Abstract

Objectives—To assess the prevalence of varicella zoster virus (VZV) antibodies in Flemish (Belgian) healthcare workers, to investigate the association between seronegativity and selected variables, and to assess the reliability of recall about disease as a predictor of immunity.

Methods—A seroprevalence study of VZV antibodies (IgG) was conducted among a systematic sample of 4923 employees in various professional groups, employed in 22 hospitals in Flanders and Brussels (Belgium). Information about sex, age, department, job, and years of employment, the country of origin, and history of varicella was obtained. The presence of VZV antibodies was investigated with the enzyme-linked immunosorbent assay (ELISA), Enzygnost anti VZV / IgG (Dade Behring, Marburg, Germany). Statistical analysis was performed by calculating prevalences and prevalence ratios (PRs) and their 95% confidence intervals (95% CIs). Sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of the recalled history were determined.

Results—The prevalence of VZV seropositivity in Flemish healthcare workers was 98.5% (95% CI 98.1 to 98.8). Seronegativity was significantly associated with age and job, increasing with both older and younger age. The prevalence of seronegative workers was significantly less in nursing staff than non-nursing staff. There was no significant difference for sex and years of employment. The PPV and NPV of recalled history were 98.9% and 3.4%. Sensitivity and specificity were 83% and 38.9%.

Conclusion—The prevalence of VZV seropositivity was very high in this sample of Flemish healthcare workers. Because of this low overall susceptibility, VZV infection seems not to be an important occupational risk among healthcare workers in Flanders. The increasing seronegativity above the age of 45 is possibly due to a loss of detectable antibodies. A positive history of varicella was a good predictor of immunity, but a negative history had no value as a predictor of susceptibility in adults.

Keywords: varicella; healthcare workers; occupational risk

Chickenpox or varicella is one of the most common acute viral infections of childhood in western countries. The varicella zoster virus (VZV) is highly contagious and is spread from person to person by contact with respiratory secretions and vesicle fluid. Varicella results from primary infection with the VZV whereas zoster or shingles occurs as a result of reactivation of latent virus. Shingles can be an important source of infection.

Until recently, mass vaccination of children was not advocated because the disease was considered to be mild in childhood, and no generally applicable vaccine was available because of problems with the stability of the vaccine. Nevertheless, varicella is not a harmless disease, especially for people at risk—for example, immunocompromised patients, premature infants, and neonates of seronegative mothers. Severe cases are also more likely to occur in healthy adults and adolescents. General symptoms and skin lesions are of greater intensity in adults. Complications include varicella pneumonia (2.5/1000), encephalitis (15/100,000) and hepatitis. The illness is more often fatal in adults, with increasing mortality as age increases.

Varicella in pregnant women is associated with a risk for VZV transmission to the fetus or newborn. Depending on the gestational age, maternal varicella causes congenital varicella syndrome, herpes zoster during infancy or early childhood, or severe neonatal varicella.

In the healthcare setting varicella is an occupational hazard for a few adults who did not contract varicella in childhood. Studies have shown that during the past 20 years, the prevalence of VZV seropositivity in young adults ranges from about 90% to 95% in temperate climates. Seroprevalence is much lower in tropical areas where figures ranged from 84% to less than 50%.

Among healthcare workers in western countries, seroprevalence rates range from 90% to 98%. Epidemiological evidence from the United Kingdom and the United States shows an upward shift in the age distribution of varicella since 1975. This could have important consequences for future morbidity and mortality due to varicella and for VZV infection in pregnant women and healthcare workers.

To obtain a more precise estimate of the susceptibility to VZV in Belgian healthcare workers, a seroprevalence study was set up.
Methods and study population
During 1996–7, a sample of employees in 21 general hospitals geographically distributed over the Flemish and Brussels region, and in one large university hospital (Leuven), was tested for the presence of VZV antibodies. Because the occupational health service (IDEWE) performs the medical surveillance for a wide variety of employers, among which are many general hospitals, the study hospitals were selected from the client hospitals. Due to these practical circumstances, it was impossible to obtain a representative sample from all the Flemish and Brussels hospitals, but a reasonable regional spread was aimed at.

