Influenza vaccination model with multiple vaccine types and waning immunity

Let us denote by $v(t, z)$ the density of vaccinated individuals with vaccine-induced immunity level $z \in [z_{min}, z_{max}]$ at time t. The parameter z describes the immune status where value z_{max} corresponds to maximal immunity and z_{min} corresponds to minimal level of immunity. The total population of vaccinated hosts is given by

$$V(t) = \int_{z_{\min}}^{z_{\max}} v(t,z)\,dz\,.$$

Vaccination infers a level of immunity z_{max}. The level of immunity of a vaccinated host tends to decay in time at some rate $g(z)$, and when it reaches the minimal value z_{min}, the host becomes susceptible again. That is,

$$dz(t)/dt = g(z),$$

with $g : [z_{min}, z_{max}] \to (0, Kg]$, $Kg < \infty$ continuously differentiable. Here, we assume $g(z) > 0$, because if $g(z^*) = 0$ for some value $z^* \in [z_{min}, z_{max}]$, there would be no change of the immunity level at z^*, contradicting the hypothesis of continuous decay of immune status.

Model equations

Our model has compartments S, I, V, and R. Let initial values $V(0) = 0$, and $R(0) = 0$, $S(0) = S_0 \geq 0$, $I(0) = I_0 \geq 0$ be given. The population of originally susceptible individuals (S) is governed by

$$S'(t) = -\phi(t)S(t) - \beta\frac{S(t)I(t)}{N(t)} + \Lambda\,,$$

where Λ represents transitions from the vaccinated compartment to the susceptible one due to immunity loss. Also, the population of infectious individuals (I) is governed by

$$I'(t) = \beta\frac{S(t)I(t)}{N(t)} - \gamma I(t) + \Omega_V\,,$$

where Ω_V represents transitions from the vaccinated compartment to the infectious one. We will specify Λ and Ω_V later.

Given any $z \in [z_{min}, z_{max}]$, denote by Gz the partition of the interval $[z_{min}, z]$ into small intervals of length Δz. Observe $Gz \in Gz_{max}$ for all $z \in [z_{min}, z_{max}]$. The total number of vaccinated individuals with immunity level in $[z - \Delta z, z]$ at time $t + \Delta t$ is given by

$$v(t + \Delta t, z)\,\Delta z = v(t, z)\,\Delta z + v(t, z)\,g(z)\,\Delta t - v(t, z- \Delta z)\,g(z -\Delta z)\,\Delta t - \{\sigma\beta I(t)v(t,z)/N(t)\}\,\Delta t.$$

The second and the third terms represent incoming and outgoing individuals due to waning immunity, respectively. We can divide the equation above by $\Delta z > 0$,

$$v(t+\Delta t, z) = v(t,z) + v(t,z)g(z)\frac{\Delta t}{\Delta z} - v(t, z-\Delta z)g(z-\Delta z)\frac{\Delta t}{\Delta z} - \sigma\beta\frac{I(t)}{N(t)}v(t,z)\Delta t$$

and compute the limit as $\Delta z \to 0$ to get

$$v(t+\Delta t,z)-v(t,z)=\Delta t\frac{\partial}{\partial z}(g(z)v(t,z))-\sigma\beta\frac{I(t)}{N(t)}v(t,z)\Delta t\,.$$

Finally, we divide by Δt and let $\Delta t \to 0$:

$$\frac{\partial}{\partial t}v(t,z)-\frac{\partial}{\partial z}(g(z)v(t,z))=-\sigma\beta\frac{I(t)}{N(t)}v(t,z),$$

where $t > 0$, $z \in [z_{min}, z_{max}]$, with the boundary condition

$$g(z_{\max})v(t,z_{\max})=\phi S(t)$$

and a nonnegative initial distribution $v(0, z) = \Psi(z) = 0(?)$, $z \in [z_{min}, z_{max}]$.

From the discrete approach derivation it becomes clear that the quantity Λ, initially introduced in the equation $S'(t)$ to represent the individuals who experience immunity loss, is given by the number $g(z_{\min})\ v(t, z_{min})$ of vaccinated individuals who reach the minimal level of immunity. Also, the quantity Ω_V, introduced in the equation $I'(t)$ to represent the individuals who are infected after being vaccinated, is given by the number $\sigma\beta\frac{I(t)}{N(t)}\int_{z_{\min}}^{z_{\max}}v(t,x)dx$ .Therefore, for $t \geq 0$, we have the system of equations:

$$S'(t)=-\phi(t)S(t)-\beta\frac{S(t)I(t)}{N(t)}+g(z_{\min})v(t,z_{\min}),$$

$$I'(t)=\beta\frac{S(t)I(t)}{N(t)}-\gamma I(t)+\sigma\beta\frac{I(t)}{N(t)}\int_{z_{\min}}^{z_{\max}}v(t,x)dx,$$

