Perspectives on optimal control of varicella and herpes zoster by mass routine varicella vaccination

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Summary

Herpes zoster arises from reactivation of the varicella–zoster virus (VZV), causing varicella in children. As reactivation occurs when cell-mediated immunity (CMI) declines, and there is evidence that re-exposure to VZV boosts CMI, mass varicella immunization might increase the zoster burden, at least for some decades. Fear of this natural zoster boom is the main reason for the paralysis of varicella immunization in Europe. We apply optimal control to a realistically parametrized age-structured model for VZV transmission and reactivation to investigate whether feasible varicella immunization paths that are optimal in controlling both varicella and zoster exist. We analyse the optimality system numerically focusing on the role of the cost functional, of the relative zoster–varicella cost and of the planning horizon length. We show that optimal programmes will mostly be unfeasible for public health owing to their complex temporal profiles. This complexity is the consequence of the intrinsically antagonistic nature of varicella immunization programmes when aiming to control both varicella and zoster. However, we show that gradually increasing—hence feasible—vaccination schedules can perform better than routine programmes with constant vaccine uptake. Finally,we showthe optimal profiles of feasible programmes targeting mitigation of the post-immunization natural zoster boom with priority.

1. Introduction

Varicella and herpes zoster (HZ) are different clinical manifestations of the varicella– zoster virus (VZV). Varicella is a highly transmissible infection occurring early in childhood [1], with 90% of European children immune by age 12 in the absence of vaccination [2]. Although recovered subjects are permanently immune to varicella, the virus remains latent in the nervous ganglia and can reactivate at later ages causing HZ, a skin disease yielding serious morbidity, first of all post herpetic neuralgia [1]. Although HZ immunology and pathogenesis are still poorly understood, since Hope-Simpson's seminal study [3,4] there has been agreement that cell-mediated immunity (CMI) plays a key role in protecting against reactivation, which therefore might occur as CMI declines. Hope-Simpson also proposed the 'exogenous boosting' (EB) hypothesis, by which CMI might be boosted by re-exposure to VZV. Evidence partly supporting the EB hypothesis has cumulated [5–7], though its actual magnitude is yet to be determined adequately [8]. A large-scale European serology has indicated a lower HZ incidence by age in countries where varicella force of infection (FOI) is higher [2]. Nonetheless, contrary evidence also exists [9]. As varicella can yield complications, such as pneumonias and congenital varicella syndrome [1], mass childhood immunization is a potentially cost-effective option [10]. Although varicella immunization is in place in the USA, Japan and Australia, in Europe only a few countries, i.e. Germany, Greece and Luxembourg, are currently vaccinating [11]. Such stalling is owing to the costs of the 'boom' in natural HZ unanimously predicted by VZV mathematical models based on the exogenous boosting hypothesis [6,12–17]. According to these models immunization programmes effectively decreasing varicella circulation would also reduce the intensity of natural boosting, yielding a large HZ wave in the early decades of the programme. Unfortunately, empirical evidence on such phenomena from currently vaccinating sites is controversial [18–20]. Although an HZ vaccine is now available [21], being licensed only for the elderly (older than 60 years), its impact might be limited as much of the HZ increase might occur at earlier ages. In this paper, we use optimal control applied to a deterministic age-structured model for VZV transmission and reactivation parametrized by real varicella and HZ data, to investigate whether there are feasible routine (i.e. at birth) varicella vaccination programmes that are optimal in controlling both varicella and HZ. Indeed, varicella programmes investigated so far in the literature [6,12–15,17] assume a constant high vaccination coverage (e.g. first dose ranging 80–95%), thereby dramatically reducing EB and promoting an increase in natural HZ. A question is therefore whether alternative, time-varying, programmes might bring about a truly better performance in controlling natural HZ. A further complication is represented by the recent evidence that HZ can also be acquired from the vaccine strain [22]. This highlights the antagonistic nature of varicella immunization when considered in a holistic perspective. Optimally controlling both varicella and HZ by means only of

routine varicella vaccination involves governing two epidemiological targets by a single control. Despite the extensive literature on optimal control of infectious diseases [23–31] this is, to our knowledge, the first investigation of the topic. In [32], varicella and HZ costs were considered based, however, on a simplified VZV model, neglecting exogenous boosting. Our formulation of the VZV optimal control problem aims to minimize discounted costs from varicella and from both natural and vaccine-induced HZ. The problem is studied numerically, discussing the role of critical parameters, such as the duration of the planning horizon and the relative cost of an HZ case, with the focus on two main issues, namely the feasibility of the programme and the mitigation of the natural HZ boom. We particularly emphasize gradually increasing varicella vaccination schedules, and programmes targeting mitigation of the post-immunization natural zoster boom with priority. A sensitivity analysis of the presence of some background HZ immunization for different target ages even outside the range for which the vaccine is currently licenced is also considered.

