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REVIEW ARTICLE

Epidemiology and factors influencing varicella infections in tropical countries including Sri Lanka

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Abstract Varicella zoster virus (VZV) infections occur worldwide but the epidemiology differs between different geographical regions. Epidemiology of varicella is partly understood in tropical and subtropical regions. Various hypotheses showing differences in exposure rates in different age groups have been proposed. Exposure to VZV during late childhood or adolescent stage causes high morbidity, especially in high school children, university students and young work force in tropical nations. Exposure to VZV infection or sero-prevalence rates through anti-VZV immunoglobulin G appears to be lower in Sri Lanka, similar to other tropical countries prior to the millennium. In contrast, a more recent study in a group of antenatal women showed a relatively higher exposure rate to VZV when compared to the exposure rates prior to 2004 in Sri Lanka. Climatic factors, socioeconomic conditions, mobility and cultural practices appear to play a role in the differences in the exposure rates to VZV infection in the tropics. In most tropical Asian countries including Sri Lanka, routine vaccination against varicella is not carried out. Individuals with negative history for varicella take the vaccine when there is a necessity. Medical and nursing students take the vaccine prior to their clinical training to avoid adulthood varicella.

Keywords Epidemiology · Varicella · Varicella zoster virus · Sero-prevalence · Sri Lanka

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Introduction

Varicella zoster virus (VZV) is an alpha herpes virus causing a self-limiting primary disease called varicella or chickenpox. Transmission of VZV occurs through respiratory aerosols and direct contact with vesicular fluid. There is a clinical attack rate of 65–85% for varicella in susceptible individuals followed by household exposure [42]. Varicella is characterized by fever concurrent with a generalized, self-limiting vesicular rash, itching and exhaustion in children but in adults and in immuno-compromised individuals the clinical severity could result in more severe and disseminated disease [34]. VZV infection may become reactivated after a period of latency to cause herpes zoster (shingles), which is characterized by a painful, localized vesicular rash involving one or more dermatomes.

Varicella has become one of the leading causes of vaccine preventable deaths in immuno-compromised children and the frequency of adulthood varicella and its complications are higher than previously estimated [9, 11]. Herpes zoster has also become a public health and social concern, mainly with increasing life spans [6]. Varicella during the first two trimesters of pregnancy can cause adverse effects to both mother as well as the foetus [13].

Varicella is usually diagnosed using the clinical features as the characteristic vesicular rash is diagnostic [34]. VZV can be isolated from the vesicular fluid in varicella and zoster 1–2 days after the onset of rash. Direct immunofluorescence (DFA) and PCR are used as successful methods of diagnosis by the detection of VZV antigen or DNA, respectively [20]. The "gold standard" for the diagnosis of VZV infection is culture of the vesicular fluid, which remains positive only during the first few days of the rash.

Treatment for VZV infections is only useful in relieving the symptoms. Both varicella and zoster can be treated with

acyclovir (ACV), depending on the severity, the antiviral may be administered orally and intravenously [58]. Antiviral drugs, famciclovir and valacyclovir can be administered orally for the treatment of zoster. Mothers and neonates who have varicella or at risk of developing varicella should be isolated on maternity wards [8]. Passive immunization with varicella zoster immuno-globulin (VZIG) is helpful in preventing or improving the clinical disease in individuals, who have a chance of developing severe cases of varicella. A live attenuated vaccine also known as "Oka vaccine" became available from late 1970s [47].

In temperate countries, children are predominantly affected by varicella and the sero-conversion to anti-VZV IgG occurs usually during late childhood and thus adults show up to 90–95% serological evidence for the past exposure to VZV [44]. Certain tropical and subtropical countries such as United Arab Emirates, Saudi Arabia and Iran show more than 80% sero-prevalence against anti-VZV IgG while a few other tropical countries like Pakistan, Singapore, India and Sri Lanka show low sero-prevalence rates making 40–60% of the adults susceptible to VZV infection [3, 38, 56].

