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Hope-Simpson's progressive immunity hypothesis explains Zoster data

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List of abbreviations:

CMI: Cell-Mediated Immunity

FOI: Force of Infection

HZ: Herpes Zoster

LRT: Likelihood Ratio Test

VZV: Varicella Zoster Virus

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Abstract.

Varicella-zoster virus (VZV) is the causative agent of both varicella and herpes zoster (HZ). After varicella infection, the virus remains dormant in the host's dorsal ganglia and can reactivate due to waning cell-mediated immunity (CMI), causing HZ. Exposure of varicella-immune individuals to VZV may boost the host's immune response, resulting in a protective effect against HZ. In this study, mathematical models of VZV transmission and HZ development are used to test the biological hypothesis of "progressive immunity", originally proposed by Hope-Simpson, that cell-mediated protection against HZ increases after each episode of exposure to VZV. Predictions from a model incorporating such hypothesis were compared to those of other models where VZV exposure only restores the initial level of CMI after primary varicella infection. The progressive immunity model explains significantly better the age profile of HZ incidence for Finland, Italy, and United Kingdom, suggesting that this mechanism is critical in shaping HZ patterns. These findings might greatly improve VZV models currently used to evaluate the impact of mass immunization programs for varicella and therefore to cope with the present decision paralysis on their introduction.

Medical Subject Headings (MeSH) (keywords):

Chickenpox; Herpes Zoster; Immunity, Cellular; Mathematical Model; Vaccination.

Varicella and herpes zoster (HZ), commonly termed as chickenpox and shingles respectively, 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). However, after recovery the virus is not fully cleared from the host's organism, but remains dormant in dorsal ganglia and reactivates as HZ in about 30% of individuals previously infected with 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 (CMI) (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 CMI specific for VZV (8, 9). However, CMI might be boosted by subclinical infections from exogenous exposure to VZV (8), as supported by several studies where the risk of HZ among those exposed to varicella cases 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 in the literature ((3), and references therein), each re-exposure to VZV, boosts the host's level of CMI to values incrementally larger than the level conferred in previous episodes (3, 8), thereby gradually reducing the risk of HZ. Thus, re-exposures provide the host with a "progressive immunity" to HZ reactivation.

In this study, we include for the first time 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 three different European countries:

Finland, Italy and United Kingdom. These three countries were selected not only for the availability of data, but also on the basis of past or ongoing mathematical modeling of varicella and HZ.

MATERIALS AND METHODS

Data

Age-specific HZ case notification data were obtained from published studies for Finland (13), Italy (14) and United Kingdom (15). Age-specific VZV-seroprevalence data for the same countries were made available from the European Seroepidemiological Network 2 (16) and used jointly with contact matrices by age to compute the force of infection (FOI) for each of the three countries considered (17). The age-specific contact matrices for each country were computed by the socio-demographic model described in (18-20). Country-specific birth rates and mortality rates by age were obtained from the Eurostat databases (21) and used to simulate the age structure of each country.

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: i) the system is at its endemic equilibrium; ii) the varicella FOI, $\lambda(a)$, is also assumed to be at equilibrium and known from seroprevalence data (17); iii) the contribution of HZ to the FOI is assumed negligible, based on the observation that HZ is rarer compared to varicella, less infectious (22), and occurs preferentially in older ages, when social contacts are much less frequent compared to younger ages (18, 23); iv) individuals immune from maternally-transferred antibodies and those in the latent and infective varicella compartments are not considered, since their time scales are negligible compared to those of HZ reactivation.

The model's structure is illustrated in Figure 1. Individuals are born susceptible to VZV infection (compartment S), which they acquire at a rate given by the FOI $\lambda(a)$. After recovery, they develop humoral protection from varicella reinfection, and become susceptible to HZ reactivation. HZ susceptible individuals can either be re-exposed, or develop shingles. Re-exposures to varicella FOI are assumed to boost the CMI response with probability z (z in [0,1]), implying a 'force of boosting' $z\ \lambda(a)$. Boosted individuals move through a cascade of HZ susceptibility states labeled as HZS_i, where i counts exposure episodes. HZ reactivation occurs at a rate $\rho_i(a,\tau)$ 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, individuals are assumed to become lifelong immune to HZ and therefore moved to compartment R ('removed'); in fact, the lifetime risk of a second HZ episode is only between 1% and 5% among immunocompetent individuals (3, 8). We refer the reader to the Web Appendix for the complete model equations and their steady-state solution.

