rate of the full seroprotection in our HCW group concurs with data on HCW from Catalonia (68.8%) [34], where, similarly to Latvia, booster vaccination against diphtheria in adults has started since 1995. At the same time, a study of paediatric HCW in Denmark [9] and in Finland [11] showed a higher rate of full seroprotection against diphtheria (80.5% and 89.9%, respectively) than in our study. In line with other studies [9,35], we have observed decreasing seroprotection against diphtheria in HCW older than 46 years and the highest potential susceptibility to diphtheria after 65 years. It should be noted that only 4.5% of HCW were seronegative for diphtheria. However, most HCW without immunity against diphtheria were younger than 65 years, and only in two cases were 74 and 78 years old.

This study revealed a higher seronegativity for measles (21.6%) in HCW than for diphtheria (4.5%). This level indicates insufficient herd immunity against measles in this group [36] and a need for clarifying results and additional immunization activities.

The rate of seropositivity for measles in HCW in Latvia was close to data on HCW from South Korea (73%) [37], but lower than in HCW from France (91.7%–93%) [67,38] and Denmark (90.3%) [9], having no mandatory vaccination against measles for this group [39], and HCW from Finland (81.5%) [11] and two other South Korean hospitals (93.1%) [32]. Similar to other studies [7–11], our results revealed the immunity gap for measles in the age of 26–35 years. It can be explained by waning vaccine-induced immunity twenty years after the last measles vaccine dose administration

Table 1
Levels of antibodies against diphtheria and measles, self-reported vaccination, and disease history in healthcare workers.

Levels of antibodies	Total	Self-reported vaccination			Self-reported disease		
		Yes	No	Unclear	Yes	No	Unclear
Anti-diphtheria IgG, IU/ml							
Positive (≥0.10)	116 (65.9%)	110 (94.8%)	2 (1.7%)	4 (3.4%)	1 (0.9%)	112 (96.6%)	3 (2.6%)
Basic (0.01–0.09)	52 (29.5%)	48 (92.3%)	3 (5.8%)	1 (1.9%)	1 (1.9%)	49 (94.2%)	2 (3.8%)
Negative (<0.01)	8 (4.5%)	7 (87.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	8 (100.0%)	0 (0.0%)
Total	176 (100%)	165 (93.8%)	6 (3.4%)	5 (2.8%)	2 (1.1%)	169 (96.0%)	5 (2.8%)
Anti-measles IgG, AU/ml							
Positive (≥16.5)	136 (77.3%)	73 (53.7%)	20 (14.7%)	43 (31.6%)	26 (19.1%)	66 (48.5%)	44 (32.4%)
Equivocal (13.5–16.4)	2 (1.1%)	1 (50.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (50.0%)	1 (50.0%)
Negative (<13.5)	38 (21.6%)	28 (73.2%)	1 (2.6%)	9 (23.7%)	4 (10.5%)	26 (68.4%)	8 (21.1%)
Total	176 (100%)	102 (58.0%)	21 (11.9%)	53 (30.1%)	30 (17.0%)	93 (52.9%)	53 (30.1%)

Table 2
Associations of the levels of antibodies against diphtheria and measles with demographics, self-reports, and *HLA-B27* in healthcare workers.

	Anti-diphtheria IgG		χ^2	**Anti-measles IgG**		χ^2
	<0.10 IU/ml	≥0.10 IU/ml		<16.5 AU/ml	≥16.5 AU/ml	
Gender			3.65			1.05
Female	58 (36.3%)	102 (63.7%)		38 (23.8%)	122 (76.3%)	
Male	2 (12.5%)	14 (87.5%)		2 (12.5%)	14 (87.5%)	
Staff group			0.24			2.35
Doctors	18 (35.3%)	33 (64.7%)		8 (15.7%)	43 (84.3%)	
Nurses	27 (35.1%)	50 (64.9%)		21 (27.3%)	56 (72.7%)	
Other	15 (31.3%)	33 (68.8%)		11 (22.9%)	37 (77.1%)	
Self-reported vaccination			3.32			6.20*
Yes	55 (33.3%)	110 (66.7%)		29 (28.4%)	73 (71.6%)	
No	4 (66.7%)	2 (33.3%)		1 (4.8%)	20 (95.2%)	
Unclear	1 (20.0%)	4 (80.0%)		10 (18.9%)	43 (81.1%)	
Self-reported disease			0.31			4.61
Yes	1 (50.0%)	1 (50.0%)		4 (13.3%)	26 (86.7%)	
No	57 (33.7%)	112 (66.3%)		27 (29.0%)	66 (71.0%)	
Unclear	2 (40.0%)	3 (60.0%)		9 (17.0%)	44 (83.0%)	
HLA-B27			1.75			0.01
Yes	5 (26.1%)	18 (73.9%)		34 (22.5%)	117 (77.5%)	
No	54 (37.1%)	97 (62.9%)		5 (21.7%)	18 (78.3%)	