The collection of blood samples occurred in two stages, because the study was set up at first to measure the prevalence of immunity to other infectious diseases. Details of this study have been published elsewhere.20 From February 1996 to June 1996, after informed consent, 3068 blood samples were collected and information was obtained by a self administered questionnaire about sex, age, department, job, duration of employment, and medical history such as blood transfusions and operations, etc. The country of origin was noted on a list of participants. To allow more specific comparisons and to evaluate the prevalence of VZV antibodies, the sample was extended with a further 2000 blood samples, which were collected from February 1997 to June 1997. A question about history of varicella was added to the questionnaire. Possible answers were yes, no, or unknown. The participants of the first part of the study were contacted and their permission was asked to test their blood samples for VZV antibodies.

The blood tests were performed during the annual occupational medical examinations of the employees. A yearly medical examination is mandatory for about 95% of all hospital employees. Medical staff are not invited for this medical examination, because they are not considered as employees. To avoid any type of selection, a fixed percentage of all the employees in each hospital were requested to participate. To reach the proposed number, the first 35% to respond in each hospital were considered eligible for the study. Because the order in which the employees are invited to the medical examination was not determined in a systematic way, the sample could be considered as approximating to a random selection. As it was not possible to interrogate the participants of the first stage about their history of varicella, this information was only available for participants of the second stage. The total number of eligible employees in the 22 hospitals was 14,998 (figure). A total of 5243 people were asked to participate. One hundred and seventy five people refused to participate. Of 3068 people in the first stage of the study, 137 did not give permission to test their blood samples for VZV antibodies. In total 312 (175+137) people refused to participate in the VZV study (5.95%). No occupational pattern was found in this group. In eight samples not enough
The study population (n=4923)

### Table 1
Prevalence ratios (PRs) of seronegative workers according to selected variables in the study population (n=4923)

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>%</th>
<th>Percentage of seronegative workers</th>
<th>PR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (y):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>240</td>
<td>4.9</td>
<td>2.08</td>
<td>1.93</td>
<td>(0.74 to 5.01)</td>
</tr>
<tr>
<td>25–34</td>
<td>1773</td>
<td>36.0</td>
<td>1.47</td>
<td>1.36</td>
<td>(0.76 to 2.42)</td>
</tr>
<tr>
<td>35–44</td>
<td>1855</td>
<td>37.7</td>
<td>1.08</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>45–54</td>
<td>904</td>
<td>18.4</td>
<td>2.10</td>
<td>1.95</td>
<td>(1.05 to 3.60)</td>
</tr>
<tr>
<td>≥55</td>
<td>122</td>
<td>2.5</td>
<td>4.10</td>
<td>3.80</td>
<td>(1.53 to 9.42)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>29</td>
<td>0.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>952</td>
<td>19.3</td>
<td>1.47</td>
<td>1.04</td>
<td>(0.62 to 1.75)</td>
</tr>
<tr>
<td>Women</td>
<td>3971</td>
<td>80.7</td>
<td>1.54</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Country of origin:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgian</td>
<td>4492</td>
<td>91.2</td>
<td>1.56</td>
<td>1.17</td>
<td>(0.16 to 8.39)</td>
</tr>
<tr>
<td>Non-Belgian</td>
<td>75</td>
<td>1.5</td>
<td>1.33</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>356</td>
<td>7.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Job or task:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing staff</td>
<td>2995</td>
<td>60.8</td>
<td>1.10</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Non-nursing staff</td>
<td>1772</td>
<td>36.0</td>
<td>2.37</td>
<td>2.15*</td>
<td>(1.38 to 3.35)</td>
</tr>
<tr>
<td>Administrative</td>
<td>412</td>
<td>8.4</td>
<td>2.91</td>
<td>2.64*</td>
<td>(1.40 to 4.96)</td>
</tr>
<tr>
<td>Maintenance and technical</td>
<td>988</td>
<td>20.1</td>
<td>2.23</td>
<td>2.02*</td>
<td>(1.19 to 3.42)</td>
</tr>
<tr>
<td>Catering</td>
<td>274</td>
<td>5.6</td>
<td>2.19</td>
<td>1.99</td>
<td>(0.85 to 4.64)</td>
</tr>
<tr>
<td>Laboratory</td>
<td>52</td>
<td>1.1</td>
<td>1.92</td>
<td>1.75†</td>
<td></td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>46</td>
<td>0.9</td>
<td>2.17</td>
<td>1.97†</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4923</td>
<td>100.0</td>
<td>1.52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Significant
†Number too small to calculate 95% CI.

