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# Predictive Value of Self-reported History of Varicella in Colombo District, Sri Lanka

[1]Hathshya M. Munasigha, [2]Ananda Amarasinghe, [3]Neelika G Malavige and [4]Nalini Sathiakumar
[1]International Health Unit, Department of Management, Development and Planning Unit, Ministry of Health, Nutrition and Indigenous Medicine, Colombo, Sri Lanka
[2]Department of Epidemology, Office-WHO, Manila, Philippines
[3]Department of Microbiology, University of Sri Jayawardenapura, Nugegoda, Sri Lanka
[4]Department of Epidemiology, School of Public Health, University of Alabama, Birmingham, USA

**Abstract:** To determine whether self-reported history of previous varicella infection is an accurate predictor of immunity to varicella. A population-based cross-sectional study of 1258 participants was conducted in Colombo District, Sri Lanka. Using interviewer-administered questionnaire, information on sociodemographic characteristics and previous history of varicella infection were obtained. A commercial enzyme-linked immunosobent assay kit was used to detect varicella zoster virus antibody IgG from serum samples. Self-reported varicella infection by the overall study group and by subgroups of adolescents, adults and women of childbearing age had a high positive predictive value (overall group, 92%; subgroups, 91-95%) for immunity to VZV. Whereas, a negative history of varicella infection was not an accurate predictor of nonimmune status, the negative predictive values were low for the overall group (76%) and subgroups (64-84%). For persons who are not at high risk of varicella infection, a positive history of varicella may be used to indicate positive immune status in lieu of serological testing. For those at high risk for varicella infection and a negative history of varicella infection, serological testing is required to determine immune status. For all those determined to the non-immune by serological testing, varicella vaccine should be offered.

**Key words:** Colombo, predictive value, self-reported, Sero-prevalence, varicella, serological testing

## INTRODUCTION

Varicella (chickenpox) infection is an infectious disease caused by primary infection with the alpha-herpes Varicella-Zoster Virus (VZV) (CDCP., 2015). The clinical course of varicella in healthy children is generally mild and self-limited (Mandell *et al*., 2010). Complications may occur and include secondary bacterial infection of skin lesions with *Staphylococcus* or *Streptococcus*, pneumonia, central nervous system manifestations (aseptic meningitis, encephalitis), Reye syndrome, haemorrhagic varicella, myocarditis etc. (Sengupta and Breuer, 2009; Mandell *et al*., 2010; CDCP., 2015) with a mortality of about 1 in 60,000 cases.

Nonimmune persons are at risk for VZV as adults with the risk of complications increasing with age. Immunocompromised persons have a high risk of disseminated disease with multiple organ system involvement and the disease may become fulminant and haemorrhagic. VZV infection in pregnancy is associated with adverse effects in both the foetus and the mother depending on the gestational period and may result in congenital varicella, neonatal varicella or maternal pneumonia (Katz *et al*., 1995; Tan and Koren, 2006; Lamont *et al*., 2011). Though varicella zoster infection provides long lasting immunity, waning of immunity occurs with age and immune deficiency conditions and leads to the development of herpes zoster (shingles). The incidence and severity of herpes zoster increases with age (CDCP., 2015).

Varicella is a vaccine preventable disease the vaccine was developed in the 1970's. High-income countries have incorporated varicella vaccine in their national immunization programs (Anonymous, 2008; CDCP., 2015). Inclusion of varicella vaccine in the national immunization schedule of most developing countries has been limited due to scarce resources and inadequate vaccine coverage. The WHO recommends that varicella can be prevented in high-risk subgroups of the population in these countries by vaccination (Marin *et al*., 2007).

**Corresponding Author:** Hathshya M. Munasigha,International Health Unit, Development and Planning Unit, Ministry of Health, Nutrition and Indigenous Medicine, No, 27/1, D.M. Colombage Mw, Nawala Rd, Nugegoda, Colombo, Sri Lanka

Prior to immunization of selected population subgroups, VZV immune status needs to be determined. Persons with past exposure to VZV either through illness, asymptomatic infection or by vaccination become seropositive for antibodies to the VZV (Anonymous, 2012) and will not require the vaccine. Single IgG tests are available to determine VZV immune status of persons. Varicella IgG serology test is cumbersome to conduct in the field and the test is not inexpensive in resource-limited countries (Munasingha *et al*., 2018). Thus, identifying non immune persons by large-scale serology testing of the population may be infeasible. Therefore we undertook to investigate whether self-reported history of VZV infection would be an accurate screening tool for determining VZV immune status among the general population in Sri Lanka, a low-middle income country in South Asia.

