Epidemics 19 (2017) 1–12

Contents lists available at ScienceDirect

Epidemics

journal homepage: www.elsevier.com/locate/epidemics

Estimation of age-specific rates of reactivation and immune boosting of the varicella zoster virus

Isabella Marinelli[a,b], Alies van Lier[c], Hester de Melker[c], Andrea Pugliese[a], Michiel van Boven[c,*]

[a] Dipartimento di Matematica, Università di Trento, Trento, Italy
[b] Basque Center for Applied Mathematics, Bilbao, Spain
[c] Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, The Netherlands

ARTICLE INFO

Article history:
Received 24 May 2016
Received in revised form 1 November 2016
Accepted 7 November 2016
Available online 22 November 2016

Keywords:
Varicella
Zoster
Transmission model
Statistical inference
Vaccination

ABSTRACT

Studies into the impact of vaccination against the varicella zoster virus (VZV) have increasingly focused on herpes zoster (HZ), which is believed to be increasing in vaccinated populations with decreasing infection pressure. This idea can be traced back to Hope-Simpson's hypothesis, in which a person's immune status determines the likelihood that he/she will develop HZ. Immunity decreases over time, and can be boosted by contact with a person experiencing varicella (exogenous boosting) or by a reactivation attempt of the virus (endogenous boosting). Here we use transmission models to estimate age-specific rates of reactivation and immune boosting, exogenous as well as endogenous, using zoster incidence data from the Netherlands (2002–2011, $n = 7026$). The boosting and reactivation rates are estimated with splines, enabling these quantities to be optimally informed by the data. The analyses show that models with high levels of exogenous boosting and estimated or zero endogenous boosting, constant rate of loss of immunity, and reactivation rate increasing with age (to more than 5% per year in the elderly) give the best fit to the data. Estimates of the rates of immune boosting and reactivation are strongly correlated. This has important implications as these parameters determine the fraction of the population with waned immunity. We conclude that independent evidence on rates of immune boosting and reactivation in persons with waned immunity are needed to robustly predict the impact of varicella vaccination on the incidence of HZ.

1. Introduction

Varicella zoster virus (VZV) is a herpes virus causing a disease known as chickenpox or varicella. After resolving of the systemic primary infection, the virus remains latently present in the host. The virus can reactivate later in life, resulting in a disease known as herpes zoster (HZ) or shingles. Dating back to the work of Hope-Simpson (1965), it has been hypothesized that boosting of the immune system of a latently infected person by contact with a person experiencing chickenpox could lower the probability of HZ developing at some point later in life (Brisson et al., 2010; Guzzetta et al., 2013; Ogunjimi et al., 2013, 2014; Thomas et al., 2002). If true, such exogenous immune boosting could have profound implications for vaccination programs aimed at reducing chickenpox, as these are expected to reduce virus transmission and exogenous immune boosting. Over the years this has become a popular hypothesis to explain and predict the dynamics of HZ in unvaccinated and vaccinated populations, and an important reserve for countries to introduce VZV vaccination (Bonanni et al., 2009; Brisson et al., 2010; Guzzetta et al., 2013; Poletti et al., 2013).

While earlier studies focused exclusively on the implications of exogenous boosting (Betta et al., 2016; Brisson et al., 2010; Guzzetta et al., 2013, 2016; Ogunjimi et al., 2015; Poletti et al., 2013; van Lier et al., 2015), Hope-Simpson's original hypothesis states that both exogenous and endogenous boosting, by reactivation attempts of the virus that are successfully countered by the immune system of the host, contribute to the maintenance of immunity. Although data are scarce, some studies indeed show subclinical reactivation in specific populations, most likely in response to stress (Cohrs et al., 2008; Ljungman et al., 1986; Mehta et al., 2004; Papaevangelou et al., 2013; Wilson et al., 1992). It is therefore of interest to evaluate the ability of endogenous and exogenous boosting together to explain the available HZ incidence data, and to obtain insight in the relative strength of endogenous versus exogenous immune

* Corresponding author.
E-mail address: michiel.van.boven@rivm.nl (M. van Boven).

http://dx.doi.org/10.1016/j.epidem.2016.11.001

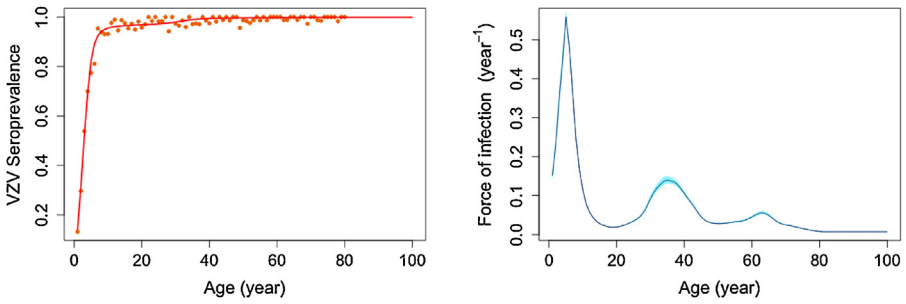

Fig. 1. Overview of varicella zoster virus (VZV) seroprevalence (i.e., fraction of the population infected) (left-hand panel) and estimated force of infection (right-hand panel) (van Lier et al., 2015). The shaded area represents the 95% confidence band of the force of infection.

