Modeling optimal vaccination strategies against pandemic influenza

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A single-out break influenza transmission model with vaccination by Gerardo Chowell et al (2006, 2009)

$$\begin{aligned}
\dot{S}(t) &= -u(t)S(t) - \beta\frac{I(t)+J(t)}{N(t)}S(t) \\
\dot{V}(t) &= \epsilon u(t)S(t) - \eta V(t) - \beta\frac{I(t)+J(t)}{N(t)}V(t) \\
\dot{F}(t) &= (1-\epsilon)u(t)S(t) - \beta\frac{I(t)+J(t)}{N(t)}F(t) \\
\dot{P}(t) &= \eta V(t) \\
\dot{E}(t) &= \beta\frac{I(t)+J(t)}{N(t)}(S(t)+V(t)+F(t)) - kE(t) \\
\dot{I}(t) &= kE(t) - (\alpha+\gamma_1)I(t) \\
\dot{J}(t) &= \alpha I(t) - (\gamma_2+\delta)J(t) \\
\dot{R}(t) &= \gamma_1 I(t) + \gamma_2 J(t) \\
\dot{D}(t) &= \delta J(t) \\
\dot{Y}(t) &= u(t)S(t)
\end{aligned} \tag{1}$$

Constrained optimal control problem

The objective functional to be minimized is

$$\mathcal{F}(u(t)) = \int_0^T [I(t) + \frac{W}{2}u^2(t)]dt \tag{2}$$

where the control effect is modeled by a quadratic term in $u(t)$. The weight constant W is a measure of the *relative* cost of vaccination over a finite time period.

The isoperimetric-constrained problem is to find $u^*(t)$ such that

$$\mathcal{F}(u^*(t)) = min_{\Omega}\mathcal{F}(u(t)) \tag{3}$$

$$\int_0^T u(t)S(t)dt = B \tag{4}$$

where $\Omega = \{u(t) \in L^1(0,T) \| 0 \leq u(t) \leq b, t \in [0,T]\}$ and subject to state systems (1).

The equality constraint (isoperimetric constraint) represents the total amount of vaccines available B over the time interval $[0, T]$.

Constraint can be reformulated in terms of the differential equation $\dot{Y}(t) = u(t)S(t)$ with the initial condition $Y(0) = 0$ and final condition $Y(T) = B$.

Pontryagin's Maximum Principle

$$\begin{aligned}
H &= I(t) + \frac{W}{2}u^2(t) \qquad (5)\\
&+ \lambda_1(t)\{-u(t)S(t) - \beta\frac{(I(t)+J(t))}{N(t)}S(t)\}\\
&+ \lambda_2(t)\{\epsilon u(t)S(t) - \eta V(t) - \beta\frac{(I(t)+J(t))}{N(t)}V(t)\}\\
&+ \lambda_3(t)\{(1-\epsilon)u(t)S(t) - \beta\frac{(I(t)+J(t))}{N(t)}F(t)\}\\
&+ \lambda_4(t)\{\beta\frac{(I(t)+J(t))}{N(t)}(S(t)+V(t)+F(t)) - kE(t)\}\\
&+ \lambda_5(t)\{kE(t) - (\alpha+\gamma_1)I(t))\}\\
&+ \lambda_6(t)\{\alpha I(t) - (\gamma_2+\delta)J(t)\}\\
&+ \lambda_7(t)\{u(t)S(t)\}
\end{aligned}$$

Theorem

There exist an optimal control $u^*(t)$ and corresponding state solutions, $X^*(t)$ that minimizes $\mathcal{F}(u)$ over Ω. It is necessary that there exist continuous functions $\lambda_i(t)$ such that