2. Material and methods

(a) The mathematical model for varicella and herpes zoster

The model forVZV transmission and reactivation has the compartmental structure of the models used in the recent public health literature [12–14,17]. The population is stationary in total size and age distribution through a constant inflow of births per year and a time-invariant age-specific mortality schedule with life expectancy equal to 75 years. Individuals are subdivided into two subgroups, those not vaccinated and those vaccinated against varicella. Varicella vaccination is administered to a time-varying fraction u(t) of newborn individuals with a 100% effective and lifelong protecting vaccine. Unvaccinated individuals are born susceptible to varicella (S), which they acquire from contacts with infective individuals at an age- (and time-) dependent FOI $\lambda_i(t)$, entering the exposed state (E). Exposed individuals become infective (I) at a constant rate σ. Infective individuals recover at constant rate γ. Recovered subjects (R) are permanently immune to varicella but lose CMI and become susceptible to HZ (ZS) at rate δ, where they either develop HZ at an age-specific rate ρ_i and become HZ cases (ZI), or receive a boost of CMI at a force of boosting (FOB) λ_i, equal to the corresponding FOI, returning to the R class. Zoster cases recover at a constant rate γZ, becoming immune to HZ (ZR). Varicella-vaccinated individuals (V) are fully immune to varicella but lose vaccine-acquired CMI at the same rate as natural CMI, becoming susceptible to HZ (VZS). VZS individuals either acquire HZ at a reduced age-specific rate $\rho_{I,v} = k\rho_i$ $(0 < k < 1)$ [24], entering the active HZ phase (VZI), or receive a boost of CMI at rate λ_i, returning to the V class. The FOI (and FOB) is age-dependent through a contact matrix C, assigning the average number of contacts between individuals of different age groups, and a constant transmission coefficient q. Transmission, CMI boosting and risk of reactivation were parametrized using age-specific data from Italy on contact patterns, VZV serology and HZ incidence. Full details are reported in the supplementary material.

(b) The basic optimal control problem

Our baseline optimal control problem seeks the time path $\tilde{u}(t) = u_{opt}$ of varicella coverage at birth that minimizes total discounted costs owing to varicella and HZ:

$$C_{[0,T]} = \int_0^T e^{-rt}(VC(t) + c_Z(NZC(t) + VZC(t)))\,dt, \qquad (2.1)$$

where r is the discount rate, [0, T] the planning horizon, VC(t), NZC(t), VZC(t), respectively, denote the number of cases of varicella, of natural HZ and of vaccine-related HZ at time t, and c_Z the cost of a unit zoster case (irrespective of whether natural or vaccine-related) relative to that of a varicella case. The cost functional (2.1) embeds the control action u = u(t) implicitly [28] via the state dynamics, i.e. $C_{[0,T]} = \int_0^T e^{-rt} f(t, x(t), u(t))\,dt$

(c) Logistic control functions

As fully optimal solutions of problem (2.1) can in practice prove unfeasible owing to possible complicated temporal behaviour (e.g. oscillations), we also considered restricted functional forms for u(t), i.e. logistic-shaped, to represent 'feasible' immunization programmes. The rationale is that, taking mitigation of natural HZ following varicella vaccination as a priority, it might be wise to allow an initial phase where boosting opportunities, and hence VZV circulation, continue to occur to some extent. In this case, optimization is carried out with respect to the parameters of the adopted logistic curve.

(d) 'Augmented' cost functional

One might expect that for long-term planning horizons, varicella elimination may be optimal regardless of the fact that it caused the natural HZ boom, thereby ignoring the chief concern of the current paralysis of varicella vaccination in Europe. To best address the above aspect, we considered this 'augmented' cost function:

$$AC(T) = \int_0^T e^{-rt}(VC(t) + c_Z(NZC(t) + VZC(t)))\,dt \quad + G\int_0^T e^{-rt} c_Z \max(0, NZC(t) - NZC_{u=0}(t))\,dt. \qquad (2.2)$$

Formulation (2.2) adds to (2.1) an 'augmenting' term (weighted by a free parameter G), which is strictly positive only during epochs where the number of natural HZ cases exceeds its pre-vaccination level (u = 0). The augmented functional adds an extra 'penalty' for policy makers who deliberately introduce varicella vaccination knowing that it will worsen, at least temporarily, the existing situation.

