Seroepidemiology of *Varicella zoster* in Israel Prior to Large-scale Use of Varicella Vaccines

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Abstract

Objectives: This large-scale study provides up-to-date estimates of *Varicella zoster* virus (VZV) age-specific seroprevalence and characteristics of VZV transmission in a representative sample of the Israeli population.

Methods: In 2000–2001, 1,642 sera collected from an age-stratified general population sample were tested for VZV antibodies using an indirect IgG ELISA system.

Results: The age-weighted VZV overall estimate was 90.2%. Seropositivity increased rapidly with age, from 68.9% at age 4 to 94.4% at age 7 and 96.6% at age 12 years. The highest force of infection was in the 4–5 years age group (0.548 per susceptible year) followed by the 6–9 years age group. Multivariate analysis revealed that VZV seroprevalence estimates were significantly associated with age and place of origin. The highest seroprevalence estimate was found among subjects of Eastern origin.

Conclusions: The seroepidemiology of VZV in Israel shows a pattern corresponding to that described for developed European countries. This study indicates that the highest force of infection is in pre-school children. Knowledge of pre-vaccination seroepidemiology is important to evaluate the effect of vaccination programs on the epidemiology of the disease.

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Introduction

The *Varicella zoster* virus (VZV), an alpha-herpes virus, can cause two distinct clinical entities: varicella (chickenpox) and herpes zoster (shingles, zoster). One attack of varicella generally confers lasting immunity to the disease, but the virus persists in latent form within sensory ganglia. The reactivation of this endogenous virus produces herpes zoster.

Varicella is an acute, highly contagious exanthema with a worldwide distribution. In metropolitan communities in temperate climates, varicella is endemic, with a regularly recurring seasonal incidence in winter and spring. In Europe and North America, varicella is primarily a disease of childhood [1]. In tropical and semitropical countries, infection is delayed and varicella is seen more often in adults. The proportion of susceptible adults is even higher in Asia, Africa, and the Middle East [2]. In immunocompetent children (2–18 years), systemic symptoms are usually mild and serious complications are extremely rare [1].

In adults, young children (<1 year) and immunologically compromised persons of any age, varicella can exhibit a spectrum of more severe presentations and complications. The mortality of varicella in adults is 25 times greater than in children [3].

Pregnant women are an additional group of specific concern since VZV infection can have adverse sequelae for both the mother and unborn child (congenital varicella syndrome and congenital varicella) [4].

In the early 1970s, Dr. Takahashi and his colleagues in Japan developed a live attenuated VZV vaccine (Oka strain) [5]. Long-term immunity of recipients of the Oka strain of vaccine has been reported to persist 20 years after vaccination [6]. Nevertheless, in immunocompetent individuals, the immunity induced by the vaccine is not as solid as that induced in wild-type VZV infection. About 25–31%

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of vaccinees lost antibodies to VZV over time but continued to experience modified disease and showed partial protection against severe varicella [7, 8]. This could have a negative consequence with an increase in the proportion of young adults susceptible to the virus resulting in a shift in case incidence towards adults where the disease is more severe and complications are more common.

The attenuated Oka VZV vaccine has been approved and recommended since 1995 in the United States for universal childhood use together with or separate from measles, mumps, and rubella vaccine [9]. The vaccine is proving to be effective and so far no age shift towards adults has been observed [10, 11].

In Europe, in July 2004, Germany introduced VZV vaccination into the routine vaccination schedule, as a single dose at the age of 11–14 months [12].

In Israel Varilrix (GlaxoSmithKline) – another vaccine also derived from the Oka strain – was introduced in June 2000 as an optional vaccination for children and has been made available through health maintenance organizations (HMO) [13]. This vaccine is, to date, not a part of routine childhood immunization schedule. Israel intends to incorporate the VZV vaccine in the routine childhood immunization, and to administer it at the same time as the MMR vaccine, as a single dose at 12 months. In addition, the vaccination will also be introduced for healthcare workers.

This is the first large-scale study to investigate the seroprevalence of VZV in the general population of Israel in the last three decades. This seroprevalence survey was conducted on sera collected in 2000–2001 within the framework of the European Sero-Epidemiological Network 2 (ESEN 2) to assess the level of immunity in the Israeli population against eight vaccine-preventable infections. Since Israel is considering the introduction of VZV vaccination into the routine immunization program, knowledge of pre-vaccination seroepidemiology is important to evaluate the effect of vaccination programs on the epidemiology of the disease [14]. Therefore, the aims of the present study were: to provide age-specific VZV seroprevalence estimates, to assess the age-specific force of infection of VZV, and to identify risk factors for VZV seropositivity.

