# Pulse Vaccination in a Polio Meta-Population Model

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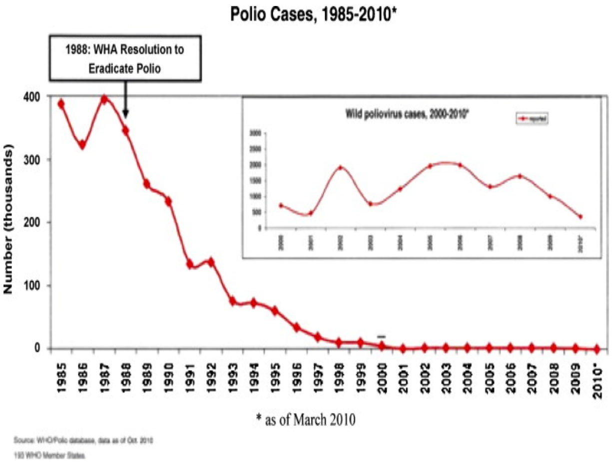
# Outline

# Global Eradication of Polio

- Global initiative to eradicate polio.



# Challenges of Eradication

- Poliovirus remains endemic in Afghanistan, Nigeria, and Pakistan.
- Difficulties posed in these countries:
  - regional instability
  - areas of low immunization
  - large population movements
  - high birth rate
  - environmental transmission

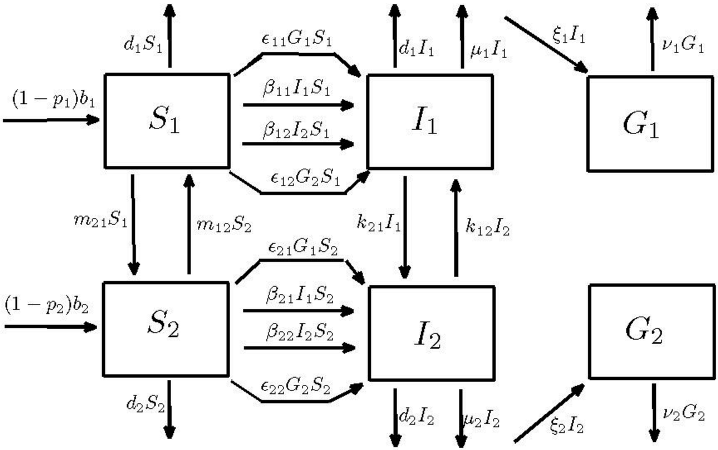
# OPV mass vaccination strategy

- Oral Polio Vaccine (OPV) is live-attenuated vaccine.
- OPV is advocated for developing countries by WHO
- Mass vaccination campaigns: a strategic way to achieve the highest possible coverage in the shortest possible time.
- Types of mass vaccination campaigns: NIDs, SNIDs.

# Meta-population models in epidemiology

- Meta-population: populations are organized in connected cities, towns, or "patches".
- Population movement:
  - short-term mobility
  - long-term migration
  - short term mobility has been modeled with *mass-action coupling*
  - long-term migration has been modeled with *linear flux terms*
- Vaccination strategy in meta-populations
  - optimal vaccine allocation
  - synchrony of population dynamics

# Model diagram (with 2 patches and no pulse vaccination)




- $S_i$ = density of susceptilbles in patch $i$.
- $I_i$ = density of infected in patch $i$.
- $G_i$ = density of virus in environmental reservoir in patch $i$.

# General $N$-patch pulse vaccination model

Let $1 \leq i \leq N$, $k \in \mathbb{N}$, and $0 < \psi_i^k \leq 1$.

