

COMPARISON OF DIAGNOSTIC ACCURACY OF
SELF-REPORTED VARICELLA HISTORY WITH SERUM
ANTI-VARICELLA-ZOSTER VIRUS IGG
AMONG HOSPITAL HEALTHCARE WORKERS,
SAMUT SAKHON PROVINCE, THAILAND
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Abstract. Varicella outbreaks in hospital settings can cause severe or disseminated disease in immunocompromised patients and vaccination of health care workers (HCWs) who lack evidence of immunity is recommended to prevent and control such outbreaks. We reviewed questionnaires from pre-vaccination protocol and result of varicella immunity from medical records of all HCWs aged ≥ 18 years who were enrolled in the varicella vaccination program at a secondary care hospital in Samut Sakorn Province, Thailand during September to October 2020. Diagnostic accuracy of self-reported varicella history compared with serum anti-varicella-zoster virus (VZV) IgG was evaluated among HCWs ($n = 654$; median age = 33 years, interquartile range = 26-41 years) with self-reported varicella disease history without medical documentation or negative or uncertain varicella disease history. Overall seroprevalence was 78.4%, which significantly increased with increasing age (p -value < 0.001). Physicians had the highest seroprevalence and nurses the lowest. Among HCWs with self-reported history of prior varicella disease ($n = 264$) and with a negative or uncertain history ($n = 390$), 4 and 33% had negative serology test respectively. Self-reported history of varicella disease showed 49% sensitivity, 92% specificity, 96% positive predictive value, and 33% negative predictive value. One in four HCWs had no detectable anti-varicella antibodies. In conclusion, a positive self-reported varicella history was a good predictor of serum anti-VZV IgG while a negative or uncertain varicella history was a poor predictor and, thus, implementation

of a policy of pre-vaccination screening for varicella for all hospital HCWs is recommended.

Keywords: anti-varicella-zoster virus IgG, diagnostic accuracy, healthcare workers, self-reported history, seroprevalence, varicella

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INTRODUCTION

Varicella (chickenpox) is a highly contagious disease caused by varicella-zoster virus (VZV) (Heininger and Seward, 2006), which can be transmitted through direct contact and airborne particulates, causing morbidity especially in adults (Rawson *et al*, 2001; Tunbridge *et al*, 2008). In a hospital setting, VZV can spread to immunocompromised patients, pregnant women and newborns (Gershon *et al*, 2015). As varicella infectivity is highest two days prior to rash onset (Weber and Rutala, 2016), diagnosis and active infection control could be delayed post-peak infectivity. Varicella outbreaks in hospitals are associated with widespread complications and increase in healthcare cost and society economic burden (Apisarnthanarak *et al*, 2007; Yang *et al*, 2019).

Vaccination of healthcare workers (HCWs) is one method for preventing nosocomial varicella transmission

(Haviari *et al*, 2015; Kim *et al*, 2018) and pre-vaccination screening provides a cost-effective approach to determining immunity (Kang *et al*, 2014). However, serology tests and vaccinations are expensive. Cost of a 2-shot VZV vaccine is THB2,180 (approximately USD70) compared to that of an anti-VZV IgG test of THB715 (approximately USD23). Vaccination against varicella is optional under the Thai National Expanded Programme on Immunization (EPI) (WHO SEARO, 2020). Collecting self-reported history of varicella infection is a potential strategy for decreasing cost of performing a pre-screening serology test and may serve as a triage method to determine whether serology testing is necessary. However, differences in diagnostic accuracy of self-reported varicella infection history compared to serology tests of HCWs have been reported (Almuneef *et al*, 2004; Wu *et al*, 2012).

Banphaeo General Hospital (BGH) (Public Organization) is a secondary care hospital located in Samut Sakhon

Province, central Thailand, which experienced a varicella outbreak in HCWs in late 2019 (BGH ICC, 2019). In order to improve outbreak control and surveillance, a pre-vaccination protocol was initiated to determine serum anti-varicella IgG among HCWs.

Thus a study was initiated to compare diagnostic accuracy of self-reported varicella history compared with serum anti-VZV IgG in HCWs at the same hospital. We hope that the results of comparison can lead up to the policy of pre-vaccination protocol for further varicella outbreak prevention.

