

## The age of infection with varicella-zoster virus in St Lucia, West Indies

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### SUMMARY

Sera from an age-stratified sample of 1810 people from the Caribbean island of St Lucia were tested for antibodies against varicella-zoster virus. The results indicate that very few infections occur in childhood, which agrees with clinical survey data from other tropical countries, but contrasts with the observed high case rate in children in temperate countries. The alternative hypotheses which may explain these results are discussed, and it is suggested that high ambient temperatures interfere with the transmission of the virus. Irrespective of the cause, the pattern of varicella incidence observed has important implications for any vaccination policy adopted in tropical countries.

### INTRODUCTION

Varicella (chickenpox), primary infection with varicella zoster virus (VZV), is a very common childhood infection in temperate countries, although the mean age of infection is significantly higher in developing countries [1–8]. This is the reverse of the age pattern observed with many other directly transmitted infections, such as measles, where the mean age of infection is typically low in developing or tropical countries because of a mixture of high population densities, which provide more opportunities for disease transmission, and high birth rates, which provide a large pool of young susceptibles [9]. The reversed age pattern of varicella infection raises questions about the nature of varicella transmission.

In order to address these questions this paper discusses the evidence that the force of infection (the *per capita* rate at which susceptibles acquire infection) of VZV is less in tropical than in temperate countries. The paper examines published reports, describes a serological investigation of the pattern of infection in the population of the Caribbean island of St Lucia and uses the survey data to estimate the age-specific force of infection.

The discussion of varicella transmission in this paper centres on differences between tropical and temperate countries. However, tropical countries are usually

Table 1. *A summary of published varicella clinical study data from tropical and subtropical countries*

Location	Approximate latitude	Date	Number of cases	Mean ( $\pm$ SD) of age of infection in years	Reference
Angoda, Sri Lanka	7° N	1955-9	5787	27.2 $\pm$ 14.6	Mauretic and Cooray, 1963 [3]
Guatemala	15° N	1963	65	3.24 $\pm$ 2.81	Salomon et al. 1966 [4]
West Bengal, India	23° N	1970-4	236	23.7 $\pm$ 17*	Sinha, 1976 [5]
Kerala, India	27° N	1976	984	20.2 $\pm$ 16.7	White, 1978 [6]
Kerala, India	27° N	1974-5	46886†	28.7 $\pm$ 18.3	White, 1978 [6]
Vellor, India	13° N	1977-82	132	22.5‡ $\pm$ 4.5	Venkitaraman and John, 1984 [7]
Ibadan, Nigeria	7° N	1970-80	2067	14.0 $\pm$ 11.8	Iyun, 1984 [8]

\* Crude estimate of the standard deviation from a graph.

† Notification data as opposed to the survey data cited from the same publication.

‡ Only adults (staff and students of the hospital) were included in this study.

also developing countries with respect to their economic and demographic characteristics while temperate countries are usually regarded as socio-economically developed. It is not clear whether the observed epidemiology of varicella is a consequence of economic, demographic or climatic conditions. Because our conclusions favour an explanation based on climate we will categorize populations as tropical or temperate, although we recognize that the alternative socioeconomic categorization (developing *vs.* developed) may have equal validity.

#### *Reports of the age distribution of cases of varicella*

Records of cases of varicella from clinical surveys in developing countries are presented in Table 1. Mauretic and Coorey [3] describe a large number of severe cases of varicella in adults amongst patients reporting to a Sri Lankan hospital. However, since the severity of the disease increases with age [10], the probability of someone with varicella seeking medical assistance could also be age related. The strength of such a bias may be greater in tropical countries where medical facilities are often less readily available.

On the basis of the high number of adult fatalities associated with varicella in rural Kerala, India, White [6] suggested that varicella is more prevalent amongst adults. This she attributed to the geographical isolation of the small communities, which would reduce the probability of individuals encountering varicella infections at a young age. This cannot, however, explain the relatively high age of the cases reported to hospitals in the densely populated Nigerian city of Ibadan [8].