## MATERIALS AND METHODS

The study was embedded in the national health care system and methods have been described in a companion paper (Munasingha *et al*., 2018). In brief, the study was a population-based cross-sectional VZV seroprevalence study conducted during 2013 in 6 of 12 Medical Officer of Health (MOH) areas in Colombo District, Sri Lanka, MOH is a health administrative unit in the national health system for implementation of primary care. The sample size was calculated based on multistage cluster sampling with probability proportionate to size, the final study included 1,258 subjects comprised of all ages and both genders. Subjects were enrolled by government public health midwives in their homes on provision of signed informed consent in the case of infants or children, informed consent was obtained from parents or guardians. The midwife then administered a structured questionnaire that elicited demographic information, collective household income and past history of varicella and herpes zoster. Interview questions:

- What is your age and DOB, sex, residence, ethnicity, religion, marital state, level of education, employment state, category of employment, monthly family income?
- Have you ever had chickenpox? If yes, at what age?
- Have you ever had shingles? If yes, at what age?
- Were you ever vaccinated with chickenpox vaccine? If yes, at what age?

A government public health nurse collected a blood sample which was then tested in a government university microbiology laboratory for VZV antibody titres. Blood samples were analysed using a commercially available validated VZV ELISA-IgG antibody test kit with a reported sensitivity of 99.4% and specificity of 97% (Anonymous, 2012). Test results were categorized into: positive-immune to VZV and negative not immune to VZV.

**Statistical analysis:** Self-reported varicella infection was compared to serologic status (immune or not immune). Agreement between both sets of information sources was determined using Cohen's kappa coefficient ($\kappa$); $\kappa$ values were interpreted according to Cohen's guidelines ($\leq$0-no agreement; 0.01-0.20-none to slight; 0.21-0.40-fair; 0.41-0.60-moderate; 0.61-0.80-substantial and 0.81-1.00-almost perfect) (McHugh, 2012). Using the serological test as the gold standard, the Predictive Value (PPV) and Negative Predictive Value (NPV) for self-reported varicella infection was computed. The PPV was calculated as the number of subjects who were immune and who also reported previous varicella infection, divided by the total number subjects who reported a previous varicella infection. The NPV was calculated as the number of subjects who were not immune and who reported no previous history of varicella infection divided by the total number of subjects who reported no previous varicella infection. Results of the above computations are presented with associated 95% Confidence Intervals (CIs). Data were analyzed using SPSS.

The study group's mean age was 31 years (standard deviation, 19.2 years, range, 6 months to 87 years) (data are not displayed in a table). Subjects were predominantly female (70%) and most (60%) resided in urban areas. About 75% had secondary to pre-university education and two-thirds were of low socioeconomic status.

## RESULTS AND DISCUSSION

All of the 1,258 subjects included in the study underwent serologic testing for VZV antibodies. Of these 682 subjects were positive yielding a VZV seroprevalence of 54.2% (95% CI = 51.5-57%). For the total study group, the overall agreement between self-reported varicella infection and serologic immune status was substantial ($\kappa$ = 0.67; 95% CI = 0.63-0.71) (Table 1). Of 560 subjects who reported a previous varicella infection, 517 were confirmed to be immune for a PPV of 92.3% (95% CI = 89.8-94.4%). Only 8% of

Table 1: Validity of self-reported varicella using serologic IgG status as the gold standard according to selected age/gender groups

| | PPV* | NPV† | Sensitivity | Specificity | |
|---|---|---|---|---|---|
| | % | % | % | % | κ |
| Variables | 95% CI | 95% CI | 95% CI | 95% CI | 95% CI |
| Adolescents | 29/32 | 78/93 | 29/44 | 78/81 | |
| 13-18 years | 90.6 | 83.9 | 65.9 | 96.3 | 0.66 |
| Adults | 470/504 | 248/385 | 470/607 | 248/282 | |
| >18 years | 93.2 | 64.4 | 77.4 | 87.9 | |
| | 90.9-95.0 | 60.8-67.8 | 73.8-80.7 | 83.5-91.5 | 0.54-0.65 |
| Females | 243/256 | 178/247 | 243/312 | 178/191 | |
| 15-45 years | 94.9 | 72.1 | 77.9 | 93.2 | |
| | 91.5-97.0 | 66.2-77.3 | 73.0-82.1 | 88.7-96.0 | 0.60-0.73 |
| Total | 517/560 | 533/698 | 517/682 | 533/576 | |
| | 92.3 | 76.4 | 75.8 | 92.5 | 0.67 |
| | 89.8-94.4 | 73.1-79.2 | 72.5-78.9 | 90.1-94.4 | 0.63-0.71 |

*PPV = Positive Predictive Value, †NPV = Negative Predictive Value

subjects who reported a previous varicella infection were found to be nonimmune. Of 698 subjects who reported no previous varicella infection, 533 were confirmed to be not immune for a NPV of 76.4% (95% CI = 73.1-79.2%). The 24% of subjects who reported no previous history of varicella infection were actually found to be immune.

