Journal of Microbiology, Immunology and Infection 56 (2023) 274—281

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Seroprevalence of varicella-zoster virus antibody and immunogenicity of live attenuated varicella vaccine in healthcare workers in Taiwan

Chen Hui Chong [a], Chun-Eng Liu [a,b], Yin-Yee Leong [c], Siang-Ying Liao [b], Huei-Wen Lai [b], Yu-Lin Lee [a,b,*]

[a] *Department of Infectious Diseases, Changhua Christian Hospital, Changhua, Taiwan*
[b] *Department of Infection Control, Changhua Christian Hospital, Changhua, Taiwan*
[c] *Department of Risk Management and Insurance, Feng Chia University, Taichung, Taiwan*

Received 5 August 2022; received in revised form 24 August 2022; accepted 23 September 2022
Available online 3 October 2022

KEYWORDS
Chickenpox;
Vaccination;
Seroresponse;
Seroconversion;
Seroreversion;
Nosocomial infection

Abstract *Background:* Healthcare workers (HCWs) without evidence of immunity to varicella-zoster virus (VZV) are recommended to undergo varicella vaccination. Immunogenicity of live attenuated varicella vaccine has rarely been investigated among HCWs in Taiwan.
Methods: Anti-VZV immunoglobulin G (IgG) titer was checked for all HCWs at Changhua Christian Hospital from 2011 to 2017. One-dose and two-dose (separated by 4—8 weeks) vaccines were administered to HCWs with equivocal and negative anti-varicella IgG results, respectively. Follow-up anti-VZV IgG was determined at least 4 weeks after completion of vaccination. Factors associated with seroconversion to varicella vaccination were analyzed.
Results: Among 2406 included HCWs, the anti-VZV IgG serostatus was tested positive, equivocal and negative in 1924 (79.9%), 117 (4.9%) and 365 (15.2%), respectively. The seroprevalence had decreased from 88.0% (235/267) in 2011 to 72.2% (270/374) in 2017 (p for trend <0.05). A total of 67.8% (327/482) HCWs completed scheduled vaccination and serological follow-up. The seroconversion rates for HCWs with baseline equivocal and negative anti-VZV IgG results were 100% (80/80) and 79.4% (196/247) after one- and two-dose vaccination, respectively. In multivariate analysis, obesity (adjusted odds ratio, 0.308; 95% confidence interval [CI], 0.11—0.94, $p = 0.039$) was the only factor statistically significantly associated with seroconversion to vaccination.
Conclusion: Decreasing trends of seroprevalence of VZV were observed among HCWs from 2011 to 2017. HCWs who were obese were less likely to respond to varicella vaccination.

* Corresponding author. Department of Infectious Diseases, Changhua Christian Hospital, No.135, Nanxiao St., Changhua City, Changhua County 500, Taiwan. Fax: +886 4 7232942.
E-mail address: leeyulin@gmail.com (Y.-L. Lee).

https://doi.org/10.1016/j.jmii.2022.09.005

Introduction

Varicella (chickenpox) is a highly contagious illness caused by the varicella-zoster virus (VZV). The infection may occur after direct contact to blisters, saliva or mucus of an infected person and transmission could also occur through airborne and droplet.[1,2] Varicella occurs predominantly in childhood and most symptoms are usually mild and self-limited, including vesicular exanthem accompanied by fever and malaise.[3] In contrast, chickenpox tends to be more severe in susceptible adults, and serious complications including neurological complications, bacterial infections, disseminated varicella and varicella pneumonia may occur and could be life-threatening.[4] Healthcare workers (HCWs) are at risk of varicella infection by airborne transmission or direct contact with VZV-infected patients in the hospital environment, which could potentially cause a nosocomial outbreak.[5,6] Therefore, the Advisory Committee on Immunization Practices (ACIP) in the United States recommends that health care institutions ensure that all HCWs have evidence of immunity to varicella.[7]

In Taiwan, a live attenuated varicella vaccine from Oka strain was first introduced in July 1997. However, it was not until January 2004 that a public free immunization program was implemented to all children aged 1 year or older. With high effectiveness of varicella vaccination (97%—100%) for preventing severe varicella, the public varicella vaccination program has led to a 75—80% decline in the incidence of varicella among children in surveillance investigations between 2000 and 2008.[8,9] Most of the HCWs in Taiwan were born before the implementation of childhood varicella vaccination program and their immunity to VZV had not been well studied. In addition, a previous study conducted by Wu et al. showed poor correlation between presence of protective VZV IgG and positive recall of previous history of varicella infection and vaccination.[10]

In this surveillance study, we aimed to investigate the trends of seroprevalence of VZV among HCWs during the health examinations on entry into workforce at the study hospital. Serological responses to varicella vaccination was investigated among all VZV-seronegative HCWs.