MATERIALS AND METHODS

Study site and research participants

The study was conducted at Banphaeo General Hospital (Public Organization) or BGH, Samut Sakhon Province, Thailand. The research protocols were approved by the director of BGH and the Human Rights and Ethics Committee of the Institutional Review Board, BGH (No 1/2564). Identities of HCWs were anonymized. We reviewed questionnaires from pre-vaccination protocol and result of varicella immunity from medical records of all HCWs aged ≥ 18 years who were enrolled in the varicella vaccination program during September to October 2020.

In pre-vaccination protocol, all HCWs ($n=1,575$) working at BGH during the study period were provided with a questionnaire on age, sex, occupation,

previous varicella infection history, and previous varicella immunization. Response on history of varicella infection consists of “yes,” “no,” or “uncertain”. Respondents with “yes” reply and provided medical documentation of previous varicella infection, together with those who had received varicella immunization, were excluded from the study because they meet the criterion of having serum anti-varicella IgG antibody as recommended by the Advisory Committee on Immunization Practices (ACIP) (Marin *et al*, 2007). HCWs with self-reported varicella disease history but without accompanying medical documentation and those with a “no” or “uncertain” reply were selected to further serology test.

Serological test

Anti VZV IgG testing were conducted by Center of Excellence in Clinical Virology, Faculty of Medicine, Chulalongkorn University. Detection of serum anti-VZV IgG was carried out using a commercial test kit namely Euroimmun anti-VZV enzyme-linked immunosorbent assay (ELISA) kit (Euroimmun, Lübeck, Germany), which is coated with purified VZV protein (Ellen strain) derived from a human fibroblast infection. Each plate contains four standard samples of known concentration and positive and negative controls. Antibody titer is expressed IU/l based on a standard curve. Samples with < 80 , 80-110 and ≥ 110 IU/l anti-VZV IgG are classified as negative,

borderline and positive, respectively (based on the manufacturer's guidelines). All samples with borderline results were subjected to repeat test and any that remained borderline are classified as negative.

Statistical analysis

Seroprevalence of anti-VZV IgG and self-reported history of varicella infection were calculated for various subgroups, according to age, sex, and occupation. A Chi-square test was used to compare differences, with significance accepted at p -value ≤ 0.05 . Sensitivity, specificity, positive and negative predictive values [95% confidence interval (CI)] were determined for ability of a self-reported history of VZV infection to predict presence of anti-VZV IgG. Statistical analysis was performed using a Stata

Version 15.1 statistical package (Stata Corp, College Station, TX).

RESULTS

Among 1,575 HCWs surveyed at BGH, 921 (58.5%) were excluded due to having documented history of varicella disease or vaccination. Median (interquartile range) age of participants was 33 (26-41) years old, most common age group being 26-35 years old, 82.9% were females, and paramedical staff [nursing assistants (49%), physician assistants (5%), medical technologists (7%), and others (39%)] was the major occupation category (42.1%) (Table 1). Non-paramedical staff consisted of cleaning personnel (23%), office personnel (19%), logistic personnel (14%), and others (44%).

Table 1

Demographic data and serum anti-varicella-zoster virus (VZV) IgG status of health care workers (HCWs) at a secondary care hospital, Samut Sakorn Province, Thailand (September - October 2020)

Characteristic	Enrolled HCW Number (%) ($n = 654$)	Positive serum anti-IgG status (%)
Female	542 (82.9)	78.6
Male	112 (17.1)	77.7
Occupation		
Physician	46 (7.0)	93.5
Nurse	171 (26.1)	72.5
Paramedical staff	275 (42.1)	78.9
Non-paramedical staff	162 (24.8)	79.6

A positive self-reported history of varicella infection was reported by 40.4% of the participants, while the remaining had no history or uncertainty in their recollection of previous varicella infection (Table 2). Overall prevalence of serum anti-VZV IgG was 78.4% (513/654), highest among physicians, and there is no significant difference between females and males (Table 1). Antibody prevalence significantly increased with age (Fig 1).

Using positive serum anti-VZV IgG as the gold standard, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of self-reported varicella infection history was only 49.3, 92.2, 95.8, and 33.3%, respectively (Table 3). Overall accuracy was 71% (95% CI: 68-74). Highest PPV and lowest NPV values were observed for age group ≥ 46 years old and among physicians.

