Vaccine Induced Pathogen Type Replacement:

Theoretical Mechanism

DIMACS Workshop on Co-evolution

October 11, 2006

*****

Maia Martcheva

University of Florida

This talk is based on various sources and three articles joint with

*****

Mimmo Ianneli
University of Trento, Italy

Xue-Zhi Li
Xinyang Normal University, China

Benjamin Bolker and *Robert D. Holt*
University of Florida

Outline

1. Introduction: Achievements of vaccination
2. Vaccination in multi-strain diseases
3. The Replacement effect
4. The Replacement effect without differential effectiveness – the case of super-infection
5. The Replacement effect without differential effectiveness – the case of coinfection
6. Theoretical mechanism of strain replacement with and without differential effectiveness
7. The Replacement effect and other trade-off mechanisms
8. Concluding remarks

Achievements of vaccination

Disease	Baseline years	Cases/year	Cases in 1998	% Decrease
Smallpox	1900-1904	48,164	0	100
Diphtheria	1920-1922	175,885	1	100
Pertussis	1922-1925	147,271	6,279	95.7
Tetanus	1922-1926	1,314	34	97.4
Poliomyelitis	1951-1954	16,316	0	100
Measles	1958-1962	503,282	89	100
Mumps	1968	152,209	606	99.6
Rubella	1966-1968	47,745	345	99.3
Hib	1985	20,000	54+71	99.7

Source: CDC, Morbidity and Mortality Weekly report (MMWR) 48 (12) 1999. *Achievements of Public Health, 1900-1999: Impact of Vaccines Universally Recommended for Children - US, 1990-1998.*

Vaccination is most effective against viruses or bacteria:

- are represented by few types that vary (mutate) little;

Vaccination in Multi-strain Diseases

If a disease is represented by many strains typically only some of the strains are included in the vaccine - *vaccine strains*. Vaccination is:

1. Against the dominant strain;
2. Against several strains which account for the most of the cases;
3. When possible against all subtypes one by one.

Examples:

- **Poliomyelitis** is represented by 3 serotypes. Vaccination against each one is necessary but produces promising results.
- **Bacterial pneumonia** is represented by 90 serotypes. Polysaccharide vaccines contain up to 23 most common serotypes.
- **Influenza:** Virus continuously mutates. Vaccine is trivalent updated every year - contains 2 type A strains and 1 type B strain.

• **Replacement effect:** The replacement effect occurs when one strain or subtype is eliminated due to vaccination and at the same time another strain or subtype increases in incidence.

Reported increases in non-vaccine strains after vaccination.

Disease	Vaccine	Increase in	Region	Refs
H. influenzae	Hib	non-type b	Alaska	3 Refs
	Hib	type f	m. states, US	1 Ref
	conj. Hib	type a	Brazil	1 Ref
	conj. Hib	noncapsulated	UK	2 Refs
S. pneumoniae	PCV-7	NVT	Finland	1 Ref
	PCV-7	NVT (carriage)	US	2 Refs
	PCV-7	Serogroups 15 and 33	US PMPSG, US	1 Ref
	PCV-7	NVT (AOM)	Pittsburgh	2 Refs
	PPV-23	12F*, 7F, 22F, 7C	Alaska	1 Ref
N. meningitidis	A-C vaccine	serogroup B	Austria	1 Ref
	A-C vaccine	serogroup B	Europe	3 Refs
	A-C vaccine	serogroup B	Cuba	1 Ref

Note: NVT = non-vaccine types, AOM = acute otitis media. The * denotes an outbreak of a strain included in the PPV-23.

What causes strain replacement?

Presumed main mechanism: *differential effectiveness of the vaccine.* In particular, for a 2 strain pathogen, a vaccine that targets the dominant strain, eliminates it and frees the ecological niche for the proliferation of the other strain.

Methods to combat strain replacement:

1. Include more strains (preferably all) strains in the vaccine.

   • This has been the case with the polysaccharide pneumococcal vaccines: Clinical trials with 6-, 12-, 14-, 15-, 17-, 23- valent vaccines. Licensed: 14-valent, and now 23-valent.

2. Target some feature common to all strains.

   • ID Biomedical announced completion of phase 1 of a **group-common** vaccine that "elicits antibodies that bind to the surface of pneumococci and that recognize strains from all 90 known serotypes".

• Differential effectiveness causes replacement.

Question: If we eliminate differential effectiveness would we eliminate pathogen strain replacement?

We considered a mathematical model of SIS type with two strains and vaccination. Assumptions:

- vaccine is 100% effective with respect to both strains "perfect vaccine";
- strain one can super-infect individuals with strain two (but not vice-versa).

• Strain i super-infects strain j if individuals already infected with strain j can get infected with strain i. Upon infection with strain i, strain i immediately "takes over" and the individual previously infected with strain j is now infected with strain i.