(e) Objective of the analysis and solution of the optimal control problem

The optimal programme is initialized at time t = 0 from the pre-vaccination endemic equilibrium of varicella and HZ. We investigated different scenarios of the two critical parameters, i.e. the length of the horizon T and the relative HZ cost c_Z. T was varied between a minimum of 20 years and a maximum up to T =100 years. The latter case represents a long-term programme covering both the expected boomin natural HZ following varicella immunization and the increase in vaccine-related HZ. As for c_Z,we took it as a simulation parameter over a very wide range ($0 < c_Z < 50$) coarsely encompassing different definitions of costs used in the literature (e.g. direct, indirect, QALY-based, etc.) [33,34]. The discount rate was set to r = 0.03/year [34]. The coverage control function u(t) is allowed to vary across different years between a minimum of 0 and a maximum of 90%, i.e. in excess of the critical coverage $p_c = 1\text{-}1/R_0$, to allow greater flexibility, but is constrained to be constant within each year, on the rationale that feasible programmes cannot be updated wildly, with 1 year taken as the minimal 'realistic' updating time. The solution of the optimality system is computed by Matlab nonlinear constrained minimization routine fmincon [35], supplemented by heuristics to cope with local minima problems (for details, see the electronic supplementary materials).

3. Results

(a) The free optimal control problem

For problem (2.1), the optimal vaccine uptake u*(t) for T = 30 years and different relative HZ costs are reported in figure 1a, together with the corresponding temporal trends of varicella and HZ (natural and vaccine-related) incidence (figure 1b–d).

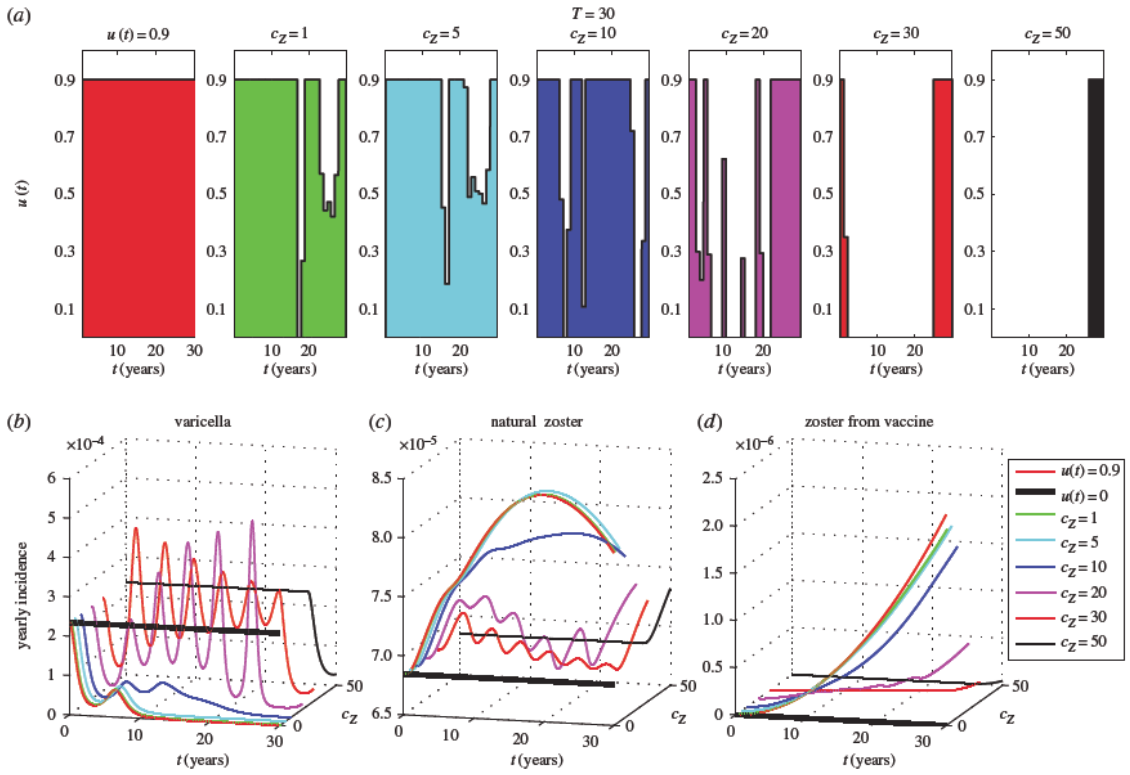

Figure 1. *The full optimal control problem for 30 years horizon and different relative HZ costs. Temporal trends of: the optimal coverage (a), varicella incidence (b), natural HZ incidence (c) and vaccine-related HZ incidence (d). The thin and thick lines at $c_Z = 0$ represent the corresponding curves under a constant vaccine uptake set at the maximal level allowed (u =90%), and without any immunization (u = 0), respectively.*

