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Modeling the impact of combined vaccination programs against varicella and herpes zoster in Norway

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ABSTRACT

Background: Adoption of varicella immunization in Europe is limited due to a predicted increase in the incidence of herpes zoster (HZ) resulting from a removal of exogenous boosting by varicella vaccination. Most available assessments of immunization strategies only considered universal varicella vaccination (alone or in combination with HZ by the live vaccine). The development of a new subunit recombinant zoster vaccine may provide new perspectives of HZ control.

Methods: We used a mathematical model for VZV in Norway based on the progressive immunity formulation of exogenous boosting. We evaluated a complete range of alternative immunization options against varicella and HZ including both universal and targeted varicella vaccination, either alone or with zoster immunization, and zoster immunization alone. We considered all values of the boosting intensity consistent with the Norwegian HZ incidence and compared the performance of the currently available live vaccine vs. a new recombinant vaccine.

Results: Universal varicella vaccination alone resulted in a marked increase in the incidence of HZ under all scenarios considered. Even under the most favorable hypotheses on the magnitude of the boosting intensity, this increase could be mitigated only by a parallel HZ immunization with a recombinant vaccine, assuming a long duration of protection. Targeted varicella immunization of adolescents resulted in a modest increase in the HZ incidence which could be counterbalanced by both the live and, especially, the recombinant vaccine.

Conclusions: Given current knowledge on HZ pathogenesis and exogenous boosting, targeted varicella vaccination of adolescents was the only strategy that was not predicted to impact the epidemiology of HZ, and therefore it may represent a suitable alternative to universal vaccination. These results are aimed to support vaccine policy decisions in Norway and other countries with a similar VZV epidemiology.

1. Background

The varicella-zoster virus (VZV) is a DNA-virus of the Herpesvirus family transmitted by direct contacts with infectious individuals. Individuals initially exposed to VZV develop varicella (chickenpox), which normally results in a life-long immunity [1]. After infection, VZV remains dormant in the dorsal root ganglia and may reactivate, following the decline of VZV-specific cell-mediated immunity, e.g., as a consequence of senescence, causing herpes zoster (shingles; HZ).

According to the "exogenous boosting hypothesis" [2], nowadays supported by several empirical studies [3–6], further exposures to VZV boost the host's cell-mediated immunity, resulting in protection against reactivation. The largest serological study on VZV in Europe [7] confirmed this assumption somewhat by suggesting that countries with a faster varicella acquisition were systematically associated with a lower age-specific incidence of HZ.

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The exogenous boosting hypothesis predicts that a reduction in the varicella incidence due to vaccination may lead to an increase of HZ in the medium-term, potentially offsetting the benefits of immunization both in epidemiological [8–16] and economic terms [16]. This concern has hindered the adoption of varicella vaccination across Europe [17].

However, the effects of varicella immunization can be reconsidered in light of the recent commercialization of a live vaccine against HZ (Zostavax®, Merck) [18] and the imminent licensing of a new one based on a subunit recombinant technology (Shingrix®, GlaxoSmithKline) [19]. Despite the considerable healthcare burden of varicella [20,21], Norway currently recommends varicella vaccination only for selected risk groups, including susceptible adolescents and adults [22]. There is currently no nationwide recommendation for HZ vaccination. Since Norway, with its state-funded voluntary national immunization program, has a capacity to achieve a sustained high coverage [23], implementation of routine childhood varicella immunization may be a feasible strategy to reduce the public health and socioeconomic burden of disease.

We used a previously developed model of natural history of VZV for Norway [24] to explore the epidemiological effects of an exhaustive range of alternative options including universal and targeted varicella vaccination, either alone or combined with zoster immunization, and zoster immunization alone.

2. Methods

Hereafter we briefly summarize the model for VZV transmission and reactivation, which is an extension of a previously published model [13,25] calibrated to VZV epidemiological data from Norway [24]. Full details are reported in the Supplementary Materials.

2.1. Natural history of VZV

The natural history of VZV was modelled [24] by an MSIR (maternal antibodies protection – susceptible – infectious – recovered) model for varicella transmission, combined with stages of susceptibility to HZ to describe reactivation (Fig. 1a). Individuals susceptible to varicella acquire infection following a force of infection (FOI) $\lambda(a, t)$, depending on chronological age, a, and time, t. Persons who recovered from varicella are susceptible to exogenous boosting at a force $z\lambda(a, t)$, where z is the boosting intensity ($0 \leq z \leq 1$), or to VZV-reactivation (HZ) at a rate $\rho_i(a, \tau)$, depending on the HZ susceptibility stage, i, and reflecting the number of effective