A Two Strain Model with Vaccination:

Variables:

t - time

$N(t)$ - total population size at time t

$S(t)$ - number of susceptibles

$I(t)$ - number of individuals infected with strain one

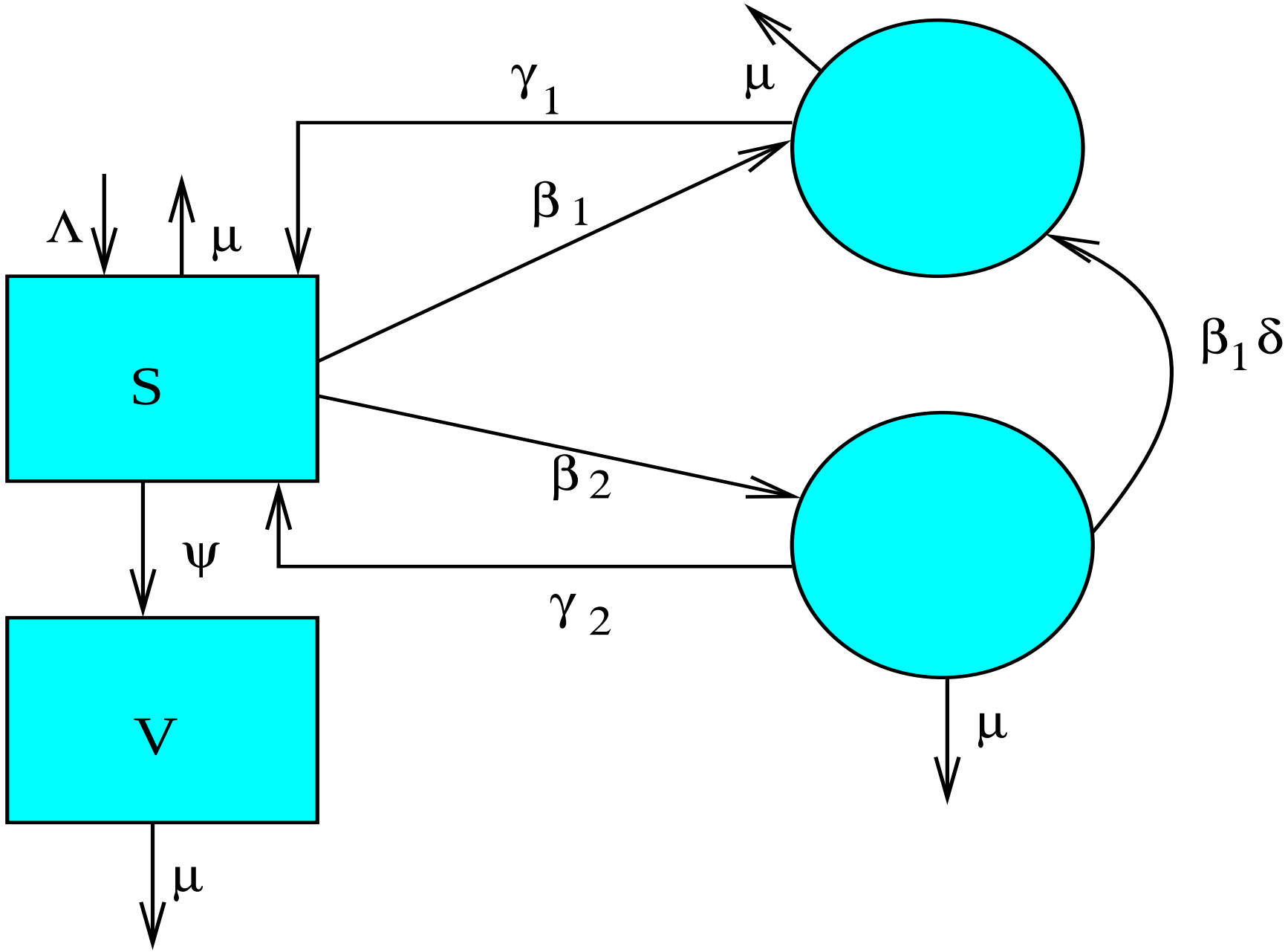
$J(t)$ - number of individuals infected with strain two

$V(t)$ - number of vaccinated individuals at time t.