$$\begin{cases} \dfrac{dS_i}{dt} &= (1-p_i)b_i - d_i S_i - S_i \displaystyle\sum_j \beta_{ij}(t) I_j - S_i \sum_j \epsilon_{ij}(t) G_j + \sum_j m_{ij} S_j \\ \dfrac{dI_i}{dt} &= S_i \displaystyle\sum_j \beta_{ij}(t) I_j + S_i \sum_j \epsilon_{ij}(t) G_j - (d_i + \mu_i) I_i + \sum_j k_{ij} I_j \\ \dfrac{dG_i}{dt} &= \xi_i(t) I_i - \nu_i(t) G_i & t \neq t_i^k \\ \dfrac{dR_i}{dt} &= p_i b_i + \mu_i I_i - d_i R_i + \displaystyle\sum_j l_{ij} R_j \end{cases}$$

$$\begin{cases} S_i\left(t_i^k\right) &= \left(1-\psi_i^k\right) S_i\left(\left(t_i^k\right)^-\right) \\ R_i\left(t_i^k\right) &= \psi_i^k S_i\left(\left(t_i^k\right)^-\right) & t = t_i^k \end{cases}$$

- $\beta_{ij}(t), \epsilon_{ij}(t), \xi_i(t), \nu_i(t)$ are assumed to be 1-periodic (to capture seasonality).

# Periodic pulses

$$\begin{cases} \dfrac{dS_i}{dt} &= (1-p_i)b_i - d_iS_i - S_i\sum_j \beta_{ij}(t)I_j - S_i\sum_j \epsilon_{ij}(t)G_j + \sum_j m_{ij}S_j \\ \dfrac{dI_i}{dt} &= S_i\sum_j \beta_{ij}(t)I_j + S_i\sum_j \epsilon_{ij}(t)G_j - (d_i+\mu_i)I_i + \sum_j k_{ij}I_j \qquad t \neq n\tau + \phi_\ell \\ \dfrac{dG_i}{dt} &= \xi_i(t)I_i - \nu_i(t)G_i \end{cases}$$

$$\begin{cases} S\left(n\tau + \phi_\ell\right) &= D_\ell \cdot S\left((n\tau+\phi_\ell)^-\right), \qquad t = n\tau + \phi_\ell \end{cases}$$

where

$$n \in \mathbb{N}, \qquad S = (S_1, \dots, S_N)^T, \qquad D_\ell = \mathrm{diag}\left(\alpha_1^\ell, \dots, \alpha_N^\ell\right),$$

$$\text{with} \quad \alpha_i^\ell = \begin{cases} 1 - \psi_i^k & \text{if } \phi_\ell = t_i^k \text{ for some } k \in \mathbb{N} \\ 1 & \text{otherwise} \end{cases}$$

and $0 \leq \phi_1 < \phi_2 < \cdots < \phi_p < \tau$ where $\tau \in \mathbb{N}$ is the fixed period.

# Disease-Free System

In the absence of infection, we obtain a linear impulsive system:

$$\frac{dS(t)}{dt} = AS(t) + b, \qquad t \neq n\tau + \phi_\ell$$
$$S\left(n\tau + \phi_\ell\right) = D_\ell \cdot S\left((n\tau + \phi_\ell)^-\right)$$

**Theorem**

*The disease-free linear impulsive system has a unique globally asymptotically stable $\tau$-periodic solution $\overline{S}(t)$.*

# Disease-Free Periodic Orbit

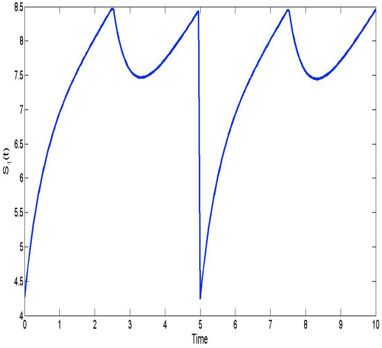



Figure: Disease-Free Periodic Orbit: The components of $\overline{S}(t)$ for certain set of parameters. ($\tau = 5$ in this simulation)

# Linearization

Consider the infectious components linearized at $\overline{S}(t)$:

$$\frac{dI_i}{dt} = \overline{S}_i(t) \sum_j \beta_{ij}(t) I_j + \overline{S}_i(t) \sum_j \epsilon_{ij}(t) G_j - (d_i + \mu_i) I_i + \sum_j k_{ij} I_j$$

$$\frac{dG_i}{dt} = \xi_i(t) I_i - \nu_i(t) G_i$$

- Let $\Phi(t)$ be the principal fundamental solution.
- Define $r$ as the spectral radius of $\Phi(\tau)$, i.e. $r = \rho(\Phi(\tau))$.