Materials and Methods

Study Design and Sampling

A cross-sectional, seroprevalence study was undertaken using stored anonymous, unlinked serum samples collected by the Israel Center for Disease Control during 2000–2001 (n = 1,642). The serum bank comprised samples from all regions of Israel from both males and females representing all age groups. The samples of the younger age group (0–18) were residual sera from diagnostic laboratories, while residual serum samples from routine screening tests of healthy blood donors comprised the adult population (18+). Both sources excluded blood samples taken from cases suspected of immunological disorders.

Samples were randomly selected from the serum bank using a stratified sampling design. The target number of samples were 50 per year of age for those aged between 1 and 19 years, 100 samples for five-yearly age groups to 35–39, then 220 samples for those aged 40 and above.

All samples were anonymized and were linked via a unique study number to demographic information recorded at time of specimen collection. Variables included patient age, sex, settlement of residence (categorized into four regions; Haifa and North, Tel Aviv and Center, Jerusalem and South, and Hasharon), country of birth (categorized into Israel or other countries), place of origin as determined by the father's country of birth (second generation Israeli, Western [Europe and the Americas] or Eastern [Africa, Asia and Middle East]) and ethnicity (Jewish or Arab). Actual data on ethnicity were collected only for the younger age groups (0–18 years). Therefore, a new variable was determined "modified ethnicity" which was deduced from the settlement of residence (coded as Jewish, Arab or mixed). There was good agreement between actual ethnicity and "modified ethnicity" when cross-referenced in the population where actual ethnicity was known.

Laboratory Methods

Sera were stored at –20°C until tested. A commercial ELISA kit (Enzygnost anti-VZV/IgG, Behring Diagnostics, Marburg, Germany) was used to measure varicella antibodies. The kit has a reported sensitivity of 99.3% and specificity of 100%. Positive and negative status of sera was determined as follows: sera with optical density (OD) less than 0.1 U (equivalent of 50 mIU/ml) were defined as negative, those > 0.2 U as positive, and those between 0.1 and 0.2 as equivocal. Equivocal samples were not retested and were excluded from further analysis (75 samples, 4.6%). The antibody status, expressed in mIU/ml, was based on the International Standard for Varicella-Zoster Immunoglobulin (50 IU) of the World Health Organization.

Quality control on the performance of the serological test was conducted in frame of the ESEN 2. A panel of 148 sera were tested in our laboratory and then at the reference laboratory in Spain (Servicio de Microbiologia Diagnostica, Centro Nacional de Microbiologia, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain) using the same ELISA system. The parallel testing was performed twice, at the beginning and end of the serosurvey. Following a regression analysis after ploting the results obtained at the two labs, the best line fit was selected and the R^2 values were calculated and found to be 0.95 and 0.92 at the two parallel runs, at the beginnig and end of the serosurvey, respectively. The qualitative analysis, around the cutoff point for seropositivity, when the test of the Spanish lab was considered the "gold standard", revealed sensitivities of 100% and 100%, and specificities of 75% and 90% for the Israeli test, in the first and second runs, respectively. These results indicate that the test used in this study may lead to a slightly overestimation of the actual seropositivity rates.

Statistical Analyses

Prevalence estimates, geometric mean concentration (GMC) and 95% confidence intervals (CI) were calculated. Seroprevalence estimates were age and sex standardized using the direct method with the Israeli population according to the Statistical Abstracts of Israel 2000 [15]. Chi-squared (χ^2) or Fisher's exact tests were used to assess the association of the various demographic correlates with the prevalence estimate of varicella antibodies while differences in GMC of varicella antibodies between groups were tested for statistical significance by the Student's t-test and one-way ANOVA.