The published data on the epidemiology of VZV in Sri Lanka is limited in the last decade and varicella was not a notifiable disease until 2006. Approximately 4000 varicella cases are notified annually in Sri Lanka (http://www.epid.gov.lk/web/index.php?option=com_content&view=article&id=148&Itemid=449&lang=en). This review focuses on the epidemiology of varicella with special reference to Sri Lanka while considering the factors affecting the epidemiology in different regions of the tropical world.

Epidemiology of VZV infections

Although VZV infections occur worldwide, there is a marked difference between the epidemiology of VZV infections among temperate and tropical regions [27]. The reason for the significant regional and seasonal variation in epidemiology is not clear. In temperate climates, VZV infection rate is high during winter and early spring. Majority of the populations in temperate countries such as the USA and UK seroconvert to anti-VZV IgG by adolescence.

Prevalence of VZV infections in temperate climates

In the USA, around 4 million annual varicella cases are reported with 100–150 deaths and > 10,000 hospitalizations [18, 32]. In the USA and UK, 90% of the population acquires VZV infection before 15 years of age [16]. In a study done by Wharton [57], only 6% of the population in the USA remains susceptible to the infection.

A similar age specific sero-prevalence pattern is seen in few other temperate countries including Slovenia, Germany, Spain and Switzerland. Among Slovenians, 75% of the varicella cases were reported in 3–4 year old children [46]. Of the overall adult population of Amsterdam, 94% have sero-prevalence for VZV IgG [53]. In Germany, children below 10 years show 94.2% sero-positivity for anti-VZV IgG [59] and in Switzerland 96.1% sero-positivity was seen among children below 12 years [1].

Data on VZV sero-prevalence among adults and children in Russia is limited, however, a study carried out by Vankova et al. [54] showed that the anti-VZV IgG level reached 90% by the age of 10 years.

The maternal immunity to varicella is more than 90% in countries like USA, Canada, UK and many parts of the Europe [24]. Prevalence of anti-VZV IgG in pregnant women in France, South-Western Finland, Ireland and Italy are 98, 96.2, 88.7 and 80.9%, respectively [4, 5, 23, 43].

Prevalence of VZV infection in sub-tropical and tropical climates

In the tropical climates, VZV infection rate is less in young children making them susceptible to infections during adulthood [29]. There is limited knowledge about the epidemiology of VZV in tropical Africa, however, 44.6% sero-prevalence among 1–4 years old in Guniea Bissau, which is not very different from the anti-VZV IgG sero-prevalence patterns in temperate regions [40].

Sero-prevalence rates of 81.3, 94.3 and 87.9% have been reported in adults in the United Arab Emirates, Turkey and Iran, respectively [25, 45, 52]. In Singapore, the sero-prevalence was 33.2% between 2008 and 2010 in 1–16-year-olds, however, the adults more than 25 years of age show 88% sero-prevalence for anti-VZV IgG from 1990 to 2010 [17]. According to Ooi et al. [38], > 90% VZV sero-prevalence is not achieved among Singaporean population until they are above 35 years. Malaysia has an anti-VZV IgG prevalence pattern similar to that of Singapore showing a low sero-conversion in children. The anti-VZV IgG prevalence rates reach > 90% in individuals more than 30 years [30]. The population younger than 20 years showed 70.4% sero-positivity for anti-VZV IgG in Bangkok, Thailand and the sero-positivity increased to 98–100% by the age of 40 [33]. In 1970 and 1980s, 83% sero-positivity for anti-VZV IgG was noted in 9–10 year olds in Japan and it rose to 100% in 25 year olds [49].

A progressive increase in the sero-prevalence for anti-VZV IgGwith age was observed in the Indian population;

16% sero-prevalence was noted in children aged 1–4 years and it progressed to 54% in 5–14 year olds [56]. During a study done in South India, a delayed sero-conversion to anti-VZV IgG was noted in 17–20-year-old nursing students and only 29.7% of the participants were sero-positive for anti-VZV IgG [55]. The Bangladeshi population in India, aged between 16–25 and 31–35 years showed 78 and 85% sero-prevalence for anti-VZV IgG, respectively [50].