# Threshold Dynamics

**Theorem (Global extinction when $r < 1$)**

*If $r < 1$, then the disease-free periodic orbit is globally asymptotically stable.*

Assume that:

(A1) There exists $\theta \in [0, \tau)$ such that the matrix $(\beta_{ij}(\theta) + k_{ij})_{1 \leq i,j \leq N}$ is irreducible.

**Theorem (Uniform persistence when $r > 1$)**

*Suppose that $r > 1$ and (A1) holds. Then the system is uniformly persistent, i.e. there exists $\delta > 0$ such that if $\beta_{ij} I_j(0) > 0$ or $\epsilon_{ij} G_j(0) > 0$, for some $1 \leq i, j \leq N$, then*

$$\liminf_{t \to \infty} I_i(t) > \delta \quad \forall i = 1, \ldots, N.$$

# Defining $\mathcal{R}_0$ (Bacaër and Guernaoui, 2006; Wang and Zhao, 2008)

- Write the "infectious component linearization" as $\dfrac{dx}{dt} = (F(t) - V(t))x$ where $F :=$ new infections.
- Let $Y(t,s)$, $t \geq s$, be the evolution operator of the linear $\tau$-periodic system: $\dfrac{dy}{dt} = -V(t)y$.
- Define the "next infection" operator $L : C_\tau \to C_\tau$ by

$$(L\phi)(t) = \int_{-\infty}^{t} Y(t,s)F(s)\phi(s)\, ds, \quad \forall t \in \mathbb{R},\ \phi \in C_\tau.$$

  where $C_\tau :=$ the Banach space of continuous $\tau-$periodic functions from $\mathbb{R} \to \mathbb{R}^{2N}$.
- $\mathcal{R}_0 := \rho(L)$
- $\mathcal{R}_0 < 1 \Leftrightarrow r < 1$ and $\mathcal{R}_0 > 1 \Leftrightarrow r > 1$.
- $\mathcal{R}_0$ is threshold with biological meaning.

# Two identical patches (with no mass-action coupling)

$$
\begin{cases}
\dfrac{dS_1}{dt} &= b - dS_1 - (1-f)\beta(t)I_1S_1 - f\epsilon G_1S_1 - mS_1 + mS_2 \\
\dfrac{dI_1}{dt} &= (1-f)\beta(t)I_1S_1 + f\epsilon G_1S_1 - (d+\mu)I_1 - mI_1 + mI_2 \qquad t \neq n \\
\dfrac{dG_1}{dt} &= \xi I_1 - \nu(t)G_1
\end{cases}
$$

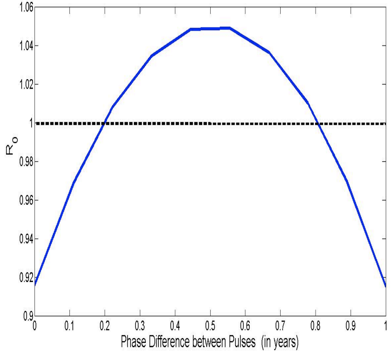
$$
\begin{cases}
\dfrac{dS_2}{dt} &= b - dS_2 - (1-f)\beta(t)I_2S_2 - f\epsilon G_2S_2 - mS_1 + mS_2 \\
\dfrac{dI_2}{dt} &= (1-f)\beta(t)I_2S_2 + f\epsilon G_2S_2 - (d+\mu)I_2 - mI_1 + mI_2 \qquad t \neq n+\phi \\
\dfrac{dG_2}{dt} &= \xi I_2 - \nu(t)G_2
\end{cases}
$$

$$
\begin{cases}
S_1(n) &= S_1(n^-), \qquad t = n \\
S_2(n+\phi) &= S_2((n+\phi)^-), \qquad t = n+\phi
\end{cases}
$$

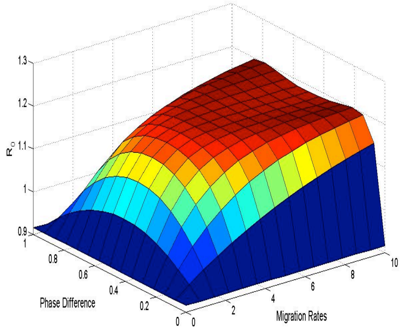
- $0 \le f \le 1$ is fraction of environmental transmission.