Methods

Study population

At Changhua Christian Hospital, a tertiary-care hospital with 1421 beds in central Taiwan, we included 2406 HCWs who underwent physical check-up before entering into workforce from August 2011 to July 2017. A standardized case record form was used to collect data including age, gender, occupation, chickenpox history, varicella vaccination history, baseline anti-VZV IgG, date of vaccination, follow-up anti-VZV IgG, height, weight, and biochemical laboratory data. The types of employment were categorized into doctor, nurse and others, the latter including paramedic, interns, administrative, and non-clinical workers.

Seroprevalence of VZV among HCWs was estimated according to the first serological result of each employee. Age compositions over the years were analyzed by Chi-square test of homogeneity to verify whether there was difference in age compositions over years and its influence on seroprevalence trend. The seroprevalence result was also compared to that of previous cohort published by Wu et al., in 2008.[10]

Determination of VZV IgG

Determination of anti-VZV IgG were performed with the use of BioPlex 2200 MMRV IgG kit (Bio-Rad Laboratories, Hercules, CA) on the BioPlex 2200 analyzer. The assay had been validated to correlate well with the sensitive VaccZyme gpEIA method, using the WHO international standard.[11,12] It has been approved by the U.S. FDA as a qualitative method showing positive, negative, or equivocal results.[13] The interpretive criteria were established by the manufacturer, and the results were defined as Negative ($\leq$0.8 antibody index (AI)), Equivocal (0.9—1.0 AI), and Positive ($\geq$1.1 AI). Both equivocal and negative results of anti-VZV IgG were defined as seronegative in the present study.

Vaccination and determination of serological response to vaccination

VARIVAX ® (Merck) is a live attenuated OKA/Merck strain with 1350 PFUs (plaque-forming units) and 0.5 mL per dose was injected subcutaneously for VZV seronegative HCWs. During a shortage of VARIVAX vaccine, VARILRIX ® (GSK), a live attenuated OKA/SmithKline Beecham strain with 0.5 mL per dose ($>10^{3.3}$ PFUs) was used as a substitute. Both monovalent vaccines are interchangeable with one another as immunogenicity and safety are well established and have been extensively reviewed.[14,15] In our study, a single dose of vaccine was provided for HCWs with equivocal anti-VZV IgG, and a second dose was provided if the follow-up anti-VZV IgG four weeks after the 1st dose was not positive. On the other hand, two doses, separated by four to eight weeks, were administered for all HCWs testing negative for anti-VZV IgG (Fig. 1).

Follow-up anti-VZV IgG titer was required for HCWs with equivocal results at baseline after receiving the first dose of vaccine, to determine the necessity to receive the second dose. For HCWs who had received 2 doses of vaccine, follow-up of anti-VZV IgG was recommended four weeks after completion of vaccination, but it was not

