Joanna Siennicka[1], Agnieszka Trzcińska[1], Magdalena Rosińska[2], Bogumiła Litwińska[1]

SEROPREVALENCE OF VARICELLA-ZOSTER VIRUS IN POLISH POPULATION*

PRZEGLĄD SEROLOGICZNY DLA WIRUSA OSPY WIETRZNEJ I PÓŁPAŚCA W POLSCE

[1]Department of Virology
National Institute of Public Health - National Institute of Hygiene, Warsaw
[2]Department of Epidemiology
National Institute of Public Health - National Institute of Hygiene, Warsaw

STRESZCZENIE

Wirus ospy wietrznej i półpaśca (VZV) jest pierwszym herpeswirusem dla którego została opracowana szczepionka. Od roku 1999 szczepionka VZV jest zarejestrowana w Polsce i zalecana do stosowania u dorosłych osób seronegatywnych (które nie przechodziły zakażenia wirusem ospy wietrznej i półpaśca) oraz u dzieci i młodzieży z ostrą białaczką w okresie remisji. Ze względu na fakt, że dane dotyczące seroprewalencji VZV są niezbędne do opracowania odpowiedniego programu szczepień, przeprowadzony został pierwszy w Polsce przegląd serologiczny na reprezentatywnej grupie osób w wieku 1-19 lat.

Próbki surowic pochodziły z banku surowic kolekcjonowanych w latach 1995-2004 z uwzględnieniem wszystkich regionów geograficznych Polski. Do badnia wybrano, wykorzystując metodę próbkowania warstwowego - stratyfikacyjnego (stratyfikacja według wieku), 1300 próbek surowic zbieranych przez okres 9 lat (1995-1996; 1998-2004). W grupie wiekowej 0-9 lat na każdy rocznik przypadało po 100 próbek surowic, a w grupie wiekowej 10-19 lat - po 40 próbek. Swoiste dla VZV przeciwciała w klasie IgG wykrywano przy użyciu testu ELISA, a poziom przeciwciał wyrażano w jednostkach międzynarodowych na ml (mIU/ml). Ogólna seroprewalencja po skorygowaniu do zastosowanej metody próbkowania dla grupy wieku 1-19 wyniosła 76,6% (95% CI: 74,6% - 78,7%). Seroprewalencja korelowała ściśle z wiekiem (p<0,0001) i w grupie osób w wieku 18 i 19 lat odpowiednio osiągała 95% i 98%, nie stwierdzono natomiast żadnego związku z płcią, miejscem zamieszkania (miasto/wieś) czy regionem geograficznym Polski. W grupie próbek zebranych w latach 2000-2004, nie zaobserwowano różnic w seroprewalencji w badanych latach. W Polsce szczepionka przeciwko VZV jest zalecana jedynie w ograniczonym zakresie, a mianowicie dla grup osób wysokiego ryzyka.

ABSTRACT

A varicella zoster virus (VZV) is the first herpesvirus for which a vaccine was developed. Since 1999, the varicella vaccine is licensed in Poland and recommended for use in adults without history of a varicella infection, and in children and young adults with remission of acute leukemia. While serological data is essential to assess the appropriate vaccination programme, we conducted the first in Poland serosurvey on a representative group of Polish population aged 1–19.

Serum samples were selected from a serum bank collected in 1995-2004 with a catchment area of the all geographical regions of Poland. A total of 1300 serum samples collected over 9 years (1995-1996, 1998-2004) were selected using a stratified sampling design (stratification by age). Samples were selected, consisting of 100 samples for each 1-year band of age groups 0-9 years, and 40 samples for each 1-year band of age groups 10-19 years. IgG serum antibodies specific to VZV were detected using an indirect enzyme immunoassay and the antibody level was expressed in international units per millilitre (mIU/ml) and was refered to the international standard for VZV immunoglobulin of 50 IU.

The overall seroprevalence estimate, adjusted for sampling design for the age group 1–19 was 76.6% (95% CI: 74.6%-78.7%). Seroprevalence correlated closely with age (p<0.0001) and among 18 and 19 year olds reached 95% and 98% respectively. No association was found between gender, rural/urban areas and geographical regions of Poland. For samples collected over the 5 year period (2000 – 2004), evidence of overall differences in seropositivity over these years was not observed.

In Poland VZV vaccination is provided only for a limited group of high risk patients. The possible updates in the immunization program are discussed and the

*) This study was financially supported by grant SP22-CT-2004-502084 of the FP7 programme of the European Commission, DG Research (POLYMOD)

Dyskutowane są ewentualne zmiany w kalendarzu szczepień, a prezentowane wyniki badań mogą mieć wpływ na kształtowanie polityki szczepień w Polsce.

