

The comparative sero-epidemiology of varicella zoster virus in 11 countries in the European region

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Abstract

The European sero-epidemiology network (ESEN2) aims to standardise serological surveillance of varicella zoster virus (VZV) in 11 participant countries. In each country, serum banks were collected between 1996 and 2003 and tested for VZV antibodies. Assay results were standardised so that international comparisons could be made. Age-specific forces of infection were calculated for three age groups (<5, 5–9 and ≥10 years of age) and used to estimate the base reproduction number (R_0) and the herd immunity threshold (H). Most VZV infection occurred in childhood, but there was a wide variation in transmissibility, with R_0 ranging from 16.9 in the Netherlands to 3.3 in Italy. Herd immunity thresholds varied from 70% in Italy to 94% in the Netherlands. There are substantial differences in VZV sero-epidemiology within the European region, which will need to be taken into account in designing national policies regarding VZV vaccination.

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1. Introduction

Infection with varicella zoster virus (VZV) results in varicella, a common and generally benign disease of childhood [1]. Although mortality is rare, varicella is responsible for an important burden of hospitalisations [2] and is more

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severe in older ages [1], pregnant women, neonates and immuno-compromised individuals [1,3,4]. Following primary infection, VZV becomes latent in the dorsal root ganglia and may reactivate at a later date resulting in herpes zoster (shingles), which is associated with depressed cell-mediated immunity found, for example, in older age [4].

A live attenuated vaccine was developed in the 1970s based on the Oka VZV strain [4] and has been incorporated in the routine paediatric immunisation schedule in the United States of America since 1995 [5]. In a recent survey of 23 countries in the European region, the inclusion of VZV vaccine in the routine paediatric immunisation programmes was reported in Germany, in the Italian region of Sicily and by some Health Maintenance Organisations (HMOs) in Israel [6].

An evaluation of the vaccine programme in the United States has reported a decrease in disease, hospitalisations and mortality [7,8]. As for many diseases, unless adequate vaccine coverage is achieved, the average age of infection will increase, with a concomitant increase in the number of severe cases. A survey of 11 day-care centres in North Carolina reported an increase in the number of susceptibles in older age groups with increased VZV vaccine coverage [9]. Modelling studies have demonstrated that there is a decrease in severe varicella disease following the introduction of mass childhood vaccination [10,11], much of which is due to the decline in hospitalisations among children. However, it is only with coverage of over 70% that there is a decrease in the hospitalisation rates for adults [11].

Epidemiological data are a vital component for the development and evaluation of vaccination programmes [12]. Case-based mandatory notification data of varicella are only available in a limited number of European countries, underlining the importance of serological data to assess the appropriateness of introducing any vaccine programme and to evaluate established programmes [6]. The European sero-epidemiology network (ESEN2), based on the previous ESEN project [13], was established in 2001 with the aim of standardising serological surveillance in 22 European countries to 8 vaccine-preventable diseases, of which 11 countries participated in the workpackage for VZV [14].

We compare the standardised VZV antibody levels reported in the national serological surveys undertaken in eleven countries in the European region, the data from which are used to estimate the key epidemiological parameters of base reproduction numbers (R_0) and herd immunity thresholds (H). These data will provide important baseline information with which to assess the appropriateness of a vaccination programme, to design the most effective strategy and to evaluate national programmes once in place.

2. Methods

2.1. Sera collection

Eleven countries in ESEN2 undertook testing for VZV antibody (Belgium, England and Wales [15], Finland, Germany [16], Israel [17], Italy [18], Ireland, Luxembourg [19], Netherlands [20], Slovakia and Spain). All countries had collected sera over limited time periods of approximately 12 months but in different years between 1996 and 2003 (Table 1). At the time of the serum bank collections, none of the participant countries had introduced an universal VZV vaccination programme, although since 2000 HMOs in Israel have recommended and partially subsidised VZV vaccination [6].