More detailed surveys from Vellore, India [7] and from rural West Bengal, India [5] show similar patterns. In the Vellore study of hospital staff and students, the incidence of varicella was considered 'remarkably high for adults' [7]. In the West Bengal study of a village population of 2248 living on  $\frac{1}{3}$  km<sup>2</sup> of land, the virus was observed to cause small epidemics of disease each year with an average age of infection of 23.4 years [5].

Table 2. A summary of published surveys of prevalence of varicella antibodies in tropical and subtropical countries

Location	Approximate latitude	Date	Number of adults (> 15 years)	Test*	Percentage adults seropositive	Reference
Brazil	2° N	1951	51	CF	41	11
St Lucia	13° N	1970	278	CF	20.9	12
Israel	32° N	1973-6	463	IFAMA	67.8	13
Israel	32° N	1980-1	176	ELISA	59	14
India	13° N	1984	24	ELISA	72	15, 16

\* CF, complement fixation; IFAMA, indirect fluorescent antibody to membrane antigen; ELISA, enzyme-linked immunosorbent assay.

The only clinical data from tropical countries which do not have the same pattern come from a study of a rainforest community of 1025 people in the Guatemalan Highlands, where only young children were infected during an epidemic of varicella [4]. Thus most clinical studies in tropical countries indicate a higher rate of infection in adults.

#### *Surveys of antibody to varicella*

Small-scale serological surveys of the prevalence of varicella antibodies with age also suggest that infection is more common in adults in the tropics, although most of the surveys suffer from methodological limitations. Two early serological surveys (Table 2) used the complement fixation (CF) test, which is useful as a diagnostic tool but is too insensitive to provide a reliable indication of past infection [1, 17]. Studies in Israel indicate that the proportion of people seropositive for varicella is low relative to prevalences in some temperate countries [2, 13, 14], but the relevance of this finding to tropical countries is difficult to assess due to the unique demographic and immigration patterns of Israel. This difficulty is illustrated by the study by Margalith, which shows a lower proportion of seropositive individuals amongst a population of 342 'western Kibbutz volunteers' than amongst the resident Israeli population [14].

A serological survey was carried out in Vellore, India [15, 16], where 171 people were tested using an enzyme-linked immunosorbent assay (ELISA). Seventy-two percent (95% confidence interval of 18%) of adults (15-24-year-olds) were seropositive, but again this result is difficult to interpret since the sample size for the adult age group was only 24.

Indirect evidence of a difference between tropical and temperate populations comes from a serological survey of pregnant women conducted in the USA by Gershon and colleagues [19]. The proportion of women with antibodies against varicella was 84% for 51 women born in the tropics and 95% for 88 women born in the United States of America. It is unclear, however, whether this difference relates to the geographical origins of the women, or to other confounding differences between immigrants and residents.

Thus, the majority of evidence points to a lower prevalence of varicella amongst children in the tropics. However, no large-scale study of the prevalence by age of

antibodies against varicella has been carried out in a tropical population using a sensitive assay. To clarify this relationship we conducted a study of VZV seroprevalence in the population of the Caribbean island of St Lucia. A total of 1810 sera, taken representatively from across ages, were tested for antibodies to varicella virus. The sera were also tested for herpes simplex type-1 (HSV-1) antibodies, because one of the possible explanations of the observed dynamics of VZV discussed below is that varicella infections are prevented by cross-immunity from antibodies acquired against HSV-1 infections.

## MATERIALS AND METHODS

### *Study design*

St Lucia is a small island (238 sq. miles) with a population, in 1984, of 134 066, and an annual population growth rate of 3% per annum [19]. The collection and storage of the serum samples is described by Cox and colleagues [19]. The 1810 samples, which include more than 1% of the entire population, were taken between September 1985 and April 1986 in work places, schools, nurseries, clinics and places of recreation chosen in order to represent the age and socio-economic distribution of the population. At each site people were selected at random from those present. The study was conducted with the agreement of the Ministry of Health and permission was received from all subjects or their guardians.