Antenatal women attending a clinic in Darwin, Australia had 92% sero-prevalence for anti-VZV IgG despite Darwin being a tropical territory of Australia. The antenatal women subjected to the study were aged between 15 and 45 years, while the 15–19 year olds showed the sero-prevalence of 90.3% and this rose to 100% in more than 35 year olds [37]. More than 86% sero-prevalence for anti-VZV IgG has been reported in pregnant women in a temperate region of Australia [10]. More than 97% of women attending prenatal clinics in Argentina were immune to VZV by 15–19 years of age [15]. Anti-VZV IgG sero-prevalence among antenatal women admitted to a hospital in Harnedan, Iran was 78.4% [31]. A 74.4% sero-prevalence for anti-VZV IgG was noted in Saudi Arabia among antenatal women [21].

The data on exposure rates for VZV in the Sri Lankan population is growing (Fig. 1). In a study carried out in a selected urban and rural population in Colombo, the capital of Sri Lanka, none of the children less than 5 years in the rural area had detectable anti-VZV IgG. In the urban children, anti-VZV IgG sero-positivity was 10%. In the same study a sero-positivity of 17 and 24% for anti-VZV IgG was observed among children less than 15 years in urban and rural areas, respectively. In those aged 60 years, 50% in the rural population and 78.9% in the urban population were immune to VZV infections [28]. A more recent study, Munasinghe et al. [35], shows an overall sero-prevalence of 54.2% for anti-VZV IgG in which 75% of the sero-positivity has been noted in individuals more than 40 years.

VZV sero-epidemiological studies on antenatal women in Sri Lanka have not been carried out at the time of Liyanage et al. [28], in that study a significant number (56.2%) of females in the child bearing age lacked immunity against VZV. However, in the recent past, one of our studies reported an increased exposure rate of 78% to VZV in a group of antenatal women aged between 18 and 45 years. Moreover, in the study sample, those that were more than 40 years had a sero-prevalence of 100% to anti-VZV IgG and thus an increment in the exposure rate to VZV was noted with increasing age [14].In a more recent study conducted in Sri Lanka, the overall anti-VZV IgG sero-prevalence in the women of childbearing age was 62% and it was as low as 37% in the 15–19 years age group [35].

A study on Sri Lankan migrant workers in Saudi Arabia aged between 21 and 30 years showed a sero-prevalence rate of 35 and 58% and the Sri Lankans were found to be at risk of acquiring VZV infections than the native Saudi population [52]. In a study on the sero-prevalence of anti-VZV IgG among the adolescents of the Kandy District of Sri Lanka, only 34% of the adolescents had sero-prevalence for anti-VZV IgG. The sero-prevalence of antibodies against VZV was low among the adolescents in the Kandy District of Sri Lanka when compared with their equivalents in temperate countries. Individuals living in urban areas has a significantly higher anti-VZV IgG positivity rate than the individuals living in rural areas [36]. In a study carried out among the new entrant university students in Sri Lanka, half of the study population was found to be susceptible to VZV infection [26]. Frequent disease outbreaks have been reported in institutional settings, but data on the outbreaks are unavailable.

Although high susceptibility rates for VZV infection have been reported, the actual morbidity and mortality data for the infection remains incomplete in Sri Lanka. In 2003, 1749 patients with VZV infections were admitted to the Government Hospitals in Sri Lanka [2] and in 2009, an outbreak with 12,000 cases were reported among internally displaced individuals in Vavuniya (http://www.internal-displacement.org/assets/library/Asia/Sri-Lanka/pdf/Sri-Lanka-November-2009.pdf). Hence, the total number of VZV infections in 2009 reached a peak of 14,407 with the outbreak reported in Vavuniya. The total number of varicella cases recorded by the Epidemiology Unit from the Government Hospitals in Sri Lanka from 2007 to 2016 are given in (Fig. 2). Overall, a significant number of varicella cases are reported every year in the country (http://www.epid.gov.lk/web/index.php?option=com_content&view=article&id=148&Itemid=449&lang=en). However, data on the incidence among high risk populations are not available but this information remains crucial for the policy making on varicella vaccination (Table 1).