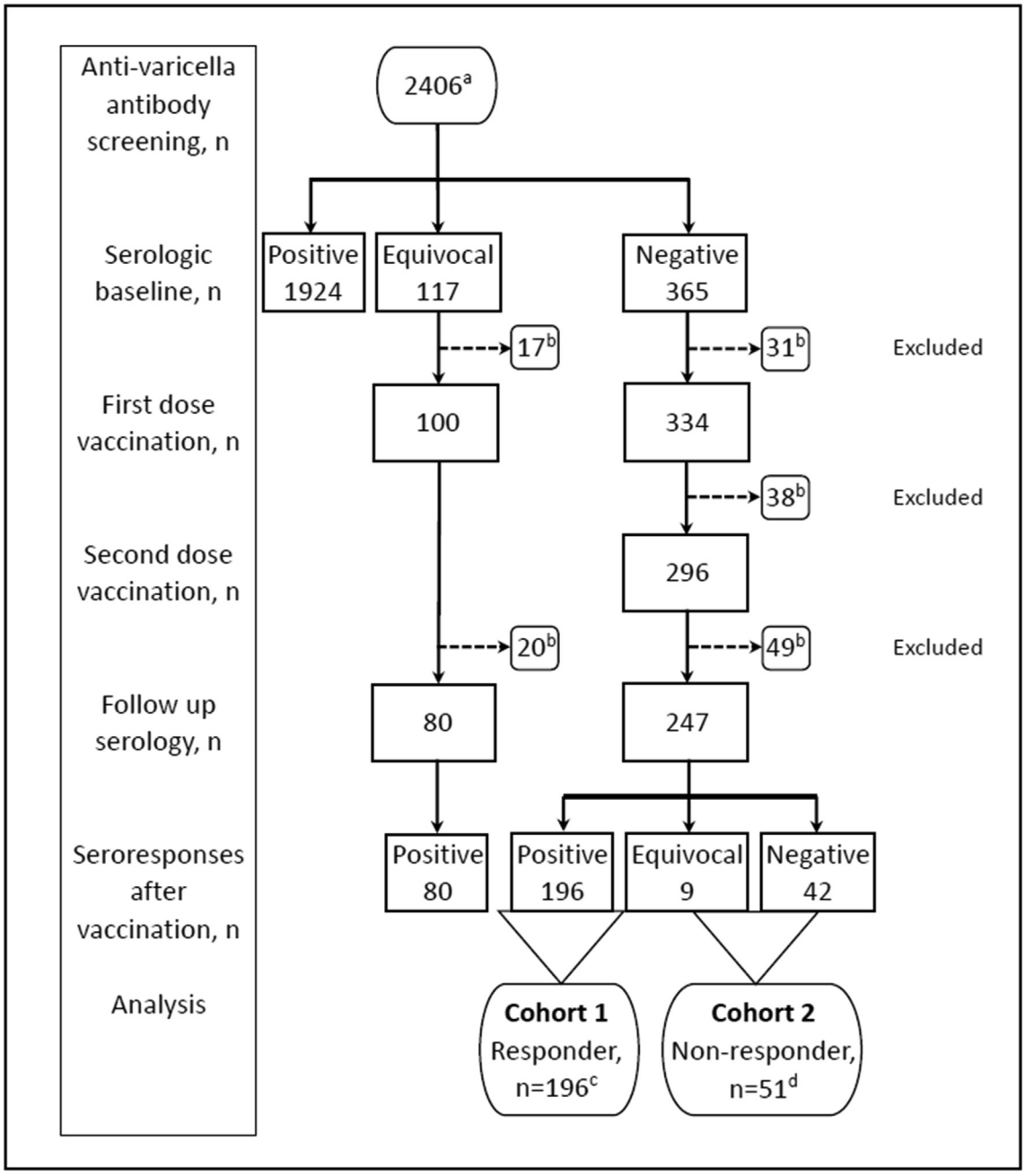

Figure 1. Study flow chart. Abbreviation: n represents number of healthcare workers. [a] represents total number of new who received blood test screening. [b] represents number of healthcare workers who loss follow-up. [c] represents number of HCWs with negative anti-VZV IgG at baseline, who gained positive serological response after varicella vaccination. [d] represents number of HCWs with negative anti-VZV IgG at baseline, who did not gain positive serological response after varicella vaccination. Arabic numeral represents number of HCWs. Dashed flow line represents exclusion of HCWs.

mandatory.[16,17] Seroresponse was defined as seroconversion from equivocal or negative serostatus at baseline to positive anti-VZV IgG results in the follow-up serological tests. A ROC curve analysis was conducted to determine the optimal cut-off level of baseline anti-VZV IgG titers (available before 2013) among HCWs with seronegativity at baseline to differentiate responders from non-responders after vaccination. Univariate and multivariate analyses were conducted to investigate factors associated with seroresponse and the variables included were gender, age, occupation (doctor, nurse and others), baseline serology (equivocal and negative), Vaccine brand (VARILRIX, and VARIVAX), and underlying diseases including obesity, hypertension, diabetes, chronic hepatitis B, hypercholesterolemia, and proteinuria. Definitions of independent variables included in univariate and multivariate analysis were as follows: obese, as having body-mass index (BMI) $\geq$30.0 kg/m^2; hypertension, systolic blood pressure

≥130 mmHg and/or diastolic blood pressure ≥80 mm Hg; diabetes, glycated hemoglobin (Hb A1c) ≥6.5%; chronic hepatitis B, reactive hepatitis B virus surface antigen (HBs Ag) for 6 months or longer; hypercholesterolemia, total cholesterol ≥200 mg/dL; and proteinuria, presence of protein in random urine samples.

Ethics

This study was approved by the Institutional Review Board (IRB) of the Changhua Christian Hospital. (IRB number: 180512). The requirement for informed consent was waived.

Statistical analysis

The statistical analyses were performed using SPSS version 19.0 and R statistical software. Categorical variables were compared with chi-square or Fisher's exact test in univariate analysis. Continuous variables were analyzed with linear regression.

Variables with *p*-value less than 0.1 in the univariate analysis were included into the multivariate model using Firth logistic regression. Odds ratio (OR) and 95% confidence interval (CI) were calculated. All statistical tests were two-tailed and $p < 0.05$ was considered statistically significant.

Results

Demographic characteristics and seroprevalence of HCWs

From 2011 to 2017, 2406 HCWs had undergone anti-VZV IgG screening, and the overall numbers of HCWs with positive, equivocal, and negative results were 1924 (80.0%), 117 (4.9%), and 365 (15.1%), respectively. The demographic and clinical characteristics are summarized in Table 1. Male HCWs had higher VZV seroprevalence than female HCWs (86.0% vs 78.3%, $p < 0.001$). The seroprevalence was noted to increase with age (p for trend <0.001). The distribution of seropositive HCWs in different age groups by gender from year 2011–2017 is illustrated in Supplementary Fig. 1. None of the HCWs were born before 2004, when universal varicella vaccination had begun. The seroprevalence for doctors, nurses and others were 88.5%, 76.6%, and 80.0% respectively, ($p < 0.001$). Both chickenpox history and varicella vaccination history had no association with serostatus of anti-varicella antibody, with *p*-value of 0.636 and 0.485 respectively.