$$\frac{\partial}{\partial t}v(t,z)-\frac{\partial}{\partial z}(g(z)v(t,z))=-\sigma\beta\frac{I(t)}{N(t)}v(t,z),$$

with the boundary condition

$$g(z_{\max})v(t,z_{\max})=\phi S(t)$$

and a nonnegative initial distribution $v(0, z) = \Psi(z) = 0$, $z \in [z_{min}, z_{max}]$. In order to include multiple vaccine types (a pentavalent vaccine (with 2 H3N2 clades); and vaccines not propagated in eggs (RIV and ccIIV)), we will expand our model to incorporate multiple vaccine variables (V^k) where superscript k denote various vaccine types. Also vaccine-related parameters will be determined according to each vaccine type and corresponding clinical trial data.

<u>Connection with ODE models</u>

Our model above can be reduced to a system of ordinary differential equations (ODEs) using the method of lines, i.e. a technique in which all but one dimension are discretized. In our case, we shall discretize the level of immunity (z) and obtain a system of ODEs in the time variable.

Let us define a sequence $\{z_j\}_{j\in \mathrm{N}}$, with $h_j := z_{j+1} - z_j > 0$, for all $j \in$ N. For simplicity, we choose a grid with few points (and we can add more later!), $z_1 := z_{min} < z_W < z_F < z_{max}$ and assume that $h_j = 1$ for all j's (after rescaling, if necessary). We define the following two subclasses of the V population:

- $V_F(t) := v(t, z_F)$, vaccinated individuals with high vaccine-induced immunity at time t. Immunity level decays at rate $\mu := g(z_F)$.

- $V_W(t) := v(t, z_W)$, vaccinees with intermediate level of immunity at time t. Immunity level decays at rate $\upsilon := g(z_W)$.

- $V_I(t) := v(t, z_{min})$, vaccinees with critically low level of immunity at time t. Immunity level decays at rate $\rho := g(z_{min})$, and V_I individuals move to S.

We now show how the PDE system can be reduced to a system of oDEs by means of the method of lines. The PDE for $v(t, z)$ is

$$\frac{\partial}{\partial t}v(t,z) - \frac{\partial}{\partial z}(g(z)v(t,z)) = -\sigma\beta\frac{I(t)}{N(t)}v(t,z),$$

with the boundary condition

$$g(z_{\max})v(t,z_{\max}) = \phi S(t)$$

and a nonnegative initial distribution $v(0, z) = \Psi(z) = 0(?)$, $z \in [z_{min}, z_{max}]$. Using forward approximation for the z-derivative in the PDE equation above, we obtain, e.g., for $V_F(t)$ the following differential equation:

$$\begin{aligned}
V_F(t)' &= \frac{\partial}{\partial t}v(t,z_F) = \frac{\partial}{\partial z}(g(z_F)v(t,z_F)) - \sigma\beta\frac{I(t)}{N(t)}v(t,z_F) \\
&\cong \frac{g(z_{\max})v(t,z_{\max}) - g(z_F)v(t,z_F)}{z_{\max} - z_F} - \sigma\beta\frac{I(t)}{N(t)}v(t,z_F) \\
&= g(z_{\max})v(t,z_{\max}) - \mu V_F(t) - \sigma\beta\frac{I(t)}{N(t)}V_F(t) \\
&= \phi(t)S(t) - \left(\mu + \sigma\beta\frac{I(t)}{N(t)}\right)V_F(t).
\end{aligned}$$

Also, for $V_W(t)$ and $V_I(t)$, we obtain the following DE's:

$$
\begin{aligned}
V_W(t)' &= \frac{\partial}{\partial t}v(t,z_W) = \frac{\partial}{\partial z}(g(z_W)v(t,z_W)) - \sigma\beta\frac{I(t)}{N(t)}v(t,z_W) \\
&\cong \frac{g(z_F)v(t,z_F) - g(z_W)v(t,z_W)}{z_F - z_W} - \sigma\beta\frac{I(t)}{N(t)}v(t,z_W) \\
&= g(z_F)v(t,z_F) - g(z_W)v(t,z_W) - \sigma\beta\frac{I(t)}{N(t)}v(t,z_W) \\
&= \mu V_F(t) - \upsilon V_W(t) - \sigma\beta\frac{I(t)}{N(t)}V_W(t) \\
&= \mu V_F(t) - \left(\upsilon + \sigma\beta\frac{I(t)}{N(t)}\right)V_W(t),
\end{aligned}
$$

