Modelling varicella vaccination in Hungary

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Varicella in Hungary

Epidemiology of the varicella-zoster virus (VZV)

- Highly contagious, primary infection causes chickenpox in (typically) children
- Upon recovery, lifelong immunity is developed to chickenpox
- But VZV stays dormant in the body, may reactivate later causing shingles
- Exogenous boosting: exposure to varicella boosts immunity to herpes-zoster

Vaccination

- Effective prevention: ~70% at one dose, ~100% at two dose vaccination
- Reduces the exogenous boosting effect; incidence of zoster may increase
- Increases the average age at infection, when risk of complications is higher.

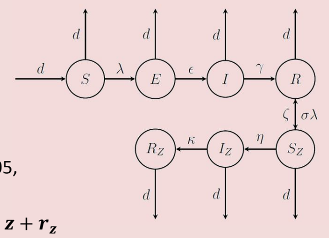
Current situation in Hungary

- Two-dose vaccination will be mandatory from August 2019, given at age 2.
- ~40000 cases of chickenpox reported annually (~40% underreporting)
- Incidence data shows oscillation with 4 years periodicity; and strong seasonality due to the school year.
- Zoster is not reported

The basic model

Assumptions, notation

- Birth and death rates are equal (d)
- Maternal immunity is neglected.
- Latent is not infectious
- Disease induced death is neglected.
- Force of infection: $\lambda = \beta(i + \nu\, i_z)$



Parameters from literature:

- $d = 0.01, \epsilon = 26, \gamma = 52, \nu = 0.07, \zeta = 0.05,$
- $\sigma = 0.7, \kappa = 40, \eta = 0.003.$

Model equations: $\mathbf{1 = s + e + i + r + s_z + z + r_z}$

$$s' = d - (\lambda + d)s, \qquad s_z' = -\sigma\lambda s_z + \zeta r - (\eta + d)s_z,$$
$$e' = \lambda s - (\varepsilon + d)e, \qquad i_z' = \eta s_z - (\kappa + d)i_z,$$
$$i' = \varepsilon e - (\gamma + d)i, \qquad r_z' = \kappa i_z - d r_z,$$
$$r' = \gamma i + \sigma\lambda s_z - (\zeta + d)r,$$

Parameters fitted:

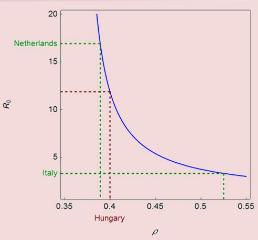
- $\beta = 770$
- $\rho = 0.4$ (underreporing ratio, see below)

Underreporting and the basic reproduction number

$$R_0 = \frac{\beta\epsilon}{(\gamma + d)(d + \epsilon)}\left(\frac{\gamma\,\zeta\,\eta\,\nu}{(d + \zeta)(d + \eta)(d + \kappa)} + 1\right)$$

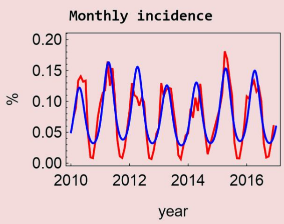
- With the fitted parameters in Hungary: $R_0 \cong 15.4$
- Assume varicella is at steady state $i_{eq}(R_0)$
- *new cases* = $\frac{\textit{rep. cases}}{\rho} = \frac{i_{eq}(R_0)}{\textit{length of infect.}} = \gamma\, i_{eq}(R_0)$
- From the Hungarian data:

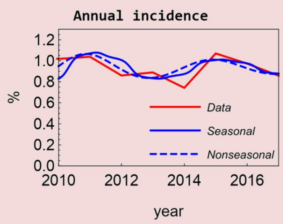
$$\frac{0.004}{\rho} = -0.017\sqrt{\frac{0.087}{{R_0}^2} + \frac{0.016}{R_0} + 0.001} - \frac{0.005}{R_0} + 0.011$$



Seasonality, model fitting

- Incidence shows strong seasonality, hence in the system $\lambda = \beta(i + \nu\, i_Z) \rightarrow \Lambda(t) = \beta\,(0.25\cos(2\pi t - 0.5) + 1)$ is used, according to the school year.
- To fit β and ρ we take the model $m(t, \beta, \rho) = \rho(\Delta i\left(t + \frac{1}{12}\right) - \Delta i(t))$, where $\Delta i'(t) = \epsilon\, e(t)$ (the growth of $i(t)$).