The VZV seroprevalence decreased from 88.0% in 2011 to 72.2% in 2017, (p for trend <0.05). The age compositions of HCWs from 2011 to 2017 were illustrated in Supplementary Table 1 and we verified that age compositions had no significant difference over the years from 2011 to 2017, ($p = 0.273$), after excluding age group of ≥50 years old due to small frequencies. Hence, the decreasing trend of seroprevalence over years was not associated with age compositions of HCWs. When compared to the seroprevalence in the study by Wu et al. in 2008–2009 (Fig. 2), we observed a decreasing trend of seroprevalence by years in our study and the differences reached statistical significance in younger age groups including HCWs aged <30 and 30–39 years (both $p < 0.05$).

Table 1 Demographic and clinical characteristics of new healthcare workers with different baseline of anti-varicella antibody patterns, 2011–2017.

	Positive	Equivocal	Negative	Total
Number, n =	1924	117	365	2406
Gender, n(%)				
Female	1470 (78.3%)	101 (5.4%)	307 (16.3%)	1878
Male	454 (86.0%)	16 (3.0%)	58 (11.0%)	528
Age group, years				
≤20, n(%)	39 (61.9%)	2 (3.2%)	22 (34.9%)	63
21～25	891 (76.9%)	55 (4.7%)	212 (18.3%)	1168
26～30	475 (84.2%)	21 (3.7%)	68 (12.1%)	564
31～35	242 (83.4%)	16 (5.5%)	32 (11.0%)	290
36～40	132 (83.0%)	10 (6.3%)	17 (10.7%)	159
41～45	58 (82.9%)	4 (5.7%)	8 (11.4%)	70
46～50	35 (79.5%)	5 (11.4%)	4 (9.1%)	44
51～55	24 (85.7%)	2 (7.1%)	2 (7.1%)	28
56～60	10 (90.9%)	1 (9.1%)	0	11
>60	18 (94.7%)	1 (5.3%)	0	19
Occupation, n(%)				
Doctor	324 (88.5%)	11 (3.0%)	31 (8.5%)	366
Nurse	735 (76.6%)	53 (5.5%)	171 (17.8%)	959
Others	865 (80.0%)	53 (4.9%)	163 (15.1%)	1081
Chickenpox history, n(%)				
No	376 (82.6%)	20 (4.4%)	59 (13.0%)	455
Yes	653 (80.5%)	38 (4.7%)	120 (14.8%)	811
No recall	895 (78.5%)	59 (5.2%)	186 (16.3%)	1140
Vaccination history, n(%)				
No	258 (80.6%)	11 (3.4%)	51 (15.9%)	320
Yes	308 (81.1%)	19 (5.0 %)	53 (13.9%)	380
No recall	1358 (79.6%)	87 (5.1%)	261 (15.3%)	1706

Seroresponse after vaccination

Of 117 HCWs with equivocal anti-VZV IgG and 365 with negative anti-VZV IgG at baseline, 100 (85.4%) and 334 (91.5%) received the first dose of varicella vaccine, respectively (Fig. 1). Thereafter, 80 (80%) HCWs with baseline equivocal anti-VZV IgG had follow-up serologicaly testing after receiving the first dose of vaccination; and 247 (74%) HCWs with baseline negative anti-VZV IgG completed follow-up serological testing after receiving 2 doses of vaccine. The serological responses of HCWs with baseline equivocal anti-VZV IgG results after one-dose vaccination and those with baseline negative anti-VZV IgG results after two-dose vaccination were 100% (80/80) and 79.4% (196/247), respectively ($p < 0.001$).

Factors associated with seroresponse to vaccination

In univariate analysis, obesity (OR, 0.229, 95% CI, 0.08–0.64, $p = 0.007$) and diabetes (OR, 0.082, 95% CI, 0.01–0.81, $p = 0.029$) were two factors associated with