For reference we also reported the trends following from (i) a constant elimination policy set at 90% coverage, and from (ii) the no-vaccination programme. Despite the complex resulting shapes of optimal paths, some clear trends may be distinguished. When the relative HZ cost is low, the optimal programme brings varicella on the path to elimination causing the natural HZ post-vaccination boom. However, the dynamics of the optimal curve are fairly complicated (consider e.g. the case $c_Z = 10$): after several years of high coverage, the optimal curve suddenly falls, to compensate the increase in HZ, but then is forced to increase again to mitigate the emergence of a varicella wave, before settling down to a prolonged period of high vaccine uptake (at the elimination level). On the other hand, for large costs of HZ—say for values greater than or equal to $c_Z = 20$ in the figure (and this is a general feature for medium-term horizons, say below 50 years)—more interesting scenarios appear where the optimal strategy must allow varicella persistence to contain the cost of natural HZ, by maintaining immunity boosting. For $c_Z = 20$, 'pulses' of vaccination are required from time to time, to contain the cost of varicella owing to varicella oscillations. For higher HZ costs, the optimal path is essentially $u^*(t) = 0$ for most of the planning horizon, with a sudden final increase in vaccine uptake to contain varicella costs when the threat of the HZ boom is over. Note that no serious concern arises from vaccine-related HZ in such a short horizon. Considering different planning horizons (from T = 20 years to T = 100 years) shows that (figure 2), overall, long horizons gradually make it optimal to achieve higher levels of varicella control, owing to the much smaller risk of vaccine-related HZ compared to natural HZ. However, considerable differences continue to occur as the HZ cost varies. For T = 50 years, optimal programmes still require increasing degrees of varicella circulation and CMI boosting for increasing values of c_Z. On the other hand, persistently high optimal varicella coverages appear for very long horizons (T = 100 years).

(b) Logistic control functions

As shown in the previous section, fully optimal programmes seem to have a number of drawbacks. For example, they tend to show dramatic variations owing to the need to mitigate varicella waves, which make them (figures 1 and 2) unfeasible from a practical public health viewpoint. We, therefore, seek instead optimal 'feasible' programmes with a non-trivial logistic temporal trend in vaccine uptake. The most interesting results still appear (see figure 3, drawn for a thin grid of the HZ relative cost in its range) for medium-term horizons ($25 < T < 50$), i.e. horizons comparable with the time scale of the natural HZ boom. Results are clear-cut in this case: (i) at low relative HZ costs ($c_Z < 10$), the optimal policy is a trivial (i.e. flat) logistic curve predicting varicella elimination by a constant vaccine uptake programme set at the maximum level; (ii) further increasing c_Z ($10 < c_Z < 35$), fully non-trivial logistic programmes (i.e. showing an increasing temporal variation in coverage as c_Z increases and reaching values around the elimination threshold) arise as a response to the need to contain HZ costs by preserving some CMI boosting; (iii) as c_Z further increases, these non-trivial logistic curves predict zero vaccination for an increasing portion of the horizon, and become trivial again when c_Z exceeds 40, when the optimal logistic programme becomes not to vaccinate. On the other hand, longer planning horizons ($T > 50$) again promote varicella elimination as the best option, confirming findings from the full optimal problem (further results in the electronic supplementary material). The relative goodness of the logistic approximation with respect to the fully optimal vaccination path proved quite variable across the different scenarios but overall quite satisfactory. In particular, over horizons with a length comparable with the duration of the natural HZ boom (e.g. 25–45 years), the logistic hypothesis was able to decrease the overall cost with respect to the hypothesis of constant coverage set at the elimination threshold by 6–12% on average.

(c) Free optimization with augmented cost index

As for problem (2.2), we only report results for a long horizon (T = 100), for which previous results showed that it is always optimal to achieve high degrees of varicella control, therefore, causing the 'perverse' boom of natural HZ, regardless of the relative HZ cost. The main result (holding for sufficiently large values of G parameter) is that an optimal programme that is able to almost completely avoid the boom of natural HZ exists (figure 4c). Notably, varicella vaccination initiates at high levels because for times close to the initiation of the programme the contribution of the 'augmented' term is necessarily small. The high initial vaccine uptake, however, triggers an initial phase where natural HZ incidence starts increasing (note that in principle by further stretching G this initial growth in natural HZ can be made as small as desired). This, in turn, inflates the 'augmented' component of costs and causes coverage to fall to low levels. Thereafter, the optimal vaccine uptake restarts increasing slowly, reaching elimination levels in several decades. Obviously, this mitigation of the natural HZ boom is only temporary as a large proportion of the cases of natural HZ avoided in the first decades of the programme are delayed to the future, rather than fully avoided (figure 4c, green curve). This is hardly surprising given that the only available control tool is the varicella vaccine. However, it has the further advantage of keeping the incidence of vaccine-related HZ lower (figure 4d, green curve).