We have

$$N(t) = S(t) + I(t) + J(t) + V(t)$$

Model Flow-chart:



The Model:

$$
\begin{aligned}
\boldsymbol{S'(t)} &= \boldsymbol{\Lambda - \beta_1 \frac{SI}{N} - \beta_2 \frac{SJ}{N} - (\mu + \psi)S + \gamma_1 I + \gamma_2 J,} \\
\boldsymbol{I'(t)} &= \boldsymbol{\beta_1 \frac{SI}{N} + \beta_1 \delta \frac{IJ}{N} - (\mu + \gamma_1)I,} \\
\boldsymbol{J'(t)} &= \boldsymbol{\beta_2 \frac{SJ}{N} - \beta_1 \delta \frac{IJ}{N} - (\mu + \gamma_2)J,} \\
\boldsymbol{V'(t)} &= \boldsymbol{\psi S(t) - \mu V(t),}
\end{aligned}
$$

$\boldsymbol{\Lambda}$ - birth/recruitment rate; $\boldsymbol{\mu}$ - natural death rate;

$\boldsymbol{\beta_1}$ - transmission coefficients of strain one;

$\boldsymbol{\beta_2}$ - transmission coefficients of strain two;

$\boldsymbol{\delta}$ - coefficient of reduction ($\boldsymbol{\delta < 1}$) or enhancement ($\boldsymbol{\delta > 1}$)

$\boldsymbol{\gamma_1}$ - recovery rate of strain one;

$\boldsymbol{\gamma_2}$ - recovery rate of strain two;

$\boldsymbol{\psi}$ - vaccination rate.

- Counter-intuitively, we observe replacement:

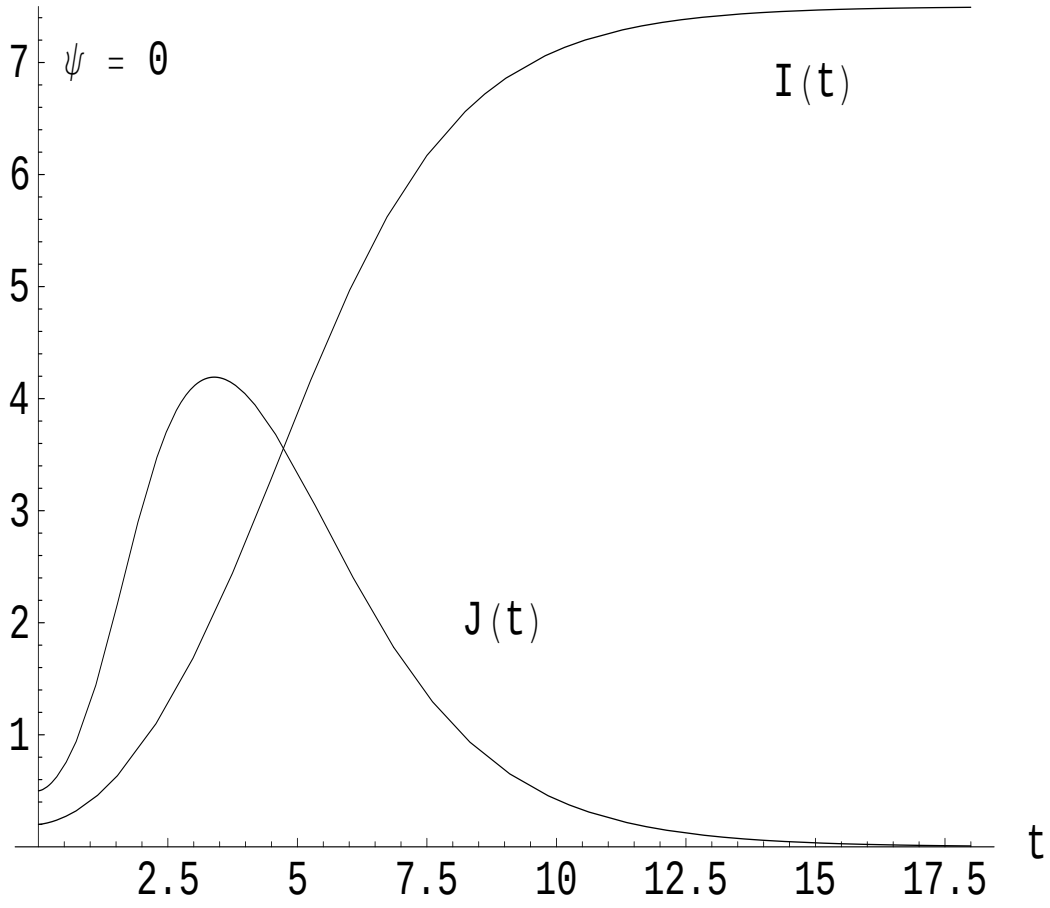


Fig.1. With no vaccination, that is $\psi = 0$, strain one eliminates strain two and dominates in the population. Here $I(t)$ is the number of infected with strain one, $J(t)$ is the number of infected with strain two, t - time, and ψ is the vaccination rate.