As for the functional forms of HZ-related parameters, a few special cases are considered. As a baseline, we choose the equivalent of a model proposed by Karhunen and colleagues (13). This model assumes a doubly exponential risk of HZ reactivation in both chronological and age since last VZV exposure, in order to incorporate the immunosenescence of the host's CMI (9) on one hand, and the cumulated exposure to HZ risk on the other hand. Therefore, the functional form assumed for the risk of HZ reactivation is $\rho_i(a,\tau) = \rho(a,\tau) = \rho_0 \times \exp(\theta_a(a-a_0)^+) \times \exp(\theta_\tau \tau)$, where ρ_0, θ_a and θ_τ are free parameters of the model and $(a-a_0)^+ = max(0,\ a-a_0)$. Note that the reactivation risk does not depend on *i* in this case. Karhunen's model also assumes a_0 fixed to 45 years and that all exposure episodes will result in boosting the exposed host (z = 1) (13). Three variants of this baseline model are then evaluated: a) one where *z* is a free model parameter, which will be referred to as the 'imperfect boosting model', since it is equivalent to assuming that only a fraction *z* of all exposure episodes will produce an effective boosting; b) one where z = 0, equivalent to the assumption that boosting plays no role for HZ ('no boosting'); c) one where θ_τ = 0, equivalent to assuming that only chronological age matters ('age only').

Our representation of Hope-Simpson's hypothesis of progressive immunity (8) departs from Karhunen (13) by making the HZ reactivation risk dependent on the infection episode *i*, through a set of scaling coefficients Q_i: $\rho_i(a,\tau) = Q_i \times \rho(a,\tau)$, where Q_i is monotonically decreasing with *i* and bound to values in [0, 1]. In particular, we choose a 'half-bell' function: $Q_i = q^{(i-1)^2}$, with i = 1, 2, ... and *q* in [0, 1]. This choice assigns a higher risk to the first few episodes of VZV exposure; the risk declines sharply with higher values of *i*, depending on the free parameter *q*. The -1 term in the exponent allows ignoring the primary varicella episode, so that the coefficient Q_1 is always 1. The baseline model (13) is a special case of the progressive immunity model when q = 1. See Web Appendix for a discussion of alternative choices of Q_i based on different values of the exponent to which $q^{(i-1)}$ is raised.

In all models, the FOI is calculated from $\lambda(a) = b\sum_x C_{a,x}\, I_x$, where *b* represents the varicella transmission rate per social contact, $C_{a,x}$ the mean number of contacts between individuals aged *a* and individuals aged *x*, I_x the proportion of varicella-infectious individuals at equilibrium. The quantities *b* and I_x were estimated for each country, by maximum likelihood fit (17) of a simple age-structured SIR model at equilibrium (18, 24, 25) to seroprevalence data (16) conditionally on the contact matrix $C_{a,x}$. The contact matrix was estimated using socio-demographic individual based models (20).

Fitting models to HZ incidence

Models were fitted by maximizing the Poisson log likelihood of observing the corresponding country-specific profiles of HZ case notifications by age (13-15) (see Web Appendix for technical details). Only a_0 was fixed (to 45 years, as in (13)) in all models and countries; depending on the model considered, a subset of the remaining parameters (z, ρ_0, θ_a, θ_τ and q) was fixed and the others were left free to vary, subject only to a positivity constraint.

Goodness of fit was assessed by the Likelihood Ratio Test (LRT), which evaluates whether the improvement in the likelihood of a given model, with respect to a nested, more parsimonious one, is significant.

In order to assess uncertainty in parameter estimates, a bootstrap procedure was implemented as follows: for each age group, the errors ε_k between best model predictions and observed data were calculated. M = 500 datasets were simulated by adding to each best fit value corresponding to a data point an error uniformly sampled from the array ε_k, and the models were then fitted against each of the M simulated datasets. The bootstrap procedure was replicated equally for each country.