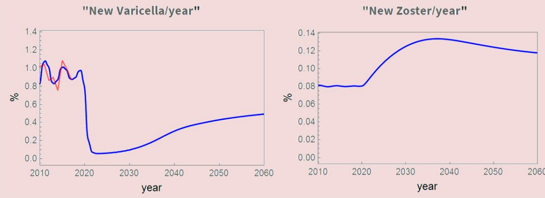




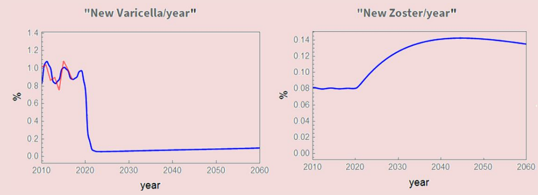
Vaccination

Vaccinations: p_b: infant; p_s: catch-up; $p_{v,s}$: adult re-vaccination

$$s' = (1 - p_b)\,d - p_s s - ds - \lambda s, \qquad v' = p_b d + p_s s + p_{v,s} s_v - \lambda\sigma_3 v - wv,$$
$$e' = \lambda s - e(d + \epsilon), \qquad s_v' = -p_{v,s} s_v - ds_v - \lambda s_v + wv,$$
$$i' = \epsilon e - i(\gamma + d), \qquad e_v' = \lambda s_v - (d + \epsilon_2)\,e_v,$$
$$r' = -r(d + \zeta) + \gamma i + \lambda\sigma s_z, \qquad i_v' = \epsilon_2 e_v - i_v\,(\gamma_2 + d)\,,$$
$$s_z' = -(d + \eta)s_z - \lambda\sigma s_z + \zeta r, \qquad r_v' = \lambda\sigma_2 s_{z,v} - (d + \zeta_2)\,r_v + \lambda\sigma_3 v + \gamma_2 i_v,$$
$$i_z' = \eta s_z - i_z(d + \kappa), \qquad s_{z,v}' = -(d + \eta_2)\,s_{z,v} - \lambda\sigma_2 s_{z,v} + \zeta_2 r_v,$$
$$r_z' = \kappa z - dr_z, \qquad z_v' = \eta_2 s_{z,v} - (d + \kappa_2)\,z_v,$$
$$r_{z,v}' = \kappa_2 z_v - dr_{z,v}.$$



Complete infant vaccination with immunity waning in 20 years: $p_b = 1; p_s = 0; p_{v,s} = 0$



Complete infant, partial catch-up and re-vaccination $p_b = 1;\ p_s = 0.2; p_{v,s} = 0.2$

The hybrid age structured model

- To capture age specific features, we use 65 age groups and a contact matrix
- Large number of compartments, high dimensional system
- Disease dynamics is continuous in time, but switching age group occurs once a year, preserving school year cohorts: a discontinuity in the model
- Model calibration to initial value is difficult, since the state of the system is not fully observable. Previous studies assumed stationary age distribution, but Hungary is in a demographic transition. We developed an iterative scheme is to find the initial values of our system.
- Novel method to calculate the basic and control reproduction numbers

$$\frac{dx}{dt} = f(x), \quad t \neq T_i,$$
$$x(T_i^+) = Ax(T_i^-),$$

C =

age of contact	00-04	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70+
	age of participant														
00-04	1,33	0,57	0,21	0,10	0,21	0,40	0,38	0,23	0,11	0,13	0,31	0,23	0,25	0,20	0,23
5-9	0,83	6,41	1,06	0,29	0,10	0,27	0,74	0,77	0,56	0,16	0,24	0,50	0,27	0,44	0,26
10-14	0,75	1,62	12,71	1,01	0,30	0,25	0,80	0,68	0,69	0,26	0,37	0,42	0,25	0,44	0,34
15-19	0,49	0,41	2,27	12,12	2,13	0,72	0,54	1,29	1,18	1,13	0,94	0,66	0,53	0,60	0,40
20-24	0,69	0,36	0,63	1,69	6,26	2,40	1,16	1,40	1,58	1,44	1,45	1,02	0,66	0,60	0,34
25-29	1,36	0,92	0,84	0,80	2,61	3,43	2,28	2,50	1,81	1,75	1,94	1,37	1,10	1,36	0,26
30-34	1,19	1,42	1,19	0,88	1,59	2,18	2,36	2,68	1,77	1,44	1,61	1,34	1,31	1,40	0,46
35-39	0,85	0,96	1,23	1,06	1,13	1,43	1,64	3,08	1,76	1,33	1,24	1,06	1,02	1,08	0,71
40-44	0,44	0,68	0,96	1,17	1,11	1,37	1,44	1,87	2,47	1,49	1,71	0,98	1,07	1,68	0,74
45-49	0,47	0,59	0,71	0,96	0,98	1,12	1,36	1,52	1,56	2,25	1,74	1,16	0,56	0,92	0,83
50-54	0,57	0,47	0,46	0,51	1,20	1,33	1,11	1,05	1,03	1,56	1,58	1,40	0,56	0,96	0,74
55-59	0,53	0,48	0,28	0,25	0,79	0,77	0,56	0,87	0,68	0,61	0,94	1,95	1,10	0,68	0,54
60-64	0,29	0,32	0,24	0,25	0,34	0,45	0,59	0,58	0,56	0,41	0,52	0,84	1,12	0,48	0,57
65-69	0,26	0,18	0,15	0,20	0,10	0,23	0,18	0,53	0,34	0,31	0,19	0,56	0,64	0,72	0,54
70+	0,28	0,36	0,38	0,23	0,30	0,40	0,30	0,71	0,55	0,67	0,71	0,77	0,64	0,80	1,23

$$\overline{A} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 & 1 \end{bmatrix} \qquad A = \begin{bmatrix} \overline{A} & 0 & 0 & 0 & 0 \\ 0 & \overline{A} & 0 & 0 & 0 \\ 0 & 0 & \overline{A} & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \overline{A} \end{bmatrix}$$

C is the contact matrix expressing mixing between age groups
A is the aging matrix expressing transition to the next age group

For R_0, we linearize the impulsive system around the discontinuous disease free periodic solution *p(t)*, and separate transmission terms from other transitions:

$$V(t) = \left[\frac{\partial \mathcal{V}_{i,j}(p(t))}{\partial x_{k,l}}\right]_{\substack{1 \leq i,k \leq n \\ 1 \leq j,l \leq m}} \qquad F(t) = \left[\frac{\partial \mathcal{F}_{i,j}(p(t))}{\partial x_{k,l}}\right]_{\substack{1 \leq i,k \leq n \\ 1 \leq j,l \leq m}}$$

R_0 is the spectral radius of a suitable operator, which can be numerically approximated from solving auxiliary impulsive periodic systems. Method is similar for control reproduction numbers.

Ongoing work, goals: reliable predicitons of chickenpox and zoster in Hungary due to the planned policy change, cost-benefit analysis and comparison of various vaccination strategies.

One of the authors in 1997

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