* $p < 0.05$.

Table 3
Spearman's rank correlations among age, IRF5, and antibodies against diphtheria and measles.

Parameters	IRF5[a]	Anti-diphtheria IgG	Anti-measles IgG
Age	0.28**	−0.34***	0.51***
IRF5[a]	–	−0.11	0.10
Anti-diphtheria IgG	–	–	−0.29***

[a] n = 127.
** $p < 0.01$.
*** $p < 0.001$.

[7,8,10,31]. At the same time, naturally acquired measles can explain a higher percent of seropositive HCW in older participants than in younger ones [7,8,10].

There was no significant association between the staff group in the full seroprotection against diphtheria and seropositivity for measles that seems positive regarding the risk of transmission of respiratory infection despite differences in frequencies and duration of patient-related contacts [4].

Self-reported immunity and objective antibodies status

Self-reported vaccination status did not provide sufficient information regarding immunity to both infections. However, the prediction of the basic clinical protection against diphtheria (95.8%) was higher than for the full seroprotection (66.7%). The better coincidence between self-reported vaccination status and immunity was applicable for diphtheria than for measles because of NPV of 4.8% for the latter. These incompatibilities can reflect remembering errors or indicate possible non-responders against vaccination. In our study, about one-third of HCW did not remember their vaccination or disease history status for measles, which is higher than, for example, 20% in the Netherlands [40]. The universal record system for registering the vaccines given to each individual should be used [11] for distinguishing the effects of remembering errors and non-responders against vaccination. Additionally, a low level of NPV for measles can reflect underestimated immunity because of using enzyme immunoassay instead of the plaque reduction neutralization as the gold standard for measuring measles immunity [40].

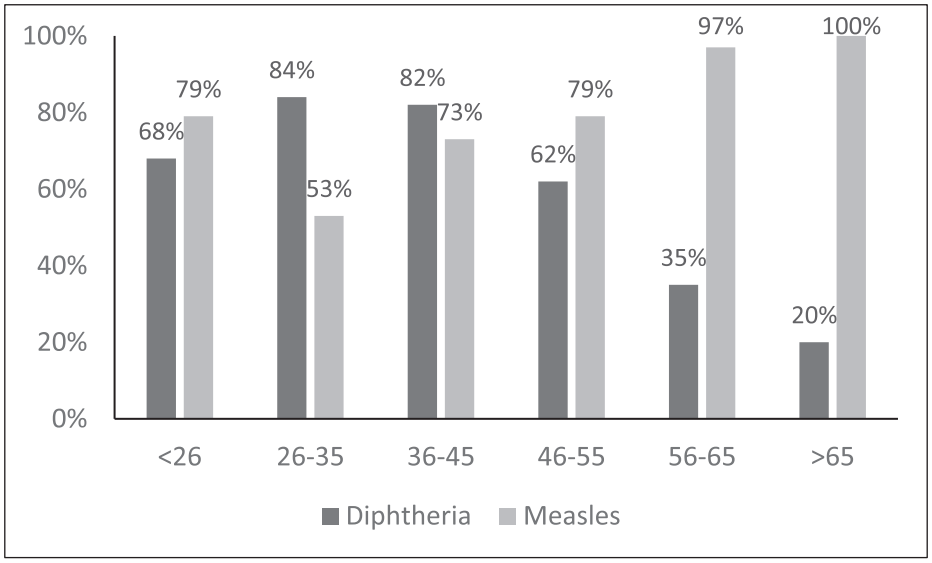

Fig. 1. Rate of full seroprotection against diphtheria and seropositivity for measles in different age groups of healthcare workers.