Słowa kluczowe:*wirus ospy wietrznej i półpaśca; seroprewalencja; epidemiologia*

results of the presented study can contribute valuable information to base the vaccination policy decisions.

Key words: *varicella zoster virus; seroprevalence; epidemiology*

INTRODUCTION

A varicella zoster virus (VZV) infection results in chickenpox (varicella), a common, highly contagious, self-limited and relatively mild disease of childhood (1). Although the course of varicella is generally mild and even subclinical, a VZV infection is responsible for a significant burden of hospitalization (2). The more severe course of chickenpox is observed in adolescents and immunocompromised patients. A VZV infection in pregnancy could be connected with congenital infection, with mortality reaching even 30% (3). Like other herpesviruses, following primary infection, VZV could establish a latent infection. Reactivation from latency results in herpes zoster (shingles), observed mainly in the elderly and immuno-compromised patients (1, 4).

VZV is the first herpesvirus for which a vaccine was developed. A live, attenuated vaccine based on the Oka strain has been available since 1974 (5). In 1995 the vaccine was incorporated into the routine childhood immunization schedule in the USA, and subsequently in many other countries (6). After the introduction of the varicella vaccination, a marked decline in the number of reported cases of chickenpox was observed as well as varicella-related hospitalizations and the number of deaths caused by complications of a VZV infection (7, 8). Since 1999, the varicella vaccine is licensed in Poland and recommended for use in adults without history of a varicella infection, and in children and young adults with remission of acute leukemia (9).

Chickenpox occurs all over the world and in non-vaccinated populations living in temperate climates, 90% of cases are observed among children aged 10 – 14 (3). However, the wide variation in the seroepidemiology of VZV was demonstrated in different countries (10, 11), which could have important implications for the design of national VZV vaccination programme. While serological data is essential to assess the appropriate vaccination programme, we conducted the first serological survey in Poland on a representative group of Polish population aged 1 – 19.

MATERIAL AND METHODS

Sera collection: Serum samples were selected from a serum bank collected in 1995-2004 with a catchment area of the all geographical regions of Poland. The bank contains residual sera from public health laboratories that offer comparable services, including diagnostic screening before surgery (~75%), health screening for new employees (~15%), diagnostics for infectious diseases and other services, including visas for international travel (~10%). A sample of 5 ml peripheral venous blood was drawn, allowed to clot and centrifuged at 1000g for 10 minutes. Sera were transferred to microtubes of 0.5 – 1ml and sent to the National Institute of Public Health - National Institute of Hygiene (NIPH-NIH) in Warsaw and stored at -70°C. All personal identifiers were removed; only age, sex, year of sampling, voyvodeship and type of residence (rural or urban) were recorded. The development of this serum bank was approved by the institutional review board of the NIPH-NIH in Warsaw, Poland.

Sampling from serum bank: A total of 1300 serum samples collected over 9 years (1995-1996, 1998-2004) were selected using a stratified sampling design (stratification by age). Weighted random samples were drawn from the serum bank with weighting designed to adjust for the sex, voyvodeship and urban/rural residence distribution of the donors of the serum bank samples as compared to the 2000 census data (Central Statistical Office). A total of 1300 serum samples were selected, consisting of 100 samples for each 1-year band of age groups 0-9 years, and 40 samples for each 1-year band of age groups 10-19 years.

Laboratory test: IgG serum antibodies specific to VZV were detected using an indirect enzyme immunoassay (Enzygnost Anti VZV/IgG ELISA test, Dade Behring). The antibody level was expressed in international units per millilitre (mIU/ml) and was refered to the international standard for VZV immunoglobulin of 50 IU. The tests were performed under the same laboratory condition using an automatic open system (ETI Star, Italy) according to the manufacturer's instructions. All samples with equivocal results (50-100 mIU/ml) were retested using the same test kit. In total, 43 samples were equivocal. After retesting, 32 remained equivocal and were excluded from analysis.

Quality control: For internal quality control the same samples (n=84) were blindly retested with the same test kit. Internal quality control showed 100% concordant results. External quality control was performed with the control panel consisting of 150 samples used for inter-laboratory standardisation of antibody titres [12]. External quality control showed 91.3% concordant results (76 positive, 1 equivocal, 60 negative). Discrepant results (n=13) were observed for samples with weak IgG level (50-100 mIU/ml).

Statistical analysis: We calculated the age specific prevalence and a common estimate for the population in Poland, assuming the inverse of sampling frequencies as weights. A design-based test for independence (Rao-Scott Chi-square test) was used for the univariate analysis and logistic model, taking into account the design for multivariate comparisons. Analysis was performed with SAS 9.1 (SAS Institute Inc.).