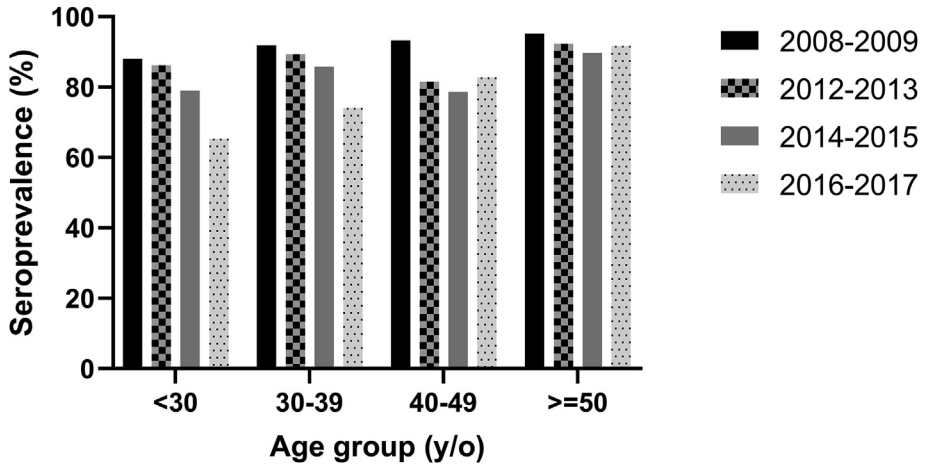

Figure 2. Trend of seroprevalence of VZV among HCWs.

Table 2 Univariate and multivariate analysis of characteristics between responders and non-responders to varicella zoster virus vaccination.

	Responsiveness to Varicella vaccine		Univariate			Multivariate		
	Responder (n = 196)	Non responder (n = 51)	OR	95% CI	p	OR	95% CI	P
Male sex, n(%)	26 (13.3)	8 (15.7)	0.822	0.35–1.94	0.651	0.922	0.39–2.39	0.858
Age, y/o, mean ± SD	25 ± 6	25 ± 6	0.989	0.941 –1.040	0.6761	0.996	0.95–1.06	0.881
Occupation, n(%)								
Doctor	15 (7.7)	4 (7.8)	0.974	0.31–3.07	1.000			
Nurse	98 (50.0)	27 (52.9)	0.889	0.48–1.65	0.755			
Others	83 (42.3)	20 (39.2)	Reference					
Vaccine brand, n(%)								
Varilrix	26 (13.3)	10 (19.6)	0.627	0.28–1.40	0.268			
Varivax	170 (86.7)	41 (80.4)	Reference					
Obese, n(%)	8 (4.1)	8 (15.7)	0.229	0.08–0.64	**0.007**	0.308	0.11–0.94	**0.039**
Hypertension, n(%)	64 (32.7)	20 (39.2)	0.752	0.40–1.42	0.409			
Diabetes, n(%)	1 (0.5)	3 (5.9)	0.082	0.01–0.81	**0.029**	0.242	0.02–1.99	0.187
Hepatitis B, (%)	6 (3.1)	1 (2.0)	1.579	0.19 –13.42	1.000			
High TC, n(%)	45 (23.0)	12 (23.5)	0.969	0.47–2.00	1.000			
Urine protein-positive, n(%)	27 (13.8)	7 (13.7)	1.004	0.41–2.46	1.000			

A responder is defined as a healthcare worker who had negative anti-varicella antibody at baseline and seroconverted after vaccination. Values in bold font indicate statistical significance.

impaired response to vaccination (Table 2). In multivariate analysis, obesity was the only factor associated with non-response to vaccination (adjusted OR, 0.308, 95%CI, 0.11–0.94, $p = 0.039$).

Baseline AI values of anti-VZV IgG were available for 44 HCWs who had negative anti-VZV IgG results at baseline. A ROC curve was plotted to evaluate if the baseline AI value could predict serological to varicella vaccine. A cut-off points of 0.115 AI (sensitivity = 0.70, specificity = 0.857) was found to have the best sensitivity and specificity (Fig. 3). HCWs with baseline AI values between 0.115 and 0.8 had a seroconversion rate of 91.3% (21/23). In contrast, the rate of HCWs with baseline AI values less than 0.115 was only 42.9% (9/21) ($p < 0.001$).

Discussion

In our study, seroprevalence of varicella among new HCWs had decreased from 88.0% in 2011 to 72.2% in 2017. The trend was prominent among HCWs aged less than 40 years. In addition, different serological responses were noted

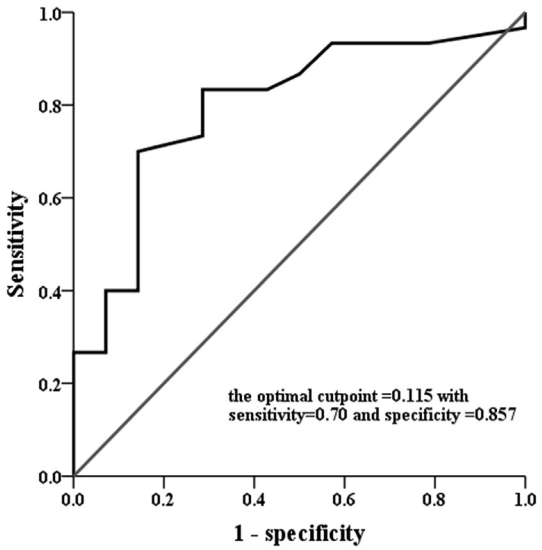

Figure 3. ROC curve of anti-VZV IgG among responders and non-responders.

between HCWs with equivocal and those with negative anti-VZV IgG results at baseline. In multivariate analyses, obesity was an independent factor associated with non-response to varicella vaccination. The different seroprevalences between sex or occupation groups could be explained by uneven age distribution (Supplementary Fig. 1).

