



Practice of Epidemiology

Hope-Simpson's Progressive Immunity Hypothesis as a Possible Explanation for Herpes Zoster Incidence Data

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Varicella-zoster virus (VZV) is the causative agent of both varicella (chickenpox) and herpes zoster (HZ) (shingles). After varicella infection, the virus remains dormant in the host's dorsal ganglia and can reactivate due to waning cell-mediated immunity, causing HZ. Exposure of varicella-immune persons to VZV may boost the host's immune response, resulting in a protective effect against HZ. In this study, we used mathematical models of VZV transmission and HZ development to test the biological hypothesis of "progressive immunity," originally proposed by Hope-Simpson (*Proc R Soc Med.* 1965;58:9–20), that cell-mediated protection against HZ increases after each episode of exposure to VZV. Predictions from a model incorporating such a hypothesis were compared with those of other concurrent models proposed for explaining HZ epidemiology. The progressive immunity model fits significantly better the age profile of HZ incidence for Finland (years 2000–2006), Italy (2003–2005), Spain (1997–2004), and the United Kingdom (1991–1992), suggesting that this mechanism may be critical in shaping HZ patterns. The model thus validated is an alternative to VZV models currently used to evaluate the impact of mass immunization programs for varicella and therefore extends the range of tools available to assist policy-makers with the present decision paralysis on the introduction of vaccination.

chickenpox; herpes zoster; immunity, cellular; mathematical model; vaccination

Abbreviations: HZ, herpes zoster; VZV, varicella-zoster virus.

Varicella (chickenpox) and herpes zoster (HZ) (shingles) are two clinical manifestations of the same pathogenic agent, the varicella-zoster virus (VZV) (1). The first infection with VZV results in varicella disease, which occurs most often in children and generally confers lifelong immunity to new episodes of varicella (1). After recovery, the virus is not fully cleared by the host but remains dormant in dorsal ganglia and reactivates as HZ in approximately 30% of persons with previous varicella (2). VZV-specific antibodies do not seem to play any role in host resistance to HZ; indeed, the critical component of the host immune response has been identified in the cell-mediated immunity (3–7) elicited by primary varicella, which is thought to constrain the virus in a latent state. The frequency and severity of HZ increase with age (2), most likely as a consequence of the decline of cell-mediated immunity specific for VZV (8, 9).

However, cell-mediated immunity might be boosted by sub-clinical infections from exogenous exposure to VZV (8), as supported by several studies where the risk of HZ among persons who had come in contact with varicella patients was significantly lower than that of the general population (10–12). According to a famous hypothesis suggested by Hope-Simpson (8) and recently re-proposed (see Oxman (3) and references therein), each re-exposure to VZV boosts the host's level of cell-mediated immunity to values incrementally larger than the level conferred in previous episodes, thereby gradually reducing the risk of HZ. Thus, re-exposures provide the host with a "progressive immunity" to VZV reactivation.

In this study, we aimed to include the progressive immunity hypothesis in a mathematical model for the natural history of varicella and HZ and investigate its ability to

explain the observed profiles of HZ incidence by age in 4 different European countries: Finland, Italy, Spain, and the United Kingdom. These 4 countries were selected for the availability of data on HZ case notifications and varicella seroprevalence by age and reliable estimates of the contact matrices by age.

MATERIALS AND METHODS

Data

Age-specific HZ case notification data were obtained from published studies for Finland (13; years 2000–2006), Italy (14; years 2003–2005), Spain (15; years 1997–2004), and the United Kingdom (16; years 1991–1992). Age-specific VZV seroprevalence data for the same countries were made available from European Sero-Epidemiology Network 2 (17) and were used jointly with contact matrices by age to estimate the force of infection for each of the 4 countries considered (18). The age-specific contact matrices for each country were computed in the paper by Fumanelli et al. (19) by applying a recent approach (20) based on routine socio-demographic data (European Commission (http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/search_database), unpublished data, 2011) used to build synthetic populations (21). We preferred these matrices to others available in the literature (e.g., the Polymod ones (22)) for various reasons: 1) they fit varicella serological data at least as well as, if not better than, Polymod ones (18); 2) being computed as descriptive statistics of census data, they do not add extra uncertainty to the estimation of the varicella force of infection; and 3) they are available in most European countries (19). Country-specific birth rates and mortality rates by age were obtained from the Eurostat databases (European Commission, unpublished data, 2011).