Factors influencing the epidemiology of VZV infections

VZV infection is more common in the winter and early spring in temperate regions [44]. Migration of populations and individuals has made a great contribution to the geographical epidemiology when it comes to the distribution of VZV strains in different regions [51]. Different reasons and theories have been proposed to reason the differences in the exposure rates to VZV infections in the tropics. Reasons for the differences in the exposure rates in temperate and tropical populations might be differences in the viral, host and geo-socio-climatic factors.

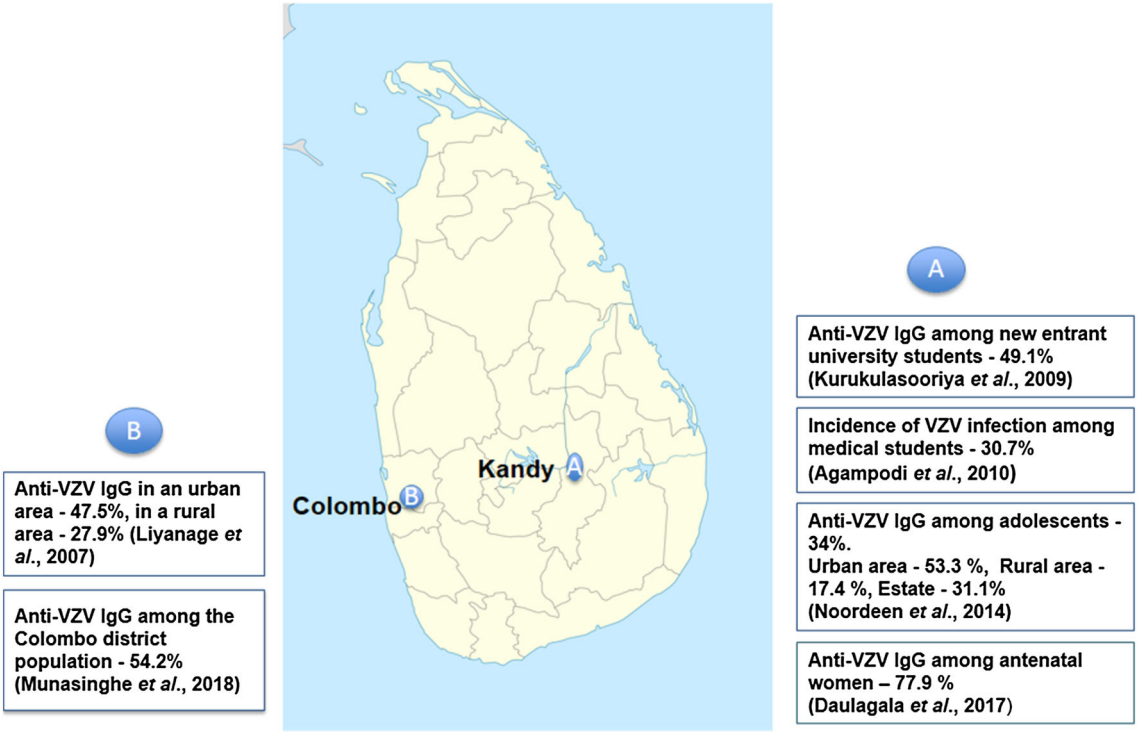

Fig. 1 Anti-VZV IgG sero-prevalence or protection rates against varicella among different age groups in Sri Lanka based on the previous studies [2, 14, 26, 28, 35, 36]

