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# Varicella zoster virus infection occurs at a relatively young age in the Netherlands☆

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ABSTRACT

*Introduction:* To date, there is no universal varicella vaccination in the Netherlands. We studied the seroprevalence of varicella zoster virus (VZV) specific antibodies and determinants for seropositivity among participants of a serosurveillance study, conducted in 2006/2007 among Dutch inhabitants 0–79 years of age.
*Materials and methods:* Serological testing of 6386 blood samples for VZV was performed with a fluorescent bead-based multiplex immunoassay. Seroprevalence and geometric mean concentration (GMC) were weighted for age, sex, ethnicity, and urbanization rate to the total Dutch population. Determinants for VZV seropositivity were identified among children younger than 6 years of age using a logistic regression model.
*Results:* The overall seroprevalence of VZV specific antibodies in the Dutch population was 94.6% (95% CI: 93.2–96.0%). This seroprevalence increased rapidly with age: at 6 years of age, more than 95% were seropositive. Determinants associated with lower VZV seropositivity were: young age, first-generation non-Dutch ethnicity, and low frequency of attendance at a day care center or nursery school. The GMC increased with age and was lower for women than for men from the age of 20 years onwards.
*Conclusions:* This study confirmed that VZV infection occurs at a younger age in the Netherlands compared to other countries, which might explain the low disease burden due to varicella. Introduction of universal varicella vaccination is not a foregone conclusion in the Netherlands. Changes in migration and day care usage will influence the age-specific risk on varicella and should therefore be monitored. Further research might elucidate the sex differences in VZV specific GMC.



## 1. Introduction

The varicella zoster virus (VZV) causes varicella (chickenpox) as well as herpes zoster (shingles). Varicella is due to the primary infection of VZV, whereas herpes zoster is caused by reactivation of latent VZV in sensory nerve ganglia. In contrast to varicella, which is mainly a childhood disease, herpes zoster predominantly affects adults 50 years of age and older. Many European countries are considering inclusion of universal varicella vaccination in their National Immunization Programme (NIP) and some countries such as Germany, Luxembourg, Latvia, and Greece already have done so. In some European countries, varicella vaccination is only offered in several regions, only in the private sector, or only to high-risk groups and/or susceptible adolescents [1–3]. In the United States, universal varicella vaccination was introduced in 1995. In the Netherlands, vaccination against varicella has not been implemented in the NIP yet. The incidence of varicella-related general practitioner consultations, hospital admissions, and deaths per 100,000 population in the Netherlands is lower than the incidence reported by other countries, but it is not likely that the severity of varicella among hospitalised patients in the Netherlands

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differs from other countries [4,5]. The European sero-epidemiology network (ESEN) demonstrated that the seroprevalence for VZV increased rapidly with age for all participating European countries. However, Dutch children are infected at a younger age as compared to children in other European countries [6]. For VZV vaccination strategies, the age of primary infection is highly relevant since the risk on varicella complications rises with age, which will influence the total disease burden in the population. A recently conducted cross-sectional serosurveillance study [7] in the Netherlands provided the opportunity to confirm the exceptional early age of infection in the Netherlands and to investigate determinants for VZV seropositivity.

## 2. Materials and methods

### 2.1. Study population and design

In February 2006–June 2007, a second cross-sectional population-based serosurveillance study (PIENTER 2) was conducted to evaluate the Dutch NIP. From 40 municipalities throughout the country (5 regions with 8 municipalities each), a sample of 19,781 Dutch inhabitants aged up to 79 years of age was invited to complete a questionnaire, to give a blood sample, and to bring vaccination certificates. Within the nationwide sample of the PIENTER 2 study, 6386 (32%) blood samples and 6351 questionnaires (of those who gave a blood sample) were collected. The questionnaire contained, among others, questions on (demographic) characteristics possibly related to VZV infection, such as age, urbanization rate, ethnicity, education, household size, and attendance at a day care center or nursery school. The study proposal was approved by the Medical Ethics Testing Committee of the foundation of therapeutic evaluation of medicines (METC-STEG) in Almere (clinical trial number: ISRCTN 20164309) and an informed consent was signed by each participant (and/or the parents depending on their age). A more detailed description of the study design and objectives of the PIENTER 2 project were reported previously [7]. The first cross-sectional, population-based serosurveillance study was performed in 1995/1996 (PIENTER 1), with a similar design [8,9].