boosting. Here we build on earlier studies (Betta et al., 2016; Brisson et al., 2010; Guzzetta et al., 2013, 2016; Poletti et al., 2013; Ogunjimi et al., 2015; van Lier et al., 2015) to obtain estimates of key parameters determining the dynamics of VZV in unvaccinated and vaccinated populations. Specifically, we use long-term HZ incidence data from the Netherlands (2002–2011, $n = 7026$ cases (van Lier et al., 2015)) to estimate age-specific rates of immune boosting, loss of immunity, and reactivation in a population without VZV vaccination. Our approach extends earlier analyses by (i) including the possibility of endogenous next to exogenous immune boosting, and (ii) allowing the age-specific rates of reactivation and immune boosting to have flexible shapes, using natural cubic splines. In this manner, the shapes and values of the rate functions are optimally informed by the data, in contrast to previous studies that have made restrictive assumptions from the onset (e.g., Guzzetta et al., 2013; van Lier et al., 2015).

The analyses reveal that rates of loss of immunity are high (0.048–0.10 per year), that reactivation rates are low up to 40 years, increase strongly to 0.03–0.10 per year at old age, and that the fraction of the population with waned immunity that is prone to HZ decreases from 45–55% at age 25 to 10–40% at age 80, and depends sensitively on whether or not endogenous boosting is taken into account. Our analyses show that exogenous boosting is stronger than endogenous immune boosting in children and adults with young children, and that it is conceivable that endogenous boosting exceeds exogenous boosting in other age strata. We discuss the implications for vaccination programs aiming to reduce chickenpox, and possible future avenues to obtain further quantitative information on the magnitude of the Hope-Simpson effect.

2. Methods

2.1. Varicella prevalence

The prevalence of VZV by age is based on Dutch serological data, derived from the second cross-sectional serosurveillance study (PIENTER2), conducted among people aged 0–79 years in the Netherlands in 2006/2007 (Van Der Klis et al., 2009). The seroprevalence of VZV in the PIENTER2 study is quantitatively very similar to the seroprevalence in the earlier PIENTER1 study (conducted in 1995/1996), indicating little change of the age at infection with VZV over the period 1996–2006 (de Melker et al., 2006; Van Lier et al., 2013). To avoid the interference of maternal antibodies we only include the 6251 samples of participants aged 6 months or older. The VZV seroprevalence data provide the basis for estimation of the basic reproduction number of VZV using the so-called social contact hypothesis (van Lier et al., 2015). Here we use the earlier estimates of the force of infection as input for estimation of the rates of reactivation and immune boosting. The data and earlier model fit are shown in Fig. 1, and can be downloaded in the data supplement of an earlier publication (van Lier et al., 2015).

2.2. Herpes zoster incidence

Sentinel data on the incidence of general practitioner (GP) consultations due to HZ by age in the period 2002–2011 (based on 7026 cases) are provided by NIVEL, the Netherlands Institute for Health Services Research (van Lier et al., 2015). The majority of HZ patients consult their GP because it is a painful condition. Because HZ complaints are highly specific and accompanied by typical lesions, with a positive predictive value of clinical judgment of 90.8% (95%CI: 87.3–94.3%), we expect that misclassification of the diagnosis by the GP is rare (Opstelten et al., 2007). Hence, we use the sentinel GP data as a proxy for the total incidence of HZ in the catchment population. The HZ data can be downloaded in the data supplement of an earlier publication (van Lier et al., 2015), and shows no increase or decrease of incidence over time, and no relative increase or decrease in any age group in the study period. The HZ data are the main source of information on which estimates of the rates of reactivation and boosting are based.

2.3. Model structure and analysis

The mathematical model to describe progression to HZ is based on earlier studies (Guzzetta et al., 2013; Poletti et al., 2013; van Lier et al., 2015). We extend these models by (i) including endogenous next to exogenous immune boosting, as in Hope-Simpson's original hypothesis (Hope-Simpson, 1965), and (ii) allowing for the rates of reactivation and immune boosting to be relatively unconstrained, using natural cubic splines.

The population is assumed to be in demographic equilibrium, and infectious contacts (i.e., contacts sufficient for transmission) between persons of different ages are made according to the social contact hypothesis. This implies that the probability of an infectious contact is proportional to observed contact patterns in the Netherlands (Mossong et al., 2008; van Lier et al., 2015). We also assume, as in earlier studies and backed by empirical evidence, that primary varicella is infectious and that infectiousness of HZ is negligible (Guzzetta et al., 2013; Seiler, 1949; van Lier et al., 2015). Next, we assume in our main analyses that reactivation can occur at most once during a lifetime (Hope-Simpson, 1965; Oxman, 2009). We have also considered an extension of the main model in which multiple reactivations are possible, and obtained similar results (Appendix E). For this reason, we focus here on the model with at most one reactivation in a person's lifetime (Fig. 2).

Further, the duration of varicella and HZ episodes (weeks to months) are short compared with the human lifespan (decades), and we may therefore use the short-disease approximation in which the varicella and HZ states are not explicitly modeled (Goeyvaerts et al., 2010). Finally, as in earlier studies (Guzzetta et al., 2013; Poletti et al., 2013) but contrasting with others (Marziano et al., 2015), we model the distribution of persons over classes by