$$
\begin{aligned}
V_1(t)' &= \frac{\partial}{\partial t}v(t,z_1) = \frac{\partial}{\partial z}(g(z_1)v(t,z_1)) - \sigma\beta\frac{I(t)}{N(t)}v(t,z_1) \\
&\cong \frac{g(z_W)v(t,z_W) - g(z_1)v(t,z_1)}{z_W - z_1} - \sigma\beta\frac{I(t)}{N(t)}v(t,z_1) \\
&= g(z_W)v(t,z_W) - g(z_1)v(t,z_1) - \sigma\beta\frac{I(t)}{N(t)}v(t,z_1) \\
&= \upsilon V_W(t) - \rho V_1(t) - \sigma\beta\frac{I(t)}{N(t)}V_1(t) \\
&= \upsilon V_W(t) - \left(\rho + \sigma\beta\frac{I(t)}{N(t)}\right)V_1(t).
\end{aligned}
$$

Also, in the differential equation for $I'(t)$,

$$\beta\frac{I(t)}{N(t)}\int_{z_{\min}}^{z_{\max}}\sigma(x)v(t,x)dx = \beta\frac{I(t)}{N(t)}\left[\sigma_1 V_1(t) + \sigma_W V_W(t) + \sigma_F V_F(t)\right]$$

Therefore, the differential equation for $I'(t)$ becomes

$$I'(t) = \beta\frac{I(t)}{N(t)}\left[S(t) + \sigma_1 V_1(t) + \sigma_W V_W(t) + \sigma_F V_F(t)\right] - \gamma I(t).$$

In summary, our PDE model can be transformed into the following system of ODE's:

$S'(t) = \theta V_L(t) - \Lambda(t)S(t) - \phi(t)S(t),$

$E'(t) = \Lambda(t)\{S(t) + V_0(t) + (1-\sigma_H)V_H(t) + (1-\sigma_M)V_M(t) + (1-\sigma_L)V_L(t)\} - \delta E(t),$

$I'(t) = k\delta E(t) - \gamma I(t),$

$A'(t) = (1-k)\delta E(t) - \gamma A(t),$

$V_0{}'(t) = \phi(t)S(t) - \{\chi + \Lambda(t)\}V_0(t),$

$V_H{}'(t) = \chi V_0(t) - \{\tau + (1-\sigma_H)\Lambda(t)\}V_H(t),$

$V_M{}'(t) = \tau V_H(t) - \{\upsilon + (1-\sigma_M)\Lambda(t)\}V_M(t),$

$V_L{}'(t) = \upsilon V_M(t) - \{\theta + (1-\sigma_L)\Lambda(t)\}V_L(t),$

$R'(t) = \gamma\big(I(t) + A(t)\big),$

$Z'(t) = \phi(t)S(t).$

where $\Lambda(t) = \beta\frac{(I(t)+\rho A(t))}{N(t)}$

If X denotes the total number of susceptible people we can vaccinate over T days, then we have an integral constraint,

$$\int_0^T \phi(t)S(t)\,dt = X.$$

Such constraints are isoperimetric constraints and can be handled by creating another state variable, such as

$$Z'(t) = \phi(t)S(t)$$
$$Z(0)$$
$$Z(T) = X.$$

Our goal is to minimize the number of infectious individuals and the overall cost of vaccination over T days. The problem is stated as

$$\min_{\phi}\int_0^T I(t) + \frac{B}{2}\phi^2(t)S(t)dt$$

where the set of controls is

$$U = \{\phi: [0,T] \to [0,\phi_{max}] \quad |\phi \text{ is Lebesgue measurable}\}$$

subject to our model equations, the equation for $Z'(t)$, and the conditions,

$$S(0) = N - I_0 - A_0,\ E(0) = 0,\ I(0) = I_0,\ A(0) = A_0,\ V_0(0) = 0,$$
$$V_H(0)=0, \quad V_M(0)=0, \quad V_L(0)=0, \quad R(0)=0, \quad Z(0)=0, \quad Z(T)=X,$$
$$S(T),\ E(T),\ I(T),\ A(T), V_0(T),\ V_H(T),\ V_M(T),\ V_L(T),\ R(T) \text{ are free.}$$

The value B in the objective functional is a balancing parameter, which determines the relative importance of the two factors.