RESULTS

Altogether 1300 samples from children and adolescents were examined for the presence of anti-VZV IgG. The number of positive samples was 805, negative 463 and equivocal 32. These 32 samples were excluded from further analysis. The overall seroprevalence estimate, adjusted for sampling design for the age group 1 – 19 in Poland, was 76.6% (95% CI: 74.6%-78.7%). Age specific data on seropositivity for VZV in the Polish population are shown on figure 1. Seroprevalence correlated closely with age ($p<0.0001$). The frequency of positive samples increased gradually from 26% among 1 year old children to 33% in 4 year olds. Afterwards, there was a steeper increase from 48% among 5 year olds to 65% among 6 year olds. By the age of 10 years, 82% of children had evidence of a past infection. Seroprevalence among 18 and 19 year olds reached 95% and 98% respectively.

Gender differences in the prevalence of ani-VZV IgG were not detected. The seroprevalence did not differ significantly between rural and urban areas (table I). Regional differences in crude seroprevalence ranged from 67.4% for the Swietokrzyskie voyvodeship to 84.3% for the Zachodnio-Pomorskie voyvodeship (table I).

For samples collected over the 5 year period 2000 – 2004, evidence of overall differences in seropositivity over these years was not observed. Above the age of 11 there is virtually no trend in seroprevalence over these years. Some variation over time is visible in the youngest age groups (figure 2). Results from 1995 – 1999 were not included in this analysis due to the small sample size.

In the multivariate analysis, age was the single most important predictor of VZV seropositivity. All other factors (sex, urban/rural residence, voyvodeship and year of sample collection), as well as the two-way interactions were not statistically significant.

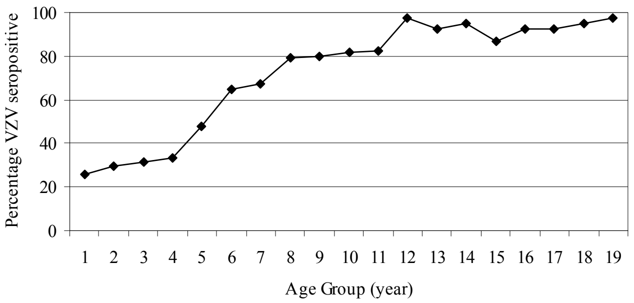

Fig. 1. Age specific seroprevalence of VZV in Poland based on sample collected 1995-2004

Ryc. 1. Występowanie przeciwciał dla VZV w różnych grupach wiekowych w Polsce na podstawie wyników badania próbek surowic zebranych w latach 1995-2004

DISCUSSION

In our study we examine prevalence of VZV antibodies in serum samples collected from general population in Poland in 1995 – 2005. Although the VZV vaccine was registered in our country in 1999, the immunity gained through vaccination is not considered to affect the results of our study since so far the vaccine was not widely used. Data on immunisation against VZV are only available since 2004 and show an increasing trend in vaccine use (13-16). However, less then 5000 people were vaccinated annually in 2004 – 2005 so in total substantially less then 1% of population could

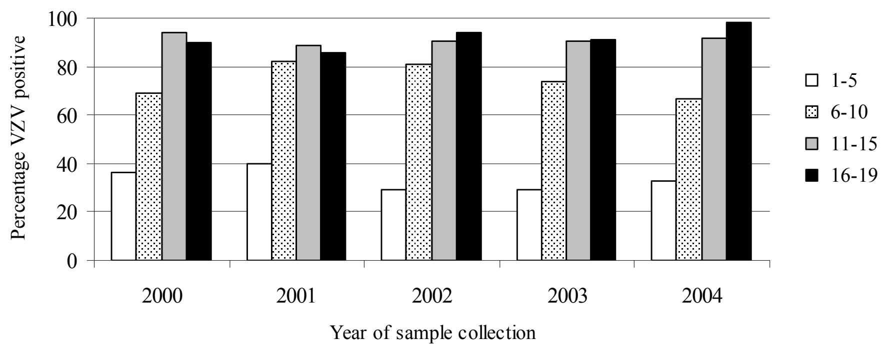

Fig. 2. VZV IgG seroprevalence in four age groups (1-5, 6-10, 11-15, 16-19) by year of sample collection

Ryc. 2. Występowanie przeciwciał IgG dla VZV w czterech grupach wiekowych (1-5, 6-10, 11-15, 16-19) w zależności od roku pobrania próbek

Table I. Estimated seroprevalence of anti-VZV IgG in Polish population by demographic features
Tabela I. Występowanie przeciwciał anty-VZV IgG w populacji polskiej