RESULTS

Table 1 reports log-likelihood values of the best fit to observed data (no bootstrap) for each model and country. The table shows that variants a), b) and c) of the baseline model do not generally improve the performance of the baseline model: in fact, the "imperfect boosting" and "no boosting" models yield a lower likelihood although using an equal or higher number of free parameters. An LRT between the "age only" and the baseline models shows that the latter performs significantly better for Italy and United Kingdom ($P < 0.01$) but not for Finland ($P = 0.1$).

The progressive immunity model presents remarkably improved performances with respect to the baseline. LRTs between the progressive immunity and the baseline models and between the progressive immunity and the age only models show that the increase in likelihood is significant (with p-values P largely smaller than 0.01) on all datasets considered, even after penalizing for the higher number w of free parameters.

Table 1. Log Likelihood of Best Fits for Each Model and Country

	w	Free parameters	Finland	Italy	United Kingdom
Baseline (13)	3	$\rho_0, \theta_a, \theta_\tau$	-124.9	-389.98	-872.48
Imperfect boosting (variant a)	4	$\rho_0, \theta_a, \theta_\tau, z$	-125.47	-387.66	-875.51
No boosting (variant b)	3	$\rho_0, \theta_a, \theta_\tau$	-126.28	-496.75	-894.39
Age only (variant c)	2	ρ_0, θ_a	-126.25	-510.4	-1388.54
Progressive immunity	4	$\rho_0, \theta_a, \theta_\tau, q$	-95.5	-120.29	-520.69

For the two best models (baseline and progressive immunity) we evaluated the variability of estimates for the goodness of fit and model parameters, using the bootstrap procedure specified in the Materials and Methods. Figure 2 compares the bootstrap log-likelihood obtained with the two models on the three datasets. The boxplot (representing quartiles and 95% confidence intervals) of log-likelihood bootstrap distributions obtained on the 500 synthetic datasets is drawn. A remarkable improvement in performance was found on all countries; the improvement is perhaps less marked for Finland, to which the baseline model was originally tailored (13). Figure 3 reports the bootstrap best fits of HZ age-specific incidence data for both models in the three countries. Unlike the progressive immunity model, the baseline model fails to capture the decline in HZ incidence at high ages that is evident in both Finnish and Italian data. The UK data do not show the same declining pattern, instead the incidence seems to saturate. While the baseline model coarsely interpolates data with an approximately linear growth, the progressive immunity model follows quite closely the observed profile, failing only to reproduce the age group of individuals older than 85 years. The greater ability of the progressive immunity model in explaining HZ incidence data compared to the baseline model can be explained by inspecting the age-specific proportions of HZ susceptible individuals, disaggregated by exposure episode. These are shown in Figure 4 for Italy (very similar graphs can be obtained for Finland and United Kingdom). As age increases, the proportion of HZ susceptible individuals having experienced a few (1 to 3) exposures declines or saturates, whereas the proportion with more than 4 re-exposure counts has an increasing age-profile (in particular HZ susceptible individuals with 7 or more re-exposures represent a negligible fraction). Therefore Hope-Simpson's progressive immunity allows to well reproduce HZ incidence data at all ages (including the declining portion at high ages) whilst maintaining an "always-increasing" zoster risk, which should be an indisputable feature of zoster development. The reason of this success is that the progressive immunity model essentially "selects" only susceptibles from the first few re-exposure episodes, or equivalently that it assigns an increasingly reduced risk to individuals with several re-exposures, on the basis of a sound biological hypothesis (8). On the other hand the baseline model fails to reproduce