The sera were obtained either by residual sera collected during routine laboratory testing (6 of 11 countries) or by population-based random sampling (5 of 11 countries; Table 1). All studies complied with national ethical requirements. Sera were collected from all age groups, were evenly distributed between males and females and were geographically representative of each country (Table 1). Project guidelines recommended that approximately 100 samples be tested in each 1-year age band of those <20 years of age [14], achieved in all countries except Ireland (where between 50 and 75 samples per 1-year age band were tested), Israel (50–60) and the Netherlands (50–75). Small numbers of samples (<100) were tested in Luxembourg in those aged <5 years and in the Netherlands in those aged 15–19 years (Table 2).

Table 1
Collection of main serum banks of participating countries and enzyme immunoassay used to test for antibodies to VZV

Country	Method sera collection	Year of collection	Age range collected	Number of samples (1–20 years)	Commercial assay
Belgium	Residual	2002	1–39	1953	Enzygnost
England and Wales	Residual	1996	1–20	2091	DiaMedix
Finland	Residual	1997/1998	1–60+	1723	Enzygnost
Germany	Residual/Population	1995/1998	1–60+	2566	Enzygnost
Ireland	Residual	2003	1–60+	1122	DiaMedix
Israel	Residual	2000/2001	1–41	1642	Enzygnost
Italy	Residual	1996/1997	1–60+	2029	Enzygnost
Luxembourg	Population	2000/2001	4–60+	1381	Enzygnost
Netherlands	Population	1996	1–60+	1016	Human
Slovakia	Population	2002	1–60+	2049	Euroimmun
Spain ^a	Population	1996	2–40	1926	Enzygnost

^a Reference centre.

Table 2
Percentage sero-negative for VZV by age group in the 11 ESEN2 countries, 1995–2003

	Percentage sero-negative for VZV by age group (n)				
	<5 years (%)	5–9 years (%)	10–14 years (%)	15–19 years (%)	20–29 years (%)
Belgium	48.8 (377)	12.6 (467)	5.8 (466)	5.1 (643)	3.2 (404)
England and Wales	52.4 (580)	21.7 (452)	10.3 (476)	8.1 (484)	7.1 (99)*
Finland	69.1 (375)	22.9 (437)	6.9 (393)	3.3 (518)	3.0 (400)
Germany	67.4 (457)	13.8 (668)	4.4 (661)	5.9 (630)	2.3 (400)
Ireland	58.7 (271)	18.3 (240)	8.1 (297)	5.7 (314)	6.2 (453)
Israel	51.0 (198)	9.4 (277)	4.7 (300)	10.8 (241)	4.9 (203)
Italy	78.3 (443)	38.9 (543)	18.3 (519)	18.1 (524)	11.2 (448)
Luxembourg	27.0 (37)**	9.9 (425)	3.4 (532)	2.8 (387)	3.2 (379)
Netherlands	49.3 (286)	2.2 (317)	1.2 (333)	1.3 (80)	0.0 (160)
Slovakia	67.1 (456)	30.1 (538)	8.8 (524)	4.9 (531)	3.7 (462)
Spain	66.8 (322)	24.1 (585)	8.3 (484)	6.2 (535)	6.9 (1106)

* Samples tested for 20-year-olds only.

** Samples tested for 4-year-olds only.

2.2. Assay standardisation

The methodology and results of the qualitative and quantitative standardisation of the VZV antibody results have been described elsewhere [21]. In brief, the reference centre (Instituto de Salud Carlos III, Madrid, Spain) prepared a panel of 148 sera, which were tested using the Behring Enzygnost enzyme immunoassay (ELISA) as negative (<100 mIU/ml), equivocal (100–500 mIU/ml) and positive (>500 mIU/ml). These panels were distributed to participant laboratories where they were tested with the quantitative ELISA normally used by the participating laboratory (Table 1).