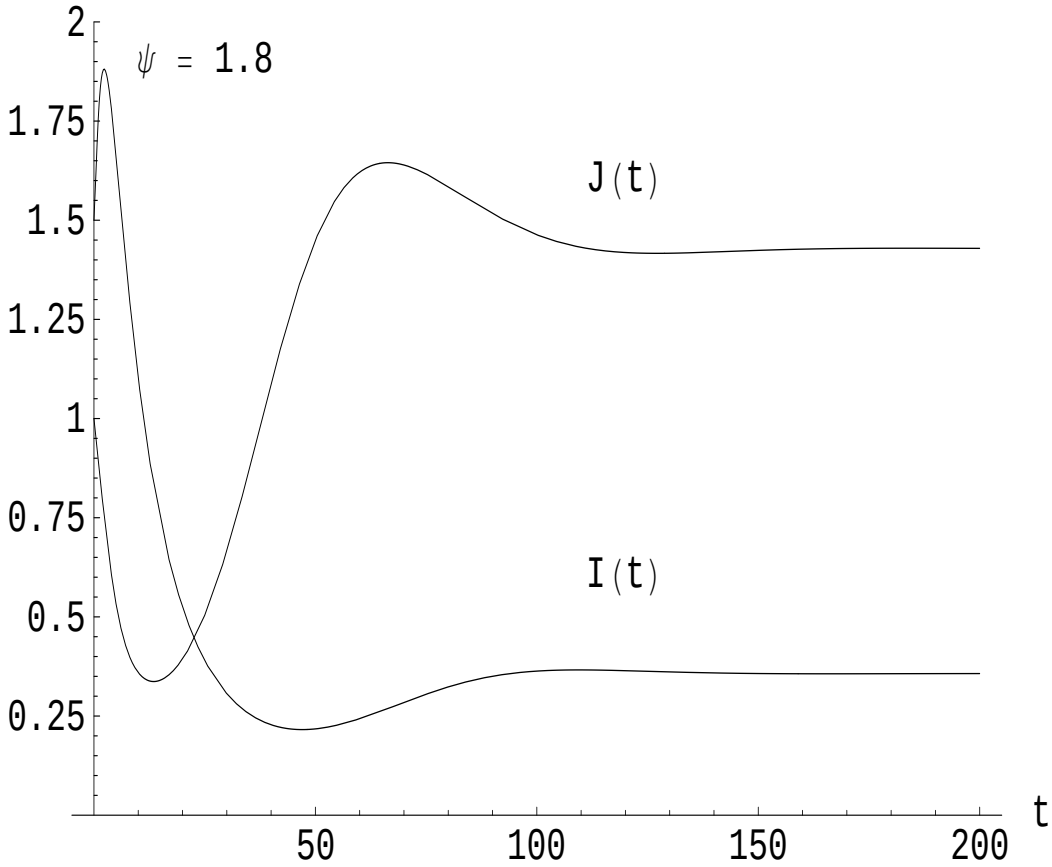


Fig.2. For medium-low vaccination levels, that is $\psi = 1.8$, strain two ($J(t)$) invades the equilibrium of strain one ($I(t)$) and the two strains coexist. Strain two ($J(t)$) has the higher reproduction number and higher prevalence.