### 2.2. Laboratory methods

In PIENTER 2, serological testing for VZV was performed with a fluorescent bead-based multiplex immunoassay using Luminex technology [10]. In this assay, VZV strain VZ-10 (GenWay, San Diego, CA) was coated to the beads and R-Phycoerythrin anti-human IgG, recognizing all IgG subclasses, was used as conjugate. Individual data were transformed into International units per ml (IU/ml) by use of the international standard for rubella as an in-house standard on each plate, and calibrated against the international standard for VZV as described [10]. To determine the cutoff for seropositivity a mixture modeling analysis was performed; this analysis resulted in a cutoff of 0.26 IU/ml (see Appendix). Seroprevalence was defined as the prevalence of a VZV-antibody concentration higher than or equal to the cutoff. In PIENTER 1, a VZV IgG ELISA kit (Human, Wiesbaden, Germany) was used to determine VZV seropositivity according to the criteria of the manufacturer [4]. In PIENTER 2, serological test results for VZV were available for 6383 individuals and in PIENTER 1 for 2044 individuals.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.08.029.

### 2.3. Data analysis

#### 2.3.1. Seroprevalence and geometric mean concentration

Because of the two-stage cluster sampling, the seroprevalence and geometric mean concentration (GMC) in IU/ml in PIENTER 2 were weighted for age, sex, ethnicity, and urbanization rate relative to the total population in the Netherlands on 1-1-2007 by taking 5 strata (regions) and 40 clusters (municipalities) into account. The seroprevalence of VZV specific antibodies in PIENTER 1 was calculated according to a similar procedure [4]. Differences in seroprevalence of VZV specific antibodies between PIENTER 1 and PIENTER 2 or between men and women were determined as follows. First, the parameters of the beta distribution for both seroprevalences were estimated using the method of moments [11]. Next, the risk ratios, the corresponding 95% confidence intervals (CI), and $P$ values were estimated with the use of Monte Carlo simulations of both seroprevalences. Differences in the GMC between men and women in PIENTER 2 were identified by calculating differences in log titers and tested by using the $t$-test. A $P$ value <0.05 was considered to be statistically significant.

#### 2.3.2. Determinants

Determinants for VZV seropositivity were identified in a subset of PIENTER 2, i.e., children younger than 6 years of age (excluding those ≤6 months of age) ($N = 788$), using a logistic regression model. We selected this age group to overcome the interference of maternal antibodies and because the majority of participants 6 years of age and older were already seropositive. The following potential determinants were included in the univariable and multivariable logistic regression analysis: age, sex, urbanization rate, ethnicity, level of education of the mother, household size, the presence of another child in the household ≤4 years of age and frequency of attendance at a day care center or nursery school by the participant. Although compulsory education in the Netherlands starts at 5 years of age, 98% of children at 4 years of age already attend school [12]. Therefore, we assumed that all children, 4–5 years old, attend school and do not attend a day care center or nursery school. Crude and adjusted odds ratios (ORs) and 95% CIs were calculated based on cases without missing answers ($N = 760$). Because of the large effect of age, crude ORs were adjusted for age. A determinant was considered to be significantly associated with VZV seropositivity if the $P$ value was <0.05.

Because of the difference between men and women over 20 years of age in the GMC for VZV antibodies, an additional analysis was conducted to see if other factors could explain these differences by sex. Determinants associated with the logarithmically transformed VZV antibody concentration were therefore identified among seropositive participants 20–79 years of age ($N = 4126$), using a linear regression model. We focused on those who were seropositive to rule out the possible influence of sporadic seronegativity on the height of the VZV antibody concentration. The following potential determinants were included in the univariable and multivariable linear regression analysis: age, sex, urbanization rate, ethnicity, level of education, household size, the presence of a child in the household ≤4 years of age and attendance at a day care center or nursery school by a child in the household. Crude and adjusted parameter estimates and 95% CIs were calculated based on cases without missing answers ($N = 3962$) (again crude parameter estimates were adjusted for age), and a $P$ value <0.05 was used to determine significance. Further, separate linear regression analyses were conducted with a model always including sex and age, plus the addition each time of one of the other potential determinants to see if the effect of sex would change more than 10%. All data analyses were performed in SAS 9.3 (SAS Institute Inc., Cary, NC, USA).