### *Serological tests*

The ELISA test has proved reliable for studies of VZV and HSV-1 antibody prevalence [20–22]. In-house ELISA tests were developed for the detection of specific anti-VZV and anti-HSV-1 antibodies using commercially available whole-virus antigen (D.M.R.Q.C. London). An indirect method was used based on that previously outlined for the detection of antibody to measles and rubella viruses [23]. Optimal dilutions of antigens and test sera were determined by 'checkerboard' titration. Plates were coated overnight with antigen at 4 °C and blocked, for 1 h, with 1% bovine serum albumin prior to the addition of sera. Incubation periods for sera and conjugate (mouse antihuman IgG, Dako Ltd) were 3 h each at room temperature. Substrate (OPD) was added for 30 min, the reaction was stopped using 5 M-H<sub>2</sub>SO<sub>4</sub> and absorbance detected at 492 nm.

A standard was produced for each specific assay (VZV and HSV), comprising a pool of high titre positive sera diluted with negative serum. This was added to each plate and used to standardize results, generating arbitrary units of antibody concentration. The dividing point between negative and positive for seropositivity was determined from the minimum of the bimodal frequency distribution of the results.

Because cross-reaction between HSV and VZV has been detected by CF tests [17] the possibility of cross-reaction detectable by ELISA was examined by pre-absorption with HSV antigen of sera positive for VZV then retesting by ELISA. Six sera, with antibody titres to VZV ranging from low to high were incubated with HSV antigen at a range of dilutions around the optimal dilution used in the HSV-1 ELISA at 37 °C for 1 h. The sera, plus non-preabsorbed controls, were then screened by ELISA for specific VZV and HSV-1 antibodies. The VZV antibody

concentrations of the preabsorbed sera remained constant and comparable with the control at all concentrations of HSV-1, suggesting no cross-reactivity between antibodies, as detected by ELISA.

## RESULTS AND DISCUSSION

The age distribution of antibody to varicella in St Lucia is shown in Fig. 1. Less than 10% of the population have experienced infection before the age of 15 years. There is then a gradual rise in seropositivity until the age of 40. The majority of cases of varicella occur in young adults, and very few children under 10 years of age are infected. This pattern is very different from that observed in countries such as Germany, Spain, USA, and Japan, where the majority of cases are found in young children [2]. To illustrate this difference Fig. 1 also shows the results of an age-stratified survey (380 randomly selected sera sent to a laboratory for diagnostic reasons unrelated to VZV infections) from West Germany [24]. The mean age at infection in St Lucia is 38.3 years, which contrasts with a mean age of 10.6 years for the West German data. Other directly transmitted viral infections do not, however, appear to exhibit this contrasting age-distribution. Fig. 2 shows that the seroprevalence of antibodies to mumps in St Lucia has a similar age-profile to those observed in England and The Netherlands [19, 23, 26, 27], with a typically low mean age at first infection [25].

### *Modelling of varicella incidence*

The difference between the age-distribution of varicella in St Lucia and in temperate countries may reflect differences in the transmission of the virus. Some estimate of the magnitude of these differences can be obtained by calculating the age-specific forces of infection using the method described by Grenfell and Anderson [28], where maximum likelihood estimates of the force of infection over age blocks are derived. The profiles of varicella seroprevalence with age for St Lucia, and an average calculated using data from Germany, Spain, Japan, USA and Israel are compared in Fig. 3. Age-specific estimates of the forces of infection for these populations are compared in Fig. 4. The forces of infection amongst children are very different, those in temperate countries being approximately 40 times those in St Lucia (Fig. 4). The forces of infection in the 15–44-year age class are also lower in St Lucia than in temperate countries, but are slightly higher than amongst St Lucian children (Fig. 4). The comparison of forces of infection for those > 45 years old is unclear because the data are unreliable for temperate countries as there are so few varicella cases in this age group. The force of infection, the rate at which susceptibles acquire infection, is a composite measure of the probability that infection is transmitted when a susceptible individual is in contact with someone infected, and of the number of contacts a susceptible will have with someone infected. In temperate countries, where the majority of varicella cases are amongst children, few adults are susceptible: thus, forces of infection experienced by adults are likely to produce few new infections. In St Lucia, transmission of varicella is low in all age groups, although there is a gradual increase in seroprevalence with age. This indicates a slight increase in the risk of acquiring varicella in adulthood.