Local titres were converted to standard titres by regressing the results of the panel testing of the national centre against those of the reference centre and thus obtaining standardisation equations which could then be applied to the results of the testing of the main serum banks [22]. The quantitative standardisations of the assays were evaluated by determining the fit of the equation using R^2 (the square of multiple correlation coefficients), especially in the equivocal range, and qualitatively by assessing the level of concordance in identifying positive, negative and equivocal results [22].

In three countries (England and Wales, Germany and Italy), the serum banks had been tested over a year before the distribution of the reference panel. A back-standardisation, described in detail elsewhere [22], was performed in those countries in order to standardise their results to common project units. In brief, approximately 150 randomly selected sera from the national serum bank were forwarded to the reference centre for testing, and the same regression analysis was conducted on the two sets of data in order to obtain the appropriate standardisation equation.

The conclusion of the assay standardisation procedure was that the results of all VZV indirect ELISA employed by participant laboratories could be successfully standardised to common units [21]. Furthermore, by comparing ELISA results with those obtained by fluorescent antibody membrane antigen (FAMA) assays, equivocal results have been

included as positive in all results from the serological surveys [21].

2.3. Main serum bank testing

Each main national bank survey was tested using the same validated assay as was used for the reference panel. The country-specific standardisation equations were then used to convert the local quantitative results of the serum survey into standardised reference laboratory units. The reference laboratory cut-offs were used to re-classify qualitatively the standardised quantitative results as negative, equivocal or positive.

2.4. Estimation of age-specific force of infection

The VZV sero-prevalence data was used to estimate age-specific forces of infection, $\lambda(a)$, a measure of the incidence of infection in a susceptible population. As nearly all children were sero-positive by late childhood, age-specific forces of infection were calculated for three age groups: <5, 5–9 and ≥ 10 years of age [23]. We assumed closed populations, mortality as type I developed countries with a life expectancy of 75 years and passive immunity in all infants until the age of 6 months. Maximum likelihood methods were used to calculate $\lambda(a)$ using the relationship between the prevalence of VZV antibodies z and $\lambda(a)$ described in Eq. (1) [24]. All forces of infection were estimated with the constraint that the value was between 0 and 1. The upper and lower 95% confidence intervals (CI) for each age-specific force of infection were estimated by a method of profile likelihood confidence intervals in which two of the three forces of infection were fixed at optimal values and for the third calculating the force of infection for which the deviance differs by 3.84 from the optimal deviance.

$$z(a) = 1 - \exp\left(-\int_0^a \lambda(a') da'\right) \quad (1)$$

2.5. Estimation of base reproduction number

The base reproduction number (R_0) is a measure of the transmissibility of an infection and is defined as the number of secondary cases that can be expected by the introduction of a single infectious case in a totally susceptible population.

We have estimated R_0 using a method assuming heterogeneous mixing in the population [24]. Age-specific forces of infection were employed to estimate transmission coefficients β in a “who acquires infections from whom” (WAIFW) matrix that reflected heterogeneous mixing between the three different age groups as described below.

	< 5 years	5 – 9 years	≥ 10 years
< 5 years	β_1	β_3	β_3
5 – 9 years	β_3	β_2	β_3
≥ 10 years	β_3	β_3	β_3

The “next generation matrix” (NGM) is then formulated, and the dominant Eigen value of the next generator operator is the expected number of new cases produced per infected individual, the base reproduction number (R_0) [24]. The upper and lower 95% CI of R_0 were calculated by using the appropriate estimate of the force of infection.

2.6. Estimation of herd immunity threshold

Herd immunity threshold (H) is the proportion of the population that needs to be immunised in order to eliminate endemic transmission of infection and thus eradication of the disease. Herd immunity threshold (H) was calculated using Eq. (2) [23] and the 95% CI obtained by employing the upper and lower estimate of R_0 .

$$H = 1 - \left(\frac{1}{R_0} \right) \tag{2}$$

3. Results

The age-specific sero-profiles of all 11 participant countries demonstrated that the vast majority of acquisition of antibodies to VZV occurred in children (Fig. 1). The rate of transmission of VZV varied so that antibodies were acquired at a much earlier age in some countries (e.g. Netherlands) than in other countries (e.g. Italy, Fig. 1). Over 50% of young children had antibodies to VZV by 5 years of age, except in Italy where only 38% of children were sero-positive (Fig. 1). In contrast, by 5 years of age, 97% of children were sero-positive for VZV in the Netherlands, and over 80% in Belgium (80.9%) and Israel (86.0%) (Fig. 1). Over 90% of adolescents aged between 10 and 15 years of age were sero-positive for VZV in all countries, except in Italy where only 78% of 15 year olds had antibodies to VZV (Fig. 1).