Feature		Number	Seroprevalence % (95% Confidence infterval)	Chi-square p-values
Age Wiek				<0,0001
	1-5	487	34.0 (29.8-38.2)	
	6-10	428	75.3 (71.0-79.7)	
	11-19	353	92.4 (89.7-95.2)	
Sex Płeć				0.7653
	Female	545	77.0 (73.6-80.4)	
	Male	723	76.3 (73.4-79.2)	
Residence Środowisko				0.8047
	Rural	97	74.2 (65.1-83.3)	
	Urban	1008	75.4 (73.0–77.8)	
	Unknown	163		
Voyvodeship Województwo				0.1992
	Dolnoslaskie	52	78.2 (65.6-90.8)	
	Kujawsko-pomorskie	90	78.6 (70.5-86.6)	
	Lubelskie	48	76.1 (63.8-88.5)	
	Mazowieckie	575	73.3 (69.7-77.0)	
	Podkarpackie	41	78.8 (66.8-90.9)	
	Podlaskie	67	78.8 (69.9-87.8)	
	Slaskie	34	83.4 (72.7-94.2)	
	Swietokrzyskie	32	67.4 (51.6-83.2)	
	Wielkopolskie	127	72.8 (65.1-80.5)	
	Zachodnio-pomorskie	147	84.3 (78.6-90.1)	
	Other	55	82.8 (72.8-92.8)	
Year of sample collection Rok uzyskania próbki				0.3103
	1995	11	73.6 (46.3-100.0)	
	1996	3	84.0 (50.2-100.0)	
	1998	27	70.3 (50.5-90.1)	
	1999	14	67.2 (42.9-91.4)	
	2000	107	75.2 (66.8-83.6)	
	2001	202	73.2 (66.6-79.9)	
	2002	275	81.7 (77.3-86.1)	
	2003	143	70.8 (63.0-78.6)	
	2004	486	76.8 (73.3-80.2)	

have vaccine-induced immunity against varicella. We demonstrate that in Poland the VZV infections usually take place during the first decade of life. Over 90% of adolescents already have antibodies against VZV.

Seroepidemiological studies conducted in different countries all over the world revealed distinct patterns of anti-VZV IgG distribution in age groups. In countries with a temperate climate, VZV seroprevalence shows rapid increase during the first decade of life, while in tropical and subtropical areas, varicella affect mainly adolescents and adults (11). Nevertheless, substantial differences in VZV sero-epidemiology within the Europe were observed (10). The large standardised study covering 11 countries in Europe showed that while in all countries most VZV infections occurred in childhood, a wide variation in transmissibility was observed. The herd immunity threshold estimated in this study for different countries varied from 70% in Italy to 94% in the Netherlands (10). The large proportion of susceptible young adults should be of concern because in this age group the clinical course of chickenpox is usually more severe, with a high rate of complications (17). The data obtained by *Nardone* et al. (10) showed that in the most investigated European population, over 50% of young children had antibodies to VZV by age 5. The exception was Italy, where only 38% of 5 year old children were seropositive (10). In the presented study, seroprevalence in the Polish population aged 5 years was 48% and resembled data from Italy. The presented study showed that chickenpox infection in Poland affects older children than in most European countries, since only 48% (95% CI: 38% - 58%) is immune at 5 years of age. Other investigated risk factors such as sex, urban/rural residence, geographic region of country did not influence the VZV seroprevalence in Poland. It is consistent with results obtained in other European countries: Switzerland (18), Spain (19), Germany (20), Italy (21). In the seroepidemiology of varicella, age is the most important predictor of VZV seropositivity. Moreover, *Heininger* et al. (18) showed that the number of siblings significantly influenced the presence of VZV antibodies; individuals who grow up without siblings have a significant risk of evading a natural VZV infection. Changes in age related seroprevalence of the antibody to VZV was also observed. In Swedish children aged 9-12 years, the seroprevalence for VZV increased from 50% to 98% over 30 years (1967-1997) (22). Similar data was obtained for the UK population, where a sharp increase in the prevalence of chickenpox in the 1 – 4 year age group over 25 years was observed (23). From 1966 to 1992, the seroprevalence rose from 7% to 51% in the youngest age group. Data presented here from Poland revealed no differences in seropositivity over 5 years. Small variations most probably reflect the cyclic occurrence of chickenpox.

A possible limitation of the study could be the collection process of the serum bank. In the sampling, people residing in urban areas were over-represented. However, we demonstrated no significant differences in

VZV seroprevalence related to the place of residence, or in any specific region of Poland. Thus these factors are unlikely to influence the overall estimates of varicella seroprevalence.

In Poland VZV vaccination is provided only for a limited group of high risk patients. The possible updates in the immunization program are discussed and the results of the presented study can contribute valuable information to base the vaccination policy decisions.

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Received: 24.07.2009
Accepted for publication: 7.09.2009

Adress for correspondence:
doc.dr hab. Joanna Siennicka
Zakład Wirusologii NIZP-PZH
ul. Chocimska 24, 00-791 Warszawa
e-mail: jsiennicka@pzh.gov.pl