$$
\begin{aligned}
\dot{\lambda}_1 &= -[\lambda_1(u(t) - \lambda_1\beta\frac{(I(t)+J(t))}{N(t)} + \lambda_2(\epsilon u(t)) \\
&+ \lambda_3((1-\epsilon)u(t) + \lambda_4\beta\frac{(I(t)+J(t))}{N(t)} + \lambda_7 u(t)] \\
\dot{\lambda}_2 &= -[\lambda_2 - \eta + \lambda_2(-\beta\frac{(I(t)+J(t))}{N(t)}) + \lambda_4\beta\frac{(I(t)+J(t))}{N(t)}] \\
\dot{\lambda}_3 &= -[-\lambda_3\beta\frac{(I(t)+J(t))}{N(t)} + \lambda_4\beta\frac{(I(t)+J(t))}{N(t)}] \\
\dot{\lambda}_4 &= -[\lambda_4(-k) + \lambda_5 k] \\
\dot{\lambda}_5 &= -[1 - \lambda_1\frac{\beta}{N(t)}S(t) - \lambda_2\frac{\beta}{N}V(t) - \lambda_3\frac{\beta}{N(t)}F(t) \\
&+ \lambda_4\frac{\beta}{N(t)}(S(t)+V(t)+F(t)) - \lambda_5(\alpha+\gamma_1) + \lambda_6\alpha] \\
\dot{\lambda}_6 &= -[-\lambda_1\frac{\beta}{N(t)}S(t) - \lambda_2\frac{\beta}{N(t)}V(t) + \lambda_3\frac{\beta}{N(t)}(F(t)) \\
&- \lambda_4\frac{\beta}{N(t)}(S(t)+V(t)+F(t)) - \lambda_6(\gamma_2+\delta)] \\
\dot{\lambda}_7 &= 0
\end{aligned} \tag{6}
$$

satisfying the transversality conditions, $\lambda_i(T) = 0,\ i = 1, \cdots, 6, \lambda_7(T) = \theta$.

Proof The existence of optimal controls is guaranteed since the integrand of J is a convex function of $U(t)$ and the the state system satisfies the *Lipschitz* property with respect to the state variables. The following can be derived from the Pontryagin's Maximum Principle:

$$\frac{d\lambda_1(t)}{dt} = -\frac{\partial H}{\partial S}, \quad \frac{d\lambda_2(t)}{dt} = -\frac{\partial H}{\partial V}, \quad \frac{d\lambda_3(t)}{dt} = -\frac{\partial H}{\partial F},$$
$$\frac{d\lambda_4(t)}{dt} = -\frac{\partial H}{\partial E}, \quad \frac{d\lambda_5(t)}{dt} = -\frac{\partial H}{\partial I}, \quad \frac{d\lambda_6(t)}{dt} = -\frac{\partial H}{\partial J}, \quad \frac{d\lambda_7(t)}{dt} = -\frac{\partial H}{\partial Y},$$

with $\lambda_i(T) = 0$ for $i = 1, ..., 6$, $\lambda_7(T) = \theta$.
The optimality conditions:

$$\frac{\partial H}{\partial u} = Wu(t) - \lambda_1(t)S(t) + \epsilon\lambda_2(t)S(t) + (1-\epsilon)\lambda_3(t)S(t) + \lambda_7(t)S(t) = 0 \text{ at } u(t) = u^*(t)$$

Solving for $u^*(t)$ we obtain

$$u^*(t) = \frac{S(t)}{W}[\lambda_1(t) - \epsilon\lambda_2(t) - (1-\epsilon)\lambda_3(t) + \lambda_7(t)].$$

By using the standard argument for bounds $0 \leq u(t) \leq b$, we have

$$u^*(t) = min\{max\{0, \frac{S(t)}{W}(\lambda_1(t) - \epsilon\lambda_2(t) - (1-\epsilon)\lambda_3(t) + \lambda_7(t))\}, b\} \qquad (7)$$

Unconstrained optimal problem using the standard two point boundary method:

- State system is solved using a forward method with given initial conditions.
- Adjoint system is solved using a backward scheme with the transversality conditions.
- Update controls using the optimality condition
- Iterate the process until a convergence criterion is satisfied

Constrained optimization problem:
$Y(t)$ is introduced in (1) from the isoperimetric constraint (5), which requires boundary conditions at $t = 0$ and $t = T$. Non-zero transversality condition at the final time T, namely that $A_7(T) \equiv \theta$. Note that θ is unknown therefore, an iteration process is needed to find the right transversality condition required to satisfy the isoperimetric constraint ($Y(T) = B$).