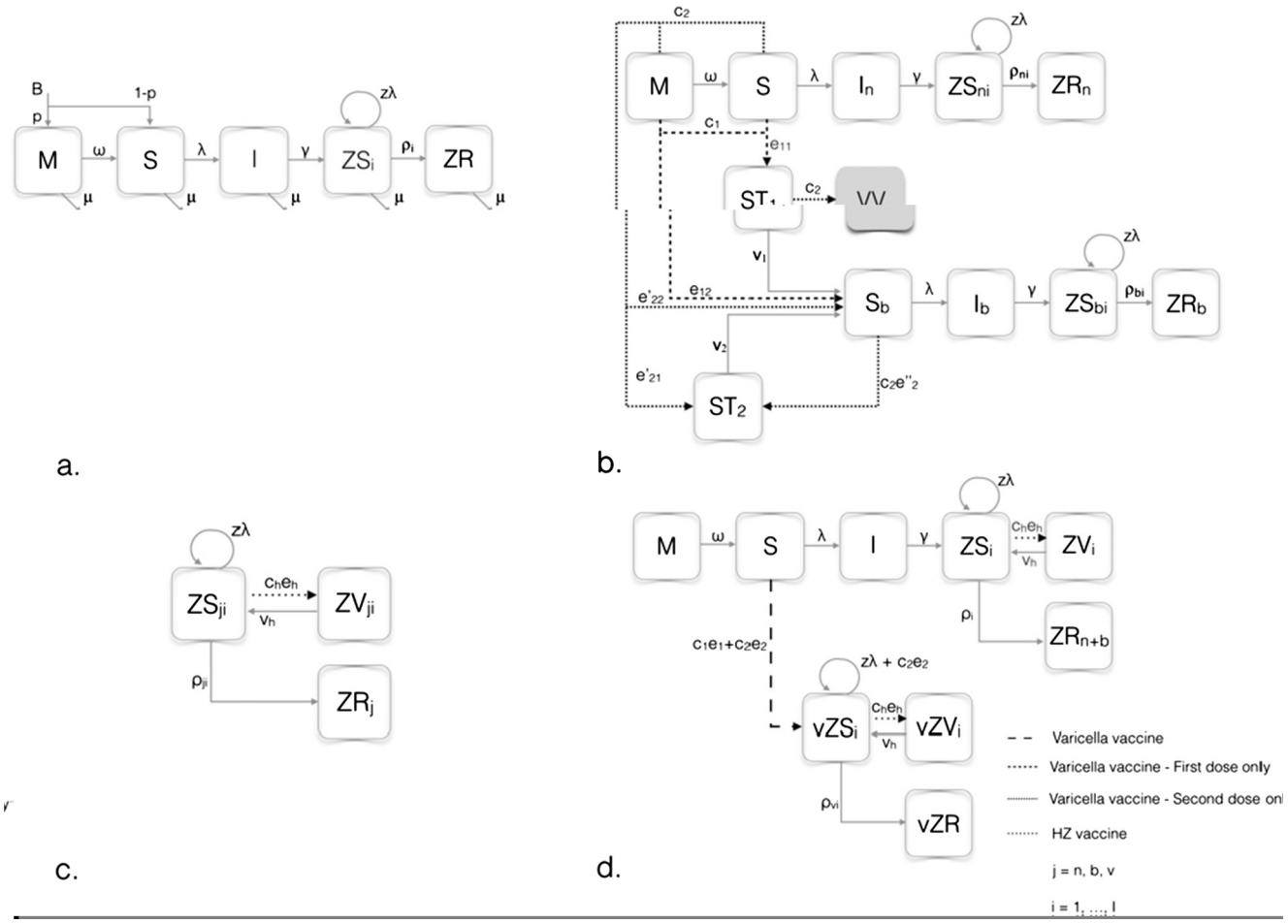

Fig. 1. Simplified modular representation of the compartmental model, stratified by 100 one-year age-classes. (a) Natural history of Varicella Zoster virus transmission and reactivation dynamics. M: Maternally immune, S: varicella susceptible, I: wildtype varicella infected, ZS_i: herpes zoster (HZ) susceptible who experienced i boosting episodes to the virus (including the varicella disease), i = 1,. . ., I, ZR: HZ removed; b) Varicella immunization model. ST_j: Fully short-term protected after jth dose of varicella vaccine, j = 1, 2, S_b: Susceptible to breakthrough disease, I_b: breakthrough varicella infected, ZS_{bi}: HZ susceptible who experienced i boosting episodes (including the breakthrough disease), i = 1,. . ., I; (c) model of HZ from vaccine strain. vZSi: HZ from vaccine strain susceptible who experienced i boosting episodes to the virus (including the second dose of varicella vaccine), i = 1,. . ., I, vZR: HZ from vaccine strain removed; (d) HZ immunization model: ZVi, ZVbi and vZVi: HZ vaccinated who had experienced i boosting episodes at vaccination (including, respectively, varicella disease, breakthrough disease, second dose of varicella vaccine), i = 1,. . ., I. Full details about model parameters and their assignments are reported in Table 1 and the Supplementary Materials.