Mathematical models

We propose a mathematical model for the natural history of varicella and HZ including Hope-Simpson's hypothesis of progressive immunity. The model is formulated as a generalization of an existing model (13), under the following simplifying hypotheses: 1) the system is at its endemic equilibrium; 2) the varicella force of infection, $\lambda(a)$, is also assumed to be at equilibrium and known; 3) the contribution of HZ to the force of infection is assumed to be negligible, based on the observation that HZ is rarer than varicella, is

less infectious (23), and occurs preferentially at older ages, when social contacts are much less frequent compared with younger ages (19, 22); and 4) persons who are immune from maternally transferred antibodies and those in the latent and infective varicella compartments are not considered, since their time scales are negligible compared with those of VZV reactivation.

The model's structure is illustrated in Figure 1. People are born susceptible to VZV infection (compartment S), which they acquire at a rate given by the force of infection $\lambda(a)$. After recovery, they develop humoral protection from varicella reinfection and become susceptible to VZV reactivation. HZ-susceptible persons can either be reexposed or develop HZ. Reexposures to VZV are assumed to boost the cell-mediated immunity response with probability z (z in $[0, 1]$), possibly dependent on age, implying a "force of boosting" $z(a)\lambda(a)$. Boosted persons move through a cascade of HZ susceptibility states labeled as HZS_i , where i counts exposure episodes. VZV reactivation occurs at a rate $\rho_i(a, \tau)$ that is dependent on i , on the host's age, a , and on the time elapsed since last exposure to VZV, τ (with $\tau \leq a$). After HZ disease, people are assumed to become lifelong-immune to HZ and are therefore moved to compartment R ("removed"); in fact, the lifetime risk of a second HZ episode is only 1%–5% among immunocompetent persons (3, 8). We refer the reader to Web Appendix 1 (available at <http://aje.oxfordjournals.org/>) for the complete model equations and their steady-state solution.

The functional form assumed for the risk of VZV reactivation is $\rho_i(a, \tau) = \rho_0 \times Q_i \times \exp(\theta_a(a - a_0)^+) \times \exp(\theta_\tau \tau)$, where $(a - a_0)^+ = \max(0, a - a_0)$. Following the formulation of Karhunen et al. (13), this form assumes a doubly exponential risk of VZV reactivation in both chronological age and time elapsed since last VZV exposure, in order to incorporate the immunosenescence of the host's cell-mediated immunity (9), on the one hand, and the cumulated exposure to HZ risk on the other hand. Unlike the formulation of Karhunen et al. (13), the functional form adopted includes the discrete function Q_i , which aims to describe the effects of the variation in the immune response with the number i of VZV reexposures according to the main hypothesis that appeared in the medical literature (8). This hypothesis, dating back to Hope-Simpson (8) and which we will call "progressive immunity," assumes that the protection provided by cell-mediated immunity increases monotonically with the number of VZV reexposures. Consistently, we represented this hypothesis by assuming a monotonically decreasing shape

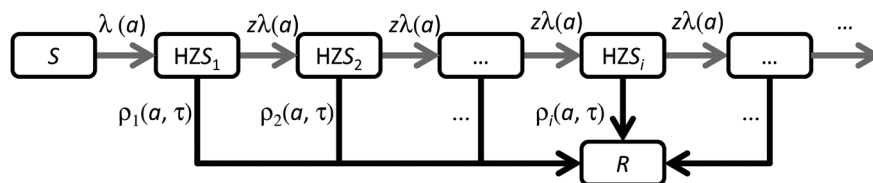


Figure 1. Compartmental structure of the proposed family of models. λ is the age-specific varicella-zoster virus (VZV) force of infection, z is the probability that reexposure results in effective boosting, and ρ_i is the VZV reactivation risk for persons exposed i times to VZV infectious cases. HZ, herpes zoster.

for Q_i according to a “half-bell” function: $Q_i = q^{(i-1)^2}$, with $i = 1, 2, \dots$ and q in $[0, 1]$. This choice (further explained in Web Appendix 2) implies that the VZV reactivation risk declines quickly after the first reexposure episodes, depending on the shape parameter q . The -1 term in the exponent allows ignoring the primary varicella episode, so that Q_1 is always 1. In the progressive immunity model, we also assume that all reexposures to the varicella force of infection result in effective boosting (i.e., $z = 1$).

We compared the progressive immunity model with a range of alternatives. As a baseline, we choose an implementation of the model proposed by Karhunen et al. (13). The baseline model is a special case of the progressive immunity model when $q = 1$, implying that Q_i remains fixed at 1 throughout the host’s entire life, independently of the number of exposures—that is, the reactivation risk does not depend on i . As in the progressive immunity model, in the baseline model z is fixed to 1 (13).