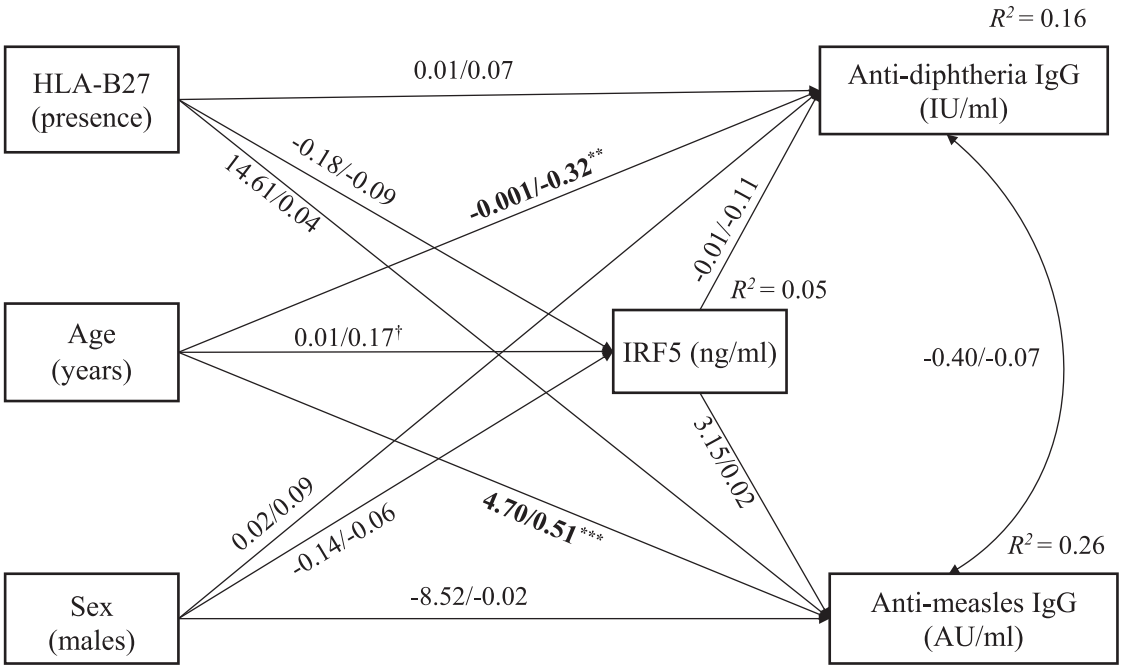

Fig. 2. Path analysis of effects of age, sex, and *HLA-B27* on anti-diphtheria and anti-measles IgG, mediated by IRF5 (n = 127). *Notes.* Coefficients include unstandardized/standardized estimates. Significant effects are highlighted in bold. *** p < 0.001. ** p < 0.01. † p < 0.10.

Our results confirmed a relatively weak association between self-reported immunity and seropositivity for measles in HCW [9,11]. It indicates that HCW operate with limited information regarding their vaccination or disease status. In addition, only half of HCW had full seroprotection against diphtheria and seropositivity for measles simultaneously. It can cause intrahospital outbreaks involving patients with chronic diseases and insufficient seroprotection against VPDs after vaccination [35]. Our findings point to the need for more attention to the protection for measles in younger and diphtheria in older HCW to close revealed immunity gaps. We recommend conducting pre-vaccination IgG screening for HCW and following booster vaccination against these VPDs in Latvia.

Immunogenetic factors and levels of antibodies

Testing the relationship between the level of antibodies against diphtheria and measles and the *HLA-B27* allele in genotype and the level of IRF5 in serum revealed no significant associations. *HLA-B27* positivity did not affect the level of antibodies against diphtheria or measles. However, previous studies reported weaker antibody responses to the diphtheria-containing vaccine in individuals with *HLA-DRB1*01* genotype [17] and the measles-containing vaccine in individuals with *HLA-DRB1*07:01, -DQA1*02:01, -DQB1*03:03* [13], *HLA-DRB1*03, -DQA1*02:01* alleles [15] or HLA homozygosity [13].