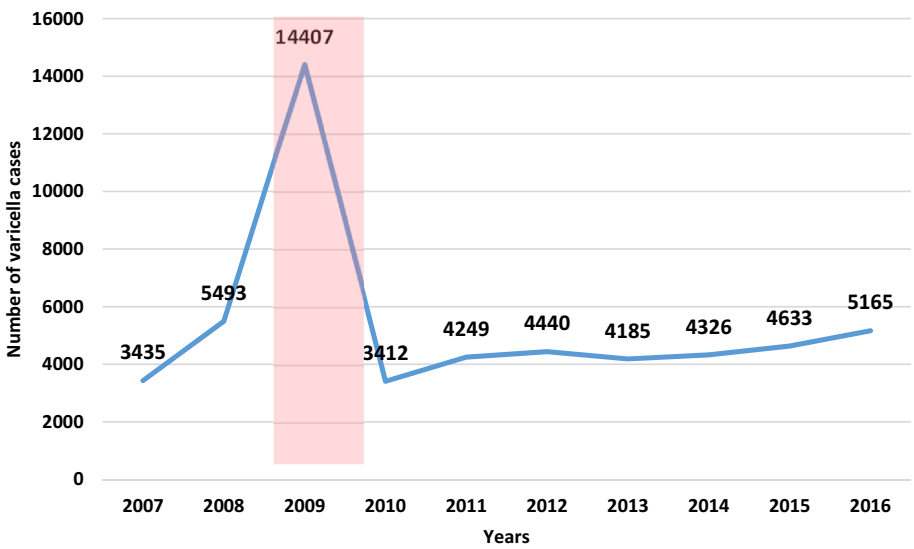

Fig. 2 Number of varicella cases reported in Sri Lanka from 2007 to 2015 (http://www.epid.gov.lk/web/index.php?option=com_content&view=article&id=148&Itemid=449&lang=en)

Taken together the viral and the host factors, VZV has been classified into different genotypes and serotypes depending on the geographical origin. Based on the geographical origin, Barrett-Muir et al. [7] has classified VZV into four genotypes, A (Africa/Asia), B and C (Europe and America) and J (Far East). The dominant genotypes circulating in most of the temperate countries are clade B and C (PstI+Bg/I-SmaI-), which have not been isolated in tropical and sub-tropical populations suggesting the involvement of the host factors. Hence, the reason for the higher sero-prevalence rates for anti-VZV IgG in temperate countries might be the circulating VZV types in those countries together with the host factors.

When considering the geo-socio environmental factors, immunity against varicella was associated with age, household exposure to varicella (as an adult), having siblings with the past history of varicella, subject/sibling attending pre-school, having a child who attended pre-

Table 1 Anti-VZV IgG sero-prevalencerates in temperate and tropical and sub-tropical countries in different populations

Country	Sample size (n)	Age (years)	Sero-prevalence (%)	Study (references)
Temperate countries				
France	486	NS	98.8	Saadatian-Elahi et al. [43]
Germany	4602	10–11	94.2	Wutzler et al. [59]
Ireland	7872	NS	88.7	Knowle et al. [23]
Italy	728	17–42	80.9	Alfonsi et al. [5]
Netherlands	1341	18–65	93.8	Van Rijckevorsel et al. [53]
Russia	2000	10	90	Vankova et al. [54]
Slovenia	3689	3–4	85.6	Sočan et al. [46]
South Western Finland	558	16–45	96.2	Alanen et al. [4]
Switzerland	256	< 12	96.1	Aebi et al. [1]
United Kingdom	NK	< 15	> 90	Fairly and Miller [16]
United States of America	NK	11–19	94	Wharton et al. [57]
Tropical and sub-tropical countries				
Argentina	2807	15–49	98.5	Dayan et al. [15]
Australia	373	14–40	86	Chant et al. [10]
	298	15–45	92	O'Grady et al. [37]
Guniea Bissau	44,034	< 4	44.6	Poulsenet al. [40]
India	102	17–20	29.7	Venkitaraman et al. [55]
	NK	5–14	54	Venkitaraman et al. [56]
India (Bangladeshi population)	NK	16–35	85	Thomas et al. [50]
Iran	635	10–40	83.6	Sharifi et al. [45]
	270	24–34	78.4	Mamami et al. [31]
Japan	1973; n = 670	25–29	100	Taylor-Wiedeman et al. [49]
	1984; n = 677			
Malaysia	2450	> 30	> 90	Malik and Bahrain [30]
Singapore	1200	1–17	50.8	Fatha et al. [17]
	1200	> 25	88	
	500	35–45	98	Ooi et al. [38]
Sri Lanka	913	1–60	47	Liyanage et al. [28]
	451	19–22	41.9	Kurukulasooriya et al. [26]
	172	30.7	25–28	Agampodi et al. [2]
	271	12–19	34	Noordeen et al.[36]
	181	18–45	76	Daulagala et al. [14]
	1258	5–60	54.2	Munasinghe et al. [35]
Thailand	NK	40	98–100	Migasena et al. [33]
Turkey	2136	> 15	94.3	Kose et al. [25]
United Arab Emirates	648	< 46	81.3	Uduman et al. [52]
	926	NS	74.4	Ghazi et al. [21]

