Challenges in the Modelling and Control of Varicella in Hungary

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Abstract The introduction of varicella-zoster virus (VZV) vaccines into the routine vaccination schedule is being under consideration in Hungary. Mathematical models can be greatly useful in advising public health policy decision making by comparing predictions for different scenarios, and by quantifying the costs and benefits of immunization strategies. Here we summarize the major challenges, most of them specific to Hungary, in devising and parametrizing dynamical models of varicella transmission dynamics with vaccination policy. We gain some important insights from a simple compartmental model regarding the seasonality and intrinsic oscillation frequency of the disease dynamics, and the sensitivity to the underreporting ratio. Finally, we discuss the ideas for a more complete, realistic model.

1 Introduction

The varicella-zoster virus is a highly contagious disease that affects a huge proportion of the population, consequently the varicella incidence is of a similar magnitude to the number of births. Although most people contract the disease in their childhood, when the symptoms are generally mild, complications may occur during the infection. Furthermore, at an older age the risk of serious complications is significantly higher.

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In many developed countries, varicella vaccination programs are already implemented. Originally one-dose programs were introduced, which have been replaced by multiple-dose vaccinations in some countries by now. In Hungary, vaccination is marketed for non-routine use, and it has been made available free of charge in a few cities in recent years. There are many country-specific studies regarding the effects and cost-effectiveness of the introduction of varicella vaccination, e.g. [1, 2, 6]. However, there are hardly any studies about Hungary ([5] is a retrospective, descriptive study), where the introduction of varicella vaccination into the routine childhood vaccination program is being considered. Given the actuality and the importance of this issue, here we summarize the challenges of such a modelling work, draw some conclusions from a simple compartmental model and devise a plan for comprehensive future work.

2 Challenges in Modeling

Latency of the Virus and Reactivation as Zoster Upon recovery from the varicella infection, VZV remains in the body in latent form. In general, the individual develops lifelong immunity to VZV. This immunity usually prevents the reappearance of varicella, however the immunity can wane over time, hence the virus may reactivate causing zoster. Zoster infected people are also infectious, but at a lower rate than varicella infected persons. The length and the efficacy of VZV immunity can show a wide interindividual variability.

The Hypothesis of Exogenous Boosting The waning immunity against VZV can be boosted if the individual has a contact with a VZV infected person. Assuming exogenous boosting, it is reasonable that after introducing vaccination, the number of varicella cases decreases and consequently the zoster incidence temporarily increases [1, 6].

Age Structure Since the virus is highly contagious and appears mainly among young children, the transmission dynamics of the virus is largely age specific. Furthermore, varicella has more severe symptoms and higher risk of complications at an older age, and reactivation in the form of zoster also occurs at older age. Hence, age-structured models are necessary to capture these phenomena.

Underreporting In Hungary, monthly reporting of varicella cases to the public health authorities is obligatory. Unfortunately, the varicella incidence appears to be much higher than reported, since the annual birth number is about 2.5-times higher than the reported varicella cases; and according to most studies, these two values should be nearly equal [6]. Among others, the main reason is that not every child is taken to the pediatrician, as there is no effective medical treatment.

Seasonality Available data also reflects a seasonal behaviour in varicella incidence. It can be traced back to the high number of infected children; consequently the

school term and vacation play an important role in the spread of VZV. To describe this phenomenon, time-dependent contact rates are needed in the model.

Lack of Zoster Data Contrary to varicella cases, it is not compulsory in Hungary to report the zoster cases. Therefore, there is no available data related to zoster. We need to make assumptions, based on studies from other countries.

Vaccines are Already Present Parents have the opportunity to buy the vaccine on the market in Hungary. Some cities have made the vaccine available for free for local children. Thus, a fraction of children have already been immunized.

Vaccination Efficacy and Waning Since varicella vaccination was licensed in the mid-80s in some European countries, the vaccine parameters are fairly reliable. In case of MMRV vaccine, 65% of the vaccinated population acquires full protection after one dose and 95% after the second dose. The vaccine-induced protection wanes in 15–20 years after one dose; while the two-dose vaccination provides lifelong immunity [6].

Long Term Dynamics Since we need predictions for many years ahead, an age-structured model should handle the transitions between age cohorts, which makes it more difficult than in models for single outbreaks, such as influenza with short-term behaviour [3]. Demographic changes also need to be taken into consideration.