(d) Logistic control functions under some background herpes zoster vaccination

In this section, we investigate how the logistic optimal control paths of the varicella vaccine uptake are affected by the presence in the population of some degree of exogenous 'background' vaccination against HZ based on a perfect vaccine. In this case, the optimal control strategy aims to control the 'residual' costs arising from varicella cases and residual HZ cases from individuals who have not been immunized against HZ. For simplicity, we assume that HZ

immunization initiates at the same time as varicella immunization using a perfect HZ vaccine, i.e. with 100% take and lifelong duration, and we consider a number of alternative HZ coverage schedules depending on two factors, namely the proportion effectively immunized p_{HZ} (taken either as 20%, 40% or 60%), and the target age at immunization (taken either as 60, 50 or 20 years). This experiment is counterfactual given that the HZ vaccine is not currently licenced for ages below 60. In particular, inclusion of the 'extreme' age of 20 years was motivated by the fact that varicella vaccinated individuals might, in a situation of sustained immunization, develop susceptibility to HZ much earlier compared with a pre-vaccination situation (in-depth discussion is reported in the electronic supplementary material). Results indicate (for T = 30 and T = 50 years; figure 5) that if some background HZ immunization can be ensured, its mitigation effects always push upward the optimal varicella vaccination path (while its temporal trend are only mildly affected) for all hypotheses considered. However, focusing on the T = 50 horizon, when the age at HZ immunization is set at 60 years this mitigation effect allows the optimal varicella vaccination to directly settle on a constant elimination path only when the HZ cost is relatively low (c_Z = 15 in figure 5) and the proportion effectively immunized against HZ is high (60%). Decreasing the age at HZ immunization from 60 to 50 years expands the window of c_Z values that yield an optimal control function promoting varicella elimination, but still requires high p_{HZ} values. This trend continues to be observed even when the age at HZ immunization is further lowered.

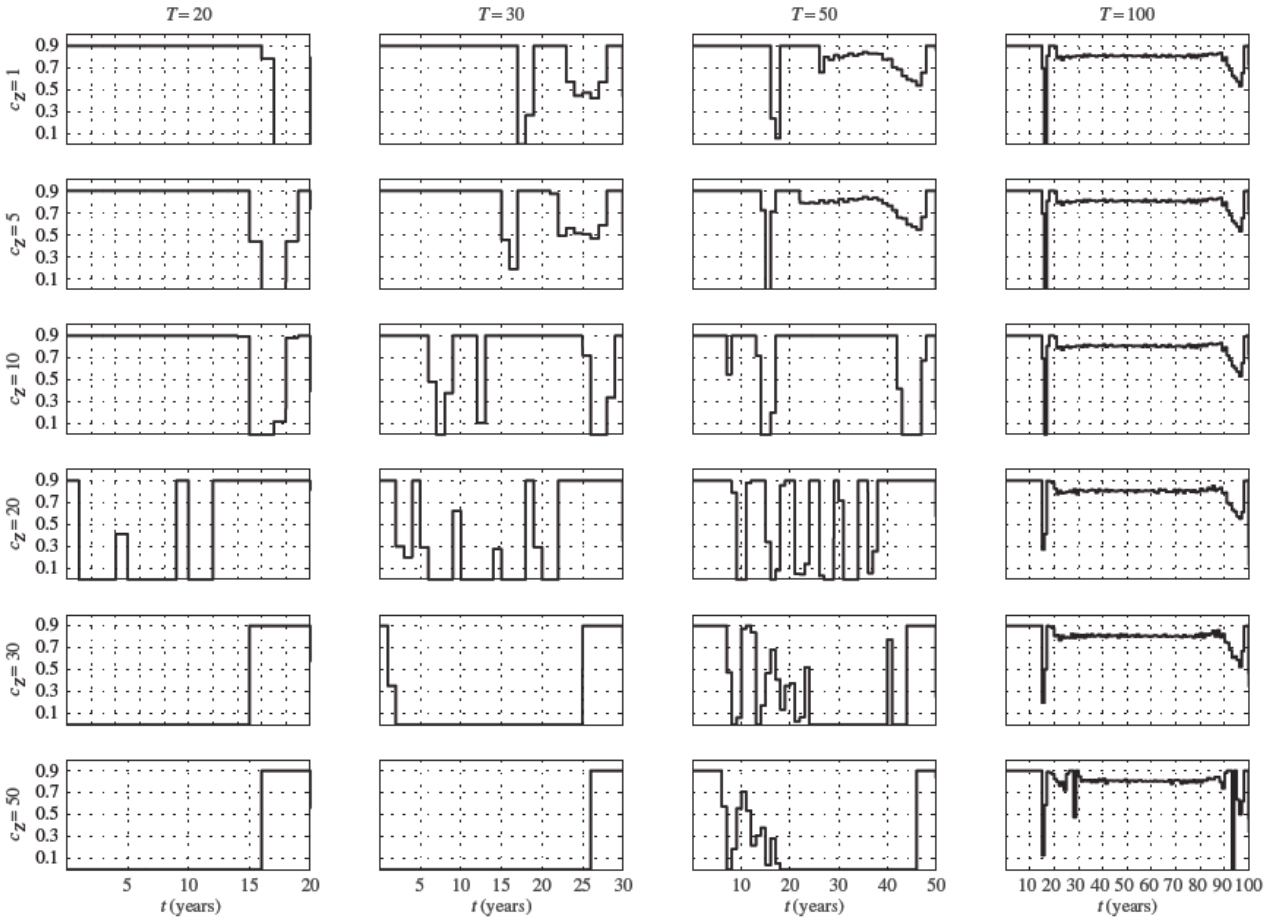

Figure 2. *The full optimal control problem (2.1). Trends of the optimal coverage u*(t) as functions of time (t) for different relative cost of HZ (rows), and different lengths of the planning horizons T (columns).*