HZ incidence at older ages due to the fact it takes as susceptible to HZ individuals from all exposure episodes, thereby eventually causing an always increasing susceptibility profile to HZ. Table 2 reports the best parameter estimates with 95% confidence interval for each dataset. 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 4.4%, the same value obtained by (13). Similarly, the estimated increase in the risk of HZ per year since last exposure, $\exp(\theta_\tau)$, is equal to 2.7%, very close to the 3.3% obtained by (13). This slight difference might be attributed to the removal of the last data point (individual older than 85) 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 FOI of VZV, as reported in subsection Models of Section Methods). As for inter-country differences in parameter estimates, there is a marked difference in ρ_0 between Finland, on one hand, and Italy and United Kingdom, on the other hand, in both the baseline and the progressive immunity models. This is explained by considering that this parameter scales the average value of HZ risk when a and τ are small: indeed, the average magnitude of HZ incidence in younger ages ($a < a_0 = 45$ years) in Finland is about one half of that in Italy and 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 three countries in the progressive immunity model, which may suggest that the components of CMI decline, regulated by these parameters, are country-independent and therefore intrinsic to the HZ biology and pathogenesis. In the baseline model, instead, considerable inter-country variability was found in estimates of θ_a, and to a lesser extent, of θ_τ, which are quite difficult to justify on biological grounds. Finally, the progressive immunity model shows a sharp variation of 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 re-exposure events. Therefore, the variability of *q* at the population level could be explained by socio-demographic factors affecting such characteristics (e.g. probability of contact, amount of viral load transferred, closeness of contacts between infectious case and boosted individual, housing density, housing ventilation).

Table 2. Parameter Estimates for the Baseline and Progressive Immunity Models

Model	Parameter	Dataset	Mean	Confidence interval
Baseline (13)	ρ_0 (1/yr)	Finland	$0.72\ 10^{-3}$	$(0.57, 0.92)\ 10^{-3}$
		Italy	$1.30\ 10^{-3}$	$(0.86, 1.83)\ 10^{-3}$
		United Kingdom	$2.19\ 10^{-3}$	$(1.43, 2.98)\ 10^{-3}$
	θ_a (%/yr)	Finland	4.28	3.45, 5.13
		Italy	0.99	0.03, 2.23
		United Kingdom	2.21	0.92, 3.54
	θ_τ (%/yr)	Finland	2.70	1.89, 3.25
		Italy	4.22	2.94, 5.38
		United Kingdom	3.21	1.51, 4.93
Progressive immunity	ρ_0 (1/yr)	Finland	$1.55\ 10^{-3}$	$(0.98, 2.23)\ 10^{-3}$
		Italy	$3.10\ 10^{-3}$	$(2.53, 3.87)\ 10^{-3}$
		United Kingdom	$3.07\ 10^{-3}$	$(2.24, 3.89)\ 10^{-3}$
	θ_a (%/yr)	Finland	7.19	5.23, 9.31
		Italy	5.23	4.14, 6.35
		United Kingdom	5.51	3. 90, 6.96
	θ_τ (%/yr)	Finland	3.77	2.57, 5.00
		Italy	3.81	3.13, 4.39
		United Kingdom	4.78	4.00, 5.70
	q (%)	Finland	60.1	45.4, 76.5
		Italy	21.0	14.7, 29.7
		United Kingdom	63.0	54.6, 72.4

DISCUSSION

Several mathematical models of VZV transmission dynamics have been proposed to describe the natural history of varicella and HZ, and to evaluate the impact of mass vaccination programs against varicella and/or HZ (11, 13, 15, 26-29). In most such models, any exposure to VZV (either primary or re-exposure) is assumed to confer temporary complete immunity against HZ reactivation, after which the host returns fully susceptible to HZ. In particular, the reactivation risk depends only on individual's age, according to a phenomenological functional form (11). This model lacks identifiability of HZ related parameters due to unobservability of the HZ susceptibility stage (30). This implies that very wide ranges of critical HZ parameters, e.g. the average duration of immunity to HZ, are consistent with data. As a consequence, model results are highly sensitive to assumptions on HZ related parameters. Unlike these works, the model in (13) does not include a compartment of complete immunity, but assumes a risk of infection dependent on both chronological age and time elapsed since last exposure to VZV. This assumption is more compliant with the currently accepted theory of VZV immunity (3, 8). In (13), the effect of boosting is to reset the time from last exposure to zero. In the present study, we propose the integration of a further noteworthy hypothesis of Hope-Simpson's (8), i.e. that each re-exposure gives an higher cell-mediated response with respect to the previous one, thereby progressively reducing the risk of HZ. The boosting of immunity through re-exposure to VZV can be investigated from many different viewpoints, e. g. by immunological studies focusing on the behavior of CMI following re-exposure to VZV (31). However, such studies do not provide information on the potential impact of re-exposure to VZV on zoster protection at the population level, for which the contribution of mathematical and statistical models remains invaluable. The 'progressive immunity model' proposed in this study is formulated as a generalization of (13). We have shown that the progressive immunity model performs significantly better than the baseline one (13) in explaining the age profiles of HZ incidence on all three datasets considered. In particular, it is better able to capture the saturating or declining trajectory of HZ incidence at older ages (13-15). Moreover, parameter estimates of the progressive immunity model provide a sharper interpretation of phenomena underlying inter-country variability of HZ incidence profiles. In fact, while the baseline model shows large inter-country variations for parameters related to the increased risk of HZ reactivation with age, the progressive immunity model yields robust figures. We do not see any obvious reason why the decline in CMI, which produces the increased risk of reactivation at older ages, should strongly differ from country to country. The progressive immunity model reproduces the inter-country differences in HZ incidence essentially by means of variations on the amount of progressive protection conferred by each boosting episode. We have suggested a list of socio-demographic factors which might justify such variability.