Several variants of the baseline model are also considered: one where only chronological age matters, which will be referred to as the “age only” model; one assuming that boosting plays no role for HZ (“no boosting”); one where boosting occurs at a rate reduced by a coefficient z independent of the person’s age (“imperfect boosting”); and one where the reducing rate z is age-dependent (“age-dependent boosting”). Finally, we consider an alternative to the progressive immunity model where the acquisition of immunity to VZV reactivation is not progressive but occurs abruptly by shifting Q_i from 1 to 0 after the H th reexposure episode (“permanent immunity model”). We refer the reader to Web Appendix 2 for details on the implementation of the different models.

In all models, the varicella force of infection is defined by the piecewise constant function $\lambda(a) = b \sum_x C_{a,x} I_x$, where b is a constant representing the varicella transmission rate per social contact (according to the social contact hypothesis (24)), $C_{a,x}$ denotes the mean number of contacts between persons aged a and persons aged x , and I_x is the proportion of varicella-infectious persons of age x at equilibrium. The force of infection was estimated for each country (displayed in Figure 2) by maximizing the binomial likelihood (18) of varicella seroprevalence data (17) using a simple age-structured susceptible–infected–removed model at equilibrium (20, 24–26) and assuming the contact matrix $C_{a,x}$ as known (19–21). Thus, statistical uncertainty in the force-of-infection estimates is limited to the uncertainty in the estimates of b only (see Web Appendix 3 for details). The fit was carried out by using serological data on all available age groups (18).

Fitting models to HZ incidence

Model parameters were estimated by maximizing the Poisson log-likelihood of observing the corresponding age-specific HZ incidence profiles in each country (13–16). Model selection was done by comparing the Akaike Information Criterion (27) scores (or a modified version for a small number of data points) of the different models; this criterion, which selects as the best-fitting model the one with the smallest score, is convenient because it allows comparing

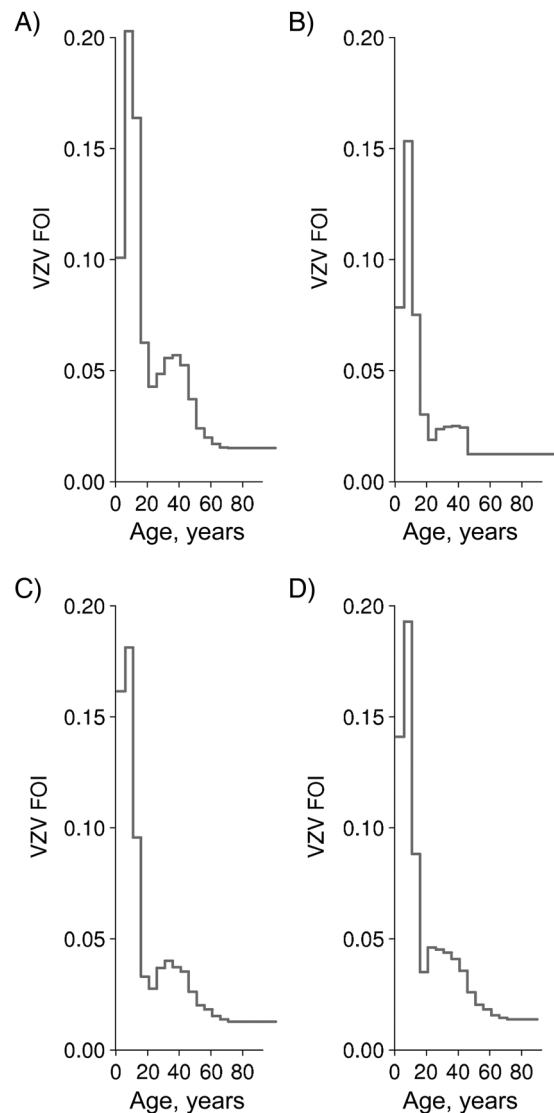


Figure 2. Varicella-zoster virus (VZV) force of infection (FOI) for the 4 countries considered in the model, by age. A) Finland (years 2000–2006); B) Italy (2003–2005); C) Spain (1997–2004); D) United Kingdom (1991–1992).

simultaneously several models with different characteristics. The likelihood ratio test (28) between nested models has also been used where feasible to evaluate the significance of fitness improvement with respect to the use of additional parameters. Web Appendix 4 provides technical details on model-fitting and model selection.