Multiple logistic regression analysis was used to determine the association between seropositivity and predictors available

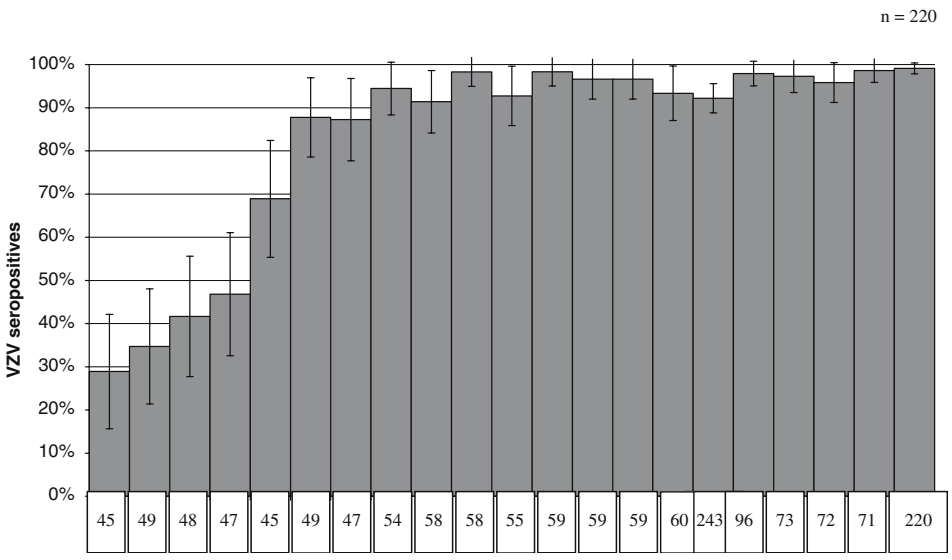

Figure 1. *Varicella zoster* virus (VZV) seroprevalence in Israel in 2000–2001 by age (in years). The numbers in the histogram bars represent the number of subjects tested.

such as: age, country of birth, place of origin etc. Odds Ratios (OR) and 95% CI are presented.

Age-specific force of infection, λ(a), is a measure of the incidence of infection in a susceptible population or in other words the rate at which susceptible individuals acquire infection. Age-specific force of infection was estimated using a likelihood method [16, 17], by maximizing the following log-likelihood function:

$$L = \sum_{j=1}^{20} Mx_j Ln(Fxj) + (Nx_j - Mx_j)(Ln(1 - Fxj))$$

where j is the index for the 20 age groups indicated in figure 1, xj is the average age in age group j, Nj is the total number of persons sampled in age group j, Mj is the number that are VZV antibody seropositive in age group j, and F(x) is the estimated proportion of individuals at age x (in years) who are VZV antibody seropositive. F(x) was assumed to be derived from constant forces of infection (λ1-λ4) for age groups 0–3, 4–5, 6–9 and ≥ 10 years, with the exception of subjects below 6 months of age who were assumed to be protected from maternal antibodies [18]:

$$Fx = \begin{cases} 1 & \text{if } x < 0.5 \\ 1 - \exp(-\lambda_1 x) & \text{if } 0.5 \le x < 4 \\ 1 - \exp(-\lambda_1(3.5 - 0.5) - \lambda_2(x - 3.5) & \text{if } 4 \le x < 6 \\ 1 - \exp(-\lambda_1(3.5 - 0.5) - \lambda_2(5.5 - 3.5) - \lambda_3(x - 5.5) & \text{if } 6 \le x < 11 \\ 1 - \exp(-\lambda_1(3.5 - 0.5) - \lambda_2(5.5 - 3.5) - \lambda_3(10.5 - 5.5) - \lambda_4(x - 10.5) & \text{if } 11 \le x \end{cases}$$

We assumed closed populations, mortality as type I developed countries and immunity through breast-feeding in all infants until the age of 6 months.

The log likelihood was maximized to obtain simultaneously point estimates of the parameters in the model and to obtain 95% CIs (assuming an approximate χ^2 distribution). Goodness of fit of the model was assessed using the deviance, i.e. the difference in 2*(log likelihood) between the saturated model and the fitted model [16, 17].

Data were analyzed using SPSS (version 12) software, and the solver add-in of Microsoft EXCEL 2003.

Results

The mean age of the 1,567 subjects tested for VZV was 20.05 years, of which 51.8% (812) were males. Data from 'inferred ethnicity' indicated that the vast majority 87.8% (1,376) were Jews and 86.9% (1,361) were born in Israel. Second generation Israelis was the most common place of origin – 49.9% (538); 30.6% (330) were of Western origin (Europe and the Americas) while the remainder 19.6% (211) were of Eastern origin (Africa, Asia and Middle East). Residents of Haifa and the North comprised 24.2%, 35.9% were living in Tel Aviv and the Center, 18.4% were from Jerusalem and Southern Israel, and 21.6% were residents of Hasharon area, covering the whole area of Israel.