For adolescents, the agreement between self reported history of varicella infection and serologic immune status was substantial (κ = 0.66; 95% CI = 0.51-0.80). Of 32 who reported a previous history of varicella, 29 were confirmed to be immune for a PPV of 90.6% (95% CI = 73.8-97.5%). The 9% of this subgroup who reported a previous varicella infection was found to be nonimmune. Of 93 who reported no previous history of varicella, 78 were confirmed to be nonimmune for a NPV of 83.9% (95% CI = 74.4-90.3%). The 16% of adolescents who reported no previous history of varicella infection were actually found to be immune.

For adults, the agreement between self-reported history of varicella infection and serologic immune status was moderate (κ = 0.59; 95% CI = 0.54-0.65). Of 504 who reported a previous history of varicella, 470 were confirmed to be immune for a PPV of 93.2% (95% CI = 90.9-95.0%). Only 7% of subjects who reported a previous varicella infection were found to be nonimmune. Of 385 who reported no previous history of varicella, 248 were confirmed to be nonimmune for a NPV of 64.4% (95% CI = 60.8-67.8%). About one-third (36%) of adults who reported no previous history of varicella infection were actually found to be immune.

For women of childbearing age, the agreement between self-reported history of varicella infection and serologic immune status was substantial (κ = 0.67; 95% CI = 0.60-0.73). Of 256 who reported a previous history of varicella, 243 were confirmed to be immune for a PPV of 94.9% (95% CI =91.5-97.0%). Only 5% of these women who reported a previous varicella infection were found to be nonimmune. Of 247 who reported no previous history of varicella, 178 were confirmed to be nonimmune for a NPV of 72.1% (95% CI = 66.2-77.3%). The 28% of this subgroup who reported no previous history of varicella infection was actually found to be immune.

Table 2: Selected characteristics of self-reported herpes zoster cases (n = 12)

| Gender M/F | Age at varicella zoster | Age at herpes zoster | VZVIgG+/- |
|---|---|---|---|
| F | 3 | 24 | + |
| F | 3 | 38 | + |
| F | 8 | 51 | + |
| F | 10 | 32 | + |
| F | 13 | 30 | + |
| F | 14 | 35 | + |
| F | 16 | 27 | + |
| F | 25 | 50 | + |
| F | 30 | 50 | + |
| M | 17 | 39 | + |
| M | 19 | 78 | + |
| M | 21 | 65 | + |

Of the overall 1,258 subjects who underwent serologic testing, 12 (1%) gave history of having had herpes zoster infection, 9 of the 12 were females. All of the 12 reported previous varicella infection which was confirmed by their immune status by the serology IgG testing, the median age of acquiring varicella infection was 15 years (range, 3-30 years). The median age of acquiring herpes zoster infection was 38.5 years (range, 24-78 years) and the median time period from the acquisition of varicella infection to the development of herpes zoster infection was 22 years (range, 11-59 years) (Table 2).

In this study, conducted in Colombo District of Sri Lanka in 2013 we found that self-reported positive history of varicella infection was an indicator of VZV antibodies with a high degree of accuracy as determined by VZV antibody titers. The PPV was high among the overall group (92%) and in subgroups of adolescents (91%), adults (93%) and women of childbearing age (95%) for immunity to VZV. Only a small proportion of subjects in the overall group (7%) and in the subgroups (5-9%) who reported a previous varicella infection were found to be nonimmune. On the other hand a self-reported negative history of varicella infection was a not an accurate indicator of varicella infection with low NPV values ranging for the overall group (76%) and subgroups (64-84%) a relatively large proportion of subjects who reported as not having had varicella were actually found to be immune (overall group, 24%; subgroups, 16-36%).

The high PPV for self-reported varicella infection noted in this study for the overall group and for

subgroups is consistent with predictive value of self-reports of varicella from other countries of selected subgroups. In Taiwan, the PPV of self-reports of varicella among health care workers was 96.3% (Wu *et al*., 2012). A study conducted in Lyons, France, noted a PPV of 99.5% among pregnant women (Saadatian-Elahi *et al*., 2007). Iranian medical students were found to have a PPV of 91% (Allami *et al*., 2014). A study of Argentinian among women 15-49 years of age found a PPV of 99.4% (Dayan *et al*., 2002).