Our results indicated a positive correlation between IRF5 and age. However, the path analysis showed the only marginal significance of this relationship. Idborg et al. [28] described the extracellular presence of IRF5 detected by sandwich ELISA. They did not define the extracellular function of IRF5 but associated the high level of IRF5 in circulation with pronounced inflammation. Ageing is often associated with chronic inflammation [41,42]. Therefore, the association between ageing, IRF5, and inflammation should be investigated in further studies.

Our study involved a relatively small number of participants, limiting the generalization of the results to the HCW population in Latvia. Another limiting issue is a disbalance between females and males, which also indicates differences in the response rate and involvement in the study. Diphtheria and measles were selected based on observed outbreaks and available resources for serological investigation. Further studies should include a broader number of VPDs in a more representative sample of HCW.

Conclusions

The study revealed a higher seroprevalence for diphtheria than for measles without differences in gender and medical staff groups. Despite this, the full seroprotection against diphtheria was lower than in other seroprevalence studies in HCW. Age was the main predictor of the level of antibodies. Considered immunogenetic factors did not affect the level of antibodies, and variability of the level of IRF5 in serum can reflect ageing processes. Self-reported vaccination status had a low informative value regarding full seroprotection against diphtheria and seropositivity for measles. Insufficient knowledge of HCW about themselves forms a risk factor in managing health-related issues. We suggest the pre-vaccination IgG screening for planning booster vaccination in HCW.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Aija Leidere-Reine reports financial support was provided by European Social Fund and Latvian state budget. The study was partially funded by the project No 8.2.2.0/20/I/004 "Support for involving doctoral students in scientific research and studies".]

References

[1] Hotez P. America and Europe's new normal: the return of vaccine-preventable diseases. Pediatr Res 2019;85(7):912–4.
[2] Kantsone I, Lucenko I, Perevoscikovs J. More than 20 years after re-emerging in the 1990s, diphtheria remains a public health problem in Latvia. Euro Surveill 2016;21(48). https://doi.org/10.2807/1560-7917.ES.2016.21.48.30414.

[3] World Health Organization (WHO). WHO vaccine-preventable diseases: monitoring system. 2020 global summary. Diphtheria and measles reported cases in Latvia. Geneva: WHO. [Accessed 06 Sept 2021]. Available from: https://apps.who.int/immunization_monitoring/globalsummary/countries?countrycriteria%5Bcountry%5D%5B%5D=LVA&commit=OK.

[4] Jiang L, Ng IHL, Hou Y, Li D, Tan LWL, Ho HJA, et al. Infectious disease transmission: survey of contacts between hospital-based healthcare workers and working adults from the general population. J Hosp Infect 2018;98(4):404–11.

[5] Shefer A, Atkinson W, Friedman C, Kuhar DT, Mootrey G, Bialek SR, et al. Immunization of Health-Care Personnel: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60(7):1–45.

[6] Berbers G, van Gageldonk P, Kassteele JVd, Wiedermann U, Desombere I, Dalby T, et al. Circulation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. Nat Commun 2021;12(1). https://doi.org/10.1038/s41467-021-23114-y.

[7] Botelho-Nevers E, Cassir N, Minodier P, Laporte R, Gautret P, Badiaga S, et al. Measles among healthcare workers: a potential for nosocomial outbreaks. Euro Surveill 2011;16(2). https://doi.org/10.2807/ese.16.02.19764-en.

[8] Kang HJ, Han YW, Kim SJ, Kim Y-J, Kim A-R, Kim JA, et al. An increasing, potentially measles-susceptible population over time after vaccination in Korea. Vaccine 2017;35(33):4126–32.

[9] von Linstow M-L, Yde Nielsen A, Kirkby N, Eltvedt A, Nordmann WT, Bybeck Nielsen A, et al. Immunity to vaccine-preventable diseases among paediatric healthcare workers in Denmark, 2019. Euro Surveill 2021;26(17). pii=2001167.