Of the 10 countries that had tested samples from young adults (20–29 years old), less than 5% of individuals were

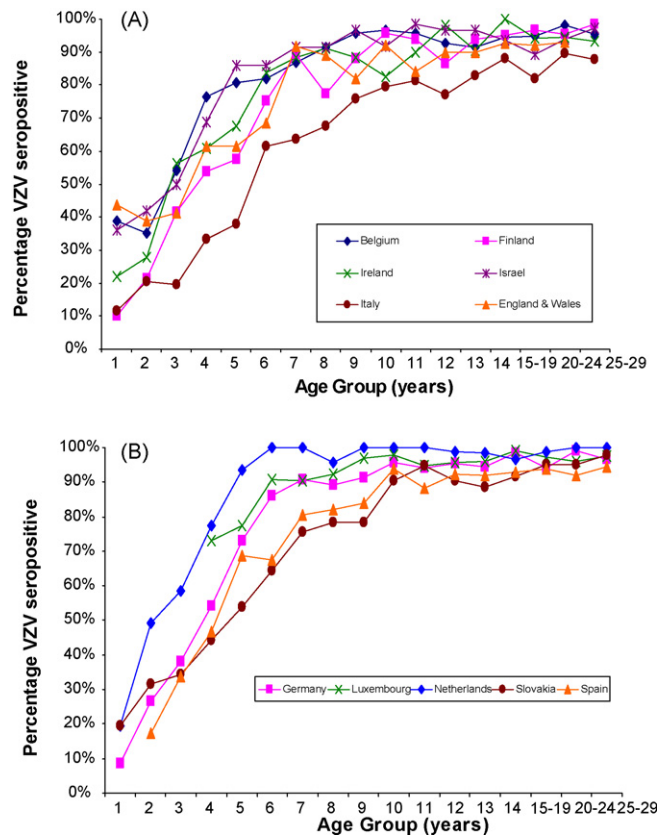


Fig. 1. Age-specific (<30 years of age) standardised sero-prevalence of VZV in 11 countries where samples were collected from either from residual sera (A) or from population sampling (B), 1995–2003.

sero-negative for VZV in 7 countries. The largest proportion of individuals sero-negative for VZV was reported in Italy (11.2%), and just over 5% in this age group were sero-negative in Ireland (6.2%), Spain (6.9%) and 7.1% of 20 year olds in England and Wales (Fig. 1 and Table 2). Amongst females of childbearing age (defined as between 15 and 39 years of age), less than 5% were sero-negative for VZV (data not shown), except in Italy (12.6%), Israel (7.6%) and Ireland (5.4%). The proportion sero-negative was highest in the youngest age group of females of childbearing age and declined in the older age groups. In Italy, nearly one-in-five (18%) of female teenagers were sero-negative for VZV (data not shown).