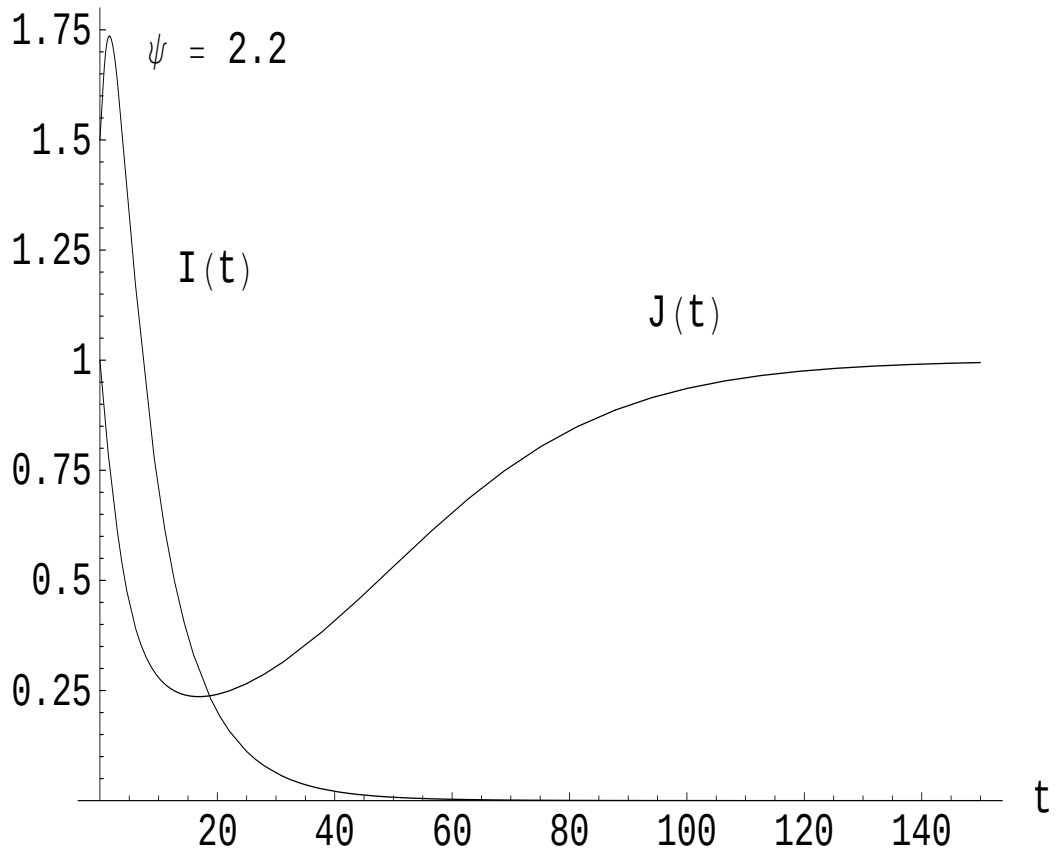


Fig.3. For medium-high vaccination levels, that is $\psi = 2.2$, strain two ($J(t)$) eliminates strain one ($I(t)$) and dominates in the population. Thus, vaccination enables the weaker strain, strain two $J(t)$, to replace the stronger strain, strain one $I(t)$ in the population.

Observation 1: Coexistence is necessary for the strains to exchange dominance.

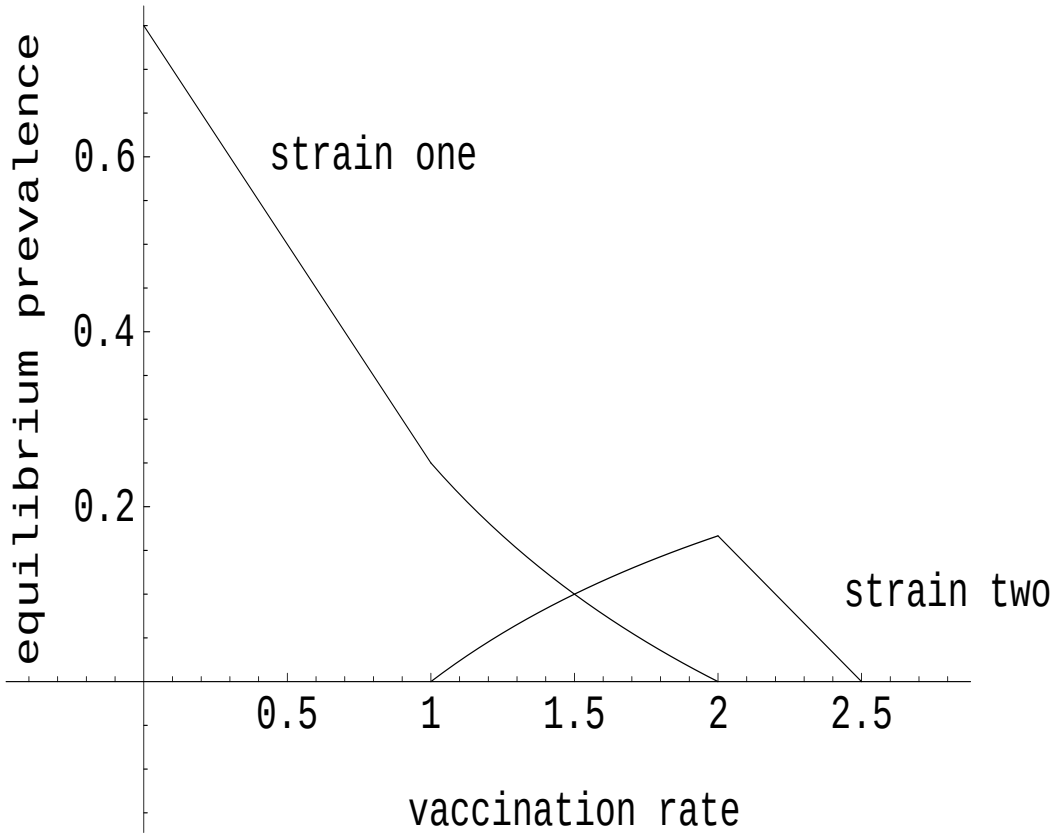


Fig.4. Graph of the equilibrium levels of the two strains in terms of the vaccination rate ψ. First, strain one dominates, then the two strains coexist. For medium-high vaccination level second strain dominates. For high vaccination rates both strains are eliminated.

• Super-infection is a well-known mechanism that leads to coexistence – *trade-off mechanism*.