Age-specific optimal vaccination

Adaptive Vaccination Strategies to Mitigate Pandemic Influenza: Mexico as a Case Study by Gerardo Chowell et al. (2009)

We used a mathematical model of the transmission dynamics of pandemic influenza which accounted for age heterogeneity in disease transmissibility ($\mathcal{R}_0$), in addition to age-specific rates of infection, hospitalization and death.

Our mathematical framework incorporated time-dependent vaccination rates in the optimal control framework.

Optimal vaccination policies were computed and analyzed under different vaccination coverage levels and the basic reproduction number ($\mathcal{R}_0$).
(1) which groups should be prioritized for influenza pandemic vaccination?
(2) how much vaccine should be allocated to each group and how do these vaccination rates vary over time?

A single-out break influenza transmission model with age groups

$$
\begin{aligned}
\dot{S}_i(t) &= -u_i(t)S_i(t) - \sum_{i=1}^{6}\beta_{ij}\frac{(I_j(t)+J_j(t))}{N(t)}S_i(t) \\
\dot{V}_i(t) &= \epsilon_i u_i(t)S_i(t) - \eta V_i(t) - \sum_{i=1}^{6}\beta_{ij}\frac{(I_j(t)+J_j(t))}{N(t)}V_i(t) \\
\dot{F}_i(t) &= (1-\epsilon_i)u_i(t)S_i(t) - \sum_{i=1}^{6}\beta_{ij}\frac{(I_j(t)+J_j(t))}{N(t)}F_i(t) \\
\dot{P}_i(t) &= \eta V_i(t) \\
\dot{E}_i(t) &= \sum_{i=1}^{6}\beta_{ij}\frac{(I_j(t)+J_j(t))}{N(t)}(S_i(t)+V_i(t)+F_i(t)) - kE_i(t) \\
\dot{I}_i(t) &= kE_i(t) - (\alpha_i+\gamma_1)I_i(t) \\
\dot{J}_i(t) &= \alpha_i I_i(t) - (\gamma_2+\delta_i)J_i(t) \\
\dot{R}_i(t) &= \gamma_1 I_i(t) + \gamma_2 J_i(t) \\
\dot{D}_i(t) &= \delta_i J_i(t)
\end{aligned}
\tag{8}
$$

The objective functional $\mathcal{F}$ to be minimized is given by the expression:

$$\mathcal{F}(U(t)) = \int_0^T \sum_{i=1}^{6} [I_i(t) + \frac{W_i}{2} u_i{}^2(t)] dt \tag{9}$$

with $U(t) = (u_1(t), ..., u_6(t))$ and $X(t) = (S_i, V_i, F_i, P_i, E_i, I_i, J_i, R_i, D_i)$.

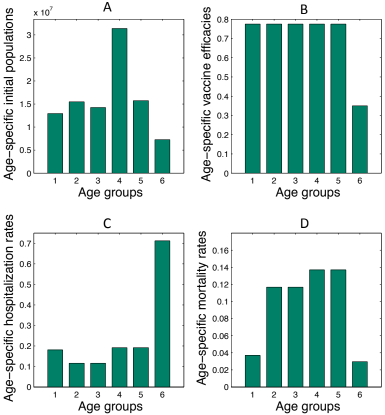
Find an optimal pair, $(U^*(t), X^*(t))$, such that

$$\mathcal{F}(U^*(t)) = min_\Omega \mathcal{F}(U(t)) \tag{10}$$

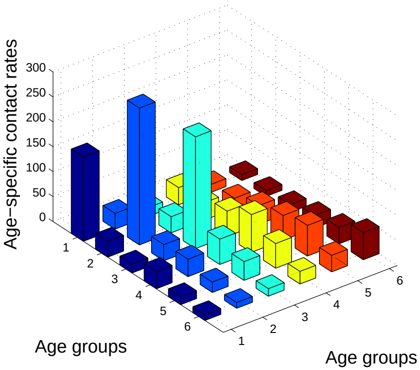
where $\Omega = \{U(t) \in L^1(0, T)^6 \| a \leq U(t) \leq b, t \in [0, T]\}$ subject to the state equations given by (8) with initial conditions. The weight constants W_i represent the desired balancing constants which measure the relative cost of vaccination.