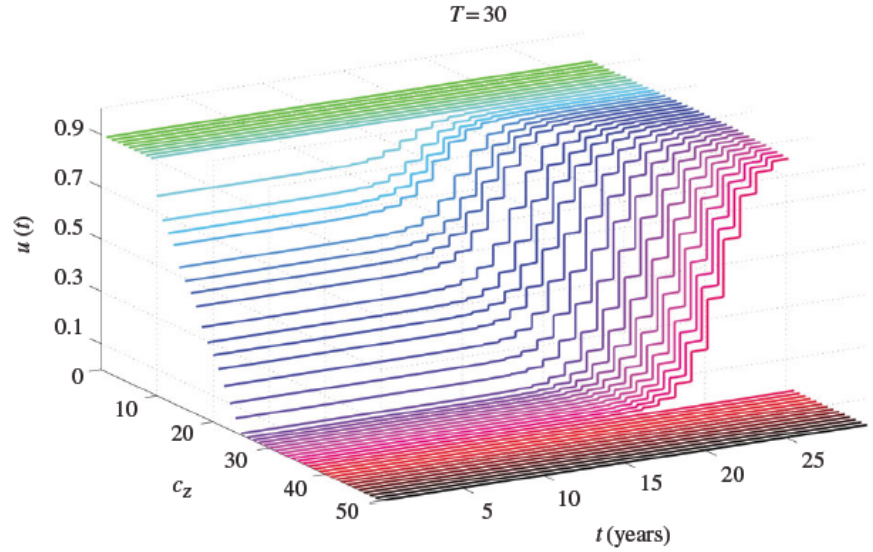

Figure 3. *The logistic control problem. Trends of the optimal coverage u*(t) as functions of time (t) for T =30 years and different values of the relative HZ costs.*