Cost-Benefit Calculations In 2017, [5] gave a comprehensive study on the economic burden of varicella in Hungary using descriptive statistical methods. There are many uncertainties related to the introduction of VZV-vaccination, for instance, the specific program, the type of the vaccination etc. are still unknown. Hence, detailed dynamic model-based studies of the economic effects can be extremely useful.

3 Insights from a Simple Compartmental Model

Based on the known models in the literature [1, 6], we use a simple compartmental system in our studies with the compartments representing the varicella disease states: *Susceptible*, *Exposed*, *Infectious*, *Recovered*, *Susceptible to Zoster*, *Zoster*, *Zoster Immune*. Maternal immunity is not taken into account in our model. Although the real situation is different, for the sake of simplicity we assume that the birth and death rates are equal (d). Then the total population is constant and a proportional model can be used where $1 = s + e + i + r + s_z + z + r_z$. The model is as follows:

$$\begin{aligned} s' &= d - \lambda s - ds, & s_z' &= -\sigma\lambda s_z + \zeta r - \eta s_z - ds_z, \\ e' &= \lambda s - \varepsilon e - de, & i_z' &= \eta s_z - \kappa i_z - di_z, \\ i' &= \varepsilon e - \gamma i - di, & r_z' &= \kappa i_z - dr_z, \\ r' &= \gamma i + \sigma\lambda s_z - \zeta r - dr, \end{aligned} \tag{1}$$

where the force of infection is $\lambda = \beta\,(i + \nu i_z)$ and $(.)'$ represents time derivative. Newborns directly become susceptible, then, one can become infected by being in contact with a varicella or zoster infectious person. Having been infected, individuals go through a non-infectious latent period, and then they will be infectious. Following the recovery, individuals acquire immunity to VZV. Immunity may wane, and then individuals become susceptible to zoster. One can either be boosted through exposure to VZV and regain immunity with efficiency σ or become zoster infectious through reactivation of VZV with the rate η. Zoster recovered individuals have lifelong immunity to VZV. The average length of the exposed, infectious, temporary immunity, and zoster states are ε^{-1}, γ^{-1}, ζ^{-1} and κ^{-1}, respectively.

The basic reproduction number R_0 is a key parameter regarding the level of virulence of the disease. In [7] the basic reproduction number was determined for a slightly different model, and the usual result holds, namely that if $R_0 < 1$ then the disease-free equilibrium is asymptotically stable, but if $R_0 > 1$ then the disease will persist. With straightforward calculations, using the same method, we obtain

$$R_0 = \frac{\beta\varepsilon}{(\gamma + d)(\varepsilon + d)} + \frac{\nu\beta}{(\kappa + d)} \cdot \frac{\varepsilon\gamma\zeta\eta}{(\varepsilon + d)(\gamma + d)(\zeta + d)(\eta + d)}, \tag{2}$$

where the terms correspond to the expected number of cases generated by a typical individual during primary varicella infection or acute herpes-zoster, respectively.

3.1 Data Analysis and Model Fitting

Annual Varicella incidence data for 20 years and monthly data since 2010 in Hungary were available to us (red curves in Fig. 1 show the incidence corrected by the fitted underreporting ratio $q = 0.4$). Since zoster incidence data is not available, the related parameters were taken from the literature. Values of $(s, e, i, r, s_z, z, r_z)$ at any time are not known, hence initial values of the solutions were taken close to

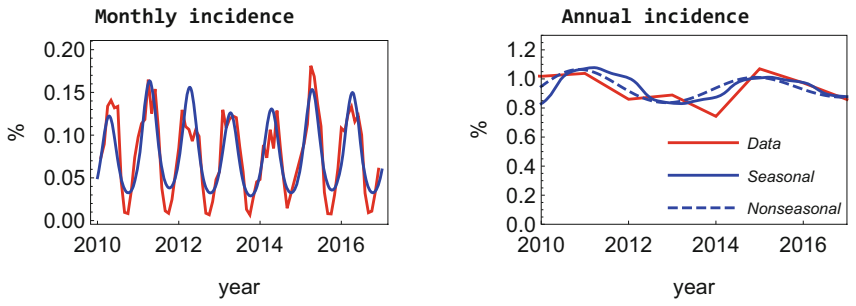

Fig. 1 Varicella incidences: data (red) and fitted model (blue)

the endemic equilibrium according to the values of parameters. Based on our former arguments, the underreporting ratio (q) is included into the fitting process.