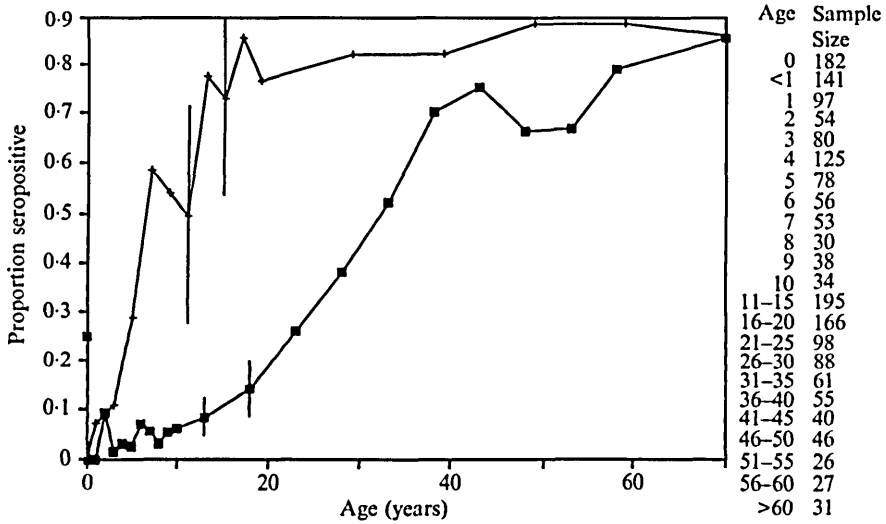


Fig. 1. The proportion of individuals with antibody to varicella-zoster virus according to age, on St Lucia (■) and in West Germany (+) [24]. The sample sizes for each age group in St Lucia are shown. The minimum sample size of each age group in the West German study was 20. 95% confidence intervals are shown on two of the points from each profile to illustrate the differences between the curves from ages 5 to 30 years. In the absence of exact sample sizes the minimum sample size of 20 was assumed in calculating the 95% confidence intervals for the results from West Germany.

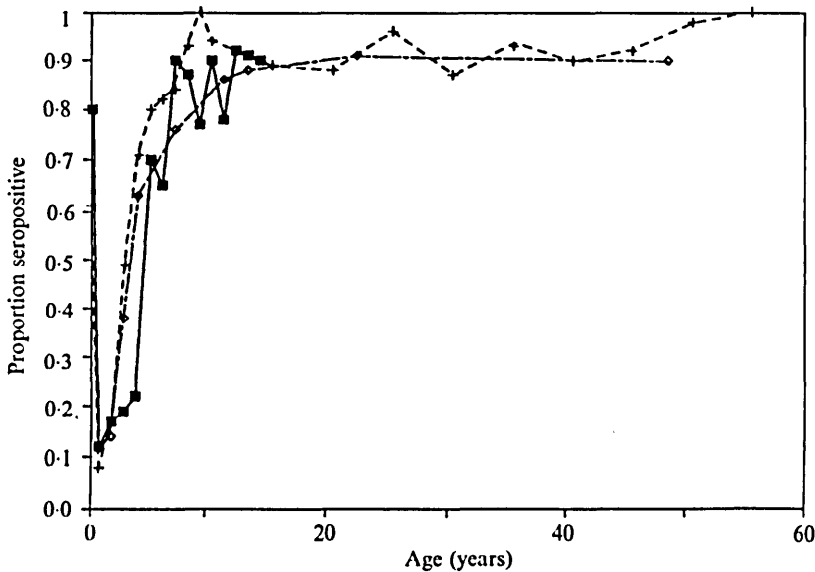


Fig. 2. The prevalence with age of antibodies against mumps shown in serological tests. A comparison of the serological profiles for St Lucia (+) [19], England (◇) [26], and The Netherlands (■) [27].