Previous studies in Sri Lanka have shown low PPV values. A study conducted in 2005 among adolescents (n = 271) in Kandy District Sri Lanka, found a PPV of 53% for self-reported varicella (Noordeen *et al*., 2014). Another study conducted in year 2000 among the same target population as the current study (Colombo District) found a PPV 72% (Liyanage *et al*., 2007). Data from the Colombo District indicate that the incidence of varicella has increased with time, the epidemiology unit of Sri Lanka reports a gradual increase of varicella cases (2010, n = 3500; 2013, n = 4500). Also, Colombo District has a higher number of reported cases compared to Kandy (Anonymous, 2013). The above findings indicate that PPV may not be a useful measure when the prevalence is low. The implications of study results in context of Sri Lanka are discussed next.

**Varicella vaccine:** The overall seroprevalence was 54.2% (Munasingha *et al*., 2018) which suggests that it would be optimal to include the vaccine in the national immunization program. Most developed countries have shown benefits of varicella zoster and herpes zoster vaccinations. As Sri Lanka has demonstrated excellent infectious disease control with other immunization programs and invests substantially for its primary health care, the inclusion of varicella vaccine in the national immunization program may be considered. At the current time, varicella vaccine is available only in the private health sector, the cost of the vaccine is Sri Lankan Rupees 3,000 (USD $20) and is not affordable to the low income population. Only 8 of 1 258 study subjects reported as having taken the vaccine. About 5 of the 8 were under 13 years of age and 5 of the 8 were in the high/middle SES group.

In the interim period, the government may consider offering the vaccine to selected subgroups of the population. As part of the child immunization program, the vaccine is given as a combined live-attenuated measles-mumps-rubella-varicella vaccine at 12 months of age or as a single vaccine at 12-24 months of age. If not vaccinated in childhood, the WHO recommends that all nonimmune persons above 13 years of age be offered the vaccine, two doses of varicella vaccine 4-8 weeks apart are required for successful vaccination (Anonymous, 2008).

The high PPV of self-reports of recall of varicella infection facilitates screening for immunity to varicella. The cost of serum testing for VZV antibodies is Sri Lankan Rupees 750 (USD $5) (Munasingha *et al*., 2018). As the test is relatively expensive, its primary value will be in individuals who do not report a previous VZV infection. Hence, self-reported varicella can be used as a zero-cost method to reduce serum testing for VZV IgG (Holmes *et al*., 2004; Holmes, 2005). The following recommendations are suggested based on the study findings:

**Positive history of varicella infection:** For persons who are not at high-risk, a positive history of varicella infection would be acceptable as an accurate indicator of positive immune status and these persons will not require the vaccine. For those at high-risk for varicella, serum-testing is suggested irrespective of history of varicella and the vaccine recommended for those who are nonimmune. Persons at high-risk for varicella infection include women of child-bearing age, adolescents and adults who have children residing in their homes, occupational environments where varicella may be transmitted (hospitals and institutions, schools, dormitories, etc.).

**Negative history of varicella infection:** For persons who are not at high-risk and report a negative history of varicella, serum testing is recommended to determine immune status and the vaccine offered to nonimmune persons. For those at high-risk for varicella, serum-testing is suggested irrespective of history of varicella and the vaccine recommended for those who are nonimmune.

**Herpes zoster vaccine:** We also noted a small percentage of study subjects reporting an episode of herpes zoster infection. As noted earlier, VZV has the capacity to persist in the body after primary infection (varicella) and become reactivated as herpes zoster. The most frequent complication is post herpetic neuralgia, chronic pain in the area where the lesions occur and resolve, ocular nerve involvement may result in vision loss (CDCP., 2015). In 2006, the US Food and Drug Administration (FDA) licensed the herpes zoster vaccine, the vaccine contains the same VZV used in varicella vaccine but at a much higher titer. The Center for Disease Control and prevention (CDC)'s Advisory Committee on Immunization Practices (ACIP)

recommends that a single dose of Herpes Zoster vaccine be given to adults 60 years and older whether or not they report a prior episode of Herpes Zoster in 2011, the FDA approved the vaccine for adults 50 years and older (Hales *et al*., 2014; Harpaz *et al*., 2008). The herpes zoster vaccine is not currently available in Sri Lanka.

## CONCLUSION

In conclusion we found that a positive history of varicella infection was an accurate indicator of VZV antibodies. For persons who are not at high risk of varicella infection a positive history of varicella may be used to indicate positive immune status in lieu of VZV serologic testing. For those at high risk for varicella infection and a negative history of varicella infection, serological testing is required to determine immune status. For all those determined to the non-immune by serologic testing, varicella vaccine should be offered.

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