Trade-off mechanism - any process that allows a competitively weak strain to coexist with a dominant strain. In the absence of a such mechanism the dominant strain must (eventually) exclude the weaker strain.

Well-known trade-off mechanisms: (not exhaustive)

1. super-infection;
2. coinfection;
3. mutation;
4. cross-immunity;
5. density-dependent host mortality;
6. exponential growth of the host population.

Questions: Is there anything special about super-infection? Do other trade-off mechanisms lead to strain replacement even with perfect vaccine?

• Does coinfection lead to strain replacement with perfect vaccination?

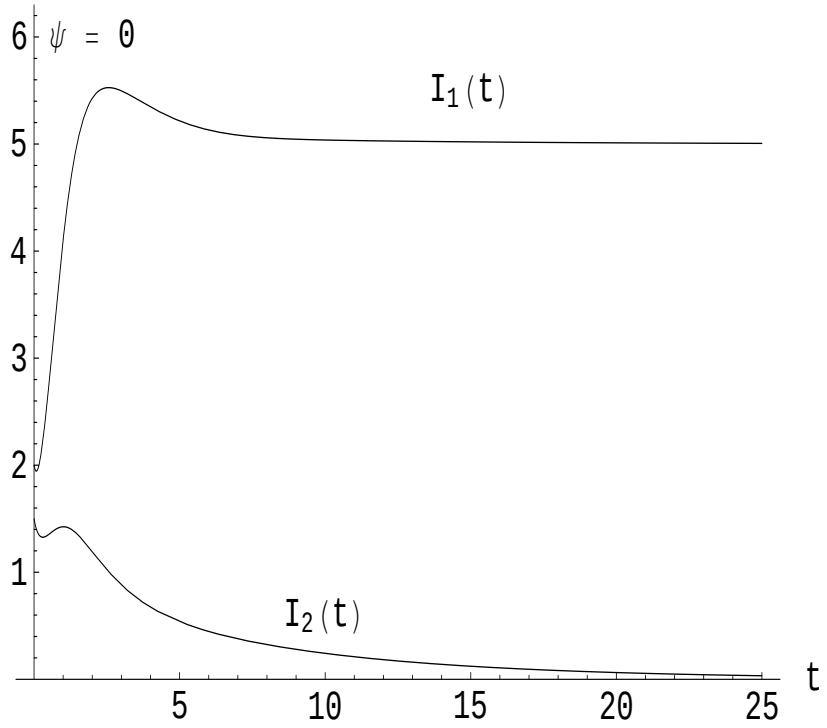
Coinfection is the simultaneous infection of a host by multiple strains.

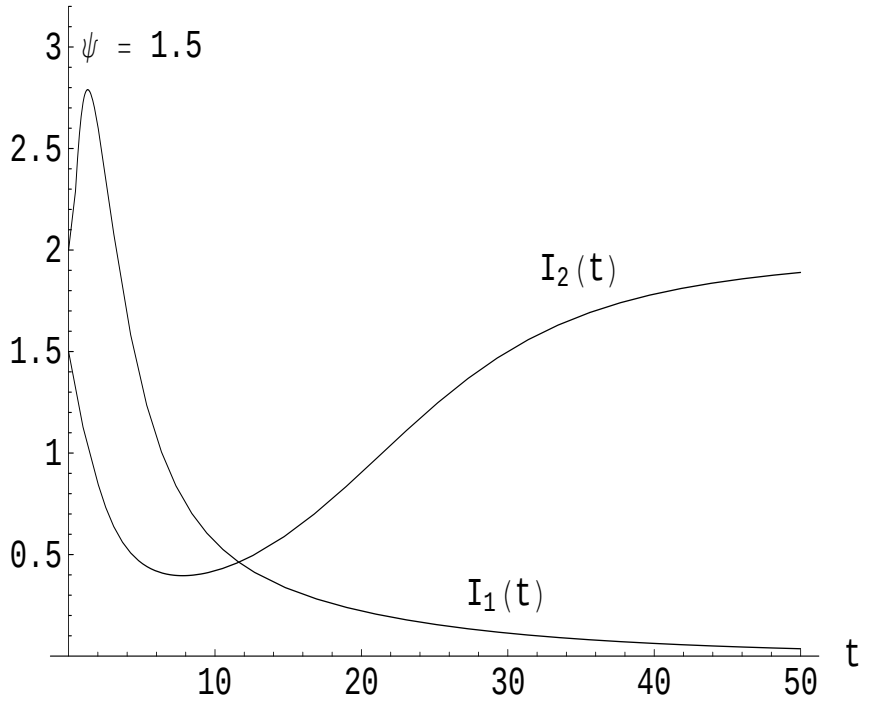
We considered a mathematical model of SIR type with two strains and vaccination. Assumptions:

- "perfect vaccine" – 100% effective with respect to both strains;
- strain two cannot coinfect individuals infected with strain one;
- jointly infected individuals cannot infect with strain two

Note: The last two assumptions make strain two weaker. While certain asymmetry between the strains seems necessary, it does not have to be this strong.