In order to assess uncertainty in parameter estimates, we implemented a parametric bootstrap procedure according to the method described in the paper by Davison and Hinkley (29). For each country, $M = 1,000$ data sets were simulated by resampling case notification data for each age group, using a Poisson distribution with mean equal to the model’s predicted value. The models were then fitted against each of the M simulated data sets, and bootstrap percentile

confidence intervals with a 95% confidence level were computed for both predictions and parameters.

RESULTS

Table 1 shows the Akaike Information Criterion scores for each model and country. The progressive immunity model fits remarkably better than all other models for all countries, with the exception of Finland, where the permanent immunity model produces a slightly better result. Overall, Table 1 shows that all hypotheses considered that do not admit a risk dependent on the number of VZV exposures fail to significantly improve the performance of the baseline model. Similar results are obtained with the version of the Akaike Information Criterion for a small number of data points (Web Table 1). On this basis, we concentrate on the comparison between the baseline model (13) and the progressive immunity model.

A likelihood ratio test was applied between the progressive immunity model and the baseline model, showing that the increase in likelihood was significant (with P values being much smaller than 0.001) in all data sets considered (see Web Table 2 for details).

For the baseline and progressive immunity models, we evaluated the variability of parameter estimates using the bootstrap procedure specified in Materials and Methods. Figure 3 reports the bootstrap best fits of HZ age-specific incidence data for both models in the 4 countries (analogous results for all models considered in Web Figure 1). Unlike the progressive immunity model, the baseline model fails to capture the decline in HZ incidence at older ages that is evident in Italian and Spanish data. The United Kingdom data do not show the same declining pattern; instead, the incidence seems to saturate. While the baseline model coarsely interpolates United Kingdom data with an approximately linear growth, the progressive immunity model follows

the observed profile quite closely, failing only to reproduce the age group of persons older than 85 years. Other European countries such as France, Belgium, and Iceland show a similar declining or saturating pattern with age in HZ incidence (Web Appendix 5), suggesting that this might be a common feature of HZ epidemiology in Europe. These countries could not be included in the analysis because of the lack either of VZV seroprevalence data or of the census data required to compute the contact matrices.

It has been proposed (13) that the HZ incidence estimated from surveillance data might be biased for persons above age 90 years due to the fact that persons living in retirement homes have in-house care and therefore do not visit general practitioners for HZ treatment. This might be the case for Finland, where, according to Eurostat census data (European Commission, unpublished data, 2011), the fraction of the population aged ≥ 90 years living in retirement homes is quite large (30%–40% of the total population aged ≥ 90 years; Web Table 3). However, data from the United Kingdom, Italy, and Spain should not suffer from this bias. HZ incidence for the United Kingdom refers to cases below age 90 years, where the proportion of the population living in retirement homes reaches, at most, 15% (see Web Table 1). As for Italy and Spain, the proportion of persons not living in private homes is below 15%, even for extreme ages (95–99 years) (for further discussion of the possible bias in reporting HZ cases, see Web Appendix 5).

At any rate, the progressive immunity model fits HZ incidence better than the baseline model even if we limit our analyses to ages below 75 years. In this case, a likelihood ratio test shows a highly significant ($P < 0.001$) improvement in likelihood for all countries (see Web Appendix 4 for details).

The greater ability of the progressive immunity model in fitting HZ incidence data compared with the baseline model can be explained by inspecting the age-specific proportions of HZ-susceptible persons, disaggregated by exposure episode. These are shown in Figure 4, part A, for Italy (very similar graphs can be obtained for the other countries). As age increases, the proportion of HZ-susceptible persons having experienced few (1–3) exposures declines or saturates, whereas the proportion with 4 or more reexposures increases (in particular, HZ-susceptible persons with 7 or more reexposures represent a negligible fraction). Therefore, in the presence of an “ever-increasing” (conditional) VZV reactivation risk with age, which should be an indisputable feature of HZ development, the decline of HZ incidence at high ages can only be observed if VZV reactivation occurs during the first few HZ susceptibility stages (Figure 4, part B). The reason for the success of Hope-Simpson's progressive immunity model in reproducing HZ incidence data at all ages (including the declining portion) is that it “selects” mainly susceptible persons with few reexposure episodes for HZ incidence. Equivalently, the progressive immunity model assigns an increasingly reduced risk to persons with several reexposures, on the basis of a sound biological hypothesis (8). On the other hand, the baseline model fails to reproduce HZ incidence at older ages because it considers persons from all exposure episodes as equally susceptible, thereby eventually causing an ever-increasing age-specific susceptibility profile to HZ.