The overall unadjusted seroprevalence estimate of VZV was 87.6% (95% CI: 85.99–89.25): 87.9% in males and 87.3% in females and increased with age. The VZV seroprevalence was 28.9% in those < 1-year-old, 41% in the 1- to 3-year-old and rapidly increased to 68.9% by the age of 4 years further reaching 94.4% at the age of 7 (Figure 1). GMC among seropositive subjects varied according to age being high in early childhood (0–9 years old), thereafter declining in teenagers (10–19 years old), increasing again in young adults (20–29 years) and peaking in those aged 30–34 years (Figure 2). The GMC of the 15–19 age group was significantly lower than that measured among 5–9 and 30–34 age groups.

Using the census population of Israel in 2000 as the reference standard [13], the age-weighted VZV overall estimate was 90.2%; 91.4% in males and 91.6% in females.

In univariate analysis, no significant association was found between seroprevalence and gender (p = 0.7); furthermore, males and females followed similar age-specific

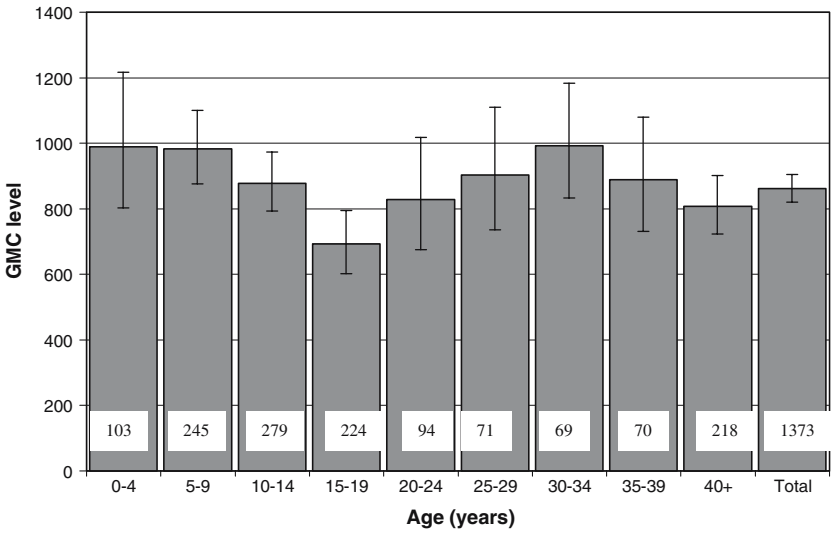

Figure 2. Geometric mean concentration (GMC) of IgG to VZV among VZV seropositives, by age-groups. The numbers in the histogram bars represent the number of subjects tested.

trends. Similarly, place of residence was not significantly associated with VZV seropositivity. The VZV antibody prevalence by age group did not significantly vary by ethnicity (p = 0.13), except when considering children in the 0–3 years age group, among whom the VZV antibody prevalence was double as higher in Arabs compared to Jewish subjects (47.8% in Arabs vs 24.0% in Jews p = 0.022, OR = 1.99, 95% CI: 1.15–3.44). Immigrants (those born outside Israel) were significantly more likely to be VZV seropositive as compared to those who were Israeli born (91.7% vs 87.0%; p = 0.05 OR = 1.66, 95% CI: 1.0–2.8). Subjects of Eastern origin were significantly more likely to be infected with VZV (97.2%) than those of Western origin (92.4%) or second generation Israeli born (87.7%) [Eastern origin vs other origin OR = 4 (95% CI: 1.66–10.29) Chi^2=12.11 p = 0.0005].

Table 1 presents the multiple logistic regression on risk analysis of factors for VZV among the whole population after adjusting for age, ethnicity, the interaction of age and ethnicity (age × ethnicity), country of birth, and place of origin. Age and family origin remained significantly associated with VZV seropositivity in these subjects. Each year of age had an 18% contribution to overall VZV seropositivity. In addition, Eastern origin was correlated with an increased risk.

The age-specific force of infection was 0.265 (95%CI 0.217–0.280) in the 0–3 years age group, 0.548 (95%CI 0.438–0.668) in the 4–5 years age group, 0.290 (95%CI 0.224–0.364) in the 6–9 years age group, and the lowest force of infection was for age groups ≥ 10 years, 0.042. (95%CI: 0.012–0.105). The deviance of this model from the saturated model was 28.9 with a p-value of 0.05.