The prevalence of VZV antibodies was investigated with the enzyme linked immunosorbent assay (ELISA), Enzygnost anti VZV/IgG (Dade Behring, Marburg, Germany). The sensitivity and specificity of this full antigen ELISA are 99.3% and 100% respectively. The limit of detection of this test is 50 mlU/ml, corresponding to a titre of 1/50. A result below this value was considered negative, a titre over 1/100 was definitely positive. Results that were classified as equivocal were retested with the ELISA test (Hycor Biomedical GmbH, Kassel, Germany). They were classified as positive or negative according to the result of this test.

The prevalence of VZV antibodies was calculated. From the data of the questionnaire and the serological survey, the percentage of seronegative was compared among different groups by calculating the prevalence ratios (PRs), defined as the ratio of the group with the highest to the lowest prevalence. The 95% confidence intervals (95% CIs) of the prevalences were calculated with the normal approximation of the binomial distribution, those of the PRs with the test based method. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the recalled history were calculated. Sensitivity was defined as the ability of a positive answer on historical enquiry to identify all immune subjects. Specificity was defined as the ability of a negative answer to identify all susceptible to VZV. The PPV is the probability, given a yes answer to the historical enquiry, that the person will be immune to VZV by serology. The NPV is the probability, given a no answer to the historical enquiry, that the person will be non-immune to VZV by serology.

Table 1 shows the distribution of selected demographical and occupational variables in the study population. The mean (SD) age was 37.2 (8.5) years, 80.7% were women, and 1.5% were of foreign origin. From the people of foreign origin only 14 were born in tropical regions. Most (60.8%) were nursing staff. The mean and median years of employment were 12.5 and 11.0 respectively.

A comparison of our sample with the total population of healthcare workers in general hospitals under medical surveillance of IDEWE (26,654 employees in 1996, which is about 38.5% of all hospital workers in Flanders and in Brussels) showed that the frequency distribution of sexes was comparable (80.7% women in the sample compared with 79.9% in the population), that younger age groups were slightly underrepresented in the sample (41.1% younger than 35 years in the sample compared with 45.7% in the population), and that nursing duties were comparable (60.8% with nursing or caring duties in the sample compared with 60.3% in the population). In the most recent official statistics (1990), the nursing staff in all Flemish hospitals account for 57.5% of the general hospital personnel.

As for the regional distribution of the people in the study, the Province of Antwerp (37% in our study versus 24% in demographic statistics), and the Province of Flemish Brabant (29% versus 15%) were overrepresented. As a consequence, the Brussels region and the other Flemish provinces were underrepresented.

### Results

The prevalence of VZV seropositivity in Flemish healthcare workers was 98.5% (95% CI 98.1 to 98.8). Only 75 out of 4923 blood samples were found to be negative.

In table 1 the PRs of seronegative workers according to the selected variables are shown. Significant PRs were found for age and job. The lowest percentage of seronegative workers (1.1%) was found in the age group 35–44 years. The PRs for the older age groups were significantly different from 1.0. Also, there was an increase in the youngest group (<25 years), but the PR of 1.93 was not significant probably due to the low number of participants in this age group. There was no significant difference for sex, duration of employment, or country of origin. In fact, the number of participants of foreign origin was too small for adequate stratified statistical analysis. Overall, nursing staff were significantly less seronegative than non-nursing staff, which means that the prevalence of seronegative workers was higher among all other job categories. The PRs were significant for administrative, maintenance, and technical personnel.

After stratification in the age groups <37 years and ≥37 years (based on the median age), the difference between nursing and non-nursing staff became more pronounced in the group of <37 years, the PR rising to 3.42 (95%
CI 1.80 to 6.48), whereas the PR for the ≥37 years olds decreased to 1.45 (95% CI 0.79 to 2.66).