Above all, the present results could be of help in coping with the current decision paralysis on the introduction of mass immunization programs for varicella and HZ. A vaccine against VZV is available since the '70s (32) and some countries (e.g. USA, Canada, Australia) have initiated varicella mass vaccination programs. There are, however, entire regions (e.g. Europe) where the decision to introduce the vaccine is stalled, largely due to the ambiguous answers of mathematical models (33). It is yet unclear whether immunizing against varicella might lead to increased incidence of HZ (34-36), due to a dramatic reduction of the boosting effect following immunization. Currently, mathematical models predict either a sharp increase of HZ incidence or no increase at all, depending on the postulated quantitative impact of re-exposures on the

HZ epidemiology. Our model addresses this problem by providing a biologically plausible description of boosting mechanisms which validates the accepted hypothesis of progressive immunity (8). Integrating these mechanisms into transmission models of varicella and HZ might greatly assist public health policy evaluation and decision.

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Figure 1. Compartmental structure of the proposed family of models.

Figure 2. Quartiles and 95% confidence intervals of log-likelihood bootstrap distributions for the baseline (13) and progressive immunity model. The purple diamond indicates the likelihood of the best fit on the original data, as reported in Table 1.

Figure 3. Model predictions of HZ age-specific incidence vs. observed data. Panels on the left side (A, C and E) refer to the baseline model (13); panels on the right side (B, D and F) refer to the progressive immunity model. Top row (A and B): Finland; middle row (C and D): Italy; bottom row (E and F): United Kingdom. Blue circles: observed data; the area of the circles is proportional to the total HZ notification cases. Red dashed lines: best fit of the model to the observed data. Black solid lines: average best fit on bootstrapped data. Gray areas: 95% confidence intervals of model projections.

Figure 4. Age-profiles of the fraction of HZ susceptible individuals over the total population, disaggregated by count of exposures, based on model estimates for Italy.

Hope-Simpson's hypothesis explains Zoster data

1. Model equations and steady state solution.

Here we report the partial differential equations that govern the family of models proposed in this paper. These partial differential equations describe the endemic equilibrium of varicella and herpes zoster under the assumption that zoster reactivation rates depend on both the chronological age of the host, *a*, and on the amount of time elapsed since last exposure, τ. Different sub-models can be obtained by substituting the appropriate functional forms of epidemiological rates and parameters, as explained in the main text.

$$S'(a) = -(\lambda(a) + \mu(a))S(a) \qquad S(0) = B$$

$$\left(\frac{\partial}{\partial a} + \frac{\partial}{\partial \tau}\right) HZS_1(a,\tau) = -(\lambda(a) + \rho_1(a,\tau) + \mu(a))HZS_1(a,\tau) \qquad HZS_1(a,0) = \lambda(a)S(a)$$

$$\left(\frac{\partial}{\partial a} + \frac{\partial}{\partial \tau}\right) HZS_2(a,\tau) = -(\lambda(a) + \rho_2(a,\tau) + \mu(a))HZS_2(a,\tau) \qquad HZS_2(a,0) = z\lambda(a)HZS_1(a)$$

...

$$\left(\frac{\partial}{\partial a} + \frac{\partial}{\partial \tau}\right) HZS_i(a,\tau) = -(\lambda(a) + \rho_i(a,\tau) + \mu(a))HZS_i(a,\tau) \qquad HZS_i(a,0) = z\lambda(a)HZS_{i-1}(a)$$

...