DISCUSSION

The study shows accuracy of undocumented self-reported or uncertain history of varicella infection compared to serum anti-VZV IgG (gold standard) among healthcare workers at a secondary care hospital in Thailand was less than 50%, although specificity, PPV, and NPV were acceptable (92, 96 and 33%, respectively). Overall seroprevalence of varicella was 78%.

Varicella seroprevalence in a general population varies between 36-99%, depending on geographic

region, population density and immunization policy, with seroprevalence being lower rate in tropical compared to temperate regions (Lolekha *et al*, 2001; Goh *et al*, 2019) *viz* 84% in Saudi Arabia (Almuneef *et al*, 2004) compared to 96% in Korea (Kang *et al*, 2014), 97.4% in Japan (Kanamori *et al*, 2014) and 91.1% of seroprevalence in Taiwan (Wu *et al*, 2012). Varicella seroprevalence from our study was comparable to previous studies among hospital HCWs in Thailand: 53% among 100 HCWs at Thammasart University Hospital, a tertiary care center located near Bangkok (Apisarnthanarak *et al*, 2007), 89% among 167 newly hired HCWs at Srinagarind Hospital, Khon Kaen Province in the northeast (Wangsan *et al*, 2019), and 84% among 107 HCWs in the Pediatrics Department, King Chulalongkorn Memorial Hospital, Bangkok (Aungulruengkitt *et al*, 2017).

Seroprevalence of anti-VZV IgG has been shown to increase with age (Migasena *et al*, 1997; Lolekha *et al*, 2001; Wu *et al*, 2012; Kang *et al*, 2014; Thantithaveewat *et al*, 2019), as was observed in the present study, which may reflect accumulation of disease exposure over time. We noted, among participating HCWs, physicians had the highest varicella seroprevalence, not unexpected as VZV vaccination is required for all incoming medical students in Thailand, although physicians enrolled in the study were those without documentation of their vaccination status. Nurses had the lowest

Table 2

Comparison between self-reported (but undocumented) history of varicella infection and presence of serum anti-varicella-zoster virus (VZV) IgG of health care workers at a secondary care hospital, Samut Sakorn Province, Thailand (September - October 2020)

History of varicella	Anti-VZV IgG status		Total
	Positive	Negative	
Positive	253	11	264
Negative	103	87	190
Uncertain	157	43	200
Total	513	141	654

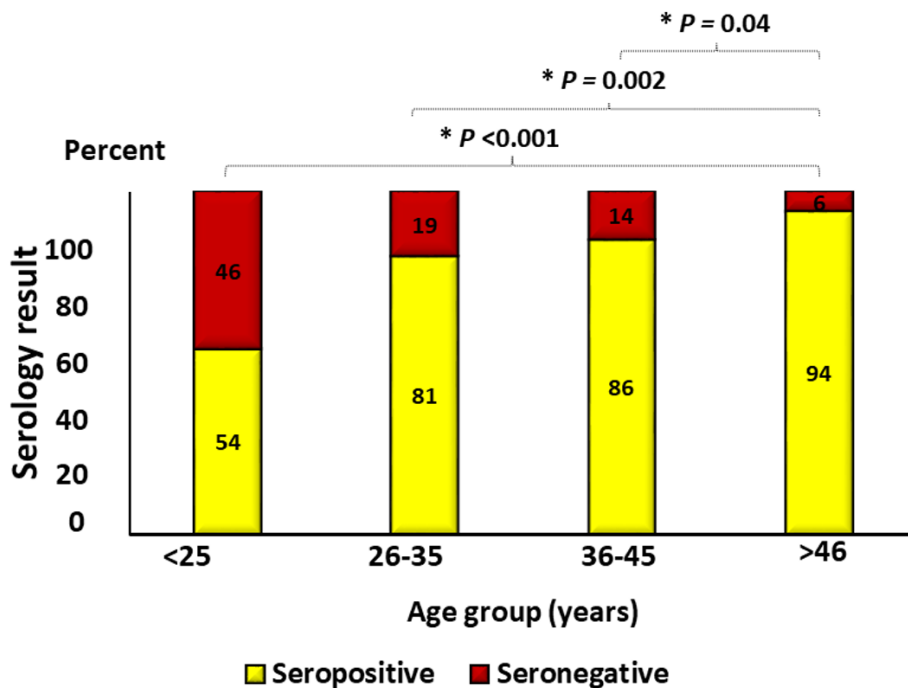


Fig 1 - Serology test for anti-varicella-zoster virus IgG in age groups health care workers at a secondary care hospital, Samut Sakorn Province, Thailand (September - October 2020).