As shown in table 2, nursing staff were less often seronegative than non-nursing staff from the beginning of their careers. The PR of seronegativity in non-nursing versus nursing staff that were employed for less than 5 years, was 3.44 (95% CI 1.30 to 9.13). There was no important decline in percentage of seronegative workers by years of employment for both groups, but the numbers were too small for statistical testing.

Workers at the paediatric department were 3.03 times more likely to be seronegative than those of other clinical departments. However, the number of participants from paediatric departments (148 people) was too small for calculating the 95% CI.

Table 3 shows the comparison between reported history of varicella and serological testing. The PPV was 98.9% (982/993), whereas the NPV was 3.4% (7/208). The sensitivity of the history to predict immunity by serological testing was 83% (982/982+201) and the specificity of history to predict susceptibility was 38.9% (7/(11+7)). These figures for sensitivity and specificity became 50.5% (982/982+201+763) and 69.4% (74+11/11+7+18), respectively, when people with unknown histories were added to those with a negative history. In the occupational health care setting, it is recommended that an uncertain history of varicella is considered as negative.

**Discussion**

The prevalence of VZV antibodies (98.5%) was high in this sample of Flemish healthcare workers. This figure is higher than those reported in similar studies of healthcare workers, where prevalences ranged from 90% to 98%. The sample size in most of these studies was small (<1000 people), except for the study of Tennenberg et al on 6664 healthcare workers of a university hospital in New York. They found a prevalence of 96.6% (estimated 95% CI 96.1 to 97.0). The lower figures in these studies could be due to a different demographic composition of the study population, in particular the presence of many workers of foreign origin. Most authors did not provide enough demographic information about their study population to confirm this hypothesis. The sensitivity of the serological assays used to detect VZV antibodies could be another explanation. We used an ELISA as opposed to an indirect fluorescent antibody (IFA) test in the study of Tennenberg et al. In our study, there was no association between seronegativity and sex or duration of employment, which was also found by other investigators. Although there is consensus that susceptibility to VZV is higher among personnel originating from tropical regions, we were not able to confirm this association because of the few participants that were of non-Belgian origin.

The association between older age (≥45 years) and seronegativity has to our knowledge not been reported previously. Although Jackson et al did not mention it, their figures on VZV antibody prevalence in 350 childcare providers, showed the same trend. The trend towards more seronegative healthcare workers in the age group of <25 years was also found in the study by Schoub et al in 244 laboratory staff members, but no statistical calculations were performed. Other investigators did not find an association between age and prevalence of VZV antibodies. An explanation for the increase of seronegative people with older age could be the loss of detectable antibodies. A lower incidence of varicella in the older birth cohorts seems less likely. Possibly the sensitivity of the serological assay, used in our study, was not sufficient to detect very low antibody titres.

The prevalence of seronegativity was significantly less in nursing staff than non-nursing staff. Age was a confounder, but cannot be the explanation for the difference between job categories. This association between job and seroprevalence was not found in other studies. Hofmann et al did not find a difference in seroprevalence between nursing staff and administrative personnel. Gallagher et al found that the proportion of susceptible clinical staff was almost identical to the proportion of susceptible staff overall. A greater risk for nurses to contract varicella during their career could be an explanation for the association found in our study. Analysis according to years of employment, however, did not show an important decline in seronegativity with increasing seniority for either nursing or non-nursing staff. Nursing staff employed for less than 5 years, were significantly more often seronegative than non-nursing staff, suggesting that the difference already exists at the beginning of their careers. Consequently, from our data we cannot conclude that there is a higher occupational risk of VZV infection in nursing staff, but the limitations of the cross sectional study design have to be kept in mind. Possibly, seronegative student nurses could already have...
contracted varicella during their training. A different socioeconomic background seems a less likely explanation because the same difference exists between nurses and administrative personnel and maintenance and technical personnel.

There was a trend to more seronegative workers in the paediatric department. By contrast with paediatric services, adults in hospital with zoster could be an important source of exposure.