• Coinfection coupled with perfect vaccination leads to strain replacement





The figure shows that strain replacement occurs in the model with coinfection. The left figure shows that strain one ($\boldsymbol{I_1(t)}$) dominates while strain two ($\boldsymbol{I_2(t)}$) is eliminated when there is no vaccination $\boldsymbol{\psi = 0}$. The right figure shows that strain two ($\boldsymbol{I_2(t)}$) dominates while strain one ($\boldsymbol{I_1(t)}$) is eliminated when vaccination is at level $\boldsymbol{\psi = 1.5}$. The reproduction numbers with $\boldsymbol{\psi = 0}$ are $\boldsymbol{\mathcal{R}_1 = 4}$ and $\boldsymbol{\mathcal{R}_2 = 5}$.

The Mechanism of strain replacement

- If the vaccination rate is ψ, the the reproduction numbers of each strain are functions of ψ

$$\mathcal{R}_1(\psi) \qquad\qquad \mathcal{R}_2(\psi)$$

- Both reproduction numbers are **decreasing** functions of ψ
- Let $\mathcal{R}_1 = \mathcal{R}_1(0)$ and $\mathcal{R}_2 = \mathcal{R}_2(0)$
- Let $\hat{\mathcal{R}}_1(\psi)$ - **invasion reproduction number of strain one**;

  Let $\hat{\mathcal{R}}_2(\psi)$ - **invasion reproduction number of strain two**.

  The invasion reproduction number (IRN) of strain i gives the number of secondary infections that one infected individual with strain i will produce in a population in which strain j is at equilibrium.

- The IRNs are functions of the vaccination rate ψ but they may be **increasing**, **decreasing**, or in general, **non-monotone**.

- Criteria for dominance and coexistence

  1. $\boldsymbol{\mathcal{R}_1(\psi) > 1}$, $\boldsymbol{\hat{\mathcal{R}}_1(\psi) > 1}$ and $\boldsymbol{\hat{\mathcal{R}}_2(\psi) < 1}$ strain one dominates.
  2. $\boldsymbol{\mathcal{R}_2(\psi) > 1}$, $\boldsymbol{\hat{\mathcal{R}}_1(\psi) < 1}$ and $\boldsymbol{\hat{\mathcal{R}}_2(\psi) > 1}$ strain two dominates.
  3. $\boldsymbol{\hat{\mathcal{R}}_1(\psi) > 1}$ and $\boldsymbol{\hat{\mathcal{R}}_2(\psi) > 1}$ the two strains coexist.

- Strain replacement will occur under the following scenario

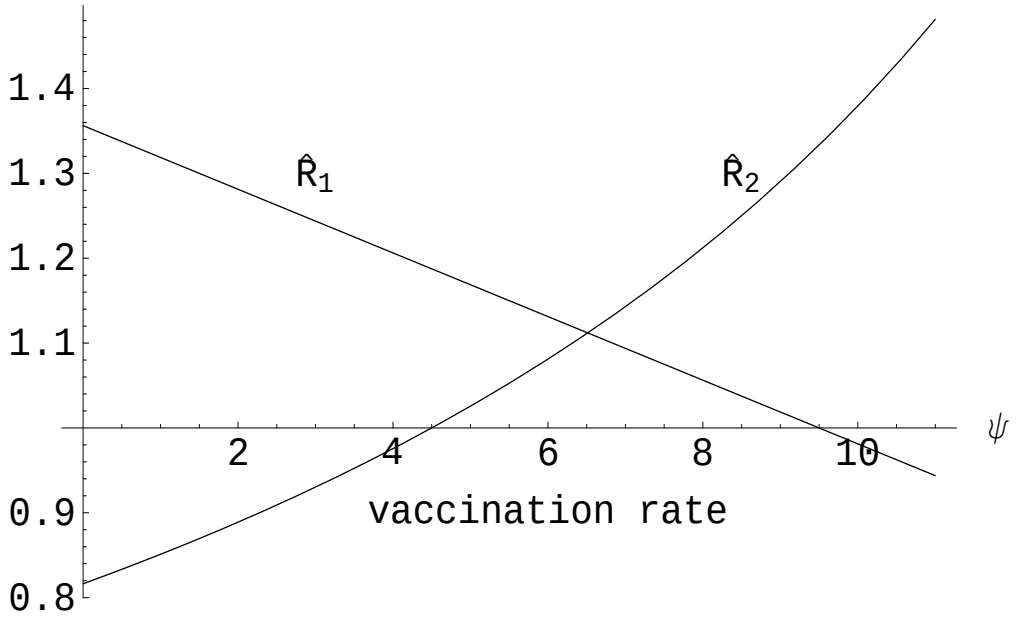
  – Suppose in the absence of vaccination $\boldsymbol{\psi = 0}$, we have $\boldsymbol{\hat{\mathcal{R}}_1(0) > 1}$ while $\boldsymbol{\hat{\mathcal{R}}_2(0) < 1 \Longrightarrow}$ strain one dominates.