Discussion

In this study we found that VZV infection increased rapidly with age in both sexes. The largest force of infection (0.548) was identified amongst 4–5 year-old, paralleling kindergarten attendance, while in the oldest age group (≥ 10 years), the estimated force of infection was 0.042. In Israel only 8.3% of the children under the age of 2 years attend pre-school facilities, rising sharply to 69.5% at the age of 4 years [15]. The early rise in VZV immunity which parallels pre-school facilities attendance indicates that earlier socialization of children in pre-school facilities play a major role on the epidemiology of VZV by keeping the age of acquisition of VZV infection and immunity low. Studies conducted in Luxemburg [19], and Belgium [20] have also identified the highest force of VZV infection among pre-school children and the values reported for this age group were similar to ours. In studies carried out in Australia [21], the United States [22], United Kingdom and Canada [23] the highest force of infection was detected among primary-school children (5–9 years old). We assume that differences between countries can result from different climatic conditions and mixing patterns, particularly in relation to childcare and pre-school attendance.

The variance in age-specific GMC levels among seropositives (illustrated in Figure 2) probably reflects the dynamics of VZV transmission in Israel. High GMC levels in early childhood (0–9 years old) parallel to high viral activity also reflected by the high force of infection in this age group. The declining GMC levels in teenagers (10–19 years old) occur when the seroprevalence is over 90% and the disease transmission is low. The GMCs increase again in young adults and childbearing years (20–29 years) peaking in those aged 30–34 years probably as a result of

Table 1
Risk factors for Varicella zoster virus (VZV) infection among the population in Israel and adjusted Odds Ratios (OR) in a multiple logistic regression analysis

Variable		VZV seropositivity		
		Adjusted OR[a]	95% CI	p-value
Age (for each year)		1.18	1.14–1.22	< 0.001
Place of origin	Israeli	1.0[b]		
	Western	2.74	1.52–4.93	0.001
	Eastern	5.51	2.07–14.65	0.001

[a] Odds Ratios were adjusted for age, age × ethnicity, country of birth, ethnicity, and place of origin; [b] reference group;
CI: confidence interval

exposure to sick children in the household then slowly decreasing.

We found that in the 0–3 years age group the VZV antibody prevalence was double as high in Arab as compared to Jewish subjects. Larger households with more children among Arabs [15] may increase the risk of exposure to older sick siblings and lower the acquisition age of VZV infection. The same explanation can be true for the finding indicating that among the Jews, those of Eastern origin had the highest risk of infection with VZV (adjusted OR = 5.5) as compared to second generation Israeli. Indeed, households of families of Eastern origin have the largest sib-size among the Jewish population in Israel [15].

In view of the serological data of the present study, the introduction of VZV vaccination into the routine immunization program, as a single dose, at the age of 12 months, before most children have started attending kindergartens seems appropriate since it will reduce the risk of exposure to the wild-type virus. We assume that the planed vaccination of healthcare workers will further reduce the circulation of the virus in the community.

It is not clear what will be the potential impact of routine VZV vaccination on the epidemiology of herpes zoster (shingles) as various reports show conflicting evidence. A major recent study provided evidence showing that VZV vaccination offers protection against zoster [24]. In contrast, others suspect that since primary repeated natural exposure to the virus might boost the immune response to chickenpox and zoster, VZV immunization will not lead to a higher long-term reduction in the incidence of zoster as compared to natural infection [25].

This study may have some limitations. First, the serum samples tested were residual sera and not samples systematically collected for this survey. We assume however that the sampling procedure of residual sera used in this study and recommended by the ESEN 1 [26] minimizes potential biases. It was previously shown that the VZV seroprevalence estimated from residual sera were comparable to the rates based on random cluster surveys [27].

Second, an important part of the blood donors among the young adult age groups (20–24 years) who were the source of the sera tested in this study, includes soldiers serving in the IDF and comprises much less Arab and orthodox religious Jewish citizens than their relative representation in the Israeli population. Also, in the older age groups, Arab citizens are under represented. Since these subpopulations tend to have larger households they are more likely to have even higher VZV prevalence rates. Therefore, our sample may slightly underestimate VZV seroprevalence in adults (≥ 18 years).

We recommend that similar seroepidemiological studies as that presented here will be re-conducted in the coming years to monitor the expected changes in the immune status and epidemiology of VZV following the planned large-scale use of the VZV vaccine in Israel.

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