Note: Detection of serum anti-VZV IgG was carried out using a Euroimmun anti-VZV enzyme-linked immunosorbent assay kit (Euroimmun, Lübeck, Germany).

Table 3
 Diagnostic accuracy of previous history of varicella infection compared to serum anti-varicella-zoster virus (VZV) IgG test of health care workers (HCWs) at a secondary care hospital, Samut Sakorn Province, Thailand (September - October 2020)

Previous history of varicella infection	Number of HCWs (%) (n = 654)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Positive predictive value (%) (95% CI)	Negative predictive value (%) (95% CI)
Age, years					
≤25	151 (23.1)	52.4 (41.1-63.6)	92.8 (83.9-97.6)	89.6 (77.3-96.5)	62.1 (52.0-71.5)
26-35	235 (35.9)	48.2 (40.9-55.5)	93.2 (81.3-98.6)	96.8 (91.0-99.3)	29.3 (21.9-37.6)
36-45	153 (23.4)	60.6 (51.7-69.0)	85.7 (63.7-97.0)	96.4 (89.8-99.2)	25.7 (16.0-37.6)
≥46	115 (17.6)	35.2 (26.2-45.0)	100 (59.0-100)	100 (90.7-100)	9.1 (3.7-17.8)
Occupation					
Physician	46 (7.0)	72.1 (56.3-84.7)	100 (29.2-100)	100 (88.8-100)	20 (4.3-48.1)
Nurse	171 (26.1)	49.2 (40.1-58.3)	95.7(85.5-99.5)	96.8 (89.0-99.6)	41.7 (32.3-51.5)
Paramedical staff	275 (42.1)	53.9 (47.0-60.7)	86.2 (74.6-93.9)	93.6 (87.8-97.2)	33.3 (25.9-41.5)
Non-paramedical staff	162 (24.8)	34.1 (26.0-43.0)	97 (84.2-99.9)	97.8 (88.2-99.9)	27.4 (19.5-36.4)
Overall	654 (100)	49.3 (44.9-53.7)	92.2 (86.5-96.0)	95.8 (92.7-97.9)	33.3 (28.7-38.3)

CI: confidence interval

seroprevalence among the HCWs, a finding previously reported in Thailand (Anugulruengkitt *et al*, 2017), a worrying observation given nurses are in consistent close contact with patients.

In the present study, PPVs of HCW with self-reported history of varicella indicated this was a high predictor of presence of serum anti-VZV IgG, in agreement with consistent with previous reports (Sam *et al*, 2008; Wu *et al*, 2012; Kang *et al*, 2014). However, a small minority of HCWs who reported a positive history of varicella were serum anti-VZV IgG negative, and thus were susceptible to infection. On the other hand, NPVs among the HCW participants who reported no or unsure history of varicella indicated that recall history was unreliable and could not be used as a basis for selection of individuals requiring serology testing. However, if individuals with uncertain history of varicella were excluded from prediction determination, sensitivity, specificity, PPV, and NPV of self-reported varicella infection history for predicting presence of serum anti-VZV IgG rose to 71.1% (95% CI: 66.1-75.7), 88.8% (95% CI: 80.8-94.3), 95.8% (95% CI: 92.7-97.9), and 45.8% (95% CI: 38.6-53.2), respectively, and accuracy was 80% (95% CI: 76%–84%), which was higher than when those with uncertain history were included. HCWs \geq 46 years of age had the highest PPV (100%) and, surprisingly, lowest NPV. This might be due to high seroprevalence in this age group and poor long-term memory

combined with poor public health education in the past.

One limitation of this study was inability to generalize these findings due to differences in hospital size and local geographic and environmental conditions. Recall bias might also affect accuracy of self-reporting.

In conclusion, the study demonstrates undocumented self-reported history of varicella among healthcare workers at a secondary care hospital in Thailand was not a reliable predictor of varicella infection status. We recommend hospitals implement a policy of pre-vaccination screening of all healthcare workers. If such a policy is not possible due to resource limitations, a pre-vaccination screening should be performed for all those with a negative or uncertain self-reported varicella history, especially among those who are in close contact with high-risk patients.

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CONFLICTS OF INTEREST DISCLOSURE

The authors declare no conflicts of interest.

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