Table 1. Akaike Information Criterion Scores for the Best Fits of 7 Models of Varicella-Zoster Virus Transmission and Herpes Zoster Development in 4 Countries (Finland (Years 2000–2006), Italy (2003–2005), Spain (1997–2004), and the United Kingdom (1991–1992))

Model	w^a	Akaike Information Criterion Score			
		Finland	Italy	Spain	United Kingdom
Progressive immunity	4	201.54	252.38	85.56	951.34
Baseline (13)	3	255.86	993.78	473.78	1,745.10
Age only	2	257.52	998.26	1,739.20	2,777.80
No boosting	3	255.90	941.56	469.96	1,746.36
Imperfect boosting	4	258.10	1,000.36	470.22	1,759.70
Age-dependent boosting	4	254.66	937.02	475.76	1,686.4
Permanent immunity	4	198.58	316.28	124.74	1,321.38

^a Number of free model parameters.

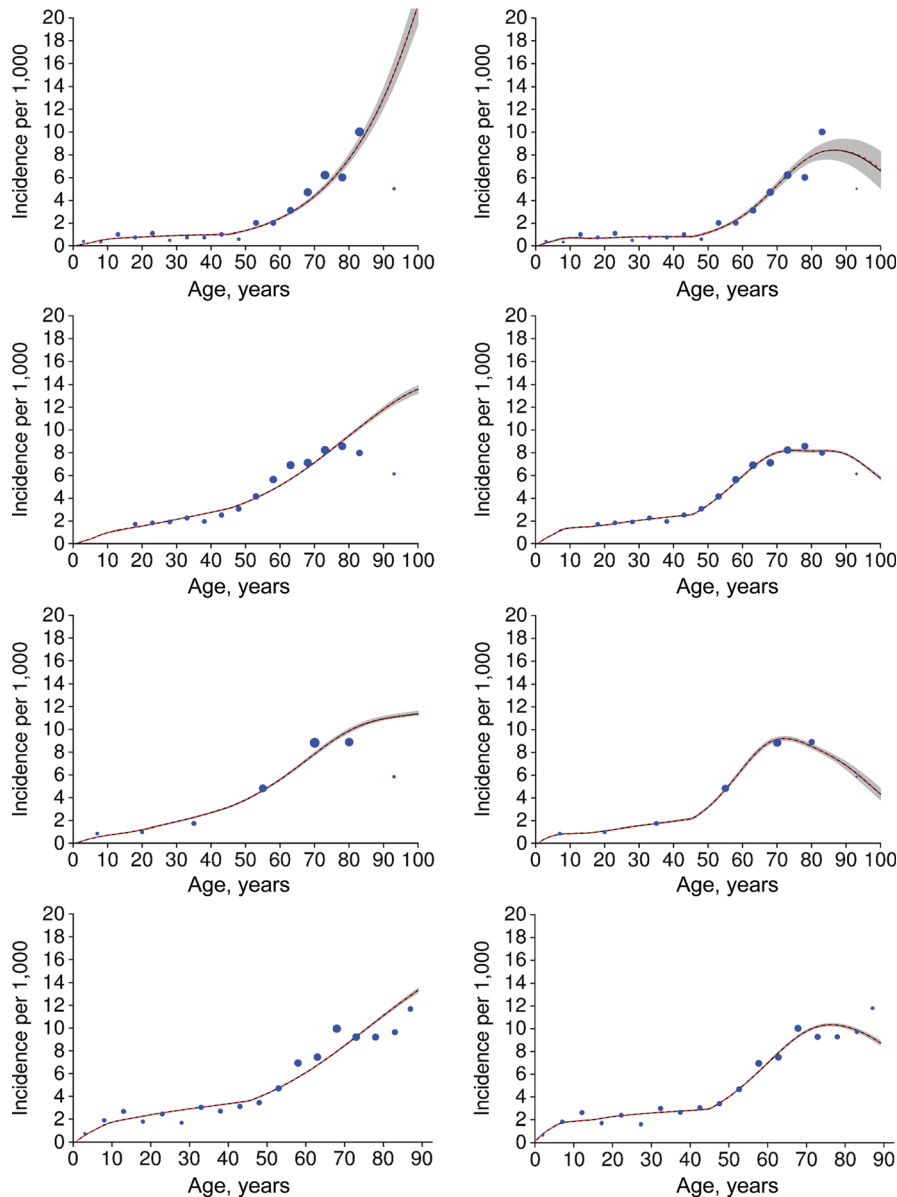


Figure 3. Model predictions of age-specific herpes zoster (HZ) incidence (per 1,000 population) versus observed data. Panels on the left side refer to the baseline model (13); panels on the right side refer to the progressive immunity model. Top row: Finland (years 2000–2006); center-top row: Italy (2003–2005); center-bottom row: Spain (1997–2004); bottom row: United Kingdom (1991–1992). Blue circles show the observed average incidence in the corresponding age group; the circles are located at the midpoint age, and their area is proportional to the total number of HZ notification cases, estimated as the product of the age-specific incidence and the population in the corresponding age group. Red dashed lines show the best fit of the model to the observed data. Black solid lines show the average best fit on bootstrapped data. Gray areas show the 95% confidence intervals for the model projections.

Table 2 shows the best parameter estimates (with 95% confidence intervals) for each data set. First, we note that the estimated increase in the risk of HZ per year of age, given by $\exp(\theta_a)$, in the baseline model for Finland is equal to 4.8%, very close to the value of 4.4% obtained by Karhunen et al. (13). Similarly, the estimated increase in the risk of HZ per year since last exposure, $\exp(\theta_\tau)$, is equal to 2.3%, which is close to the 3.3% obtained by Karhunen et al. (13). The difference might be attributed to the removal of the last data