  – Suppose $\boldsymbol{\hat{\mathcal{R}}_1(\psi)}$ is a decreasing function of $\boldsymbol{\psi}$ while $\boldsymbol{\hat{\mathcal{R}}_2(\psi)}$ is an increasing function of $\boldsymbol{\psi}$.

  – Then for some $\boldsymbol{\psi^*}$ large enough we will have $\boldsymbol{\hat{\mathcal{R}}_1(\psi^*) < 1}$ and $\boldsymbol{\hat{\mathcal{R}}_2(\psi^*) > 1 \Longrightarrow}$ strain two dominates

  – provided $\boldsymbol{\mathcal{R}_1(\psi^*) > 1}$ and $\boldsymbol{\mathcal{R}_2(\psi^*) > 1}$.

- This is the case both with super-infection and coinfection:



Graph of the invasion reproduction numbers in terms of the vaccination rate ψ in the case of coinfection with perfect vaccine. Figure shows that $\hat{\mathcal{R}}_1(\psi)$ is a decreasing function while $\hat{\mathcal{R}}_2(\psi)$ is an increasing function. For $\psi < 4.5$ we have $\hat{\mathcal{R}}_1 > 1$ while $\hat{\mathcal{R}}_2 < 1$ and strain one will competitively exclude strain two. For $4.5 < \psi < 9.5$ we have $\hat{\mathcal{R}}_1 > 1$ and $\hat{\mathcal{R}}_2 > 1$ and the two strains coexist. For $\psi > 9.5$ we have $\hat{\mathcal{R}}_1 < 1$ while $\hat{\mathcal{R}}_2 > 1$ so strain two prevails.

Question: Does "perfect" vaccination' coupled with all trade-off mechanisms lead to strain replacement.

Answer: No. Coupled with cross-immunity it does not.

We considered a mathematical model of SIR type with two strains and vaccination. Assumptions:

- "perfect" vaccine – 100% effective with respect to both strains;
- **cross-immunity**: individuals who have recovered from the first strain can get infected by the second with reduced transmissibility; and vice-versa.
- individuals who have had both strains are completely removed.

The IRN are (c_1, c_2 constants dependent on the parameters):

$$\hat{\mathcal{R}}_1(\psi) = \frac{\mathcal{R}_1}{\mathcal{R}_2} + \mathcal{R}_1 c_1 \left(1 - \frac{1}{\mathcal{R}_2(\psi)}\right) \quad \hat{\mathcal{R}}_2(\psi) = \frac{\mathcal{R}_2}{\mathcal{R}_1} + \mathcal{R}_2 c_2 \left(1 - \frac{1}{\mathcal{R}_1(\psi)}\right)$$

- Both IRN are **decreasing** functions of ψ.

Question: Which trade-off mechanisms lead to replacement with "perfect" vaccination and which do not?

Several hypotheses:

1. **Hypothesis 1:** Possibility of "perfect" vaccine-induced type replacement depends on the details of the competitive outcomes at the within-host level.

2. **Hypothesis 2:** In the absence of vaccination, super-infection and coinfection allow for dominance of the strain with the lower reproduction number.

   Assume $\mathcal{R}_1 > \mathcal{R}_2$.

   $$\text{strain 1} \xrightarrow[\textit{super-infection}]{\textit{coinfection}} \text{strain 2}$$

   Vaccination restores the dominance of the strain with larger reproduction number:

   $$\text{strain 1} \xrightarrow[\textit{super-infection}]{\textit{coinfection}} \text{strain 2} \xrightarrow{\textit{vaccination}} \text{strain 1}$$

Concluding remarks

1. Strain replacement can occur even when vaccine protects 100% against each strain ("perfect" vaccine).

2. When the vaccine is "perfect" some trade-off mechanism is necessary for the replacement effect to occur.

3. "Perfect" vaccines lead to strain replacement with super-infection and coinfection.

4. "Perfect" vaccines do not lead to strain replacement when the trade-off mechanism is cross-immunity.

5. Mechanism: Vaccines (even "perfect" vaccines) differentiate between the strains by decreasing the invasion capabilities of the stronger strain and increasing the invasion capabilities of the weaker strain.

6. We have **two hypotheses** on which trade-off mechanisms may lead to replacement with "perfect" vaccination. Further studies are necessary to evaluate which one is true.