[10] Smetana J, Chlibek R, Hanovcova I, Sosovickova R, Smetanova L, Gal P, et al. Decreasing Seroprevalence of Measles Antibodies after Vaccination – Possible Gap in Measles Protection in Adults in the Czech Republic. PLoS ONE 2017;12(1):e0170257. https://doi.org/10.1371/journal. pone.0170257.

[11] Koivisto K, Puhakka L, Lappalainen M, Blomqvist S, Saxén H, Nieminen T. Immunity against vaccine-preventable diseases in Finnish pediatric healthcare workers in 2015. Vaccine 2017;35(12):1608–14.

[12] Zimmermann P, Curtis N. Factors that influence the immune response to vaccination. Clin Microbiol Rev 2019;32:e00084–e118.

[13] Haralambieva IH, Ovsyannikova IG, Pankratz VS, Kennedy RB, Jacobson RM, Poland GA. The genetic basis for interindividual immune response variation to measles vaccine: New understanding and new vaccine approaches. Expert Rev Vacc 2013;12(1):57–70.

[14] Linnik JE, Egli A. Impact of host genetic polymorphisms on vaccine induced antibody response. Human Vacc Immunotherapeut 2016;12(4):907–15.

[15] Poland GA, Ovsyannikova IG, Jacobson RM, Vierkant RA, Jacobsen SJ, Pankratz VS, et al. Identification of an association between HLA class II alleles and low antibody levels after measles immunization. Vaccine 2001;20(3-4):430–8.

[16] Ovsyannikova IG, Shane Pankratz V, Vierkant RA, Jacobson RM, Poland GA. Consistency of HLA associations between two independent measles vaccine cohorts: A replication study. Vaccine 2012;30(12):2146–52.

[17] Ferlito C, Biselli R, Mariotti S, von Hunolstein C, Teloni R, Ralli L, et al. Tetanus-diphtheria vaccination in adults: the long-term persistence of antibodies is not dependent on polyclonal B-cell activation and the defective response to diphtheria toxoid re-vaccination is associated to HLA-DRB1*01. Vaccine 2018;36(45):6718–25.

[18] Bowness P. HLA-B27. Annu Rev Immunol 2015;33(1):29–48.

[19] Hertzell KB, Pauksens K, Rombo L, Knight A, Vene S, Askling HH. Tick-borne encephalitis (TBE) vaccine to medically immunosuppressed patients with rheumatoid arthritis: A prospective, open-label, multi-centre study. Vaccine 2016;34(5):650–5.

[20] Rondaan C, Furer V, Heijstek MW, Agmon-Levin N, Bijl M, Breedveld FC, et al. Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations. RMD Open 2019;5(2):e001035. https://doi.org/10.1136/rmdopen-2019-001035.

[21] Elkayam O, Amir S, Mendelson E, Schwaber M, Grotto I, Wollman J, et al. Efficacy and Safety of Vaccination Against Pandemic 2009 Influenza A (H1N1) Virus Among Patients With Rheumatic Diseases. Arthritis Care Res 2011;63(7):1062–7.

[22] Heijstek MW, van Gageldonk PGM, Berbers GAM, Wulffraat NM. Differences in persistence of measles, mumps, rubella, diphtheria and tetanus antibodies between children with rheumatic disease and healthy controls: a retrospective cross-sectional study. Ann Rheum Dis 2012;71(6):948–54.

[23] Guo L, Hao R, Tian F, An N, Wang K. Interferon regulatory factor 5 (IRF5) regulates the expression of matrix metalloproteinase-3 (MMP-3) in human chondrocytes. Int Immunopharmacol 2018;55:231–6.

[24] De S, Zhang B, Shih T, Singh S, Winkler A, Donnelly R, et al. B Cell-Intrinsic Role for IRF5 in TLR9/BCR-Induced Human B Cell Activation, Proliferation, and Plasmablast Differentiation. Front Immunol 2018;8. https://doi.org/10.3389/fimmu.2017.01938.