# Importance of Synchronizing Pulses

Example with no seasonality or environmental transmission.

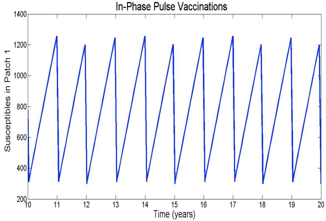



(a) $\mathcal{R}_0$ vs Phase difference $\phi$

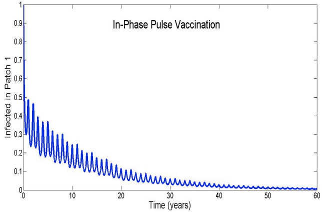



(b) $\mathcal{R}_0$ vs Phase difference $\phi$ and migration rate $m$

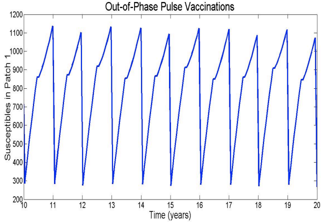
# Simulations of Impulsive Model



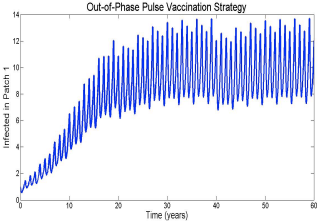

(c) In-phase (susceptibles)




(d) In-phase (infected)



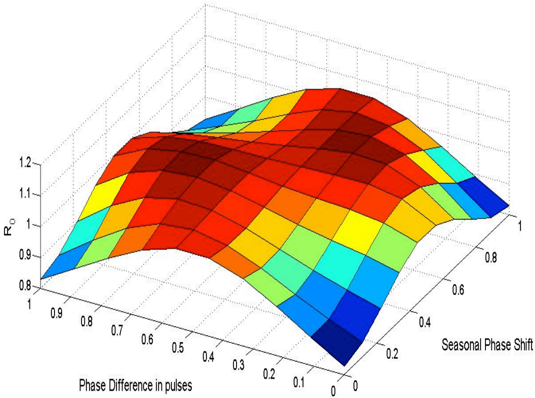

(e) Out-of-phase (susceptibles)




(f) Out-of-phase (infected)

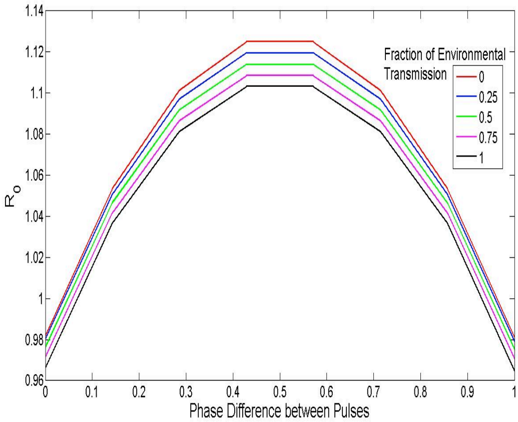
# Effect of Seasonality

Let $\beta(t) = \beta(1 + a\sin(2\pi(t - \theta)))$.




It is best to synchronize pulse vaccinations during the season before the high-transmission season.

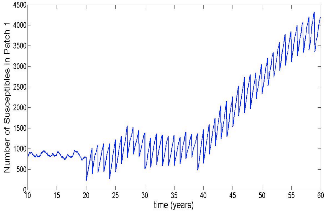
# Environmental Transmission



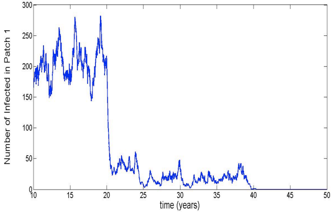
# Pulse Vaccination vs Continuous Vaccination Strategy

- Compared pulse vaccination and continuous vaccination strategy in terms of $\mathcal{R}_0$ for a given expected number of vaccinations per year.
- Simulations show that synchronized pulse vaccination and continuous vaccination are essentially equal.
- Similar to recent result in *SIR* model (Onyango and Müller, 2013).
- Should pulse vaccination have any advantage over continuous vaccination?