The PPV of a reported history of varicella (98.9%) was high and corresponds to the results of other investigators.\(^{11}13\) The NPV (3.4%) was low compared with similar studies where this figure varied from 11.1% to 60%. Our very low NPV could be due to the fact that historical information was obtained by a self administered questionnaire and not by a face to face interview of the participants, during which additional information on the illness could have been provided. From the figures of Schoub et al,\(^{17}\) who questioned their participants about a history of varicella, we calculated a NPV of 33.3%. Other explanations could be that we only asked for varicella or chickenpox and not for zoster or shingles and that our study population was rather old (mean age 37.2 years). The PPV and NPV were higher in younger people, especially in those younger than 18 years.\(^{25}26\) A positive history of varicella was able to identify 83% of healthcare workers that were immune. A negative history was able to identify 39% of those that were not immune. Eleven of 993 people (1.1%) with a positive history of varicella were seronegative. This could partly be due to the sensitivity of the ELISA test. As five of these 11 people (45%) were older than 45 years, whereas this age group only accounted for 21% of the participants, this finding also suggests the loss of detectable antibodies. Fifty five per cent of these people were younger than 45 years. Evidence was found in other studies that a positive history of varicella is not a reliable predictor of immunity in young adults.\(^{24}\) A negative or uncertain history of varicella was able to detect 69% of the seronegative workers, which means, however, that 31% (11/36) of seronegative workers were not detected by history.

Almost all investigators agree that healthcare workers should be immune to VZV to prevent VZV infection in susceptible employees, and to decrease the likelihood of nosocomial transmission of VZV to patients.\(^{2}399131825\) Therefore, advice has been given to screen for VZV immunity at the time of initial employment and to vaccinate employees that are not immune.\(^{39}\) Most of them consider a positive history of varicella sufficiently predictive for immunity and restrict serological screening and subsequent vaccination to those with a negative or uncertain history of varicella.\(^{2}31131825\) They also assume that screening of this group is cost effective because the negative predictive value of history is low. Only a few authors consider the risk of missing non-immune employees unacceptable and advise testing all healthcare workers irrespective of their history.\(^{91524}\) In Belgium the varicella vaccine is 20 times more expensive than a serological test for VZV antibodies and our data showed that the NPV of a history of varicella is very low. Therefore, we calculated that it would be cost effective to test people with a negative or uncertain history before vaccination. Nevertheless, according to our results, one third of seronegative people (31%) have a positive history of varicella and will not be detected and vaccinated with this strategy. Detection of all seronegative workers implies a doubling of serological tests (1982 vs 989) and increases costs by 80%. Another option is to test healthcare workers with a negative or uncertain history of varicella and to test those with a positive history, if they have an increased risk.\(^{2125}\) This can be defined as higher risk of exposure (services for infectious diseases, contact with immunocompromised patients), higher personal risk (non-pregnant women of childbearing age) or expected lower prevalence of VZV antibodies (foreign origin).

Finally, taking a history during a face to face interview, probably would increase the NPV and subsequent costs of testing.

Because part of the negative serological results in employees with a positive history of varicella could be due to the loss of detectable antibodies in older people, further investigations are necessary on cases of secondary varicella in elderly people. More sensitive tests can be used to examine negative serum samples.\(^{27}\) Cases of secondary varicella have already been described.\(^{19}\) If there were evidence that secondary varicella could be severe or complicated, it might be necessary to repeat serological screening and vaccination after 45 years.

A final remark concerns the external validity of our study. Even though it is a large sample which is geographically well spread, representation for all healthcare workers in Flanders and in Brussels cannot be guaranteed.

In conclusion, our study shows that the prevalence of VZV antibodies in Flemish healthcare workers is high. Therefore, the overall occupational risk of VZV infection for healthcare workers is low at this moment. This could change in the future as epidemiological studies in the United Kingdom and the United States show an upward shift in the age distribution of varicella cases over the past 20 year.\(^{7}\) Mass vaccination of young children also can influence the VZV epidemiology. Follow up of the seroprevalence rates of VZV antibodies will therefore be necessary in the future.

We thank everybody who collaborated in the study, particularly the hospital staff and personnel, the occupational physicians and nurses, the IDEWE central secretarial service, especially N Gevers, the documentation center of IDEWE, and J Dewijngeerts (IDEWE). We thank SmithKline Beecham (Belgium) and the Scientiﬁc Institute for Public Health—Louis Pasteur (Brussels, Belgium) for ﬁnancial support.


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