In Taiwan, the universal varicella vaccination program was implemented among all preschool children since 2004.[9] With the implementation of varicella vaccination program, the peak incidence of VZV in children had decreased from 66 per 1000 in 2003 to 23 per 1000 in 2008.[18] Similarly, decreasing trends were also observed in other countries. In Sicily, Italy, the annual incidence declined 90.6% after introduction of 1 dose varicella vaccination, from 95.7 per 1000 in 2004 to 9.0 per 1000 in 2007.[19] In West Philadelphia, Pennsylvania in the U.S., where 1-dose varicella vaccination program was implemented since 1997, VZV incidence had decreased by 90.4%, from 4.1 cases per 1000 in 1995 to 0.4 cases per 1000 in 2005.[20] In the era before universal varicella vaccination in Taiwan, Tseng at el had found infants had a peak rate of hospitalization due to varicella infection followed by a second peak in adults aged 30—44 years.[21] The second peak of varicella infection in adults suggested risk of domestic exposure to infected children. Another study conducted by Ogunjimi et al. also found a tendency toward higher antibody concentrations in the asymptomatic parents who were exposed to varicella in household compared to the healthy young or old control group.[22] Exposure to VZV-infected children increased in both cellular and humoral immunity in VZV-immune adults.[23] The significant reduction of varicella incidence among children after implementation of the national varicella vaccination program among children in Taiwan decreased the possibility of domestic exposure for adults. Therefore, a decreasing trend of seroprevalence among HCWs with time was found in our study. Similarly, universal varicella vaccination was introduced since 2006 in Italy, a seroprevalence survey in 2011—2012 among adults also revealed the pattern of decreasing seroprevalence in the population aged <35 years.[24] All HCWs were born before the universal vaccination era. The seronegative HCWs could be due to missed vaccination and disease in childhood, or lacking boosting opportunities with waning immunity.[20,25,26]

Overall serological response to vaccination in our study (84.4%) was lower compared to the seroconversion rate reported by varicella vaccine manufacturers (99.9% among seronegative children after 2nd dose of VARIVAX; 100% among healthy children after 2nd dose of VARILRIX).[27,28] Similar to our results, serological response rate (88.1%) among 101 vaccinated healthcare personnel was reported by Behrmen et al. in 2005—2007 in the U.S.[29] Another study in the U.S. prior to the implementation of nationwide varicella vaccination, a seroconversion rate of 82% after 1 dose and 94% after two doses was observed among 187 healthy susceptible adults.[30] The lower seroconversion rate after varicella vaccination in our study could be explained by selection bias because only seronegative HCWs were recommended to receive varicella vaccination and included to the analysis of serological response. These seronegative HCWs with equivocal or negative anti-VZV IgG at baseline had either experienced waning of immunity years after primary VZV infection or vaccination, lack of previous VZV infection, or failure to mount antibody response to previous VZV infection or vaccination (non-responders). The proportion of non-responders would be higher among seronegative adults than all population including seropositive ones. To the best of our knowledge, this was the first study comparing serological responses after varicella vaccination between HCWs with baseline equivocal and those with negative anti-VZV IgG results. Our analysis provided evidence that 1 dose of varicella vaccination is sufficient for HCWs with equivocal baseline of anti-VZV IgG. Moreover, among HCWs with negative anti-VZV IgG results (<0.6 AI), those with higher baseline anti-VZV IgG values (>0.115 AI) had better serological response than those with values < 0.115 AI (91.3% vs. 42.9%). We considered that seronegative HCWs with higher baseline anti-VZV IgG results were more likely due to waning of immunity years after primary VZV infection or vaccination without subsequent booster vaccination in adulthood.