point (patients older than 85 years) in the original work (13) and to some approximations in our model with respect to the original one (e.g., the removal of HZ from the force of infection of VZV, as reported in the “Mathematical models” subsection of Materials and Methods).

As for intercountry differences in parameter estimates, there is a marked difference in ρ_0 between Finland and Spain, on the one hand, and Italy and the United Kingdom, on the other hand, in both the baseline and the progressive immunity

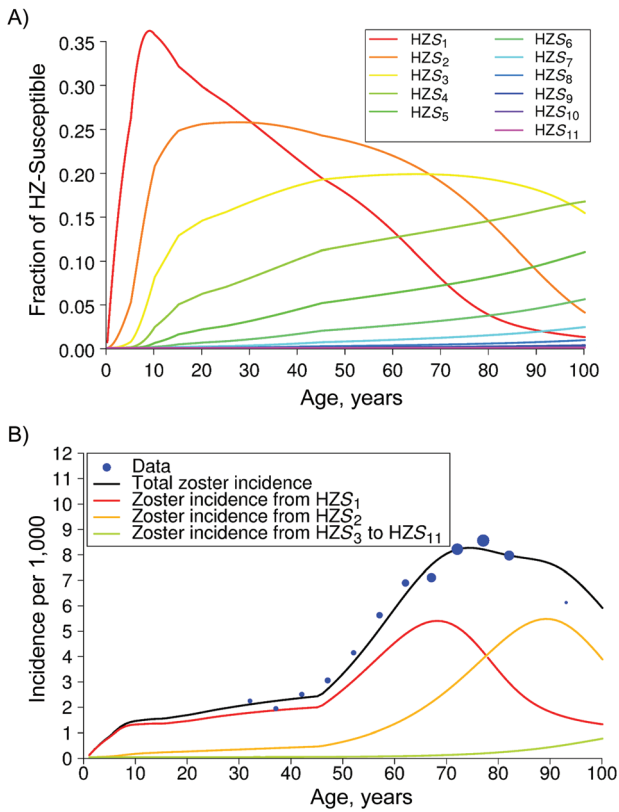


Figure 4. Model estimates based on data from Italy (2003–2005). A) Age profiles of the fraction of herpes zoster (HZ)-susceptible persons (HZS) over the total population, disaggregated by exposure count (number of reexposures, indicated by the subscripts 1–11); B) age profiles of HZ incidence, disaggregated by exposure count.

models. This can be explained by considering that this parameter reflects the average value of HZ risk when a and τ are small: Indeed, the average magnitude of HZ incidence at younger ages ($a < a_0 = 45$ years) in Finland and Spain is about one-half that in Italy and the United Kingdom, which is consistent with the ratio of the corresponding ρ_0 values.

We also note that estimates for θ_a and θ_τ are substantially stable across the 4 countries in the progressive immunity model, which may suggest that the components of cell-mediated immunity decline, regulated by these parameters, are country-independent, and therefore are intrinsic to HZ biology and pathogenesis. In the baseline model, instead, considerable intercountry variability was found in estimates of θ_a and θ_τ , which are quite difficult to justify on biological grounds.