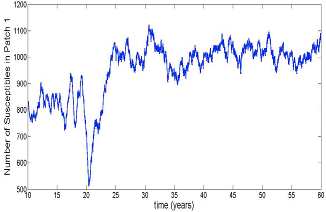
# Stochastic Simulations



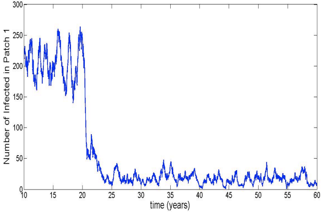

(g) Pulse Vaccination (susceptible)




(h) Pulse Vaccination (infected)

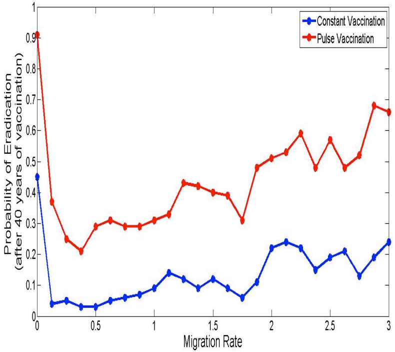



(i) constant vaccination (susceptible)

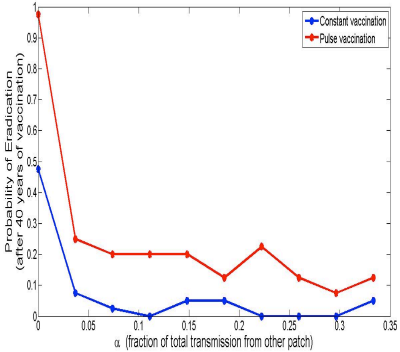



(j) constant vaccination (infected)

# Probability of Eradication

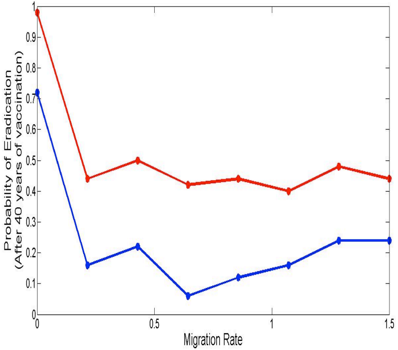



(k) Probability of eradication vs migration rate

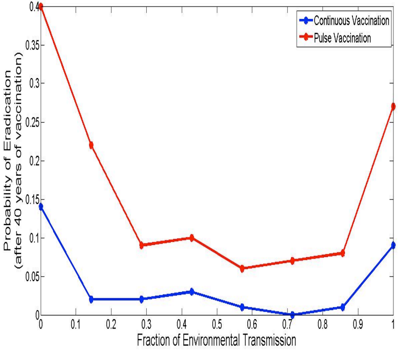



(l) Probability of eradication vs mass-action coupling

# Probability of Eradication




(m) Probability of eradication vs migration rate
(with seasonality)




(n) Probability of eradication vs fraction of environmental transmission

# Summary and Conclusions

- We consider an impulsive *SIR*-type meta-population model with seasonality, environmental transmission, and arbitrary pulse vaccination schedules in each patch.
- A basic reproduction number, $\mathcal{R}_0$, is defined and proved to be a global threshold for the system.
- Numerical calculations show the importance of, both, synchronizing the pulse vaccinations between the patches.
- When including stochasticity, it is found that pulse vaccination has a major advantage over a continuous vaccination strategy in terms of the probability of eradication.

# Ongoing and Future Work

- Include multiple susceptibility classes to capture the fact that multiple doses of OPV are needed to gain immunity.
- Investigate reversion of vaccine virus to wild-polio virus and the effect on eradication.
- Parametrize model.

# Acknowledgments

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Thank you for your attention!

Questions?

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