Obesity was an independent factor negatively associated with responsiveness to varicella vaccination. Reduced immune responses to vaccination of other diseases like hepatitis B, tetanus and rabies in obese population were also observed.[31—33] A possible explanation is that obesity causes low-grade inflammation, and has direct effects on the immune system rendering immunosuppression.[34,35] Adipocytes in white adipose tissue secrete multiple pro-inflammatory cytokines (e.g. tumor necrosis factor (TNF)-α, Interleukin (IL)-6) and acute phase proteins (e.g. Haptoglobin, Serum amyloid A) for stimulation of angiogenesis locally, possibly as a result of hypoxia due to insufficient vasculature within expanding adipose tissue.[36] Despite local effect, these adipocyte-generated pro-inflammatory signals have several systemic effects: stimulate the production of inflammatory markers from the liver; disrupting insulin signaling and glucose transport which could cause insulin resistance at myocyte, adipocyte and hepatocyte level; and may play a role in atherogenesis.[37] Several mechanisms of dysregulation of immune system by chronic inflammation state found by mouse studies are:

altered production of cytokines and T cells, diminished natural killer cell activity, and poor response to antigens.[38,39] Nevertheless, the exact mechanism in human has yet to be identified. Leptin is another adipokine which gained much attention as it had pleiotropic effects on immune cell activity due to presence of leptin receptors on all immune cells of both innate and adaptive immunity.[40]

There were several limitations in our study. First, this was a study conducted at a tertiary hospital and the findings might not be able to be generalized to other settings. Besides, the national varicella vaccination program in Taiwan was implemented in 2004, the VZV seroepidemiology would be different when more people born in the vaccination era enter our hospital as HCWs. Third, the majority of HCWs in our study were of younger age groups, and, therefore, the proportion of HCWs having certain variables of interest such as diabetes, malignancy, and obesity were relatively low.

In conclusion, decreasing seroprevalence of VZV IgG with years observed among HCWs might be partly due to decreasing opportunity of booster vaccination, as a result of increasing herd immunity that developed years after universal varicella vaccination for children since 2004. Obesity was an important factor associated with non-responsiveness to varicella vaccination.

Declaration of competing interest

All authors declared no conflicts of interest.

Acknowledgements

No funding was received in this study.

References

1. Viner K, Perella D, Lopez A, Bialek S, Newbern C, Pierre R, et al. Transmission of varicella zoster virus from individuals with herpes zoster or varicella in school and day care settings. *J Infect Dis* 2012;**205**:1336—41.
2. Gustafson TL, Lavely GB, Brawner ER, Hutcheson RH, Wright PF, Schaffner W. An outbreak of airborne nosocomial varicella. *Pediatrics* 1982;**70**:550—6.
3. Asano Y. Clinicopathologic understanding and control of varicella-zoster virus infection. *Vaccine* 2008;**26**:6487—90.
4. Heininger U, Seward JF. Varicella. *Lancet* 2006;**368**:1365—76.
5. Ku CH, Liu YT, Christiani DC. Case report: occupationally related recurrent varicella (chickenpox) in a hospital nurse. *Environ Health Perspect* 2005;**113**:1373—5.
6. Aly NY, al Obaid I, Al-Qulooshi N, Zahed Z. Occupationally related outbreak of chickenpox in an intensive care unit. *Med Princ Pract* 2007;**16**:399—401.
7. Advisory Committee on immunization Practices; Centers for disease control and prevention (CDC) USA. Immunization of health-care personnel recommendations of the advisory Committee on immunization Practices (ACIP). *MMWR Recomm Rep* 2011;**60**:1—45.
8. Seward JF, Marin M, Vázquez M. Varicella vaccine effectiveness in the US vaccination program: a review. *J Infect Dis* 2008;**197**: S82—9.
9. Chao DY, Chien YZ, Yeh YP, Hsu PS, Lian IB. The incidence of varicella and herpes zoster in Taiwan during a period of increasing varicella vaccine coverage, 2000—2008. *Epidemiol Infect* 2012;**140**:1131—40.
10. Wu MF, Yang YW, Lin WY, Chang CY, Soon MS, Liu CE. Varicella zoster virus infection among healthcare workers in Taiwan: seroprevalence and predictive value of history of varicella infection. *J Hosp Infect* 2012;**80**:162—7.
11. McLachlan E, Scholz H, Bolotin S, Crowcroft NS, Hatchette TF, Jackson C, et al. Calibration and evaluation of quantitative antibody titers for varicella-zoster virus by use of the BIOPLEX 2200. *J Clin Microbiol* 2019;**57**. e00296-19.
12. Kim YH, Hwang JY, Shim HM, Lee E, Park S, Park H. Evaluation of a commercial glycoprotein enzyme-linked immunosorbent assay for measuring vaccine immunity to varicella. *Yonsei Med J* 2014;**55**:459—66.
13. Binnicker MJ, Jespersen DJ, Rollins LO. Evaluation of the bio-rad BioPlex measles, mumps, rubella, and varicella-zoster virus IgG multiplex bead immunoassay. *Clin Vaccine Immunol* 2011;**18**:1524—6.
14. Wutzler P, Bonanni P, Burgess M, Gershon A, Sáfadi MA, Casabona G. Varicella vaccination - the global experience. *Expert Rev Vaccines* 2017;**16**:833—43.
15. Clements DA. Varicella vaccination in children. *BioDrugs* 2000; **14**:49—60.
16. Bolyard EA, Tablan OC, Williams WW, Pearson ML, Shapiro CN, Deitchman SD, et al. Guideline for infection control in health care personnel, 1998. *Infect Control Hosp Epidemiol* 1998;**19**: 407—63.
17. Taiwan C.D.C. *Healthcare personnel vaccination recommendations*. Taiwan Centers for Disease Control; 2019. https://www.cdc.gov.tw/File/Get/4os2clUwkwKAZ_4W0JIOUA. [Accessed 17 January 2022].
18. Chang LY, Huang LM, Chang IS, Tsai FY. Epidemiological characteristics of varicella from 2000 to 2008 and the impact of nationwide immunization in Taiwan. *BMC Infect Dis* 2011;**11**: 352.
19. Helmuth IG, Poulsen A, Suppli CH, Mølbak K. Varicella in Europe-A review of the epidemiology and experience with vaccination. *Vaccine* 2015;**33**:2406—13.
20. Guris D, Jumaan AO, Mascola L, Watson BM, Zhang JX, Chaves SS, et al. Changing varicella epidemiology in active surveillance sites - United States, 1995-2005. *J Infect Dis* 2008;**197**:s71—5.
21. Tseng HF, Tan HF, Chang CK. Varicella epidemiology and cost-effectiveness analysis of universal varicella vaccination program in Taiwan. *Southeast Asian J Trop Med Publ Health* 2005; **36**:1450—8.
22. Ogunjimi B, Smits E, Hens N, Hens A, Lenders K, Ieven M, et al. Exploring the impact of exposure to primary varicella in children on varicella-zoster virus immunity of parents. *Viral Immunol* 2011;**24**:151—7.
23. Arvin AM, Koropchak CM, Wittek AE. Immunologic evidence of reinfection with varicella-zoster virus. *J Infect Dis* 1983;**148**: 200—5.
24. Tafuri S, Gallone MS, Cappelli MG, Gallone MF, Larocca AMV, Germinario C. A seroprevalence survey on varicella among adults in the vaccination era in Apulia (Italy). *Vaccine* 2014;**32**: 6544—7.
25. Luyten J, Ogunjimi B, Beutels P. Varicella-zoster virus vaccination under the exogenous boosting hypothesis: two ethical perspectives. *Vaccine* 2014;**32**:7175—8.
26. Talbird SE, La EM, Mauskopf J, Altland A, Daniels V, Wolfson LJ. Understanding the role of exogenous boosting in modeling varicella vaccination. *Expert Rev Vaccines* 2018;**17**:1021—35.
27. *Prescribing Information/Insert Varivax*. https://www.merck.com/product/usa/pi_circulars/v/varivax/varivax_pi.pdf. [Accessed 15 November 2021].
28. *Prescribing Information/Insert Varilrix*. https://gskpro.com/content/dam/global/hcpportal/en_BD/PI/Varilrix_IPI_14_1_03_2019.pdf. [Accessed 15 November 2021].