[25] Cui C, Wang S, Lu W, Wang Y, Li J, Qu K, et al. The adjuvanticity of manganese for microbial vaccines via activating the IRF5 signaling pathway. Biochem Pharmacol 2021;192:114720. https://doi.org/10.1016/j.bcp.2021.114720.

[26] Almuttaqi H, Udalova IA. Advances and challenges in targeting IRF5, a key regulator of inflammation. The FEBS Journal 2019;286(9):1624–37.

[27] Yang Y, Zhang C, Jing D, He H, Li X, Wang Y, et al. IRF5 Acts as a Potential Therapeutic Marker in Inflammatory Bowel Diseases. Inflammat Bowel Dis 2021;27(3):407–17.

[28] Idborg H, Zandian A, Ossipova E, Wigren E, Preger C, Mobarrez F, et al. Circulating Levels of Interferon Regulatory Factor-5 Associates With Subgroups of Systemic Lupus Erythematosus Patients. Front Immunol 2019;10:1029.

[29] Ipsen J. Circulating antitoxin at the onset of diphtheria in 425 patients. J Immunol 1946;54:325–47.

[30] World Health Organization. The immunological basis for immunisation. Diphtheria. Update 2009. [Accessed 10 Jan 2021]. Available from: http://apps.who.int/iris/bitstream/handle/10665/44094/9789241597869_eng.pdf?sequence=1.

[31] Bianchi FP, Stefanizzi P, De Nitto S, Larocca AMV, Germinario C, Tafuri S. Long-term immunogenicity of Measles vaccine: An Italian retrospective cohort study. J Infect Dis 2020;221(5):721–8.

[32] Kwak YG, Song JE, Oh G-B, Jeong IH, Cho CR, Kim N, et al. Comparison of the seroprevalence of measles antibodies among healthcare workers in two Korean hospitals in 2019. Infect Chemotherapy 2020;52(1):93. https://doi.org/10.3947/ic.2020.52.1.93.

[33] Rosseel Y. lavaan: An R package for structural equation modeling. J Stat Softw 2012;48(2):1–36. https://doi.org/10.18637/jss.v048.i02.

[34] Esteve M, Carreras R, Casas I, Peña P, Guixeras A, Torrecillas S, et al. The immune status against tetanus and diphtheria in healthcare workers in Catalonia. Vaccine 2020;38(12):2646–50.

[35] Boey L, Bosmans E, Ferreira LB, Heyvaert N, Nelen M, Smans L, et al. Seroprevalence of Antibodies against Diphtheria, Tetanus and Pertussis in Adult At-Risk Patients. Vaccines 2021;9(1):18. https://doi.org/10.3390/vaccines9010018.

[36] Plans P. Prevalence of antibodies associated with herd immunity: A new indicator to evaluate the establishment of herd immunity and to decide immunization strategies. Med Decis Making 2010;30(4):438–43.

[37] Jung J, Kim SK, Kwak SH, Hong MJ, Kim SH. Seroprevalence of measles in healthcare workers in South Korea. Infect Chemotherapy 2019;51(1):58–61.

[38] Freund R, Krivine A, Prévost V, Cantin D, Aslangul E, Avril M-F, et al. Measles immunity and measles vaccine acceptance among healthcare workers in Paris, France. J Hospital Infect 2013;84(1):38–43.

[39] Maltezou HC, Botelho-Nevers E, Brantsæter AB, Carlsson R-M, Heininger U, Hübschen JM, et al. Vaccination of healthcare personnel in Europe: Update to current policies. Vaccine 2019;37(52):7576–84.

[40] Dorigo-Zetsma JW, Leverstein-van Hall MA, Vreeswijk J, de Vries JJC, Vossen ACTM, ten Hulscher HI, et al. Immune status of health care workers to measles virus: evaluation of protective titers in four measles IgG EIAs. J Clin Virol 2015;69:214–8.

[41] Pawelec G, Goldeck D, Derhovanessian E. Inflammation, ageing and chronic disease. Curr Opin Immunol 2014;29:23–8.

[42] Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol 2018;15(9):505–22.