The results of the serological survey and the calculation of transmission intensity demonstrate a much lower rate of varicella transmission in St Lucia compared with that in temperate countries such as Germany and the USA. Because the transmission of other directly transmitted viral infections, such as mumps and

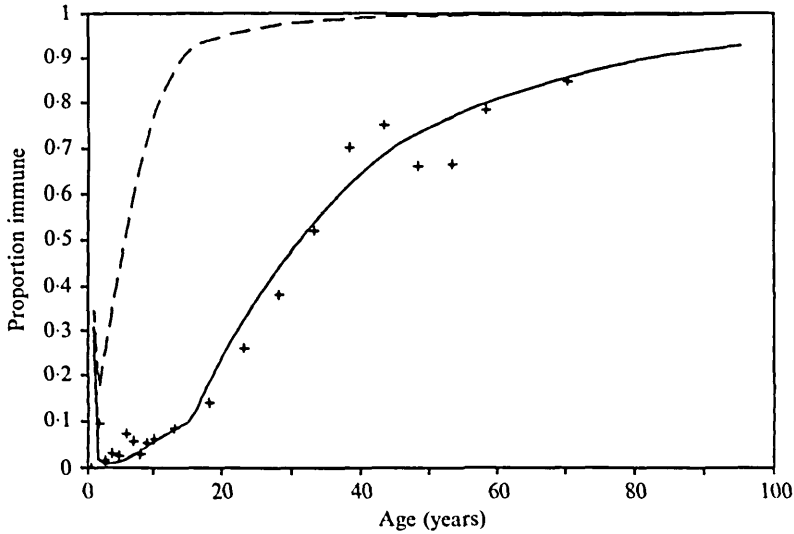


Fig. 3. The proportion of particular age groups seropositive to VZV on St Lucia (+) with the profile which best describes the pattern (solid line). The dashed line is the equivalent profile derived from epidemiological data from Germany, Spain, USA and Japan [2]. Both profiles were calculated using the method of Grenfell and Anderson [28].

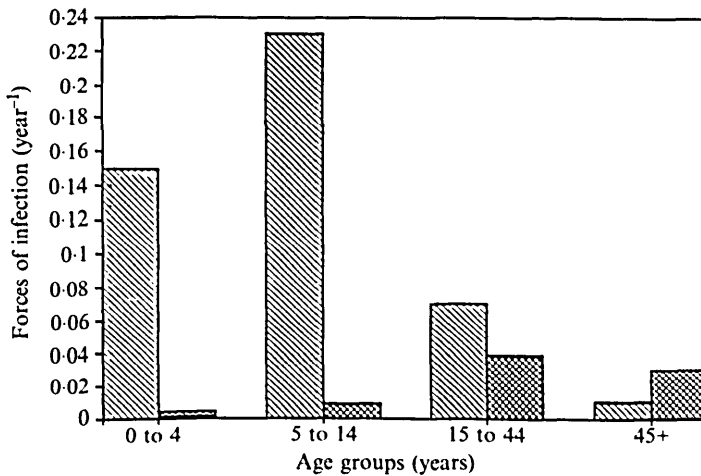


Fig. 4. The force of infection per year calculated in age blocks for St Lucia (▨), calculated from the profile in Fig. 3 following the method of Grenfell and Anderson [28], and for Germany, Spain, USA and Japan (■) taken from Garnett and Grenfell [2].

measles, remains high in tropical countries such as St Lucia, it is perhaps useful to look at how varicella transmission differs from that of other directly transmitted viruses.

Varicella infections are often acquired without direct contact between susceptible and infected individuals [29, 30], which suggests airborne transmission. It is generally accepted that the main source of infectious VZV is from



respiratory aerosols, since infection is sometimes transmitted before the onset of skin lesions in index cases [31–33] and because the seasonal incidence of varicella is similar to that of other infections spread by respiratory aerosols such as measles and rubella [1]. However, the relative importance of virus shed from the respiratory tract and from skin lesions is unclear. In local studies of the probability of transmission it was found that, within households, the transmission of varicella is almost as likely as the transmission of measles, but that the transmission of varicella to the wider community is much lower for varicella than for measles [34]. This suggests that proximity may be more important for the transmission of varicella than for measles. In addition, high levels of live virus can be found in fresh cutaneous lesions [35], whereas attempts to isolate the virus from the respiratory tract have failed [36, 37].