Of the three age groups, the largest forces of infection were amongst 5–9 year olds in all countries except in Belgium and Israel, where it was in the under 5 age group (Table 3). The largest estimated force of infection in the youngest age group (1–4 years) was observed in the Netherlands (0.35) and the lowest in Italy (0.10, Table 3). In the 5–9-year old age group, the estimated forces of infection for each country was greater than 20/100, of which the largest was estimated in the Netherlands (0.67) and the lowest in Italy (0.20, Table 3). In the oldest age group (≥10 years), the estimated forces of infection were low, with a force of infection of greater than 10/100 being reported only in Slovakia (0.137) and two

Table 3

Age-specific estimates of force of infection of VZV in three age groups (<5, 5–9 and 10+) in 11 ESEN2 countries, 1995–2003

	Age-specific forces of infection (95% CI)		
	<5 years	5–9 years	≥10 years
Belgium	0.312 (0.285–0.341)	0.275 (0.237–0.315)	0.051 (0.027–0.078)
England and Wales	0.208 (0.190–0.228)	0.226 (0.195–0.259)	0.044 (0.044–0.044)
Finland	0.162 (0.141–0.183)	0.358 (0.318–0.399)	0.096 (0.068–0.128)
Germany	0.189 (0.180–0.197)	0.431 (0.415–0.447)	0.038 (0.027–0.049)
Ireland	0.235 (0.209–0.263)	0.295 (0.260–0.334)	0.023 (0.004–0.044)
Israel	0.314 (0.279–0.352)	0.285 (0.239–0.336)	0.000 (0.000–0.000)
Italy	0.099 (0.087–0.112)	0.203 (0.183–0.223)	0.072 (0.058–0.086)
Luxembourg	0.326 (0.285–0.370)	0.357 (0.307–0.413)	0.052 (0.018–0.090)
Netherlands	0.351 (0.305–0.402)	0.673 (0.545–0.830)	0.000 (0.000–0.061)
Slovakia	0.156 (0.140–0.174)	0.253 (0.223–0.286)	0.137 (0.111–0.165)
Spain	0.153 (0.137–0.171)	0.326 (0.300–0.353)	0.051 (0.051–0.051)

Table 4

Estimated base reproduction number (R_0) and herd immunity thresholds for VZV in 11 ESEN2 countries, 1995–2003

	Base reproduction number (95%CI)	Herd immunity threshold (95% CI)
Belgium	6.47 (5.62–7.55)	84.5 (82.2–86.8)
England and Wales	3.83 (3.32–4.49)	73.9 (69.9–77.7)
Finland	4.85 (3.89–6.04)	79.4 (74.3–83.4)
Germany	5.46 (5.16–5.76)	81.7 (80.6–82.6)
Ireland	5.22 (4.53–6.14)	80.8 (77.9–83.7)
Israel	7.71 (6.01–10.06)	87.0 (83.4–90.1)
Italy	3.31 (2.82–3.83)	69.8 (64.5–73.9)
Luxembourg	8.28 (6.74–10.42)	87.9 (85.2–90.4)
Netherlands	16.91 (11.5–24.18)	94.1 (91.3–95.9)
Slovakia	5.72 (4.72–6.81)	82.5 (78.8–85.3)
Spain	3.91 (3.53–4.38)	74.4 (71.7–77.2)

countries (Israel and the Netherlands) with forces of infection of zero (Table 3).

The largest estimated R_0 was reported in the Netherlands (16.9) and the lowest in Italy (3.3). The estimated R_0 for the Netherlands was nearly twice that of the next highest (Luxembourg; 8.28) and 7 of the 10 countries had R_0 of less than 6 (Table 4). The largest H was estimated in the Netherlands (94%), and estimates of between 80 and 90% were reported for six countries and less than 80% in four countries, of which the lowest was estimated in Italy (70%, Table 4).

4. Discussion

We report on the first international study that compares the standardised pre-vaccination serology of VZV in the European region. Unlike other studies [25,26], the VZV antibody titres have been standardised to common units, thereby controlling for possible inter-assay and inter-laboratory variations and allowing for international comparisons to be made [21,22]. Although serum banks were compiled by either residual sera collection or population sampling, data from Australia demonstrated that the VZV sero-prevalence

estimated from either method was similar [27]. However, residual sera methods are thought to be more open to selection biases as they are collected from those attending medical services, even though population surveys are open to important non-response biases [28].