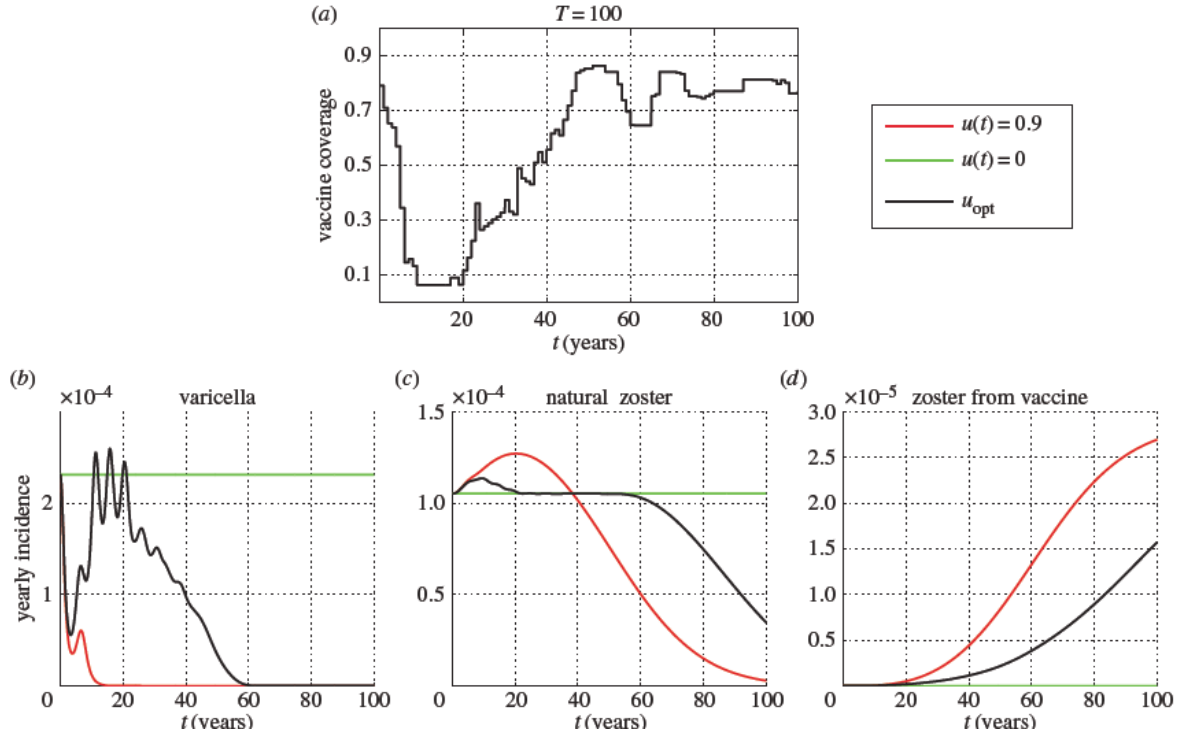

Figure 4. *Optimal control under the augmented cost index (2.2) for T = 100 years, c_Z = 35 and G = 5. (a) Temporal trend of the optimal coverage u*(t): (b) Temporal trends of varicella incidence, (c) natural HZ incidence and (d) vaccine-related HZ incidence. Corresponding trends for the cases of absence of any immunization and of an elimination programme with constant vaccine uptake set at the elimination threshold pc are also reported for reference.*

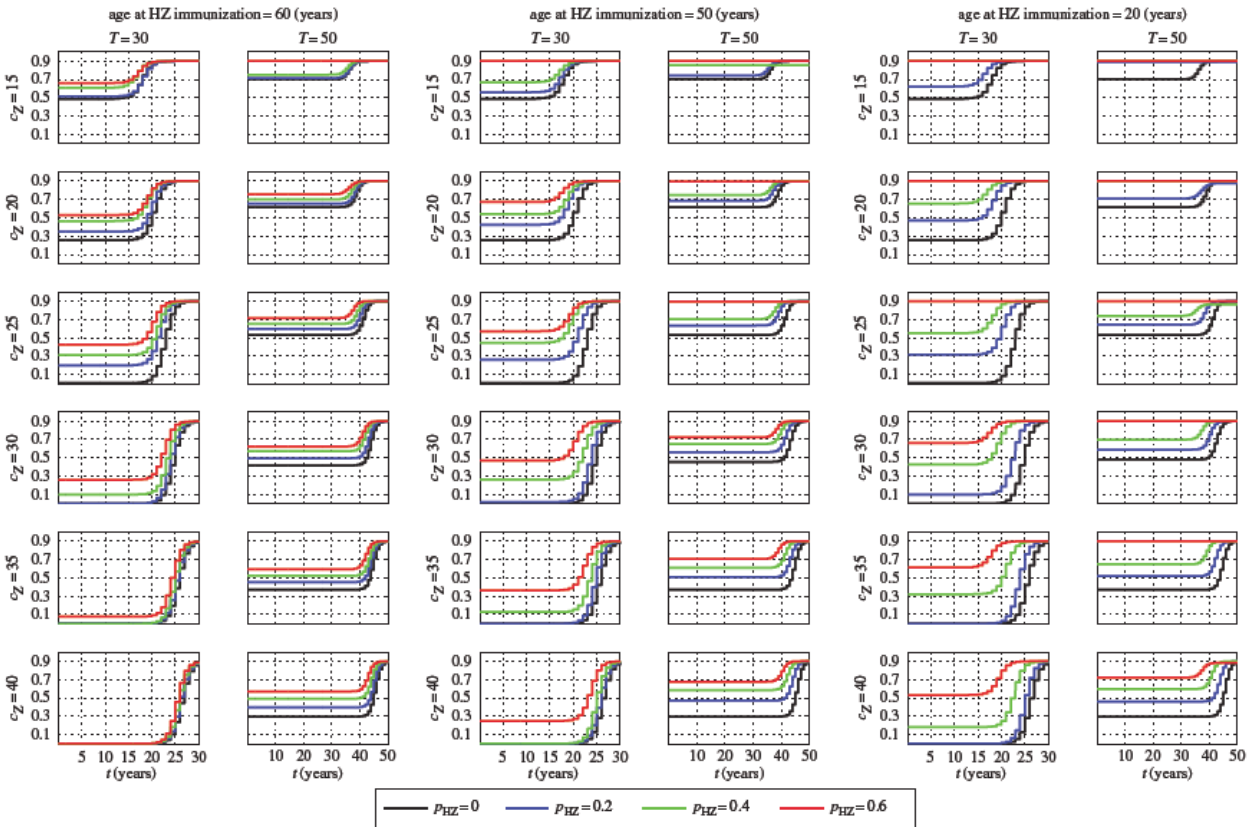

Figure 5. *The logistic control problem for some background levels of the HZ vaccine coverage. The figure reports trends of the optimal varicella coverage as functions of time (t), for two different horizons (T = 30 years, T = 50 years), for different values of the relative HZ cost c_Z (reported on the different rows of the figure), for three different ages at HZ immunization (60 years versus 50 years versus 20 years) and for different levels of the proportion p_{HZ} effectively immunized against HZ (p_{HZ} = 0, p_{HZ} = 0.2, p_{HZ} = 0.4, p_{HZ} = 0.6, reported by lines of different colours).*