If varicella transmission occurs from virus shed from lesions as well as from aerosols then a possible explanation of a low transmission probability of VZV in tropical countries is that the virus in exposed cutaneous lesions is inactivated by the ambient tropical temperatures. It may be that some proportion of varicella infections transmitted from cutaneous lesions in temperate communities is prevented in tropical communities. It is also feasible that ambient tropical temperatures inactivated virus in respiratory aerosols although this would have to occur on a shorter time scale. It has been observed that VZV is inactivated if kept at 60 °C for 30 min [38]. However no systematic attempt has been made to look at the influence of temperature on the virus or to compare the temperatures need to inactivate VZV with those needed to inactivate other viruses.

If temperature is responsible for slowing the spread of varicella then we would expect the majority of cases in tropical communities to occur when seasonal temperatures are low. This may be illustrated by the time series data from the clinical study in the Vellore hospital [7] where the seasonal peak incidence of varicella coincides with the minimum temperatures and maximum humidity (Fig. 5a). In Kerala the highest levels of varicella associated mortality are around January, the coolest part of the year [6, 39]. Other time series show a more confused picture. In Sri Lanka (Fig. 5c) the peak incidence of varicella is during the dry season but the relationship with temperature, which varies little in Sri Lanka [39], is unclear. Neither is the relationship clear in Ibadan (Fig. 5b), where the peak incidence is in the cool dry season, but the minimum temperature coincides with a rise in incidence [8, 39]. It is recognized, however, that the apparent concordances of time series could be confounded by seasonally varying social factors, such as school terms, which play an important role in varicella epidemiology in developed countries [40].

Other hypotheses, although in our view less likely, could also explain the observed low forces of infection in St Lucia.

*St Lucia as an isolated community.* VZV is a typical herpes virus, which can persist in small isolated populations [42], because it has a latent phase which can reactivate as infectious herpes zoster. Thus, because VZV is endemic there, the island's geographical isolation cannot explain the observed prevalence of varicella.

*Interference from other pathogens.* It has been suggested that there could be 'epidemiological interference' from other infections which inhibits varicella infection in the tropics [1, 5, 35]. It is thought that 'intense transmission of viruses