In Europe, the sero-epidemiology of VZV was characterised as a disease of childhood with a rapid acquisition of antibodies to VZV, so that by early adolescence most individuals were sero-positive for VZV, a profile similar to that reported by other studies undertaken in Europe [29,30,26]. The large proportion of susceptible young adults in Italy is of concern as in this age group varicella disease is more severe and the incidence of complications is very much higher [31]. Even though the risk of congenital syndrome is small following infection in pregnancy [3,32], the large pool of susceptible females of childbearing age in Italy is a cause for concern [18].

The transmission of highly infectious infections, such as VZV, is highly dependent on the pattern and intensity of mixing in the population, and especially in the younger age groups [23,26,33,34]. The highest age-specific forces of infection for VZV were found those aged 5–9 years old, which incorporates the start of primary school, and has been also reported in Canada [33] and Australia [34]. Only in Belgium and Israel was the highest force of infection observed in pre-school age groups, and this has also been reported in other studies in Europe [19,26,33]. These differences may be accounted for by either the use of alternative data sources [26,33] or methods (i.e. different age groups) [19]. In Belgium and Israel, the higher force of infection was attributed to the early age at which pre-school commences and the larger proportions of infants and pre-school children in child-care starting at 3 months of age [17,26].

There was a wide variation in the estimated R_0 , and thus consequently also in herd immunity thresholds (H), for the individual countries, although the range was within that reported in the literature [23]. Even so, the estimate of R_0 for the Netherlands was higher [20] and for Italy lower than other countries. Such a difference is unlikely to be due to different sampling methodologies, as the R_0 estimated from

residual sera or population surveys overlapped or to differences in assays as the antibody titres were standardised [21]. However, the estimated R_0 is dependent on the mixing matrices employed [35], thus the use of a single matrix may not have been appropriate for all 11 countries. A wide variation in the estimated R_0 for rubella was reported in different European countries, but not for measles and mumps [36]. Thus, the epidemiology of VZV, like that of rubella, may be more sensitive to differences in mixing patterns. Nonetheless, the impact of different social structures on the epidemiology of VZV in different European countries is now being actively investigated.

The variability in the reported R_0 and herd immunity thresholds have important implications for the epidemiology of varicella in each country and thus the design and implementation of a VZV vaccination programme. Although international comparisons of varicella epidemiology can be hampered by differences in the surveillance [37] or lack of data [6], it has been reported that in the Netherlands, where there is high VZV transmission, there are lower rates of varicella complications and zoster than countries with lower transmission of VZV [20]. Such countries will need to ensure that the vaccine programme is introduced with an adequate coverage to avoid a risk of increased incidence of severe varicella in older age groups. Before vaccination, it is possible that those countries with low transmission (such as Italy) are more likely to have an increased incidence of severe complications linked to varicella infection in adults. Therefore, in these countries, adolescent vaccination campaign may be more cost-effective than in high transmission countries [38]. Certainly the introduction of universal VZV vaccination in such countries will also require an adolescent catch-up campaign, as undertaken in Sicily and Germany [6].

The WHO has recommended that VZV vaccine should only be introduced in those countries that can maintain a sustained and high (i.e. 85–95%) coverage [39], higher than the estimated herd immunity threshold of seven of the 11 countries. Recent infant MMR vaccine coverage can be used as an indicator of the ability of national immunisation programmes to deliver VZV vaccine; especially as a combined MMR-VZV vaccine is being developed [40]. This level of MMR vaccine coverage has not been reported in four of the participant countries (Belgium, England and Wales, Ireland, and Italy) [41]. Furthermore, the acceptance of a VZV vaccine by the wider public, especially as chickenpox is not viewed as a serious disease by some parents and medical professionals [42,43], may further reduce the coverage of any VZV vaccine.

We have demonstrated wide variations in the sero-epidemiology of VZV in 11 different countries in Europe and its environs. The possible introduction of childhood vaccination for VZV vaccine remains the responsibility of each participant country. However, the use of serological data is essential to assess the appropriateness of a vaccination programme, to design the most effective strategy and to evaluate the programme once in place.

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