NK not known; *NS* not specified in the study

schooland previous or current employment of the parent/s. Geo-socio environmental factors were noted by a study conducted in a population of immigrant Bangladeshi women and the British women [48]. The socio-economic standards play a role in the VZV epidemiology in certain countries [12, 39]. In that context, there is a difference between VZV epidemiology in urban and rural settings of the tropical countries such as India and Sri Lanka. Number of siblings and residential area (urban, estate and rural) showed a statistical association with the presence of anti-VZV IgG among adolescents in the Kandy District of Sri Lanka. This could be due to high population density in urban areas enabling higher transmission rates [36].

In Sri Lanka, more urban adults are immune to VZV infection compared their counterparts in the rural areas [28]. Many other studies also suggested that delayed onset

of VZV infection in rural tropical areas is purely a rural phenomenon. However, no differences in prevalence rates for VZV was analyzed for rural and urban areas in studies conducted in Switzerland [22] and Argentina [15]. The reason for this may be differences in population density, movement of people in rural areas for better employment in the cities or any other differences in the urban and rural populations in these countries [15].

When considering the climatic factors, high ambient temperature and humidity might affect the VZV transmission [19] and it is believed that the virus gets inactivated at higher temperatures [41]. According to another hypothesis ultra-violet (UV) radiation shows a major difference between tropical and temperate zones and it inactivates the virus in vesicles before or after they rupture and thus reducing the infectivity of the virus. This hypothesis explains why transmissibility in the tropics are low throughout the year and why the incidence of varicella hits a peak during winter and spring in temperate zones, when the effect of UV radiations are at its lowest [41]. The seasonal and regional variations in acute VZV infections within some Southeast Asian countries support this argument. According to Lee [27], VZV infection occurs during cooler months in more temperate regions of Southeast Asian countries. In the southern part of India the highest level of varicella associated morbidity and mortality were observed in the coolest months of the year [19], similar observations were made in Thailand during 1995–1997 [33].

Although socio-cultural factors might be playing a role in VZV infections especially in South Asia, there are no documented evidence to support how they contribute to the control of VZV infections in childhood. Compared to other South Asian countries, VZV sero-prevalence is lower in Sri Lanka and the reasons for these differences are also unclear. However, being an island near to the equator, Sri Lanka experiences the tropical climate year around, hence, the high temperature and humidity might be affecting the virus transmission adversely. Higher morbidity rates associated with VZV in adults are recorded in Sri Lanka. Due to the seriousness of illness, as a cultural practice most Sri Lankans isolate infected patients to reduce the transmission of the infection to other children. Whereas, in the Western countries 'varicella parties' are considered as a way to protect children from more severe infections during adulthood [28].

Concluding remarks

Varicella is a major public health concern in the tropics including Sri Lanka. Sri Lanka shows lower sero-prevalence rates than some other tropical countries making a significant proportion of adults in the country susceptible to VZV based on data prior to the millennium. Although the most recent data on antenatal women show a relatively higher exposure rates by anti-VZV IgG, a significant number of varicella have been reported in the island. Varicella and its complications poses an economic drain to the country, however, currently the economic impact of varieclla is not estimated. To evaluate the epidemiological impact of VZV infection and its complications, establishing the active and passive surveillance systems will be useful in the tropics. Substantial economic and health benefits can be enjoyed with vaccinating the non-immune adolescents routinely. In countries like Sri Lanka vaccination policies should be made and implemented for the routine vaccination of risk groups including the immunocompromised, young women, health care workers and neonates exposed to the virus at birth. Childhood varicella should be encouraged to minimize the risk of adulthood varicella and its complications.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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