Using Pontryagin's Maximum principle to find the optimal vaccination schedule, we first define the Hamiltonian as

$$\begin{aligned} H = I(t) + \frac{B}{2}\phi^2(t)S(t) + \lambda_1(\theta V_L - \Lambda S - \phi S) \\ + \lambda_2\big(\Lambda(t)\{S(t) + V_0(t) + (1-\sigma_H)V_H(t) + (1-\sigma_M)V_M(t) + (1 \\ - \sigma_L)V_L(t)\} - \delta E(t)\big) + \lambda_3\big(k\delta E(t) - \gamma I(t)\big) + \lambda_4\big((1-k)\delta E(t) - \gamma A(t)\big) \\ + \lambda_5\big(\phi(t)S(t) - \{\chi + \Lambda(t)\}V_0(t)\big) \\ + \lambda_6\big(\chi V_0(t) - \{\tau + (1-\sigma_H)\Lambda(t)\}V_H(t)\big) \\ + \lambda_7\big(\tau V_H(t) - \{\upsilon + (1-\sigma_M)\Lambda(t)\}V_M(t)\big) \\ + \lambda_8\big(\upsilon V_M(t) - \{\theta + (1-\sigma_L)\Lambda(t)\}V_L(t)\big) + \lambda_9\Big(\gamma\big(I(t) + A(t)\big)\Big) \\ + \lambda_{10}\big(\phi(t)S(t)\big)\,. \end{aligned}$$

The values λ_1, λ_2, λ_3, λ_4, λ_5, λ_6, λ_7, λ_8, λ_9, and λ_{10} are the associated adjoints for the states *S*, E, *I*, A, V_0, V_H, V_M, V_L, *R* and *Z*, respectively. By differentiating the Hamiltonian with respect to each state variable, we find the differential equation for the associated adjoint. Also, because states *S*, *I*, *E*, A, V_0, V_H, V_M, V_L, and *R* do not have fixed values at the final time, the values of the associated adjoints at the final time is zero. Since *Z* has initial and terminal conditions, λ_{10} has no transversality condition.

Therefore, the adjoin system is

$$
\begin{aligned}
\lambda_1' &= -\frac{B\phi^2(t)}{2} + (\lambda_1 - \lambda_2)\Lambda(t) + (\lambda_1 - \lambda_5 - \lambda_{10})\phi(\mathrm{t}),\\
\lambda_2' &= \delta(\lambda_2 - k\lambda_3 - (1-k)\lambda_4),\\
\lambda_3' &= -1 + \frac{(\lambda_1 - \lambda_2)\beta S}{N} + \frac{(\lambda_5 - \lambda_2)\beta V_0}{N} + \frac{(\lambda_6 - \lambda_2)(1-\sigma_H)\beta V_H}{N}\\
&\qquad + \frac{(\lambda_7 - \lambda_2)(1-\sigma_M)\beta V_M}{N} + \frac{(\lambda_8 - \lambda_2)(1-\sigma_L)\beta V_L}{N} + (\lambda_3 - \lambda_9)\gamma,\\
\lambda_4' &= \frac{(\lambda_1 - \lambda_2)\beta\rho S}{N} + \frac{(\lambda_5 - \lambda_2)\beta\rho V_0}{N} + \frac{(\lambda_6 - \lambda_2)(1-\sigma_H)\beta\rho V_H}{N}\\
&\qquad + \frac{(\lambda_7 - \lambda_2)(1-\sigma_M)\beta\rho V_M}{N} + \frac{(\lambda_8 - \lambda_2)(1-\sigma_L)\beta\rho V_L}{N} + (\lambda_4 - \lambda_9)\gamma,\\
\lambda_5' &= \frac{(\lambda_5 - \lambda_2)\beta(I + \rho A)}{N} + (\lambda_5 - \lambda_6)\chi,\\
\lambda_6' &= \frac{(\lambda_6 - \lambda_2)(1-\sigma_H)\beta(I + \rho A)}{N} + (\lambda_6 - \lambda_7)\tau,\\
\lambda_7' &= \frac{(\lambda_7 - \lambda_2)(1-\sigma_M)\beta(I + \rho A)}{N} + (\lambda_7 - \lambda_8)\nu,\\
\lambda_8' &= \frac{(\lambda_8 - \lambda_2)(1-\sigma_L)\beta(I + \rho A)}{N} + (\lambda_8 - \lambda_1)\theta,\\
\lambda_9' &= 0,\\
\lambda_{10}' &= 0,
\end{aligned}
$$

with $\lambda_j(T) = 0$ for *j*=1,…,9.

By the optimality condition, we have $\frac{\partial H}{\partial \phi}|_{\phi^*} = 0$ on the interior of the control set, where ϕ^* denotes the optimal control. Solving ϕ^* on the interior of the control set gives

$$\phi^* = \frac{(\lambda_1 - \lambda_5 - \lambda_{10})}{B}.$$

Taking the bounds into account, we conclude

$$\phi^* = min\left[\phi_{max}, max\left[0, \frac{(\lambda_1 - \lambda_5 - \lambda_{10})}{B}\right]\right].$$