29. Behrman A, Lopez AS, Chaves SS, Watson BM, Scott Schmid D. Varicella immunity in vaccinated healthcare workers. *J Clin Virol* 2013;**57**:109—14.
30. Gershon AA, Steinberg SP, Larussa P, Ferrara A, Hammerschlag M, Gelb L, et al. Immunization of healthy adults with live attenuated varicella vaccine. *J Infect Dis* 1988;**158**:132—7.
31. Fan W, Chen XF, Shen C, Guo ZR, Dong C. Hepatitis B vaccine response in obesity: a meta-analysis. *Vaccine* 2016;**34**: 4835—41.
32. Eliakim A, Swindt C, Zaldivar F, Casali P, Cooper DM. Reduced tetanus antibody titers in overweight children. *Autoimmunity* 2006;**39**:137—41.
33. Banga N, Guss P, Banga A, Rosenman KD. Incidence and variables associated with inadequate antibody titers after preexposure rabies vaccination among veterinary medical students. *Vaccine* 2014;**32**:979—83.
34. Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-α and IL-6. *Diabetes Res Clin Pract* 2005;**69**:29.
35. Young KM, Gray CM, Bekker LG. Is obesity a risk factor for vaccine non-responsiveness? *PLoS One* 2013;**8**:e82779.
36. Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr* 2004;**92**: 347—55.
37. Yudkin JS. Adipose tissue, insulin action and vascular disease: inflammatory signals. *Int J Obes (Lond)* 2003;**27**:S25—8.
38. Karlsson EA, Beck MA. The burden of obesity on infectious disease. *Exp Biol Med (Maywood)* 2010;**235**:1412—24.
39. Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. *Int J Obes (Lond)* 2013;**37**:333—40.
40. Procaccini C, Jirillo E, Matarese G. Leptin as an immunomodulator. *Mol Aspect Med* 2012;**33**:35—45.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2022.09.005.