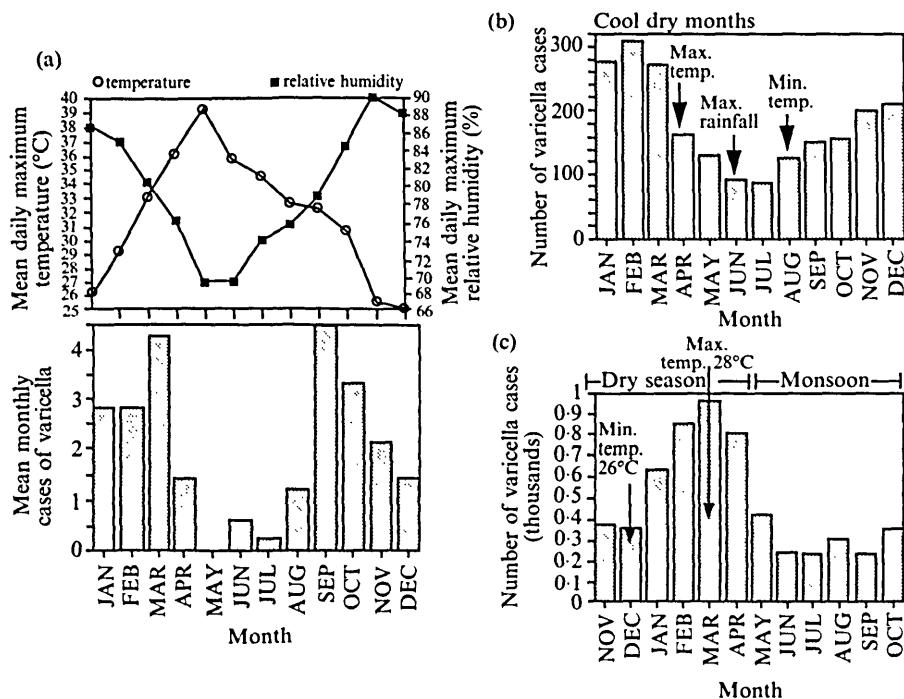


Fig. 5. (a) Mean monthly case reports of varicella, maximum daily temperature and maximum daily relative humidity for the Christian Medical Hospital in Vellore, 1977-81 (from Venkitaraman and John, [7]). (b) The total number of cases reported in each month to the Infectious Disease Hospital, Ibadan, 1970-80 (from Iyem, [8]). (c) The total number of cases of varicella by month, for the fever hospital Angoda, Sri Lanka, 1955-9 [3]. Maximum and minimum temperatures are for the nearest site for which they are recorded in the Times World Atlas [39].

among children may create competition among the viruses for the same "soil" and may therefore postpone some common infectious diseases to a later age' [5]. A possible way in which viruses could influence each other is through the stimulation of non-specific immune mechanisms such as the production of interferon, which may prevent the establishment of another virus. Although this effect has been used to explain the poor performance of oral polio vaccine in tropical countries [42], it is difficult to see why varicella should be more affected than other virus infections transmitted by the same route.

*Cross-immunity from herpes-simplex infections.* It seems unlikely that non-specific interactions between viruses are responsible for preventing infections with VZV. However, it may be more probable that closely related infections could lead to immunity against some common antigens which may generate cross-immunity. Herpes simplex virus (HSV) is the virus most closely related to varicella-zoster virus, and there is some evidence of cross-antigenicity between these viruses in serological tests [43-45] and Wolff and colleagues [46] present data which could be interpreted as indirect evidence that varicella incidence is influenced by the presence of antibodies against HSV. In St Lucia, herpes simplex infections occur at a very young age, and by the age of 7 years > 90% of the children have been infected, which compares with 25-50% infection in 5-9-year-old children in

temperate countries [22]. This degree of difference between HSV prevalence in children in tropical and temperate areas is difficult to reconcile with the very large difference in VZV prevalence.

*Host genetic resistance.* The differences between the ethnic composition of temperate and tropical communities might be seen as one explanation for differences in susceptibility. However, recent research on the seroprevalence of varicella antibodies amongst pregnant women who had lived all their lives in London found that the proportion of seropositives was independent of ethnic groupings (personal communication, Nokes DJ, 1991).

*Sociological isolation of varicella cases.* Varicella has similar symptoms to smallpox and it is possible that residual fear of the latter may still lead to the rejection and effective isolation of infected individuals. Such isolation is unlikely to have a major effect, but it may contribute to the slight increase in the force of infection amongst adults, since it is more difficult for those adults responsible for the care of the sick to isolate themselves from infection.

### Conclusion

This study has generated a reliable indication of the mean age of varicella incidence in a tropical country. These results suggest that there is a substantial difference in the transmission of varicella in tropical and temperate populations. Of the possible explanations presented, the most convincing is that some combination of ambient temperatures and humidity inactivates the virus and reduces transmission in the tropics. This suggests that cutaneous lesions may play a role in transmission, and further studies which compare transmission within and between households might help elucidate this role.

This study has highlighted differences in VZV epidemiology in different geographical regions. These differences may have important implications for the use of the newly developed varicella vaccine [47] in tropical countries. In addition, the difference in age of initial infection observed in tropical and temperate countries may influence the timing of the reactivation of zoster. If time since initial infection is more important than age in this reactivation then we could expect a much lower incidence of zoster in tropical countries. At present there are no data available on the incidence of zoster in tropical communities and this also might reward investigation.

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