Parameter definitions and baseline values

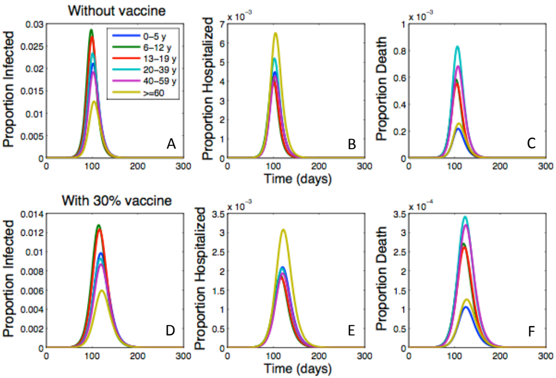
Parameter	Description	Value
k	Rate of progression from latent to infectious (days^{-1})	$1/1.9$
γ_1	Recovery rate (days^{-1}) for infectious class (days^{-1})	$1/1.5$
γ_2	Recovery rate for hospitalized class (days^{-1})	$1/1.5$
η	Rate of progression from vaccinated to protected (days^{-1})	$1/10$
α_i	Age-specific diagnostic rate (days^{-1})	$0.12 - 0.7$
δ_i	Age-specific mortality rate (days^{-1})	$0.03 - 0.14$
ϵ_i	Age-specific efficacy of vaccinations	$0.3 - 0.8$
$I_i(0)$	The initial values (i=2,3)	$1, 5$
T	The simulated duration (days)	300
b	The upper bound of control (vaccination rates, days^{-1})	0.02
W_i	Weight constants on controls	$10^9 - 10^{15}$



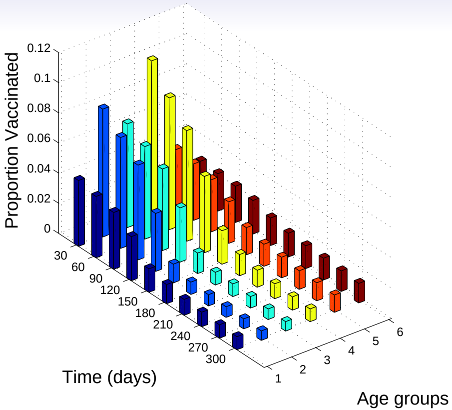
Age-dependent parameters (calibrated for the 2009 A (H1N1) outbreak in Mexico) are shown($1 = 0 - 5y, 2 = 6 - 12y, 3 = 13 - 19y, 4 = 20 - 39y, 5 = 40 - 59y, 6 => 60y$).



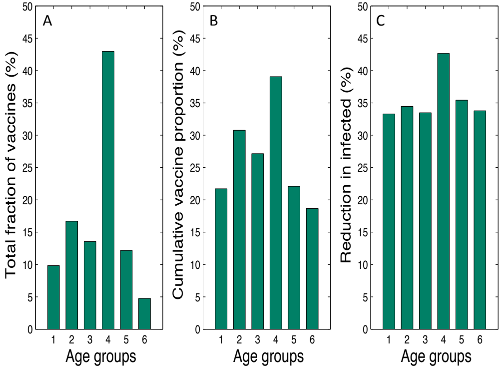
The age-specific contact rate matrix c_{ij} between age groups i and j is illustrated in the bottom panel. The contact rate among the 6-12 y age group is the highest while it is lowest among seniors ($> 60y$).



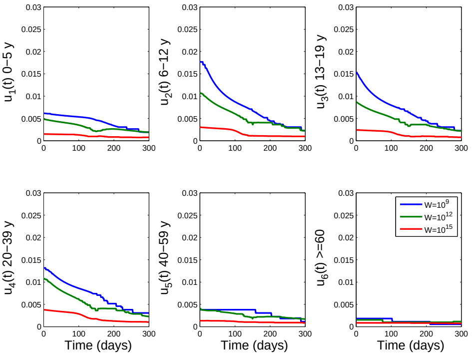
Age-specific incidence curves of clinical cases, hospitalizations and deaths are displayed when $\mathcal{R}_0$=1.8.