4. Discussion

Motivated by the current European public health debate on the stalled introduction of varicella immunization owing to the fear of the 'boom' in natural HZ predicted by mathematical models, we used optimal control applied to an age-structured model to investigate the extent to which varicella vaccination can effectively control both varicella and HZ. This is a case where optimal control might aid the design of vaccination schedules, given the 'antagonistic' effects of the varicella vaccine. Indeed, on the one hand, VZV immunization during childhood might increase natural HZ incidence in the short–medium term. On the other hand, in the medium–long term, when the benefits of varicella immunization increase because the natural HZ boom is over, the challenge of the increase in vaccine-related HZ emerges. Given our focus on the varicella–zoster conflict, we deliberately omitted vaccine costs in the performance functional to avoid inclusion of confounding factors. Results from the free optimal control problem show complicated patterns with abrupt changes in the optimal coverage, possibly arising from the underlying bang–bang nature of the problem hidden by the realistic constraint of updating the policy only yearly. This makes such programmes unfeasible from the public health viewpoint. Nonetheless, some clear indications arose. A main one is that varicella elimination by a constant high coverage programme is optimal either for low relative costs of HZ or for long horizons (owing to the lower risk of vaccine-induced HZ compared with natural HZ). Motivated by the need to identify 'feasible' programmes, particularly in relation to the control of the post-vaccination natural HZ boom, we considered a simpler problem where the optimal time path of vaccine uptake is restricted to logistic- type curves. The rationale is that it might be wise to allow an initial phase where boosting opportunities, and hence VZV circulation, continue to occur. Here the results are clearcut for planning horizons with a length comparable with the time scale of the natural HZ boom: (i) at low relative HZ costs the optimal logistic policy is a trivial one predicting varicella elimination by an essentially constant vaccine uptake programme; (ii) at high relative HZ costs the optimal logistic programme is not to vaccinate; (iii) at intermediate relative HZ costs non-trivial logistic programmes, showing a marked variation within the planning horizon, are selected instead. Furthermore, given that for long horizons varicella elimination always proves the optimal choice irrespective of the fact it caused the boom in natural HZ,we considered the issue of controlling the natural HZ boom as a key priority even in the long term. This is done by augmenting the cost functional by an extra 'penalty' for policy makers who deliberately start a vaccination programme though aware of its perverse public health implications. This analysis shows that gradually increasing logistic-shaped optimal coverage functions also appear over long-term horizons when control

of the natural HZ is taken as a priority, and allow the natural HZ boom to be almost entirely avoided. Although this outcome appears through the postponement of natural HZ cases to the future, it nonetheless suggests the existence of alternative policies. In passing we note that the augmented 'policy-penalizing' functional is a parsimonious manner to discover logistic-like optimal paths, instead of postulating them. Finally, mitigation of HZ by some 'external' HZ immunization can push the optimal varicella vaccination path upward. However, this effect becomes really important by steadily allowing the optimal varicella vaccination to directly set on a constant elimination path, only for ages well below those for which the HZ vaccine is currently licenced (60 years) and for quite high HZ vaccine uptake (60%), which seems hard to achieve given the current estimates of HZ vaccine effectiveness [16]. Despite some clear-cut indications, the present results can only be considered a departure point given their form of 'what if' scenarios for different levels of the costs of varicella and HZ cases. Although some available estimates of costs were used to specify the range used in the simulation, to assess the importance of the different scenarios a much deeper integration with economic analyses would be necessary. Moreover, though the adopted epidemiological model is fully age-structured, we used fixed, age-independent costs of varicella and HZ. As such costs are known to be age-dependent [33,34], this is a potential limitation requiring careful investigation. Further sources of structural uncertainty are represented by the many current unknowns in VZV, particularly in relation to CMI boosting and reactivation. The paper focused on the 'fullboosting' hypothesis considered by recent public health modelling [12,13,15,17], according to which each re-exposure to varicella yields a CMI boosting event. As the exact magnitude of the boosting effect is still unclear [7] this might be debatable. However, this choice deals with the most interesting situation, i.e. the 'worst-case', which magnifies the impact of varicella immunization on zoster burden. Still, we relied on a number of conservative hypotheses, e.g. by assuming that varicella vaccinated individuals lose vaccine-acquired CMI at the same rate as naturally immune individuals, and that CMI boosted at the same rate in these two groups. Unfortunately, we continue to be forced to parametrize our mathematical models by resorting to conservative assumptions, or to poorly identified parameters to fill gaps in direct empirical epidemiological and immunological evidence. Last, the modelling side should be made more robust to deal more appropriately with those situations where varicella is close to elimination by the use of stochastic modelling.

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