In particular, *B* represents the yearly number of newborns, μ(*a*) the death rate by age of the individual and the other quantities are specified in the main text. The boundary conditions for τ = 0 in HZ susceptible compartments represent the effect of boosting: individuals who are re-exposed to VZV are moved into the next susceptibility compartment and their time since last exposure is reset to zero.

Given the steady state approximation (indicated with (i) in section Material and Methods of the main text) and the hypothesis that λ(*a*) is known, the linear equations here described can be solved recursively by integration along the characteristic lines $a = \tau + x$, obtaining:

$$S(a) = B\, e^{-\int_0^a \lambda(x)+\mu(x)dx}$$

$$HZS_1(a) = HZS_1(a-\tau,0)\; e^{-\int_0^\tau \lambda(a-\tau+x)+\mu(a-\tau+x)dx} e^{-\int_0^\tau \rho_1(a-\tau+x,x)dx}$$

$$HZS_2(a) = HZS_2(a-\tau,0) e^{-\int_0^\tau \lambda(a-\tau+x)+\mu(a-\tau+x)dx} e^{-\int_0^\tau \rho_2(a-\tau+x,x)dx}$$

…

$$HZS_i(a) = HZS_i(a-\tau,0)\; e^{-\int_0^\tau \lambda(a-\tau+x)+\mu(a-\tau+x)dx} e^{-\int_0^\tau \rho_i(a-\tau+x,x)dx}$$

…

From the age profiles of susceptibility by episode of exposure, *HZS*$_i$, we can calculate the episode-specific absolute incidence of HZ by age as: $HZI_i(a) = \int_0^\infty \rho_i(a,\tau) HZS_i(a,\tau)d\tau$ and therefore the total age profile of zoster incidence $HZI(a) = \sum_i HZI_i(a)$. The latter quantity, aggregated by 5-years age-groups (except for the age group of individuals older than 85), defines the predicted incidence p_k appearing in the Poisson log likelihood (see next section).

2. Log likelihood maximization

The Poisson log likelihood is defined as follows:

$$L = \log\left(\prod_{k=1}^{N} \frac{e^{-p_k} {p_k}^{O_k}}{O_k!}\right) = \sum_{k=1}^{N} (O_k \log(p_k) - p_k - \log(O_k!))$$

where *N* is the number of age-groups, O_k is the observed number of HZ cases in the *k*-th age-group and p_k is the corresponding model prediction, computed by solving the model analytically. The function was maximized using a standard Nelder-Mead algorithm [S1].

3. Sensitivity analysis on the functional form of Q_i

The form proposed in the main text for Q_i is only one of the possible formulations of Hope-Simpson's hypothesis of progressive immunity. The choice $Q_i = q^{(i-1)^2}$ with $q \leq 1$ is justified by the need of having a strictly decreasing function. The rate at which this 'half-bell' function decays with the episode of infection *i* depends on *q*, which is a free parameter, and on the exponent of (*i* - 1), which was fixed to 2 in the main text. We tested the performance of the same model under different integer values of this exponent (generally denoted by κ); Table S1 gives a summary of the log-likelihood obtained with different values of κ. It shows that κ = 2 is the best choice for all datasets, except for the United Kingdom where κ = 1 performs better (however, the log likelihood for κ = 2 is very close to the best score). It also shows that for κ ≥ 3 the best log likelihoods saturate to suboptimal values: this is due to the fact that Q_i falls to zero so quickly that only the first HZ susceptible compartment contributes to the total HZ incidence (i.e., Q_i is negligible for $i \geq 2$).

Table S1. Comparison of Log-Likelihood Scores Obtained with Different Values of κ.

κ	Finland	Italy	United Kingdom
1	-108.95	-169.93	-486.94
2	-95.5	-120.29	-520.69
3	-173.87	-137.42	-5075.66
5	-177.62	-137.87	-5174.24
10	-177.62	-137.62	-5180.07

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