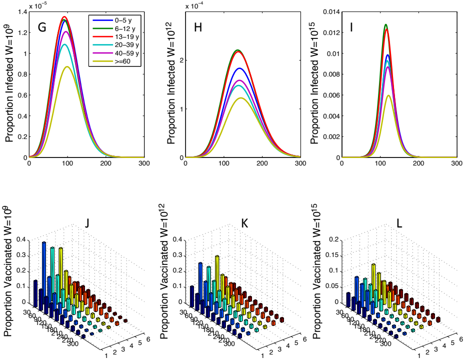
The time series of age-specific vaccinated proportion is shown for each age group.



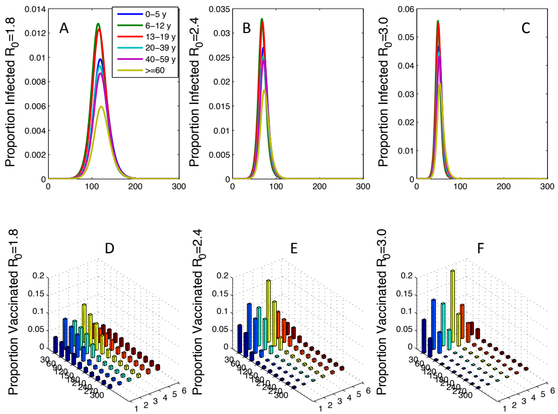
Age-specific fractions of total vaccines, cumulative proportions of vaccinated cases and reductions are illustrated in the graph A, B, C, when $\mathcal{R}_0$=1.8.



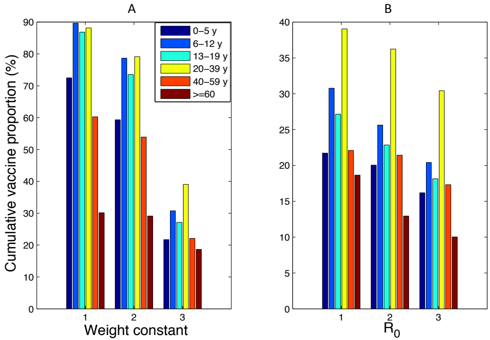
The impact of weight constants on age-specific incidence of infected and vaccinated are explored when $\mathcal{R}_0$=1.8 under three different weight constants $W = 10^9$, $W = 10^{12}$, and $W = 10^{15}$. Age-specific vaccination controls are compared in top six graphs (A-F).



The corresponding age-specific incidence curves of clinical cases are illustrated in the middle three graphs (G-I). Age-specific vaccinated proportions are displayed in the bottom three graphs (J-L). Total vaccine coverages are 77%, 67% and 30% for $W = 10^9$, $W = 10^{12}$, and $W = 10^{15}$, respectively.



Age-specific incidence curves of clinical cases are plotted under three different $\mathcal{R}_0 s$: $\mathcal{R}_0 = 1.8$, $\mathcal{R}_0 = 2.4$, and $\mathcal{R}_0 = 3.0$ (A-C). Total vaccination coverages are 30%, 26% and 21% for $\mathcal{R}_0 = 1.8$, $\mathcal{R}_0 = 2.4$, $\mathcal{R}_0 = 3.0$, respectively.



Cumulative proportions of vaccinated ($\mathcal{R}_0$=1.8 A, 1:$VC = 77\%$, 2:$VC = 67\%$, 3:$VC = 30\%$). B: 1:$\mathcal{R}_0 = 1.8$, 2:$\mathcal{R}_0 = 2.4$, 3:$\mathcal{R}_0 = 3.0$).

Summary

- Monotonic decreasing vaccination rates (the highest rate at the beginning) are optimal for all $\mathcal{R}_0$.
- The total vaccination coverage of 70 %: The school age group (6-12y) is the main target.
- The total vaccination coverage of 30 %: The maximum vaccination coverage is allocated in the age group in the 20-39 y.
- Our analysis demonstrate that high contact rates (6-12y) and the high population density (20-39y) contributed the most to the overall transmissibility of influenza.
- Overall, the optimal vaccination strategy provide relatively high reductions of 36, 37 and 38 %, respectively, in the number of infected, hospitalized and dead, respectively, when $\mathcal{R}_0 = 1.8$ and vaccination coverage of 30%.