Finally, the progressive immunity model shows a sharp variation in q across countries. This parameter modulates the protective effect of boosting events on the immune response of the host. It is plausible to assume that this parameter depends, at the single host level, on characteristics of reexposure events. Therefore, the variability of q at the population level could be explained by micro- and macro-level sociodemographic factors affecting such characteristics, as suggested by Silhol et al. (30). For example, higher housing

Table 2. Parameter Estimates for Varicella-Zoster Virus Reactivation Risk in the Baseline and Progressive Immunity Models for Finland (Years 2000–2006), Italy (2003–2005), Spain (1997–2004), and the United Kingdom (1991–1992)

Parameter and Country	Mean Estimate	95% Confidence Interval
<i>Baseline Model (13)</i>		
ρ_0 , ^a 1 per year		
Finland	0.73×10^{-3}	$0.66 \times 10^{-3}, 0.69 \times 10^{-3}$
Italy	1.31×10^{-3}	$1.22 \times 10^{-3}, 1.39 \times 10^{-3}$
Spain	0.72×10^{-3}	$0.67 \times 10^{-3}, 0.77 \times 10^{-3}$
United Kingdom	1.98×10^{-3}	$1.92 \times 10^{-3}, 2.05 \times 10^{-3}$
θ_a , ^b 1 per year		
Finland	4.74	4.42, 5.07
Italy	1.11	0.87, 1.34
Spain	0.12	0.05, 0.29
United Kingdom	1.98	1.82, 2.12
θ_τ , ^b 1 per year		
Finland	2.28	2.08, 2.46
Italy	4.10	3.86, 4.37
Spain	6.46	6.28, 6.62
United Kingdom	3.56	3.41, 3.73
<i>Progressive Immunity Model</i>		
ρ_0 , ^a 1 per year		
Finland	1.15×10^{-3}	$0.95 \times 10^{-3}, 1.41 \times 10^{-3}$
Italy	2.91×10^{-3}	$2.71 \times 10^{-3}, 3.15 \times 10^{-3}$
Spain	1.42×10^{-3}	$1.30 \times 10^{-3}, 1.57 \times 10^{-3}$
United Kingdom	2.95×10^{-3}	$2.84 \times 10^{-3}, 3.06 \times 10^{-3}$
θ_a , ^b 1 per year		
Finland	6.52	5.48, 7.69
Italy	5.35	4.86, 5.82
Spain	6.01	5.33, 6.70
United Kingdom	4.86	4.60, 5.15
θ_τ , ^b 1 per year		
Finland	4.47	3.81, 5.15
Italy	4.21	3.99, 4.44
Spain	6.09	5.80, 6.38
United Kingdom	4.55	4.42, 4.68
q , ^c %		
Finland	64.4	56.5, 72.7
Italy	19.4	16.7, 22.6
Spain	52.4	48.4, 56.7
United Kingdom	69.6	67.9, 71.2

^a ρ_0 represents risk at birth.

^b θ_a and θ_τ represent rates of exponential growth with chronological age a and time since last exposure τ , respectively.

^c q is the parameter of risk reduction due to boosting.

density and increased frequency and closeness of contacts between infectious cases (typically children) and boosted persons (typically adults) may increase the probability of exposure and the amount of viral load transferred, and

therefore the effectiveness of boosting, which is translated into lower values of q in our model. Indeed, housing density is higher in Italy than in the other countries of this study (the average number of rooms per person in households, as an inverse proxy for housing density, was estimated at 1.4 for Italy, 1.8 for the United Kingdom, and between 1.8 and 1.9 for Spain and Finland in 2006–2010 (European Commission, unpublished data, 2011)). Moreover, data from the Polymod Study (22) show that Italian children have more frequent in-household contacts with their grandparents than their Finnish and British counterparts (see Web Appendix 6; Spain was not involved in the Polymod Study); the closeness of contacts may be estimated as the frequency of skin-to-skin contact over all contacts from the same study, and it was found to be significantly higher for Italy (52%) than for the United Kingdom and Finland (43% and 36%, respectively) (22). These factors might partially explain, on the basis of biological considerations, the lower value of q found in Italy as compared with Finland and the United Kingdom.

Finally, we observe that parameter estimates for the progressive immunity model are quite robust with respect to uncertainty in the force-of-infection estimates (Web Appendix 3).