Due to the strong seasonality of varicella, we replaced the constant β in the system by a periodic function $\hat{\beta}(t) = \beta(1 + b\cos(2\pi t - c))$ with $b = 0.25$ and $c = 0.5$ chosen by a separate fitting process. The seasonal system with parameters β (transmission rate) and q (underreporting ratio) was fitted to the monthly data. The fitting model is simple: the cumulative growth of $i(t)$ is measured by $\hat{i}(t)$ with $\hat{i}'(t) = \varepsilon e(t)$, and hence the monthly and annual incidences are modeled by $MM(t) = q(\hat{i}(t + 1/12) - \hat{i}(t))$ and $AM(t) = q(\hat{i}(t + 1) - \hat{i}(t))$, respectively.

Fitting was performed by the sophisticated and well-tested command NonlinearModelFit in Wolfram Mathematica 11.3, which can be applied to implicitly defined models such as numerical solutions of differential equations, and it can measure the goodness of the fit. Default options and $ConfidenceLevel \to 0.95$ were used.

After iteratively applied fitting and some fine-tuning, the final rounded values of fixed parameters are $d = 0.01$, $\epsilon = 26$, $\gamma = 52$, $\nu = 0.07$, $\zeta = 0.05$, $\eta = 0.003$, $\sigma = 0.7$, $\kappa = 40$. The goodness of the fit was measured by the adjusted $R^2 = 0.933$. The fitted values are $q = 0.398$ (standard error: 0.012, 95%, confidence interval: [0.374, 0.422]); $\beta = 768.94$ (standard error: 54.27, 95%, confidence interval: [660.88, 877]). The result can be seen on Fig. 1. The monthly incidence data and fitted model $MM(t)$ can be found on the left side, while the right one contains the annual data and the fitted model $AM(t)$ as well as the corresponding autonomous model with the same parameters. Finally, we emphasize that although the seasonality is very strong, both the monthly and annual incidence models show a multi-annual periodicity. The yearly peaks have maxima approximately at every 4 years. This phenomenon is known in the epidemiology of varicella and the value agrees the practice. The same period can be obtained by the autonomous model.

3.2 Sensitivity to Underreporting Ratio

According to the previous section, varicella cases are likely to be seriously underreported in Hungary ($q \approx 0.4$). The model fitting is coherent with what the serological studies suggest. In this section we investigate, how sensitive our model is to the ratio of the reported and total cases, i.e., we examine dependence of the basic reproduction number R_0 (see Eq. (2)) on this ratio q at the parameters fitted above.

Assuming that in Hungary the population is at the endemic equilibrium and using the equality $n_V/q = \gamma i^*$ (where n_V is the average annual reported varicella incidence since 2010 and i^* is the endemic equilibrium of i), we obtain the relation between q and R_0 depicted in Fig. 2. Note that in the literature a wide variety of different R_0 values can be found for the VZV. In [4], the highest value is 16.91 (Netherlands) and the lowest is 3.31 (Italy). According to these values, the

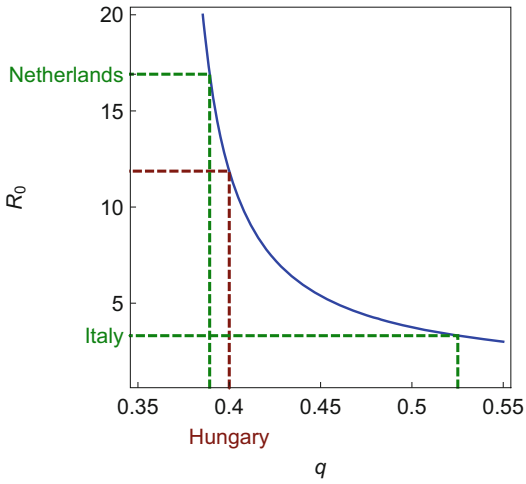

Fig. 2 Relation between the underreporting ratio q and the basic reproduction number

underreporting ratio in Hungary would change between 0.39 and 0.53. As we found above, the fitted value of q is about 0.4 and the corresponding R_0 is 11.87.

4 Conclusion

We gave an overview of the main challenges in the modelling of varicella in Hungary. We fitted a very simple model to the available data, and found that the strong seasonality of varicella infections and the underreporting are essential. The main aim of our research is to forecast the impact of vaccination in Hungary. Based on our simple model the global effects and strategic goals can be already visible. To build a realistic model which can be used to evaluate the impact of vaccination policies, the simple compartmental system should be significantly extended by vaccination, seasonal effects and age structure with age specific parameters and contact patterns.

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