DISCUSSION

A vaccine against VZV has been available since the 1970s (31), and some countries (e.g., the United States, Canada, and Australia) have initiated varicella mass vaccination programs. However, there are entire regions (e.g., almost all of Europe, with the exceptions of a few national and local settings (32)) where the decision to introduce the vaccine is stalled. The paralysis is largely due to the fear of a massive increase in HZ incidence following the reduction of VZV circulation (33–37), which is systematically predicted by mathematical models (11, 13, 16, 38–41). Countries where VZV mass vaccination is in place (35) report ambiguous trends in HZ incidence (36, 37).

In this paper, we propose a new model for HZ epidemiology which includes the number of reexposure episodes experienced by an individual as a determinant of the hazard of VZV reactivation (8). This “progressive immunity model” performs better than competing models in explaining the age-specific HZ incidence profiles on all data sets considered. In particular, it captures better both the declining or saturating behavior of HZ at older ages, where present, and the age profiles at younger ages. Moreover, the model seems to provide a neater interpretation of phenomena underlying intercountry variability in HZ incidence profiles. In fact, the progressive immunity model yields robust estimates with respect to intercountry variability of parameters related to the age components of the VZV reactivation risk. The amount of progressive protection q conferred by each reexposure episode is predicted to be, jointly with the baseline age risk, a main determinant of the intercountry differences in HZ incidence. We have suggested a number of sociodemographic determinants of the intercountry differences estimated for q . Our future work will be aimed at better understanding the role of biological parameters and the intercountry differences by simultaneous multicountry fit, constraining parameters

having a stronger biological basis to assume the same value in the different countries.

A main feature of the progressive immunity model is that it yields a possible explanation for a counterintuitive phenomenon: the decrease in HZ incidence among very old persons, which is apparent in data from Italy and Spain. According to the model, this decrease is due to a lower HZ risk in elderly persons, determined by a higher number of reexposures during their lifetimes. Nonetheless, the progressive immunity model fits HZ data better than competing models even in settings, such as Finland and the United Kingdom, where this decrease is less obvious.

Especially in these 2 countries, the interpretation of results might be complicated by a potential bias arising in very old persons, a significant proportion of whom live in retirement homes (up to 50% among persons aged 95–99 years) and were therefore not included in the surveillance data used in this study. If, in particular, HZ incidence among persons living in retirement homes is higher than that in the general population, the figures provided by surveillance systems would underestimate the true overall incidence of HZ. There is currently no detailed information available on HZ incidence in retirement homes in the countries considered. Therefore, it would be worth collecting this information in future studies. However, a scenario analysis (Web Appendix 5) suggests that quite large values of excess incidence among persons living in retirement homes would be required to make the overall HZ profiles by age nondecreasing. At any rate, the progressive immunity model better fits HZ incidence data even after excluding data on the very old (persons aged ≥ 75 years) (Web Tables 4 and 5).

We acknowledge that Hope-Simpson’s progressive immunity hypothesis (8) is not necessarily the unique possible explanation for the decline in HZ incidence among the very old. An alternative explanation might be decreasing average population frailty with increasing age, in which survival to high ages is associated with better general health and immunity status. A further related point deserving scrutiny in future studies is the role of mortality among the very old.

More generally, HZ immunology and pathogenesis are complex and still only partially understood, challenging epidemiologic interpretation and mathematical modeling. Advances in our understanding of the mechanisms underlying exogenous boosting—for example, by immunological studies focusing on the behavior of cell-mediated immunity following reexposure to VZV (42)—are needed. Nonetheless, such studies would hardly provide information on the potential impact of reexposure to VZV on HZ protection at the population level, and thus, lacking large-scale epidemiologic studies of the matter, the contribution of mathematical and statistical models remains essential.

Clearly, mathematical models based on epidemiologic data are not intended to replace direct immunological evidence for pathogenic mechanisms. Therefore, we cannot conclude that Hope-Simpson’s progressive immunity hypothesis is the true mechanism underlying VZV reactivation. However, the current lack of precise knowledge about the immunology and pathogenesis of HZ increases the need for developing reasonable and testable alternative hypotheses that might suggest further research directions. The model developed here supplies a

counterintuitive suggestion, namely that repeated exposures to VZV outbalance, in very old persons, the increase in VZV reactivation risk due to immunosenescence. This result is immunologically testable by comparing cell-mediated immunity levels in the very old with those of younger persons, and therefore is deserving of further investigation.

Lastly, current uncertainty about HZ pathogenesis makes it unavoidable to explore a range of alternative hypotheses and related models when considering public health policy evaluations, such as the impact of immunization programs. The two models compared in this study represent alternative viewpoints on HZ onset among the very old which are reasonable in structure and compatible with data, and therefore are useful in bounding the range of alternative models of HZ development.

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